Quantitative Genetic Models for Genomic Imprinting

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Abstract

A gene is imprinted when its expression is dependent on the sex of the parent from which it was inherited. An increasing number of studies are suggesting that imprinted genes have a major influence on medically, agriculturally and evolutionarily important traits, such as disease severity and livestock production traits. While some genes have a large effect on the traits of an individual, quantitative characters such as height are influenced by many genes and by the environment, including maternal effects. The interaction between these genes and the environment produces variation in the characteristics of individuals. Many quantitative characters are likely to be influenced by a small number of imprinted genes, but at present there is no general theoretical model of the quantitative genetics of imprinting incorporating multiple loci, environmental effects and maternal effects. This research develops models for the quantitative genetics of imprinting incorporating these effects, including deriving expressions for genetic variation and resemblances between relatives. Imprinting introduces both parent-of-origin and generation dependent differences in the derivation of standard quantitative genetic models that are generally equivalent under Mendelian expression. Further, factors such as epistasis, maternal effects and interactions between genotype and environment may mask the effect of imprinting in a quantitative trait. Maternal effects may also mimic a number of signatures in variance and covariance components that are expected in a population with genomic imprinting. This research allows a more comprehensive understanding of the processes influencing an individual’s characteristics.
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Supplementary Material

A CD is enclosed on the back page. This CD contains summaries of Mathematica® files used to derive the quantitative genetic expressions for variances and covariances in Chapters 3, 4, 5 and 6, saved in pdf format. A more comprehensive index is included on the CD.


Manuscripts

Chapter 3 “Intergenerational effects imposed by genomic imprinting invalidate some simple derivations of variance components in quantitative genetic models” [AW Santure and HG Spencer] has been submitted to Theoretical Population Biology and the editor has requested that some revisions be made.

Chapter 6 “Quantitative genetic models for maternal effects and genomic imprinting” [AW Santure and HG Spencer] is in press for Genetics.

Chapters 2, 4, 5 and 8 are also intended for publication.
1. Introduction

Genomic imprinting

In general, mammals inherit two copies of each gene (each copy termed an allele) – one from their father and one from their mother. Genes may be active or inactive in an organism through developmental stages or in different tissue types, and usually either both maternally and paternally inherited alleles will be expressed, or both will be inactive. In contrast, a gene is imprinted when its expression is dependent on the sex of the parent it was inherited from. Thus, unlike the majority of other genes, one allele may be silent while the other is expressed. A well-characterised example of an imprinted gene is insulin-like growth factor II (\textit{IGF2}), which is expressed predominantly from the paternally inherited allele in both eutherian and marsupial mammals [Morison et al., 2001; www.otago.ac.nz/IGC], including mouse [DeChiara et al, 1991], deer mouse [Vrana et al., 1998], human [Giannoukakis et al., 1993; Rainier et al., 1993; Ogawa et al., 1993; Ohlsson et al., 1993], sheep [McLaren and Montgomery, 1999], cow [Dindot et al., 2004], rat [Pedone et al., 1994] and pig [Nezer et al., 1999; Jeon et al., 1999], and wallaby [Suzuki et al., 2005] and opossum [O’Neill et al., 2000].

Genomic imprinting represents a spectrum of unequal expression of maternal and paternal alleles, from one allele always being expressed and the other repressed, through to very slight differences in the timing or amount of expression of maternal and paternal alleles, or tissue-specific monoallelic expression. For example, the imprinted gene \textit{Ipl} (Imprinted in Placenta and Liver) is expressed predominantly from the maternal allele in mouse placenta and yolk sac, fetal liver and lung and adult spleen, but in the brain and adult kidney \textit{Ipl} is expressed from both maternal and paternal alleles, although paternal expression is lower [Qian et al., 1997]. As well as tissue specific expression, a gene may show variable imprinting status among individuals within a species, termed polymorphic imprinting [Naumova and Croteau, 2004]. For example, in humans a small proportion of individuals express only the maternally inherited allele of \textit{IGF2R} (insulin-like growth factor II receptor) [Xu et al., 1993] but it is generally transcribed from both alleles in the rest of the population [Kalscheuer et al., 1993]. Most generally, therefore, imprinting results in the functional non-equivalence of reciprocal heterozygotes, where the phenotype of
individuals with a maternally derived $A_1$ allele and a paternally derived $A_2$ allele is not equivalent to the phenotype of individuals with the reverse inheritance pattern [Spencer et al., 1999].

The first evidence for genomic imprinting in mammals arose from pronuclear transplantation studies in mice, where all nuclear genes are either maternally (gynogenetic) or paternally (androgenetic) derived. Gynogenetic embryos develop normally but membrane and placenta development is poor, while androgenetic mice develop normal membranes and placentas but embryo structures do not develop [Surani et al., 1984; McGrath and Solter, 1984; Cattanach and Kirk 1985; reviewed in Reik and Walter, 2001]. Early evidence for the separate and complementary roles of maternally and paternally derived genomes also includes study of human triploids, uniparental chromosome disomies, chromosome duplications and deletions and analysis of transgene expression [reviewed in Hall, 1990]. For example, DeChiara et al. [1990] derived transgenic mice with a targeted mutation in $IGF2$ designed to disrupt expression of the gene. Heterozygous mice that inherited the disrupted copy of $IGF2$ from their father exhibited significant growth retardation, while those with maternally inherited copies of the mutation grew normally [DeChiara et al., 1991]. Biochemical studies confirmed exclusive paternal expression, and silencing of maternal alleles, in the majority of embryonic tissues [DeChiara et al, 1991]. Approximately 83 imprinted genes have now been identified in mammals, including 41 in humans [Morison et al., 2005].

**Establishment and maintenance of imprinting**

The manifestation of genomic imprinting requires that maternal and paternal genomes are distinguishable at their fusion and remain so to the death of the organism. In addition, in germ cells these parent-of-origin indicators must be erased and reset according to the sex of the individual, so that children of that individual will have appropriate maternal and paternal imprints [reviewed in Bartolomei and Tilghman, 1997]. Both DNA methylation and histone acetylation, known to regulate normal gene activation and inactivation by modulating DNA packaging, have been linked to the establishment and maintenance of parental imprints [reviewed in Reik and Walter, 2001]. DNA methylation and histone deacetylation tend to be associated with inactive alleles at an imprinted locus. Interestingly, the majority of imprinted
genes occur in clusters with other imprinted genes, likely to aid in coordinated regulation of these genes. Further, imprinted genes contain a high proportion of CG dinucleotides, the DNA sites subject to DNA methylation [Bartolomei and Tilghman, 1997].

**Evolution of imprinting**

One of the most interesting features of genomically imprinted genes is their role in growth and development. Of the 83 transcripts currently known to be imprinted, biological processes such as organogenesis, cell cycle regulation, cell growth and maintenance and chromatin architecture are represented [Morison et al., 2005]. Evidence suggests that in general maternally expressed genes inhibit growth of offspring, while paternally expressed genes are growth enhancers [Barlow, 1995]. There are a number of hypotheses for the evolution and maintenance of imprinting in mammals, many of which exploit the idea of imprinted genes impacting the growth of offspring. Examples of these theories are the genetic conflict, ovarian time bomb, X-linked sex-specific selection and sexually antagonistic selection hypotheses [see Morison et al., 2005].

The genetic conflict hypothesis [Haig and Westonby, 1989; Haig 1992] is perhaps the most prevalent hypothesis for the evolution of imprinting. A mother will be related equally to all of her offspring in a litter, but if there is any degree of multiple paternity a father cannot be sure that all offspring in a litter are his. The hypothesis states that to maximise the growth, and hence survival and fitness, of offspring in a litter, a mother wishes to partition her resources equally to all offspring. In contrast, fathers wish to enhance the survival of their own offspring in a litter, at the expense of unrelated offspring in the same or subsequent litters. Thus genes influencing resource provision and growth of offspring during pregnancy will be imprinted, with maternally inherited alleles active in genes suppressing growth, and paternally inherited alleles active for genes enhancing growth. However, this hypothesis is not supported by examples of growth genes that are maternally active, for example *Mash2* in mice [Guillemot et al., 1995]. Mathematical modelling suggests that multiple paternity may not be necessary for the emergence of imprinting at a locus, and that polymorphic imprinting is possible under this hypothesis [Spencer et al., 1998].
In contrast, the ovarian time bomb hypothesis [Varmuza and Mann, 1994] supposes that imprinting evolved to prevent the spontaneous development of unfertilized eggs in the ovaries, causing ovarian trophoblastic disease. Inactivation of the maternal allele of a gene necessary for egg growth would prevent such development, requiring a paternal contribution before growth would begin. This hypothesis, however, is less consistent with multiple imprinted loci evolving than the genetic conflict hypothesis [Weisstein et al., 2002].

The X-linked sex-specific hypothesis [Iwasa and Pomiankowski, 1999] was developed to account for the observation that a number of genes on the X chromosome may be imprinted in females. As males have only one copy of the X chromosome, one of the X chromosomes in females is generally inactivated, a process termed dosage compensation [Lyon, 1961]. For eutherian females, this inactivation is random, so that females are a mosaic of paternally and maternally derived active X chromosomes. However, a number of genes show imprinted rather than random inactivation – for example, Xist, a gene influencing X inactivation, is expressed only from the paternal X chromosome in embryos [Kay et al., 1994]. The X-linked sex-specific hypothesis supposes that imprinting on the X chromosome is likely to evolve when selection favours different embryonic gene expression patterns in males and females.

Finally, the sexually antagonistic selection hypothesis [Day and Bonduriansky, 2004] extends the X-linked sex-specific hypothesis to autosomal loci; imprinting is likely at loci where the optimal levels of expression are different for males and females. If the benefits to one sex outweigh the costs to the other sex, imprinting will evolve. This hypothesis also predicts that gene expression may be sex as well as parent-of-origin dependent; male and female offspring may show different levels of inactivation of a given allele. Evaluation of these and other hypotheses for the evolution of genomic imprinting will improve as knowledge of the total number and specific function of imprinted genes advances.

**Quantitative genetics**

Much of the discussion above has focused on single genes and their significance for the phenotype of an individual. In general, however, many genes influence the phenotype of an individual. Any phenotype that cannot be attributed to
the action of a single locus is termed a complex trait [Lander and Schork, 1994]. The interaction between multiple genes and the environment produces continuously varying characteristics, termed quantitative traits [Fisher, 1918; Wright, 1921]. Quantitative traits are generally described in terms of the mean phenotypic value of an individual with a given genotype, the mean value observed when all individuals with a certain genotype are measured for the trait of interest. The phenotype may be dissected into genetic and environmental components, and gene by environment interactions [Fisher, 1918; Falconer and Mackay, 1996; Lynch and Walsh, 1998].

Quantitative genetics is in general the statistical study of quantitative traits in populations, considering aspects such as the mean phenotypic value of individuals, the variability in a population, and the correlations and covariances between individuals sharing genetic information or sharing environments. The variation in a population may be written as the sum of the variation in genetic and environmental factors, plus variation in the interaction between these factors and potentially correlations between genes and environment [Falconer and Mackay, 1996; Lynch and Walsh, 1998].

As discussed by Mackay [2001], full understanding of a quantitative trait requires knowledge of aspects such as the number and individual effects of loci, how these loci vary within and between populations and between species, how loci interact with each other and with particular environments, and the rate at which new mutations occur at loci and how they affect the trait. As a consequence, quantitative genetic theory for population variances and resemblances between relatives is extensive. Dissecting the genetic and environmental influences on the phenotype of individuals remains a significant challenge for evolutionarily, medically and agriculturally important traits [Mackay, 2001]. A particular obstacle is that because effects of individual loci may be small and sensitive to environmental conditions, it may not be possible to estimate the number and effect of loci contributing significantly to a quantitative trait, particularly in human populations where sample sizes are small [Lander and Schork, 1994; Barton and Keightley, 2002].

**Imprinting and quantitative genetics**

Given the relatively small number of imprinted genes in the mammalian genome, it is unlikely many of the genes influencing a quantitative trait will be imprinted, but one or two may be. Indeed, much of quantitative genetics is focused on
aspects related to growth, survival and fitness (especially in human health and disease and for agriculturally important traits) [Mackay, 2001] and there is growing evidence that numerous such traits are influenced by genomic imprinting [see Chapter 2 for an overview]. Quantitative genetics of imprinting, then, is concerned with determining how an imprinted gene might contribute to a quantitative trait, and how the influence of imprinting may be detected. Of particular interest, therefore, is assessing how population variances and resemblances between relatives change when imprinting is added to a simple quantitative genetic model, and how, in the presence of imprinting, adding multiple loci, environmental effects and maternal effects might impact these population variances and covariances. Such investigation has been limited to an additive multi-locus analysis of complete inactivation [Hill and Keightley, 1998] and a single locus model deriving expressions for the components of genetic variance and measures of resemblances between relatives [Spencer, 2002]. The following chapters incorporate two loci, environmental and maternal effects into a standard quantitative genetic model, and assess how they impact the signatures in population variances and covariances that are expected if imprinting is acting. This research therefore expands quantitative genetic theory and aids a more comprehensive understanding of the processes influencing a population’s characteristics.
References


2. Detecting Genomic Imprinting in Complex Traits: A Comparison of Statistical Approaches

Abstract

Expression of an imprinted gene depends on the sex of the parent from which it was inherited. Consequently, reciprocal heterozygotes may display different mean phenotypes and this difference affects many genetic properties of both natural populations and experimental crosses. Although the mammalian genome contains a relatively small number of imprinted genes, many of these contribute significantly to important aspects of the phenotype, including growth and development. The past few years has seen development of an increasing number of methods aiming to identify imprinting at loci involved in the development of complex traits. This review considers a number of such approaches, including cases where marker information is and is not available. The application and utility of these approaches is also discussed.

Introduction

A gene is imprinted when its level of expression is dependent on the sex of the parent from which it was inherited. Imprinted loci are characterized by the reduced or absence of expression of either the paternally or maternally derived allele at a particular developmental stage or in a specific tissue type. Complete inactivation of an imprinted gene results in functional haploidy, with only one of the two copies of a gene expressed. More generally, however, imprinting results in the functional non-equivalence of reciprocal heterozygotes: inheriting an $A_1$ allele from one’s mother and an $A_2$ allele from one’s father gives a different phenotype, on average, than the reverse inheritance pattern.

Approximately 83 imprinted genes have been identified in mammals, including 41 in humans, and many of these genes are thought to be involved in traits such as growth and development [Morison et al., 2005]. A number of approaches have been used to demonstrate imprinting of specific genes or chromosomal regions, including examining differences between gynogenetic and androgenetic embryos, differences between triploids where the extra set of chromosomes are maternally or paternally derived, chromosome deletions, uniparental disomies, transgene expression
and specific gene expression (see Hall [1990a; 1990b]; Chatkupt et al. [1995] for reviews of these approaches).

Single genes may have a significant effect on the phenotype of an individual, but in general traits are influenced by a large number of loci. Any phenotype that cannot be attributed to the action of a single gene locus is termed a complex trait [Lander and Schork, 1994]. The interaction between many loci, each with small effects on the phenotype, and with the environment, may produce either continuously varying characters, termed quantitative traits, or discrete traits, such presence or absence of disease [Lander and Schork, 1994]. Of course, many cases of disease may be thought of as a quantitative character in terms of affection severity. Of the large number of genes involved in a particular complex trait, whether continuous or discrete, it is possible that some number of them are imprinted. It is therefore of interest to assess whether imprinted genes have a significant effect on a trait thought to be influenced by many genes; this chapter provides a review of current statistical methods for detecting imprinting in complex traits. Nevertheless, it should be noted that in many circumstances such statistical methods will not be able to differentiate imprinting effects from other parent-of-origin effects such as mitochondrial inheritance, maternal genetic effects or differential expansion of trinucleotide repeats in maternal and paternal germlines [Davies et al., 2001].

A number of models and methods for detecting imprinting in complex traits are outlined below, for both studies with and without marker information available. See Table 1 for a brief overview of these approaches.
A. Detecting imprinting effects for studies without marker information

A number of approaches have been used to demonstrate parent-of-origin or imprinting effects in complex traits in the absence of genotypic information, generally in human disease or livestock improvement programs. These approaches include assessing parent-of-origin effects such as transmission of disease susceptibility and phenotype severity from parent to offspring, the use of general mixed models incorporating imprinting to estimate genetic variances, and theoretical calculation of correlations and covariances between animals.

A1. Parent-of-origin effects

Three methods have been employed to assess how the sex of a transmitting parent influences the phenotype of offspring for the trait of interest: predominant transmission of a trait from one parent, differences in risk to offspring of developing the disease when a trait is maternally compared to paternally inherited, and differences in phenotype when a trait is maternally compared to paternally inherited.

For discrete complex traits such as presence or absence of disease, parent-of-origin effects may be assessed using two approaches. Given an affected offspring with an affected parent, parental transmission of the trait to offspring can be compared by contrasting the number of affected fathers versus affected mothers using $t$ tests or, based on the expectation that male and female parents should each transmit the trait half of the time, a $\chi^2$ statistic, binomial test or two tailed Fisher exact test may be used (see Table 2 for examples).

Alternatively, parent-of-origin effects may manifest in differences in the risk to offspring of developing the disease, based on which of their parents are affected. This approach takes into account both affected and unaffected offspring in calculating risk statistics or penetrance parameters. Differences in penetrance across maternal and paternal inheritance may again be evaluated using $t$ tests, using $\chi^2$ statistics and Fisher’s exact test for comparison to expected distributions, or by contrasting risk to offspring when inherited maternally or paternally using approaches such as univariate and multivariate regression analysis (see Table 2 for examples).

For quantitative traits, perhaps the most straightforward statistical approach to demonstrate a parent-of-origin effect is to examine differences in the phenotype of
offspring when a trait is maternally compared to when it is paternally inherited. Such comparisons may involve simple $t$ tests comparing differences in the offspring mean values of a particular trait when inherited maternally or paternally. Conditional regression and analysis of variance approaches may also highlight the sex of the transmitting parent as a significant predictor for phenotype, with post-hoc $t$ tests comparing maternal and paternal phenotype differences (see Table 2 for examples).

**Summary**

Of these three approaches: parental transmission of the discrete trait from one parent, differences in risk to offspring of developing the disease when a discrete trait is maternally compared to paternally inherited, and differences in phenotype when a quantitative trait is maternally compared to paternally inherited, none are able to differentiate imprinting from other parent-of-origin effects. Nevertheless in combination with other evidence such as linkage or quantitative trait loci (QTL) mapping studies, these may be valuable approaches in adding evidence to a proposed parent-dependent mode of expression for complex traits.

**A2. General mixed models incorporating imprinting**

General mixed models are commonly utilized in livestock genetics for estimating genetic variances, observing selection response and selecting individuals for breeding programs as these models allow for complicating factors such as extended families, unequal family sizes, assortative mating and selection [Lynch and Walsh, 1998]. The general mixed model describes the phenotypic values of the trait for individuals in the population ($y$) as the sum of fixed effects ($\beta$), random effects ($u$) and residual errors ($e$):

$$y = X\beta + Zu + e$$

Fixed effects ($\beta$) include factors such as population mean, gender, location and year of birth while random effects ($u$) incorporate genetic effects such as additive genetic values [Lynch and Walsh, 1998]. $X$ and $Z$ are incidence matrices. The general mixed model also requires the definition of covariance matrices for $u$ and $e$. For $e$, the covariance matrix is related to the total environmental variation while for $u$, the covariance matrix is derived using covariances between relatives.
There are a number of ways to formulate the general mixed model, including an animal model and a gametic model [Tier and Solkner, 1993]. Animal models are employed to estimate breeding values for each individual, while gametic models estimate breeding values in terms of the sum of parental contributions [Lynch and Walsh, 1998]. An animal model expresses the random effects covariance matrix in terms of the population’s additive genetic variance and a matrix of relatedness between individuals, termed the additive genetic relationship matrix. In contrast, the corresponding random effects covariance matrix for the gametic model is expressed as a variance-covariance matrix among gametes, or gametic relationship matrix, that computes probabilities among individuals that genes are identical by descent.

**Addition of imprinting to general mixed model: Gibson et al. [1998]**

Gibson et al. [1988] included imprinting in the general mixed model framework by partitioning the random effects into additive genetic effects expressed regardless of parental origin (a) and genetic effects expressed only when inherited maternally (or paternally) (g):

\[ y = X\beta + Za + Wg + e \]

where \( X, Z \) and \( W \) are incidence matrices. This model requires both an additive genetic relationship matrix and a gametic relationship matrix and so combines animal and gametic models in the same analysis.

**Extensions to and properties of Gibson et al. imprinting model:**

Schaeffer et al. [1989] extended this work to include a method for deriving the gametic relationship matrix. Each individual is expressed as two gametes, one maternally and the other paternally inherited. The gametic relationship matrix is then derived based on the sharing of gametes between related individuals. Although this approach involves expression of only maternal or paternal alleles, separate maternal and paternal contributions may be estimated. Stella et al. [2003] applied this method to simulated data and found that although the model was able to detect imprinting where it was simulated, spurious detection of imprinting effects is possible in situations where imprinting is not present.

To avoid the computationally-intensive derivation of both gametic and additive genetic relationship matrices in the model of imprinting as outlined by Gibson et al. [1988], Tier and Solkner [1993] extended the model to allow inclusion of parent-offspring gametes into the additive genetic relationship matrix. For example, if expression from only the maternal allele is being considered, the relationship matrix
contains entries for each individual and their relatedness to all other individuals, plus additional entries representing the transfer of gametes from all mothers to each of their offspring. Tier and Solkner [1993] demonstrated that this approach gave the same fixed and additive effects as the method of Gibson et al. [1988] and Schaeffer et al. [1989]. Nevertheless, solutions for imprinting effects were found to be the average of maternal and paternal gametic effects derived using the approach of Schaeffer et al. [1989], and so do not allow estimation of male and female gametic effects separately. Use of a single relationship matrix rather than two matrices allows inclusion of covariances between additive and gametic effects, and eases addition of imprinting into computer programs based on an animal model [Tier and Solkner, 1993].

Following the revised method of Tier and Solkner [1993], de Vries et al. [1994] tested for imprinting in backfat thickness and growth rate in pigs. Paternal and maternal inactivation were fitted separately and compared by a likelihood ratio test to a model with no imprinting. Including maternal environmental effects in the model showed a similar effect to fitting maternal expression (paternal inactivation) for the two traits, as both components contribute to covariance between maternal half-sibs. It was also shown that phenotypic selection for traits of interest might be up to 50% less efficient when an imprinted gene influences the trait. As a result, imprinting will contribute to lower than expected selection responses in genetic improvement schemes [de Vries et al., 1994].

Essl and Voith [2002a] used a simulation approach to determine the estimation properties of the method of Tier and Solkner [1993]. It was found that only half of the real gametic effect is identified in variance component estimation, and the method of Tier and Solkner [1993] was therefore revised to include this correction.

The approach of Tier and Solkner [1993] only allows estimation of a combined imprinting effect that is the average of the gametic effects of maternal and paternal gametes separately [Tier and Solkner, 1993]. Essl and Voith [2002a] therefore also used sire and dam models to assess imprinting effects. A dam (sire) model includes additive effects of only the dam (sire) into the approach, and a significant difference in the estimation of the variance of the realized dam and sire effects indicates differential expression of maternal and paternal genes provided common environmental effects are not biasing estimates of the covariance between half sibs [Essl and Voith, 2002a]. See Table 2 for applications of the above approaches.
Summary

General mixed model approaches are common in livestock genetic programs because they allow the estimation of genetic variance components and breeding values [Lynch and Walsh, 1998]. The three approaches of Gibson et al. [1988], Tier and Solkner [1993] and Essl and Voith [2002a] demonstrate that although formulating animal models to include maternal or paternal gametic effects is possible, the confounding effect of maternal environment cannot be dissected from maternal gametic expression. Further, none of these models include both maternal and paternal gametic inheritance and so are restricted by the assumption that variability in gametic effects for the trait of interest is only observed through either maternal or paternal transmission [Stella et al. 2003].

A3. Correlations and covariance

In a more theoretical framework, Hill and Keightley [1988] examined the influence of imprinting on the covariance of relatives for multiple loci. Covariances were derived by defining $m$ as the proportion of the genetic variance expressed from paternally expressed genes, $f$ as the proportion from maternally expressed genes and $(1-m-f)$ from Mendelian expression. The derivations failed, however, to incorporate incomplete inactivation. Further, in addition to imprinting, there may be a number of possible explanations when an offspring’s phenotype is more similar to one parent than the other, such as maternal or cytoplasmic inheritance [Hill and Keightley, 1988].

A recent theoretical paper [Spencer, 2002] was the first to incorporate imprinting into a standard single locus, two allele quantitative genetic model and to derive expressions for additive and dominance components of variance and correlation between relatives. Spencer [2002] derived mean genotypic value and the genotypic deviations of each of the four genotypic classes ($A_1A_1$, $A_2A_2$, and reciprocal heterozygotes $A_1A_2$ and $A_2A_1$) and hence also the breeding values. Further, expressions for total, additive and dominance genetic variances were calculated, and the covariance between breeding values and dominance deviations derived. In contrast to Mendelian expression, breeding values and additive genetic variances are different for males and females, and additive and dominance deviations are correlated. Using a regression approach, a test statistic for imprinting was derived by calculating the correlations between relatives. Unfortunately, the standard error of the test statistic for
imprinting is likely to be large in most situations, resulting in reduced power to detect imprinting effects. Santure and Spencer [in press] recently added maternal effects into the model.
B. Detecting imprinting effects for studies with marker information

A wide variety of methods have been employed to demonstrate imprinting effects in complex traits for which marker information as well as phenotype is available. In general, these methods are extensions to existing approaches for estimation of the genetic contribution to complex traits. These approaches include parametric linkage analysis, allele-sharing linkage methods, association studies, and QTL mapping as described in Lander and Schork [1994].

B1a. Linkage analysis: Parametric

Parametric linkage analysis is a model-based pedigree approach for assessing the likelihood that a particular trait of interest is influenced by a genetic factor at a specific locus, given genetic markers in the region. A number of genetic models may be assessed against the hypothesis that there is no relationship between the trait of interest and the locus. Models can include parameters such as the mode of expression of the disease trait (for example, recessive or dominant), the penetrance of the trait, the distance between markers and the trait locus, and allele frequencies at marker and trait loci [Lander and Schork, 1994]. Penetrance is defined as the probability that a trait will be expressed given a specific genotype [Strauch et al., 2000].

The observed genotypic and phenotypic data in the pedigree are used to assess how well a particular model fits the data, compared to a model without linkage, usually by calculating the maximum likelihood of each model and comparing them by a likelihood ratio [Lander and Schork, 1994] or a LOD (Logarithmic Odds) score, which is log base 10 of the likelihood ratio [Morton, 1955]. The maximum likelihood for each model is found by maximizing over free parameters included in the model [Ghosh and Collins, 1996]. Other methods such as odds ratios may also be used to assess support for a given model. If a correct genetic model is employed, parametric analysis has more power to detect linkage than approaches that are model-free [Strauch et al., 2000].

Addition of imprinting to parametric linkage analysis: Heutink et al. [1992]

Although linkage analysis was performed for a single-gene trait, Heutink et al. [1992] were the first to investigate an imprinting model in parametric linkage analysis. Two models were compared in an extended Dutch pedigree with heredity
paragangliomas exhibiting exclusive paternal inheritance. The first model assumed an autosomal dominant mode of inheritance with penetrance of the gene incomplete and age-dependent. The second model incorporated genomic imprinting by assuming no expression of the phenotype when inherited maternally. Although both models found significant evidence for linkage on Chromosome 11, the imprinting model gave much stronger support.

**Addition of imprinting to parametric linkage analysis: Nothen et al. [1999]**

In comparison to fitting an imprinting model to parametric linkage analysis, in a study of bipolar affective disorder Nothen et al. [1999] performed separate analyses after subdividing families into transmitting male and female parents. Examining only maternal transmissions found no linkage to markers along chromosome 18. Nevertheless for all families, paternal transmission families and those families for which transmission could not be determined, there was suggestive evidence for linkage at one, five and five markers respectively on chromosome 18, implying the contribution of imprinted loci to this trait.

Large differences in the predicted male and female recombination frequencies between marker loci may be a consequence of imprinting [Smalley, 1993]. Conversely, it is possible that for chromosomal regions where male and female recombination rates do differ, stronger evidence for linkage to the trait of interest may be seen in transmitting families for which the parental sex has a lower recombination rate [Nothen et al., 1999]. There are differences in the male and female recombination rates across chromosome 18 [Straub et al., 1993].

To assess whether different recombination rates in males and females would have a significant affect on the detection of linkage when families were divided based on sex of the transmitting parent, Nothen et al. [1999] simulated pedigrees for which a single marker was linked to the disease trait, with different male and female recombination rates between trait locus and marker. It was found that the power to detect a significant deviation from random allele sharing was higher for all families combined than it was for paternal families [Nothen et al., 1999]. An excess of allele sharing in affected individuals is evidence for linkage between the marker and trait of interest [Ghosh and Collins, 1996]. This higher power in families implies that if differences in male and female recombination rates affected linkage analyses on chromosome 18, the five markers demonstrating suggestive linkage in paternal transmissions would also be likely to be seen in linkage analysis using all families,
which was not the case [Nothen et al., 1999]. Nevertheless, it should be noted that this argument certainly does not exclude the possibility of different male and female recombination rates affecting linkage analyses.

Addition of imprinting to parametric linkage analysis: Strauch et al. [1999; 2000]

Strauch et al. [1999] and Strauch et al. [2000] presented a theoretical extension to parametric linkage analysis to detect parent-of-origin effects in disease, and the inclusion of this approach into the software GENEHUNTER [Kruglyak et al., 1996], termed GENEHUNTER-IMPRINTING. Generally, a genetic trait model for a two-allele, single locus parametric analysis consists of the disease allele frequency and penetrance parameters for the heterozygote and the two homozygotes. Extension to include imprinting requires separate penetrance parameters for the two classes of heterozygote, dependent on the parental origin of the disease allele [Strauch et al., 1999]. For each of the markers across the genome, the maximum likelihood of the four penetrance-parameter model with linkage to the locus is then compared to the maximum likelihood of the same model without linkage. Likelihoods are maximized to find the most likely recombination fraction between the marker and the disease locus.

Extension to two-allele, two disease loci for parametric analysis requires allele frequencies at both disease loci and definition of 16 different penetrances, dependent on allele combination and parental origin of each allele [Strauch et al., 2000]. The two disease loci are assumed to be unlinked. The likelihood for the 16-penetrance-parameters model is again maximized over the recombination fraction between disease and marker loci for the two genomic disease locations. A significant imprinting effect is proposed if the difference between LOD scores for imprinting and nonimprinting models is more than 2.5, following the criteria suggested by Greenberg and Berger [1994]. It is not clear, however, whether these thresholds are fully applicable when comparing imprinting and nonimprinting models as Greenberg and Berger [1994] only examined differences between dominant and recessive models when suggesting significance values.

Strauch et al. [1999] simulated two pedigrees for a paternally expressed disease and analyzed the pedigrees with a number of different models, including an imprinting model and a model with separate recombination rates in males and females. In one of the pedigrees the LOD score support for an imprinting model was the same as that for the model incorporating sex differences in recombination rates,
highlighting the observations of Nothen et al. [1999] and Smalley [1993] that it may be difficult to dissect imprinting from differential recombination rates in males and females. See Table 3 for applications of the approaches described above.

B1b. Linkage analysis: Allele-sharing methods

Allele-sharing methods are based on the premise that, if a particular genetic locus is linked to a trait of interest, affected individuals will inherit identical copies of the locus more often than would be expected by chance [Lander and Schork, 1994]. Pedigree-based analysis is employed to compare the frequency of alleles shared identical by descent (IBD) in affected relatives, compared to expected IBD sharing if the locus is not linked to the trait of interest. Allele-sharing methods do not require specification of a genetic model; consequently they are more robust than parametric methods although may not have the same power to detect linkage [Lander and Schork, 1994].

Allele-sharing methods for discrete traits

A number of methods are employed to assess the significance of the degree of allele sharing between affected relatives, including a simple $\chi^2$ statistic comparing observed with expected IBD allele-sharing for one locus or the use of an IBD-affected pedigree member (IBD-APM) statistic incorporating IBD sharing across many loci and all members in a pedigree [Lander and Schork, 1994]. It has also become common to utilize likelihood-based statistics in assessing the degree of allele sharing between affected relatives to allow comparison with parametric linkage analysis [Risch, 1990c; Kong and Cox, 1997]. In contrast to parametric linkage analysis where LOD scores are maximized over parameters such as recombination rates and penetrance parameters, allele-sharing LOD statistic are generally maximized over the proportion of alleles IBD, compared to expected allele sharing in the absence of linkage.

Addition of imprinting to allele sharing analysis: transmissions

For discrete traits and single loci, differences in allele-sharing between male and female transmissions are an indication of a parent-of-origin effect. A number of studies have demonstrated excess allele sharing when inherited through only one parental line using a $\chi^2$ statistic comparing male and female transmissions to an
expected transmission of 50% from each parent. Exact binomial tests of the equality of proportions of grandparental alleles and parental alleles have also been used to demonstrate a parent-of-origin dependent transmission of alleles to affected offspring (see Table 3 for examples).

For discrete trait and whole-genome or multiple marker loci genetic studies, a number of approaches have been used to demonstrate excess allele sharing through only one parent. Loci linked to the trait of interest may be examined \textit{a posteriori} for differences in allele sharing between male and female transmissions. Maternally and paternally transmitted chromosomes may be considered separately and evidence for imprinting suggested by an excess in allele sharing from only one parent. Finally, separate calculation of nonparametric LOD scores enables comparison of male and female allele transmissions, and the significance of differences in the likelihood statistics between males and females assessed by simulation (see Table 3 for examples).

\textit{Addition of imprinting to multipoint analysis: Rice [1997]}

Parent-of-origin effects may also be examined using an extension to multipoint analysis [Rice, 1997]. Multipoint analysis utilises IBD sharing simultaneously for several markers and provides a region-wide test for differences in allele sharing [Lynch and Walsh, 1998]. Parametric analysis including recombination rates can be used to locate the most likely position for a trait locus [Kruglyak et al., 1996].

\textit{Extensions to and properties of Rice imprinting model:}

Following the outline of Rice [1997] for including parent-of-origin effects in multipoint analysis, McInnis et al. [2003] performed a genome-wide scan in sib pairs for loci linked to bipolar disorder. In each sib pair for markers across the genome, the probability of sharing alleles IBD was determined separately for maternal and paternal transmissions. Differences in IBD sharing between maternal and paternal pedigrees were evaluated by comparing the maximum LOD score for a single IBD sharing probability with the LOD score allowing separate IBD sharing probabilities for maternal and paternal transmissions. The significance of the LOD score difference was assessed by randomly assigning parental allele transmission and comparing the simulated LOD difference to the observed value. McInnis et al. [2003] found a significant difference in allele sharing between maternal and paternal alleles for two
loci, located on chromosomes 1 and 13, with chromosome 13 showing increased sharing of maternal alleles across three markers.

Addition of imprinting to allele sharing analysis: Holmans [2002]

Holmans [2002] derived a likelihood method for testing differences in affected sib allele sharing between maternal and paternal inheritance. Separate probabilities are defined for sibs sharing a paternal or maternal allele IBD, and these probabilities used to maximize the likelihood of the observed IBD maternal and paternal sharing, compared to the likelihood that the sharing probabilities are equal. An alternative approach is to define a “patLOD” (“matLOD”) statistic by setting the paternal (maternal) IBD sharing probability to the expected value of 0.5, and maternal (paternal) IBD probability to the maximum sharing probability assuming imprinting. The absolute difference between patLOD and matLOD scores then provides a test for imprinting [Holmans, pers comm.].

Affected sib pairs were simulated to assess the performance of the likelihood and |patLOD-matLOD| imprinting tests [Holmans, pers comm.]. Both the likelihood ratio and absolute difference tests misspecified imprinting in around 5% of replicates. The power to detect imprinting when it was present was at most 67%, although this power is comparable to power levels detecting linkage in the same sample [Holmans, pers comm.].

Allele-sharing methods for quantitative traits

Lindsay et al. [2000a] and Lindsay et al. [2000b] extended methods for nonparametric linkage analysis of quantitative traits to include parent-of-origin effects. These extended methods are described more fully in Hanson et al. [2001]. For quantitative traits, a variance components method [Amos, 1994] and a regression method [Haseman and Elston, 1972] are two common approaches for linkage analysis [Hanson et al., 2001]. Both are based on the principle that, for the trait of interest, relatives sharing a large proportion of the same alleles will be more similar compared to those relatives sharing a small proportion of alleles. Allele sharing may be calculated or estimated, and can be partitioned into maternal and paternal contributions to total allele sharing [Hanson et al., 2001].

Variance components approach:

The variance components method involves fitting a linear model that estimates the trait mean, and partitions the variance into a number of components. For each
individual, a trait value ($z_i$) is represented as the sum of the overall mean of the pedigree ($\mu$), a major gene component ($A_i$), a random polygenic effect ($A_i^*$), a shared environmental component ($E$) plus a residual effect ($e_i$) [Amos, 1994]:

$$z_i = \mu + A_i + (A_i^* + E) + e_i$$

The total variance in the pedigree can then be partitioned into components representing the influence of the QTL for the trait of interest (monogenic component) ($\sigma^2_A$), the effects of unlinked genes and environmental factors shared by families (polygenic component) ($\sigma^2_{A+E}$), and the environmental components unique to an individual (environmental component) ($\sigma^2_e$) [Hanson et al., 2001]. The covariance between relatives may be calculated based on the relationship between individuals and observed allele-sharing at a major gene locus or marker linked to the major gene [Amos, 1994]. A number of statistical approaches may be used to assess the support for linkage [Hanson et al., 2001], including likelihood-based tests to compare evidence for linkage against evidence for no linkage to the trait of interest.

Addition of imprinting to the variance components approach: Hanson et al. [2001]

A parent-of-origin effect may be included by partitioning the monogenic component of variance ($\sigma^2_A$) into components that represent the influence of the QTL carried on the paternal (male) chromosome ($\sigma^2_{Am}$) and the influence of the QTL carried on the maternal (female) chromosome ($\sigma^2_{Af}$) [Hanson et al., 2001]. The presence of imprinting may then be tested either by comparing the likelihoods of a model incorporating imprinting to a model without imprinting, or by testing for a QTL across the genome separately for paternally- and maternally-derived alleles [Hanson et al., 2001].

Haseman-Elston regression method:

The Haseman-Elston regression method [Haseman and Elston, 1972] involves regressing the squared difference between phenotypic trait values for a pair of relatives ($z_i - z_j$) against the proportion of alleles they share IBD at a marker ($\pi_{ij}$):

$$(z_i - z_j)^2 = \alpha + \beta \pi_{ij}$$

If a gene in the region influences trait levels, siblings who share more alleles are expected to show closer phenotype similarity. A negative value for the regression slope $\beta$ suggests linkage between the trait and the marker.
Addition of imprinting to the Haseman-Elston regression method: Hanson et al. [2001]

Parent-of-origin effects may be included by estimation of separate male and female slope coefficients, according to the source of allele sharing:

\[(z_i - z_j)^2 = \alpha + \beta_f s_{ij} + \beta_m s_{mij}\]

Linkage with maternally or paternally derived chromosomes can be tested by whether one or both slope coefficients (\(\beta_f\) and \(\beta_m\)) are significantly different from zero using a likelihood-based approach. Based on the variances of these slope coefficients, a \(t\) test may be used to calculate the significance of the difference between the coefficients [Hanson et al., 2001].

Extensions to and properties of Hanson et al. imprinting models:

Hanson et al. [2001] simulated data for sibships to assess the performance of the variance components and regression analysis models including parent-of-origin effects. Incorporating parent-of-origin effects resulted in substantially increased power to detect linkage to imprinted loci. A variance-components approach was found to be more powerful in general than a regression method, perhaps due to the failure of the regression method to account for interdependence within families with more than two siblings (and hence more than one sib pair) [Hanson et al., 2001]. Removal of this interdependence by restricting analysis to a single pair from each sibship also results in a loss of power to detect linkage due to the loss of information from excluding additional siblings from analysis. Extension to include other relatives is also likely to be more straightforward for the variance components method [Almasy and Blangero, 1998]. Simulation results suggested that the two methods are not sensitive to moderate differences in recombination rate [Hanson et al. 2001].

Methods for detecting imprinting may have reduced power to detect linkage because assessment of parent-of-origin effects requires genetic data from at least one parent in order to determine allele inheritance, resulting in a number of cases that need to be excluded from analysis [Hanson et al., 2001]. The optimal strategy to detect imprinting may therefore depend on the genetic information available. Without prior evidence for imprinting, an initial scan using a general model may be optimal to detect regions with evidence for linkage. These regions may then be analysed further with models incorporating parent-of-origin effects to determine whether the loci are imprinted [Hanson et al., 2001].
Shete and Amos [2002] extended the variance components imprinting model of Lindsay et al. [2000b] and Hanson et al. [2001] by partitioning the monogenic phenotypic variance for a locus ($\sigma^2_A$) into three parts: an additive component from the paternally derived allele ($\sigma^2_{Am}$), an additive component derived from the maternally inherited allele ($\sigma^2_{Af}$), and a dominance component ($\sigma^2_D$). Interestingly, this partitioning contradicts the finding of Spencer [2002] that for an imprinted locus, an additional covariance between additive and dominance effects exists, and hence additive and dominance effects are correlated. The effect of imprinting may be assessed by a likelihood ratio test for the equality of the two parent-specific additive variances [Shete and Amos, 2002]. Again, this approach is not valid if the recombination rates between the trait locus and the marker are different between the sexes [Shete and Amos, 2002].

By examining the statistical properties of the approach, Shete and Amos [2002] also derived an expression for the sample size required in order to attain a certain power for a given significance level. They showed that for a given significance level, the required sample size is smaller for a standard variance-components model compared to a model incorporating imprinting, unless the imprinting effect is large. The small number of imprinted genes in the mammalian genome suggests that it is best to perform genome scans with the usual variance-components model and then test for imprinting in areas where significant linkage is observed, instead of initially applying the imprinting model and then testing for Mendelian or imprinted expression [Shete and Amos, 2002], as also suggested by Hanson et al. [2001].

Shete et al. [2003] extended the imprinting variance components approach to include extended pedigrees, as dividing large pedigrees into sibships may result in loss of power to detect linkage [Wijsman and Amos, 1997]. See Table 3 for applications of these approaches.

**B1c. Combined parametric and allele-sharing linkage analysis**

For dichotomous disease traits, Knapp and Strauch [2004] derived a further approach for assessing imprinting in linkage analysis based on allele sharing. This method is an extension of the linkage method derived by Risch [1990a; 1990b; 1990c] and Holmans [1993] and differs from the parametric approach of Strauch et al. [1999]. Risch [1990c] defined a maximum LOD score criterion for affected relative pairs,
dependent on the observed allele sharing at a marker locus, to assess the significance of linkage. This method includes estimating probabilities for two relatives sharing zero, one or two alleles IBD given that they are both affected [Risch, 1990b; Holmans, 1993] to give a maximum likelihood. The LOD scores for each marker can then be assessed for evidence for linkage. Penetrance parameters may also be defined for each combination of alleles at the disease locus [James, 1971; Risch, 1990a].

*Addition of imprinting to linkage analysis: Knapp and Strauch [2004]*

For affected sib pairs, Knapp and Strauch [2004] extended this approach to include imprinting. For a diallelic disease locus, four separate penetrance parameters are defined for homozygotes and the two reciprocal heterozygotes. Separate probabilities for affected sibs sharing zero, two, one maternal or one paternal marker allele IBD plus separate recombination rates between marker and disease locus for males and females are also defined. These parameters allow derivation of population prevalence (mean value) and additive and dominance variance components [Knapp and Strauch, 2004] following the approach of Kempthorne [1957]. Using the additive and dominance variance components to estimate marker allele sharing between affected sibs, likelihood for linkage allowing for imprinting is then assessed against the likelihood of no linkage. Criteria to assess the significance of the likelihood ratio statistic and corresponding LOD score are also outlined [Knapp and Strauch, 2004] for different numbers of alleles at the marker locus. Although the imprinting likelihood ratio test assesses evidence for linkage including imprinting rather than testing for imprinting, it is possible to test an imprinting against no-imprinting hypothesis using a restricted likelihood ratio test [Knapp and Strauch, 2004]. In simulations including different degrees of imprinting, allowing for imprinting in the likelihood calculations gave much higher power to detect linkage. Further, if no imprinting effect was modelled, there was only a slight reduction in power to detect linkage using an imprinting approach compared to a non-imprinting approach [Knapp and Strauch, 2004].

**Summary: linkage analysis**

Model-based linkage analysis is a powerful method for detecting linkage provided the correct genetic model is employed [Strauch et al., 2000]. Separate examination of maternal and paternal transmission is likely to reduce the power of the model to detect linkage, due to exclusion of some individuals when inheritance of
traits is unclear. Defining separate penetrance parameters for reciprocal heterozygotes appears a successful method for detecting parent-of-origin effects in complex traits, nevertheless it is not clear whether this approach is able to differentiate imprinting from other parent-of-origin effects. Also, caution should be taken in concluding imprinting where there is evidence of different male and female rates of recombination, that could equally be a consequence of imprinting [Smalley, 1993] or provide spurious evidence for imprinting [Nothen et al., 1999]. Finally, it should be noted that comprehensive investigations of the appropriate threshold values for genome-wide significance have not been undertaken; certainly these values will be dependent on whether imprinting is being tested against a no-linkage or a no-imprinting hypothesis.

Allele-based methods for linkage analysis are more robust than parametric methods and hence are popular options when trait inheritance is unclear. Parent-of-origin effects may be apparent where excess allele-sharing is seen from only one parent, or LOD scores are different when maternal and paternal pedigrees are examined separately. Extension to regression and variance-components approaches detecting linkage in quantitative traits has successfully detected imprinting in a number of traits. Nevertheless, as with parametric linkage analysis, allele-sharing methods are sensitive to differences in recombination rates between the sexes. The power to detect linkage for methods incorporating imprinting is dependent on the number of cases for which parental origin of alleles can be determined. Nevertheless, it may be possible to incorporate likelihood methods for deducing parental origin of allele to improve the power to detect linkage.

B2. Association studies

Association methods rely on the concept that, given loci that are linked to a trait of interest, certain alleles will be associated with phenotypes such as disease status more often than would be expected by chance. In contrast to linkage studies that scan the whole genome with relatively few markers, association studies are more often used to confirm the involvement of a particular susceptibility allele at one locus [Elston, 2000], or tight linkage between a marker and disease allele. In general, association studies are case-control studies based on comparison of unrelated affected and unaffected individuals in a population [Lander and Schork, 1994]. Nevertheless,
difficulty in matching cases and controls and concern over population structure affecting association has led to development of family-based tests to assess association between trait and locus [Whittaker and Morris, 2001]. Among these methods include likelihood ratio tests, case/psuedocontrol analyses, the Transmission Disequilibrium Test (TDT), [Whittaker and Thompson, 1999], and extensions of the TDT, predominantly using “case-parent triads” of affected patients and their parents.

For a diallelic locus, the TDT [Spielman et al., 1993] measures the inheritance of alleles from heterozygous parents to affected offspring [Spielman and Ewens, 1996]. If one allele at a locus is associated with the disease, it will be transmitted preferentially to affected offspring, compared to random transmission of alleles if there is no association. Transmission distortion may be tested by $\chi^2$ or similar tests. The TDT tests for both linkage and association [Spielman and Ewens, 1996], is robust to population stratification, and may be extended to multiple alleles [Self et al., 1991; Schaid, 1996; Clayton, 1999].

**Association studies for discrete traits**

*Addition of imprinting to TDT: Weinberg [1999]*

For alleles associated with the trait of interest, Weinberg [1999] derived a TDT-like statistic to test for parent-of-origin effects in allele transmission. The $TDT_{MvsF}$ tests whether there is stronger evidence of transmission distortion to affected offspring from one parent, suggestive of a parent-of-origin effect [Weinberg et al., 1998]. A test for differences in parental transmission may be based on Fisher’s exact test or a $\chi^2$ test for testing the equality of the maternal and paternal proportions [Weinberg, 1999]. In addition, Weinberg et al. [1998] proposed a Transmission Asymmetry Test (TAT) that omits data from parents who are both heterozygous. This approach circumvents the statistical dependency between allele transmissions of two heterozygous parents. Equality of transmissions from mothers and fathers may then be tested using a $\chi^2$ statistic.

*Log-linear likelihood approach:*

Weinberg et al. [1998] also extended a log-linear likelihood approach in case-parent triads [Weinberg et al., 1998; Wilcox et al., 1998] to include parent-of-origin effects. The standard log-linear likelihood approach considers a single locus, with either two alleles, one of which is a trait-associated variant, or multiple alleles grouped into “associated” and “not-associated” categories. Given an affected child,
this classification allows 15 child-parent outcomes and six mating types, dependent on parental genotype [Schaid and Sommer, 1993]. Without assuming Hardy Weinberg equilibrium for the allele frequencies, conditional probabilities of each of the 15 outcomes may be defined as the product of a risk parameter and a mating class parameter. The risk parameters are similar in concept to the penetrance parameters of linkage analysis (see Strauch et al. [1999]) and define risk of developing the trait, given the number of variant alleles. A maximum likelihood approach may then be used to estimate these risk parameters given the observed counts of case-parent triads, by fitting a log-linear model. The log-linear model in this case expresses the expected value of each of the 15 outcomes as the exponential of the sum of the natural log of the mating class parameter and the natural log of the risk parameter. Maximum likelihood estimation for log-linear models is available in standard statistical packages and generally involves an iterative process fitting the best model to marginal totals in a frequency table [Knoke and Burke, 1980], from which parameters may be estimated. The fit of the model is then tested using a $\chi^2$ or similar statistic comparing expected with observed cell counts.

Addition of imprinting to log-linear likelihood approach: Weinberg et al. [1998]; Wilcox et al. [1998]

The log-linear approach for case-parent triads was extended to include maternal and parent-of-origin effects [Weinberg et al., 1998; Wilcox et al., 1998] through additional parameters in the model. For maternal effects, the mother’s genotype provides an additional risk parameter, while for imprinting separate risk parameters are defined for maternally and paternally inherited susceptibility alleles. While the maternal effects model parameters may be estimated using a standard maximum likelihood approach, the imprinting model requires an extra step to maximize the likelihood given the parameter estimates. This extra step is necessary because it is not possible to deduce parental origin of alleles for heterozygous children with heterozygous parents. The EM algorithm [Dempster et al., 1977] is therefore employed to estimate the imprinting relative risk parameters for the father and mother [Weinberg et al., 1998]. The EM algorithm is a general method for finding the maximum-likelihood estimates for parameters in a model when the data is incomplete [Dempster et al., 1977].
Properties of TAT and log-linear likelihood imprinting models:

Weinberg et al. [1998] simulated population data to examine the performance of the log-linear likelihood and TAT approaches for detecting imprinting. The likelihood of imprinting models was assessed by the change in maximum likelihood both when imprinting is added to a basic model, and when imprinting is removed from a full model including mating class, genotype, maternal effects and imprinting terms.

The log-linear likelihood approach had high power to conclude the correct imprinting model against a background model, although power was poor in rejecting a fully parameterized model including maternal effects in favor of the correct imprinting model, and a drop in power was observed when both paternal imprinting and maternal effects were simulated. The TAT had low power in detecting a parent-of-origin effect for all models [Weinberg et al. 1998], most likely due to the exclusion of the heterozygous x heterozygous mating pairs from analysis.

In the presence of maternal effects the TAT and TDT_{MvF} tests are not valid because an excess transmission of maternal alleles may be a result of maternally mediated genetic effects [Weinberg, 1999]. Further, although the likelihood approach has high power to detect imprinting effects, it may not be strictly valid if the locus being investigated is a linked marker rather than the actual susceptibility locus [Weinberg, 1999], due to recombination between the two affecting the risk parameter when the allele is maternally and paternally inherited.

Addition of imprinting to association studies: Weinberg [1999]

Weinberg [1999] proposed an additional model to account for maternal as well as imprinting effects and allow for analysis of a marker rather than susceptibility locus, termed the Parent of Origin Likelihood Ratio Test (PO-LRT). The PO-LRT considers only the three mating types for which the mother and father do not carry the same number of susceptibility alleles. Offspring are then stratified according to the number of copies of the allele, which removes any dependence between numbers of parental and offspring alleles. The probability of the number of maternally inherited alleles being greater than the number of paternally inherited alleles is then calculated for each combination of parent-offspring triad, conditional on mating types. Finally, these probabilities may be transformed into odds that maternal is greater than paternal transmission. The model for the data is then written in terms of the log of the odds as the sum of one imprinting parameter and two maternal effects parameters, dependent
on whether the mother carries one or two copies of the susceptibility allele. A likelihood ratio test may then be used to test the significance of including the imprinting term in the model and to estimate the parent-of-origin and maternal effect parameter [Weinberg, 1999]. Nevertheless it should be noted that because the model conditions on mating type and child’s genotype, it is not possible to estimate the genotype risk parameters.

If it is assumed there are no maternal effects, only cases consisting of offspring with only one susceptibility allele are informative. The PO-LRT reduces to a TDT-like statistic testing whether there is an excess of maternal transmission, utilizing a $\chi^2$ statistic, which Weinberg [1999] terms the Parental-Asymmetry Test (PAT).

Properties of TAT, PAT and PO-LRT imprinting models:

Case-parent triad data was simulated with maternal and/or imprinting contributions to risk, and the performance of the TAT, PAT and PO-LRT was assessed [Weinberg, 1999]. Triads for which all individuals were heterozygous were excluded from analysis.

For no imprinting and no maternal effects, all tests performed well at detecting association. Adding maternal effects decreased the power of TAT and PAT to detect association. The PO-LRT, TAT and PAT were successively more powerful in detecting imprinting in the absence of maternal effects. Only the PO-LRT is valid for testing a combined maternal effect and imprinting model, and the power to detect imprinting effects was seen to be dependent on the underlying model parameters; for example power to detect imprinting was higher for an over-expressed maternally inherited allele compared to paternal allele [Weinberg, 1999].

Weinberg [1999] suggested that, if maternal effects are unlikely, the PAT is the most powerful method for detecting imprinting effects. Nevertheless, although the PO-LRT has low power to detect true imprinting effects, it is the only valid test if maternal effects are present and the allele locus under study may only be linked to the true susceptibility locus. Further extension to include heterozygous triads could improve the power of the PO-LRT [Weinberg, 1999]. See Table 4 for applications of the approaches described above.

Case/psuedocontrol analysis:

Cordell et al. [2004a] presented further methods to model parent-of-origin effects in association studies of discrete complex traits. These methods are based on
case/psuedocontrol analysis, which is an extension of the genotype relative risk method of Schaid and Sommer [1993] and Schaid [1996]. The genotype relative risk method conditions both on the fact that offspring are affected and on the parental genotypes, and is easily extended to include multiple loci, genotype/environment interactions and larger family structures [Cordell and Clayton, 2002].

Addition of imprinting to Case/psuedocontrol analysis: Cordell et al. [2004a]

To fit models including parent-of-origin effects, each case-parent triad is genotyped and the parental origin of alleles determined; if parent-of-origin cannot be inferred the triad must be discarded [Cordell et al., 2004a]. From the informative triads, sibling “pseudocontrols” are constructed using the remainder of alleles not transmitted to the affected offspring. Again pseudocontrols are discarded if parental origin of alleles cannot be determined. This method is termed the “Conditioning on Parental Genotypes” (CPG) approach [Cordell et al., 2004a].

For these combined affected offspring and pseudocontrols sets, risk parameters are estimated by maximizing the likelihood of these risks using a logistic regression approach. The likelihood for the whole data set (and hence the likelihood of the model given the data) is the product of the likelihoods for each case-parent triad. Imprinting is added to the model by defining separate genotype relative risks parameters for reciprocal heterozygotes.

A second approach, “Conditioning on Exchangeable Parental Genotypes” (CPEG), is also described that generates additional pseudocontrols by exchanging maternal and paternal haplotypes [Cordell et al., 2004a]. This method allows both examination of parent-of-origin effects on genotype relative risk and inclusion of triads that may be excluded in the CPG approach because parent-of-origin cannot be inferred [Cordell et al., 2004a]. Both the CPG and CPEG approach exclude families with heterozygous offspring and parents, although these families may be included using the EM likelihood approach described by Weinberg et al. [1998].

Properties of imprinting models for association studies:

Cordell et al. [2004a] simulated data to evaluate the properties of the CPG and CPEG approaches. Using CPG and CPEG approaches with parent-of-origin effects specified, estimates for risk parameters were unbiased and confidence intervals on the estimates smaller for the CPEG approach. Using the CPG approach without imprinting, estimates for heterozygotes were the average of reciprocal heterozygotes in the underlying model [Cordell et al., 2004a].
Data was also simulated to compare performance of the CPG and CPEG approaches and the log-linear and PO-LRT approaches of Weinberg et al. [1998] [Cordell et al., 2004a]. All methods displayed unbiased parameter estimation, and standard errors on estimates were smaller for the CPEG and log-linear models compared to the CPG and PO-LRT methods. As suggested by Weinberg et al. [1998], models including parent-of-origin effects may be tested against a background model and likelihoods compared. Nevertheless, simulations suggest that if an effect is not included in the model parameterization, it is likely to be detected as an effect included in the model – for example imprinting effects may be detected as maternal effects if maternal effects are incorrectly specified by the model [Cordell et al., 2004a]. Therefore there may not be sufficient power in conditional likelihood-based tests to distinguish between parent-of-origin or maternal effects, or other effects such as mother-child genotype interactions [Cordell et al., 2004a].

Cordell [2004b] examined the properties of the log-linear, PO-LRT, CPG and CPEG approaches for analysis of a marker linked to the trait locus, rather than the trait locus itself. The CPG approach underestimated true parameters, with power to detect effects and parameter underestimation worsening with increasing distance between marker and locus. The CPEG, log-linear and PO-LRT approaches gave similar results in the absence of imprinting effects, but detection of (absent) maternal effects increased with increasing distance between marker and locus [Cordell, 2004b]. Although the PO-LRT was derived to account for consideration of a marker rather than trait locus, it appears not to perform any better than the other two approaches [Cordell, 2004b].

**Association studies for quantitative traits**

A number of methods have been developed for association studies of quantitative traits, including the use of mixture and linear models.

*Addition of imprinting to association studies: van den Oord [2000]*

van den Oord [2000] developed an approach for testing maternal and parent-of-origin effects in quantitative traits using case-parent triads. Following the approach of Weinberg et al. [1998], for a diallelic locus, fifteen triads corresponding to six mating classes are defined. In contrast to a cell count structure [Weinberg et al., 1998], however, mean offspring values are defined as the sum of parameters such as mating type means, own genotype effects, maternal effects plus a parent-of-origin
effect, and variances across each mating type are estimated. The model was specified as a normal mixture model to allow for a mixture of complete and incomplete case-parent triads across different mating types. A number of approaches may be used to estimate the parameters of mixture models; in this case van den Oord [2000] uses a maximum likelihood approach. Likelihood ratio tests may be used to test the significance of parameter estimates compared to the null hypothesis that parameters are zero [van den Oord, 2000].

To assess the mixed model approach, van den Oord [2000] simulated data for case-parent triads assuming no genetic effects, gene-dose effects, parent-of-origin effects or maternal effects, including cases where paternal genotypes were missing. In the absence of a genetic component, genetic effects were detected in between 5.0 and 5.8% of simulations, corresponding well to the underlying Type I error of 5% even with large numbers of missing paternal genotypes. Error rates appeared slightly lower when incomplete data was omitted. There was high power to detect offspring genetic effects when they were simulated, and parameter estimates for genotype effects, maternal effects and parent-of-origin effects were unbiased. Including incomplete data using the mixed model approach gave more power to detect genetic effects. Nevertheless, there was very low power (29.5-43.8%) to detect parent-of-origin effects.

Linear model for quantitative traits:

In contrast to the mixture model approach of van den Oord [2000], Whittaker et al. [2003] derived a linear model to describe parent-of-origin effects for quantitative traits. Again, a diallelic locus is considered for case-parent triads. The expected phenotypic value in the offspring given the number of offspring and parent variant alleles ($z_{ijk}$) is written as a linear combination of the mean value of combined parent genotype ($\beta_{ij}$) and the mean value of offspring genotype ($\gamma_k$):

$$z_{ijk} = \beta_{ij} + \gamma_k$$

where $i$, $j$ and $k$ refer to the number of variant alleles in father, mother and offspring respectively. If there is no association between the marker and the trait locus, there will be no effect of offspring genotype [Whittaker et al., 2003]. The significance of association between marker and a quantitative trait may be assessed using a generalized TDT type test [Allison, 1997]. Maternal effects are added by allowing the combined parent genotype parameter to take different values if alleles are maternally or paternally derived.
Addition of imprinting to a linear model: Whittaker et al. [2003]

A parent-of-origin effect may be included in the linear model by adding a parameter representing the change in mean from inheriting a variant allele from the father (or mother):

\[ z_{ijk} = \beta_i + \gamma_k + \tau_j (or + \tau_f) \]

Inheritance of alleles from heterozygous parents to heterozygous offspring may be estimated using an EM algorithm [Weinberg et al., 1998] or other estimation procedures [Whittaker et al., 2003].

Whittaker et al. [2003] analysed data from 118 triads to assess the association between infant body size at 6 months and alleles at the insulin locus. Previous studies have suggested association between paternal transmission of class III alleles and type II diabetes [Huxtable et al. 2000]. Fitting a full linear model including maternal and imprinting effects gives a negative parameter estimate for inheriting a class III allele paternally, corresponding to smaller body size. Nevertheless, it is difficult to assess the significance of including an imprinting term as the model improved when parent-of-origin effects are added to a model with only child genotype, but did not improve when parent-of-origin effects and child genotype are added to a model with maternal effects. Simulations, based on full-model parameter estimates from the real data, suggest that power to detect child genotype effects may indeed be enhanced by inclusion of parent-of-origin effects in the model [Whittaker et al. 2003]. Because simulations were based on non-zero parameter estimates for both imprinting and maternal effects, it is not possible to assess how well this approach may differentiate between the two.

Summary

The use of association studies in genetic analysis is common for analysis of human disease traits and for detecting disease-susceptibility genes once a chromosomal location has been indicated by linkage analysis. Imprinting and parent-of-origin effects have been incorporated into a number of association approaches and have been reasonably successful at detecting imprinting using simulation testing and analysis of real data. It is not clear whether it is best to test a model incorporating imprinting against a reduced background model, or test the significance of imprinting by removing it from a fully parameterized model including maternal effects. It appears likely that if maternal effects are present, they will be detected as imprinting.
if maternal effects are not included in the model parameterisation. Further, where the locus being considered is a marker linked to the trait locus, a number of approaches are invalid and likely to lead to spurious detection of maternal effects.

B3. QTL mapping

Quantitative Trait Locus (QTL) mapping is a genome-wide approach to studying association and linkage between alleles at a locus and a trait of interest [Lynch and Walsh, 1998] and has become increasingly popular in analysis of quantitative traits with the improving density of genetic linkage maps [Falconer and Mackay, 1996]. A number of approaches may be used to support association between genetic locus and trait; perhaps the simplest is to compare phenotypic means for different marker classes [Falconer and Mackay, 1996]. Maximum likelihood may be used to compare the hypotheses of presence or absence of a QTL in a genomic interval.

QTL mapping may be performed both in inbred and outbred line crosses. Inbred crosses are based on the assumption that different marker and QTL alleles are fixed in the two lines and, given association between marker and trait locus, F2 or backcrossed individuals will be more similar in phenotype to one or other inbred line according to the origin of their alleles. The same concept is applied to mapping QTLs in outbred crosses, nevertheless in this situation many alleles may be segregating that may not necessarily be associated with the same QTL allele in all individuals. QTLs detected in inbred crosses represent differences between lines while outbred crosses detect QTLs segregating within populations [Lynch and Walsh, 1998].

QTL mapping for inbred lines

Addition of imprinting to inbred line QTL mapping:

Imprinting or parent-of-origin effects at a QTL become apparent where there are differences in phenotype when a linked allele is maternally or paternally derived. There have been a number of parent-of-origin effects demonstrated in fully inbred lines (see Table 4 for examples).
QTL mapping for outbred lines

Least-squares regression:

For general pedigrees, a least-squares regression framework may be used to test for presence of QTL in crosses between two genetically divergent but outbred lines [Haley et al., 1994]. This method assumes that outbred lines are fixed for QTLs of moderate or large effect, but marker alleles need not be unique. The phenotypic value of an individual with a given genotype is expressed as the sum of an overall mean, an additive component, a dominance component and a residual error. To estimate the additive and dominance coefficients, the phenotypes of individuals are regressed on additive and dominance variables; these variables are functions of the conditional probability of the individual being a heterozygote or one of two homozygotes for the QTL, given flanking marker genotypes [Lynch and Walsh, 1998]. The ratio of the regression mean square to the residual mean square provides an F statistic that can be calculated across a region to determine the most likely position for the QTL, alternatively a maximum likelihood approach may be used to estimate the position of the QTL [Haley et al., 1994].

Addition of imprinting to least-squares regression: Knott et al. [1998]

An extensive QTL mapping study in a cross between wild boar and large white pigs was the first to address the possibility of an imprinting effect based on a linear regression approach [Knott et al., 1998]. Putative QTLs for fitness traits such as growth rate and fat measurements were first located by searching the genome to identify regions where including markers explains significantly more of the phenotypic variance compared to a model without linkage. QTLs were then tested for an imprinting effect by utilizing information about the parental origin of alleles at the putative QTL [Knott et al., 1998]. Individuals may be classified according to the population and parent-of-origin of each allele, and evidence for imprinting seen in significant differences between the least-squares means of reciprocal heterozygotes. For each QTL, a model fitting an imprinting term in addition to additive and dominance components was compared to a model with no QTL. If significant, this imprinting model was then compared to the best QTL model without imprinting to see whether the imprinting effect was significant, using simulation to assess the level of significance [Knott et al., 1998]. One locus on chromosome 4 showed significant improvement when an imprinting model was a compared to fitting only additive and dominance terms. Wild boar alleles inherited through the male parent were found to
increase the percentage of abdominal fat, suggesting the locus may be maternally inactivated.

**Extensions to and properties of Knott et al. imprinting model:**

Rattink et al. [2000] extended this approach of Knott et al. [1998] to classify QTL with evidence of imprinting using a reduced model incorporating only maternal or paternal expression.

de Koning et al. [2000] also built on the approach of Knott et al. [1998] to derive a direct test for the separate contribution of the paternally and maternally inherited effects, for a cross between Chinese Meishan pigs and commercial Dutch pigs. Following the least-squares approach, the probability of inheriting two Meishan QTL alleles, two Dutch QTL alleles, or one of each allele was calculated at intervals across the genome for each F\textsubscript{2} individual. To separate the contribution of the parents, separate probabilities were introduced for whether an individual inherited a Meishan QTL allele from its mother or from its father. A model including a paternal, maternal and dominance component was then fitted at intervals across the genome and significance inferred from comparison to a no-QTL model at each locus [de Koning et al., 2000]. The mode of expression of the QTL was inferred based on the contribution to total sum of squares for each of the three components. If both maternal and paternal effects were significant, diallelic expression is inferred, whereas the imprinting is predicted if only one effect is significant, and no dominance is present.

This model of analysis assumes that there was only one allele at each QTL locus in each of the two parental lines. If more than one allele was segregating in Meishan or Dutch pigs, the power to detect a QTL for the trait would be reduced and its effect underestimated [Alfonso and Haley, 1998]. Further, extreme allele frequency differences between male and female parents could lead to false identification of imprinting for a Mendelian QTL. These problems are both unlikely given the significant morphological differences between Meishan and Dutch pigs and random selection of both male and female parents from the F\textsubscript{1} generation [de Koning et al., 2000].

Lee et al. [2001] noted that the approach of de Koning et al. [2000], by testing the hypothesis of an imprinted QTL against the hypothesis of no QTL, fails to test an imprinting model against a model of Mendelian expression. Lee et al. [2001] propose assessing a number of models, including Mendelian expression, maternal and paternal components plus dominance, only paternal effects and only maternal effects, by
testing against a no-QTL model and testing a full imprinting model against Mendelian and the two reduced imprinting models. To assess the significance of the full imprinting model against Mendelian expression, maternal and paternal coefficients were permuted to give a chromosome-wide significance level. The maternal and paternal models were assessed by randomly changing the sign of the model coefficients. A number of imprinted loci were detected using this approach [Lee et al., 2001].

Further to this reduced model approach suggested by Lee et al. [2001], Thomsen et al. [2002] suggested a “decision tree” method to testing first whether a Mendelian QTL is present, followed by testing the full imprinting approach against both a Mendelian model and a no-QTL model. If the full imprinting approach is significant, maternal and paternal reduced models may be tested against the full model to determine whether maternal, paternal or partial imprinting is most likely [Thomsen et al., 2002]. For a Berkshire-Yorkshire swine cross, a large number of QTL for growth and meat quality were detected across the genome, nevertheless only a few of these QTL showed significant evidence for imprinting when compared to Mendelian expression. In contrast, using the approach of de Koning et al. [2000] testing imprinting against a hypothesis of no QTL, a large proportion of imprinted QTL were seen [Thomsen et al., 2002]. This result highlights the importance of testing against the correct null hypothesis. It should be noted, however, that failing to include separate maternal and paternal contributions in the initial genome QTL scan may miss imprinted loci, especially those loci with small effects on the phenotype. As discussed above [Cordell et al., 2004a], there is likely to be a trade-off between detecting true effects with small effect by including many parameters in the model, and concluding incorrect effects when the model is over-parameterized.

de Koning et al. [2002] examined the quantitative genetic aspects of an imprinted QTL and performed a simulation study to examine the properties of the regression approach for detecting imprinting that was earlier developed by Knott et al. [1998] and de Koning et al. [2000]. The objective of the simulation study was to determine the power for detecting imprinted QTL under imprinting and Mendelian models, and determine the rate of falsely identifying an imprinted QTL.

Expressions for the total genetic variance at a diallelic, imprinted locus were derived and can be shown to be equivalent to Spencer [2002]. Assuming additive but no dominance effects, complete dominance, or complete silencing of one allele, it can
be shown that the total genetic variance under an imprinting model is twice that under an additive model and, provided equal numbers of each line are mated, 4/3 that under a dominance model [de Koning et al., 2002].

An extensive F$_2$ cross was simulated and an additive, a dominant, a paternally expressed and a maternally expressed QTL were modeled separately. In addition, founder lines were either fixed for alternative QTL alleles or a single favorable allele was set at high frequency in one founder line and low frequency in the other. Support for a Mendelian QTL was assessed using a standard model incorporating the conditional probability of inheriting one or two alleles from a particular founder line. Whereas de Koning et al. [2000] extended this model to incorporate separate conditional probabilities for reciprocal heterozygotes, de Koning et al. [2002] estimated the best imprinted QTL by comparing two reduced models, one with exclusive maternal expression and the other with exclusive paternal expression of the QTL, and no dominance term, against the hypothesis of no QTL. For each of the three models, a genome-wide 5% threshold was applied against the null hypothesis of no QTL.

Replicates with significant evidence to support an imprinted QTL against the hypothesis of no QTL were tested using two approaches: testing the null hypothesis of a Mendelian model against a full model incorporating imprinting, and testing the null hypothesis of a reduced imprinting model (with only paternal or maternal expression) against a Mendelian model. Imprinting was inferred when both Mendelian expression was rejected and imprinting failed to be rejected [de Koning et al., 2002].

For simulated imprinted and Mendelian QTLs with the same total effect on phenotype, there was higher power to detect imprinted QTL, due to the variance explained by a fully imprinted QTL model being larger than that explained by a QTL modeled as additive or dominant [de Koning et al., 2002]. Performing QTL analyses with reduced imprinting models revealed imprinted QTLs whose effects were too small to detect using a standard Mendelian model of analysis. A small number of F$_1$ sires was found to have significant effect on the power to detect paternal compared to maternal expression of a QTL. Further, modeling a non-imprinted QTL with small effects, a small number of F1 sires or where the same alleles are segregating in both founder lines may produce spurious detection of imprinting, despite testing both null and alternative hypotheses of Mendelian expression against imprinting [de Koning et al., 2002]. Study designs incorporating a small number of F1 sires or with QTL alleles
segregating in both founder lines are therefore unsuitable for the detection of an imprinted QTL. In addition, uninformative markers and partially imprinted QTLs are likely to compromise the correct characterization of imprinted QTL.

**Addition of imprinting to least-squares regression: Nezer et al. [1999]**

Nezer et al. [1999] utilized an alternative regression approach to test for imprinting on pig chromosome 2 for an intercross between Large White and Pietrain strains. Evidence for a QTL influencing musculature and fat deposition traits was seen near the IGF2 locus on chromosome 2. IGF2 is expressed exclusively from the paternal allele in many mammals [Morison et al., 2001]. Maternal and paternal expression were separately incorporated into the regression analysis in the region by assuming the QTL had only two possible genotypes, dependent only on the maternal (or paternal) allele. Using a microsatellite marker in the region, the hypothesis that an imprinted gene affects musculature and fat deposition was tested by comparing the LOD scores when the QTL was assumed to be maternally (or paternally) expressed compared to biparental expression. A significant LOD score was obtained when testing for a paternally, but not maternally, expressed QTL [Nezer et al., 1999]. See Table 4 for further applications of the above approaches.

**Summary**

If it can be assumed that QTL alleles are fixed in separate populations, crosses between inbred lines, or outbred but genetically distinct lines, are a powerful method for detecting imprinting. Crosses in animals such as pig and mouse where large numbers of offspring and short generation times allow large F\textsubscript{2} designs are ideal for genetic dissection of complex traits. Studies in the future will benefit from careful tracking of parental origin of alleles, as differences in mean phenotypes are unlikely to be due to maternal effects or mitochondrial inheritance where backcrosses to both parental lines have been performed.

Nevertheless, as with the linkage and association approaches described above, it may be difficult to distinguish imprinting from other parent-of-origin effects and, indeed, imprinted loci may not be detected at all in genome scans if the effect of the locus is small when averaged across maternal and paternal contributions, even if one of these contributions individually is significant. The current drawback in imprinting analysis of QTLs is the lack of methods to examine outbred crosses where a number of QTL alleles are likely to be segregating in each population. Where a small number
of sires are available, both spurious detection of and failure to detect imprinting effects is possible and it may be that some common crosses in agricultural species are unsuitable for detecting imprinting effects.

B4. Other approaches

Addition of imprinting to full likelihood model: Haghighi and Hodge [2002]

For a single diallelic locus underlying a complex trait, Haghighi and Hodge [2002] derived a full likelihood model for parent-of-origin effect in nuclear families, and included different ascertainment probabilities for males and females. In contrast to defining four penetrance parameters dependent on genotype [Strauch et al., 2000], Haghighi and Hodge [2002] define three - a maternal transmission penetrance, given that the disease allele is inherited from the mother, a paternal transmission penetrance, given that the disease allele is inherited from the father, and a combined penetrance, given that the disease allele is inherited from both mother and father. The exact likelihood of transmission of disease allele and the penetrance of disease for offspring for the four phenotypic parental mating types is then calculated: affected mother x unaffected father, unaffected mother x affected father, unaffected mother x unaffected father, and affected mother x affected father. It should be noted that exact likelihoods were calculated only for an autosomal dominant model of inheritance and, further, the three penetrance parameters do not allow for incidence of disease in the absence of disease alleles, which may be included in the approach of Strauch et al. [2000].

This likelihood model incorporating parent-of-origin effects was also extended to include ascertainment, to allow assessment of the effect ascertainment bias has on detecting a parent-of-origin effect [Haghighi and Hodge, 2002]. Ascertainment bias is common in complex disease analysis and may result from recruitment of families to studies through affected offspring, or higher likelihood of one sex reporting affection.

The likelihood models were assessed by simulated data sets covering a range of disease penetrances, imprinting effects and ascertainment models. Estimates for the difference between maternal and paternal transmission penetrances were unbiased when the correct model was analysed, but biased when ascertainment was ignored or incorrectly specified. The power to detect a parent-of-origin effect was higher when the correct model was specified, and power increased with increasing difference between maternal and paternal penetrances [Haghighi and Hodge, 2002]. When data
were simulated assuming a high disease allele prevalence, power to detect parent-of-origin effects decreased, as the parental origin of alleles was not able to be determined for the increased number of homozygous offspring. This likelihood approach may be extended to two loci to allow linkage studies, and is in principle equivalent to the approach of [Strauch et al., 2000] if ascertainment is excluded. Such likelihood derivations may also be useful in tests for imprinting for a locus known to be associated with a trait of interest.

**Marker Association Chi-Squares (MASC) method:**

Clerget-Darpoux et al. [1988] derived a method to test genetic models in diseases known to be associated with particular genes. This approach, known as the Marker Association Chi-Squares (MASC) method, takes into account information on both the segregation of a known marker with the disease and the risk of relatives of a patient also being affected with the disease. The method is based on minimizing a sum of independent chi-squares over three parameters: the allele frequencies at the disease locus, the risk of developing the disease given inheritance of alleles at the marker locus and the recombination fraction between the marker and disease alleles. Using this method, it is possible to test the support for a proposed genetic model by comparing the observed allele frequencies at the marker locus, the probability that parents of a patient are also affected and the probability that siblings of a patient are affected with those probabilities expected under the proposed model.

**Addition of imprinting to MASC: Clerget-Darpoux et al. [1991]**

Clerget-Darpoux et al. [1991] applied the MASC approach to test a number of genetic models for Type 1 insulin dependent diabetes mellitus (IDDM) at the HLA locus. Three genetic models were tested: one disease locus with two alleles, one disease locus with three alleles and a complementation model with two susceptibility alleles at two loci in the HLA region. A maternal effect was proposed if adding an additional parameter to each of the models increased the support for that model. The maternal effect parameter is a measure of the increase in risk to an individual of developing IDDM, given that they have inherited a susceptibility allele from their mother.

The data did not support either the single locus models with and without maternal effects and the complementation model without maternal effects. A complementation model including a maternal effect was found to best explain the observations. Although Clerget-Darpoux et al. [1991] concluded as a result that this
model fitted the data, it is only possible to conclude that there is not enough evidence to reject the model. The MASC method is therefore only valid for rejecting proposed models. Further, it is also not possible to reject the hypothesis that maternal genetic environment has an effect on susceptibility for IDDM.
Conclusion

A number of questions remain to be resolved for detection of imprinting in complex traits.

*What is the appropriate null hypothesis to be testing against? Is it best to test a model including imprinting against a null hypothesis of no linkage or association, or to test the significance of imprinting by removing it from a fully saturated model?*

There are concerns with both of these approaches. Rejecting a null hypothesis of no linkage/association is not evidence to accept an imprinting hypothesis. Similarly, greater support for a model including imprinting does not necessarily mean that an imprinting model is the best option, especially if other influences such as maternal effects are present and not being tested. Conversely, testing many models and picking the “best” raises concerns of multiple testing and significant results may be unlikely to be replicated in further studies.

*Is the best approach to first detect linkage or association, and then search for an imprinting effect, or to include parent-of-origin terms in analysis from the outset?*

Many methods require full knowledge of parental origin of alleles to test for an imprinting effect. In these circumstances, it may be that the most powerful method to detect linkage/association and imprinting is first to follow a standard approach for linkage/association, then test for the influence of imprinting. It is of concern that some initial linkage/association scans will fail to detect loci that are in fact imprinted, as the “average” signal from these loci may be weak. Full knowledge of parental origin of alleles, or likelihood-based methods for “best-guessing” origin, allow inclusion of parental terms in initial analysis, and are likely to be the most powerful approach for detecting linkage/association with imprinting effects.

*What is the appropriate level of significance for testing an imprinting hypothesis?* In the absence of rigorous significance thresholds, perhaps the best approach for testing significance is simulating data, although this procedure returns to the problem of the appropriate null hypothesis to be testing against. Simulated data should be similar to the investigator’s own; randomly assigning male and female transmissions of alleles to offspring provides an appropriate test of imprinting in the presence of linkage/association.
What effect do differences in recombination rates for males and females have on detecting imprinting? Moderate differences in recombination rate appear not to have an influence on the detection of imprinting, although use of sex-averaged recombination rates may incorrectly lead to the conclusion that imprinting is significantly affecting the trait. A number of methods have already incorporating separate recombination rates for males and females into imprinting analyses, and further studies will benefit from routinely including different male and female recombination rates.

Is it possible to dissect maternal (genotype) effects and imprinting? In theory, if maternal effects are assumed to depend only on maternal genotype, it should be possible to dissect the combined effect of maternal genotype from the single allele effect of imprinting, even where one allele is not completely silenced at the imprinted locus. Nevertheless, it appears that for the majority of approaches, especially in the absence of marker information, this dissection will not be possible. Parametric linkage analyses and linkage analysis from observed differences in IBD allele sharing between male and female transmissions should exclude maternal effects, although it is possible they will not differentiate imprinting from other parent-of-origin effects such as higher rates of trinucleotide expansion in the male germline. Likelihood-based methods may have very low power to distinguish between maternal and imprinting effects. QTL analyses of inbred lines for which a large number of crosses are possible are likely to be a very powerful method for dissecting imprinting from maternal effects.

Clearly the most appropriate and powerful statistical approach for detecting imprinting in a complex trait is dependent on the research question, the study design and the assumptions that can be made regarding inheritance and influence of maternal effects. The challenge for the future will be to develop statistical methods with power to detect imprinting even for trait loci with very small effects or that show variation in imprinting status between subpopulations. Certainly the ultimate aim in studying a complex trait is to understand the processes transforming an individual’s genes into its phenotype, and detecting imprinting is an important step towards this aim.
References


Strauch K, Fimmers R, Kurz T, Deichmann KA, Weinker TF, Baur MP. 2000. Parametric and nonparametric multipoint linkage analysis with imprinting and


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<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
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<tbody>
<tr>
<td>Without marker information</td>
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</tr>
<tr>
<td>Parent-of-origin effects: transmission from one parent (discrete traits)</td>
<td>Given an affected offspring with an affected parent, compare the number of affected fathers versus affected mothers. Predominant transmission from one parent suggests a parent-of-origin effect for the trait.</td>
</tr>
<tr>
<td>Parent-of-origin effects: risk (discrete traits)</td>
<td>Given parents affected with disease, calculate the risk to offspring of developing this disease, based on which of the parents are affected. Higher risk from one parent suggests a parent-of-origin effect.</td>
</tr>
<tr>
<td>Parent-of-origin effects: different phenotype (quantitative traits)</td>
<td>Examine differences in the phenotype of offspring when a trait is maternally compared to paternally inherited.</td>
</tr>
<tr>
<td>General mixed models</td>
<td>Phenotype of individual described in terms of fixed effects, additive genetic effects expressed regardless of parental origin, genetic effects expressed only when inherited maternally (or paternally) and residual errors. Estimate additive effects to assess impact of parental effects.</td>
</tr>
<tr>
<td>Correlations and covariance</td>
<td>Use of different correlations between relatives to assess impact of imprinting.</td>
</tr>
<tr>
<td>With marker information</td>
<td></td>
</tr>
<tr>
<td>Linkage analysis: parametric</td>
<td>Model the relationship between a trait of interest and a given genetic locus. Assess whether trait is influenced by an imprinted locus by comparing likelihood of model including imprinting to that without.</td>
</tr>
<tr>
<td>Linkage analysis: allele-sharing methods (discrete traits)</td>
<td>If a particular genetic locus is linked to a trait of interest, affected individuals will inherit identical copies of the locus more often than would be expected by chance. Assess imprinting by</td>
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| **Linkage analysis: allele-sharing methods (quantitative traits)** | For quantitative traits, relatives sharing a large proportion of the same alleles will be more similar compared to those relatives sharing a small proportion of alleles. Variance components method partitions variance into the major gene effect plus other genetic and environmental factors and tests likelihood of model using observed allele sharing. Imprinting is added by splitting major gene effect into male and female transmissions. Regression approach involves regressing the phenotype of relatives against the proportion of alleles they share IBD at a marker. A negative value for the regression slope suggests linkage between the trait and the marker. Imprinting is added by estimating separate male and female slope coefficients. |
| **Association studies (discrete traits)** | Given a locus linked to a trait of interest, certain alleles will be associated with phenotypes such as disease status more often than would be expected by chance. Assess imprinting by testing transmission distortion; by comparing separate risk parameters for maternally and paternally inherited susceptibility alleles; or by comparing separate genotype relative risks parameters for reciprocal heterozygotes. Alternatively models including parent-of-origin effects may be tested against a background model and likelihoods compared. |
| **Association studies (quantitative traits)** | Define offspring value as the sum of parameters such as mating type means, offspring own genotype effects, maternal effects plus a parent-of-origin effect. Alternatively define offspring value as sum of mean parent and offspring genotype plus parent-of-origin effect. If there is no association between the marker and the trait locus, there will be no effect of offspring genotype. Assess likelihood of model including parent of origin effects against model without these effects. |
QTL mapping (inbred lines) | QTL mapping is a genome-wide approach to studying association and linkage between alleles at a locus and a trait of interest. Given association between marker and trait locus, individuals will be more similar in phenotype to one or other inbred line according to which inbred line their alleles originate from. Assess imprinting by comparing differences in phenotype when a linked allele is maternally or paternally derived.

QTL mapping (outbred lines) | Express the phenotypic value of an individual with a given genotype as the sum of an overall mean, an additive component, a dominance component and a residual error. Imprinting tested by comparing means of reciprocal heterozygotes, or alternatively by adding a parent of origin term to the expression for phenotypic value and assessing the likelihood of model.
Table 2: Applications – No marker information

<table>
<thead>
<tr>
<th>Approach name and reference</th>
<th>Species</th>
<th>Trait</th>
<th>Reference</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Parent-of-origin effects</td>
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<tr>
<td>Transmission from one parent</td>
<td>Human</td>
<td>Albright's hereditary osteodystrophy</td>
<td>Davies and Hughes [1993]</td>
<td>Two tailed Fisher exact test for difference in maternal and paternal transmissions</td>
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<td>Arthritis</td>
<td>Rahman et al. [1999]</td>
<td>Normal approximation to binomial to test proportions</td>
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<td>Atopy</td>
<td>Aberg [1993]</td>
<td>$\chi^2$ comparing maternal and paternal history</td>
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<tr>
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<td>Bipolar affective disorder (BPAD)</td>
<td>McMahon et al. [1995]</td>
<td>$\chi^2$ testing parental transmission</td>
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<td>Gershon et al. [1996]</td>
<td>$\chi^2$ testing parental transmission</td>
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<td>Kato et al. [1996]</td>
<td>$\chi^2$ testing parental transmission</td>
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<td>Kornberg et al. [2000]</td>
<td>$\chi^2$ testing parental transmission</td>
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<td>Crohn's disease</td>
<td>Akolkar et al. [1997]</td>
<td>Two tailed binomial test on parental transmission</td>
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<td>Chatkupt et al. [1992]</td>
<td>$\chi^2$ testing parental transmission</td>
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<td>Type I insulin dependent diabetes mellitus (IDDM)</td>
<td>Warram et al. [1984]</td>
<td>Log-rank test on affected offspring of mothers and fathers across time points</td>
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<td>Risk</td>
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<td>Ruiz et al. [1992]</td>
<td>Fisher’s exact test on risk</td>
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<td>Different phenotype</td>
<td>Human Alzheimers</td>
<td>Farrer et al. [1991]</td>
<td>Conditional logistic models including parental sex and age</td>
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<td>Bipolar I disorder</td>
<td>Grigoroiu-Serbanescu et al. [1995]</td>
<td>Survival function comparison using LD statistic; $t$ test on affected parent; multiple regression on sex of parent</td>
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<td>Birth weight and type II diabetes</td>
<td>Lindsay et al. [2000c]</td>
<td>General linear model with influence of parental diabetes status on birth weight</td>
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<td>Huntington’s disease</td>
<td>Roos et al. [1991]</td>
<td>ANOVA on age of onset for sex of parent and sex of individual</td>
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<td>Farrer et al. [1992]</td>
<td>$t$ test on age of onset against parental sex; least-squares regression models including parental sex</td>
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Kuehr et al. [1993] $\chi^2$ testing relative risks from parental transmission

Epilepsy Ottman et al. [1998] Univariate and multivariate regression analysis

Psoriasis vulgaris Traupe et al. [1992] Fisher’s exact test on risk

Burden et al. [1998] $t$ test on affected parent

Tourette’s syndrome Lichter et al. [1995] $\chi^2$ testing relative risks from parental transmission

Huntington’s disease Roos et al. [1991] ANOVA on age of onset for sex of parent and sex of individual

Birth weight and type II diabetes Lindsay et al. [2000c] General linear model with influence of parental diabetes status on birth weight
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<tr>
<th>Condition</th>
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<td>Neurofibromatosis</td>
<td>Miller and Hall [1978]</td>
<td>t test on morbidity against parental sex</td>
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<td>Periodic catatonia</td>
<td>Stober [1998]</td>
<td>Wilcoxon matched pair statistic on age at onset</td>
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<td>Psoriasis</td>
<td>Traupe et al. [1992]</td>
<td>t test on birth weight against parental sex</td>
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<td>Burden et al. [1998]</td>
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<td>t test on age of onset against parental sex</td>
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<td>Schizophrenia</td>
<td>Ohara et al. [1997]</td>
<td>t test and $\chi^2$ on age of onset against parental sex</td>
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<td>Tourette’s</td>
<td>Lichter et al. [1995]</td>
<td>$\chi^2$ on phenotype against parental sex; MANCOVA factor analysis including parental sex</td>
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<td>Turner syndrome</td>
<td>Skuse et al. [1997]</td>
<td>t test on phenotype against parental sex</td>
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<td>Bishop et al. [2000]</td>
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<td>ANCOVA and t test comparison of group means including parental sex</td>
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<td>Mouse Egg traits</td>
<td>Bander et al. [1989]</td>
<td>t test comparison of reciprocal heterozygotes</td>
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<td>Susceptibility to valproic acid teratogenicity</td>
<td>Beck [2001]</td>
<td>t test comparison of reciprocal heterozygotes</td>
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**General Mixed Model**

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<td>Gibson et al. [1988] and Cattle</td>
<td>Dairy Cattle Milk yield Schaeffer et al. [1989] Estimate mean, additive effects and maternal expression effects</td>
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<td>Schaeffer et al. [1989]</td>
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<td>Gibson et al. [1988] and Tier and Sökner [1993]</td>
<td>Beef Cattle</td>
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<td>Dairy Cattle</td>
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<td>Milk yield</td>
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<td>Backfat thickness and growth</td>
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<td>Linkage analysis: parametric</td>
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<td>One gene trait</td>
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<td>Complex trait</td>
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<td>Linkage analysis: allele sharing methods</td>
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<td>Atopy</td>
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<td>Bipolar disorder I and II</td>
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<td>Embryo growth and development</td>
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<td>Embryo, single</td>
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<td>Polycystic ovary syndrome</td>
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<td>Paterson et al. [1999a]</td>
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<td>Obesity</td>
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<td>Multipoint Analysis [Rice, 1997]</td>
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<td>Body mass index, obesity and type II diabetes</td>
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Table 4: Applications – Marker information; Association studies, QTL mapping and other methods

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<th>Approach name and reference</th>
<th>Species</th>
<th>Trait</th>
<th>Reference</th>
<th>Comments</th>
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<td>Association Studies</td>
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<td>PO-LRT [Weinberg et al. 1998]</td>
<td>Human</td>
<td>Type II diabetes</td>
<td>Huxtable et al. [2000]</td>
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<td>Log-linear likelihood, TDT&lt;sub&gt;MvsF&lt;/sub&gt;, TAT, PO-LRT [Weinberg et al. 1998]</td>
<td>Childhood obesity</td>
<td>Le Stunff et al. [2001]</td>
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<td>QTL mapping</td>
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<td>Inbred lines</td>
<td>Mouse</td>
<td>Alcohol preference</td>
<td>Melo et al. [1996]</td>
<td>Significant difference in phenotype of B/B and B/D females only when father was B/B. No examination of differences in alcohol tolerance between reciprocal F&lt;sub&gt;1&lt;/sub&gt; mice.</td>
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<td>Study</td>
<td>Trait</td>
<td>Reference</td>
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<td>Banko et al. [1997]</td>
<td>Audiogenic seizures</td>
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<td>Significant differences ($\chi^2$ statistic) between E/D and E/E mice only with a D/E father and E/E mother. No examination of differences in seizure rates between reciprocal F1 mice.</td>
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<td>Clapcott et al. [2000]</td>
<td>Trypanosomiasis susceptibility</td>
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<td>Significant difference in survival for B/C heterozygotes was seen dependent on whether the strain C parent was male or female ($\chi^2$ statistic); large difference in LOD scores at one locus, based on whether the C strain parent was maternal or paternal.</td>
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<td>Milan et al. [2002]</td>
<td>Pig Carcass composition</td>
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<td>Jeon et al. [1999]</td>
<td>Skeletal and cardiac muscle</td>
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<td>Paternally expressed QTL mapping to $IGF2$</td>
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<td>Lee et al. [2003]</td>
<td>Pig Growth</td>
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<td>Test hypotheses of Mendelian against no QTL, and imprinting against no QTL.</td>
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<td>Jungerius et al. [2004]</td>
<td>Pig Backfat thickness</td>
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<td>Notes</td>
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<tr>
<td>Body composition</td>
<td>de Koning et al. [2000]</td>
<td>Significant evidence for linkage at some loci found only under imprinting model: including more parameters may increase power to detect QTL.</td>
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<td>Coat Colour</td>
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<td>Growth, backfat, litter size</td>
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<td>Pig growth and meat quality</td>
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<td>One maternally expressed QTL on chromosome 8.</td>
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<td>Mouse body mass</td>
<td>Rance et al. [2005]</td>
<td>Utilized Thomsen et al. [2002] decision tree to detect 33 QTL with parent-of-origin effects; significance thresholds derived using permutation tests.</td>
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</table>
Heterozygotes for QTL take trait values outside the range of the homozygotes. Very high error rate – as the model became overspecified nearly all QTL showed evidence for imprinting.

<table>
<thead>
<tr>
<th>de Koning et al. [2002]</th>
<th>Reproduction</th>
<th>Holl et al. [2004]</th>
<th>Other approaches</th>
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<td></td>
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<td>Human IDDM Margaritte-Jeannin et al. [1995]</td>
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</table>

**Other approaches**

MASC [Clerget-Darpoux et al., 1988] | Human | IDDM | Margaritte-Jeannin et al. [1995] |
3. Intergenerational Effects Imposed by Genomic Imprinting Invalidate Some Simple Derivations of Variance Components in Quantitative Genetic Models

Abstract

The level of expression of an imprinted gene is dependent on the sex of the parent from which it was inherited. As a result, reciprocal heterozygotes in a population may display different mean phenotypes for quantitative traits. Using four standard quantitative genetic methods for deriving breeding values, population variances and covariances between relatives, we demonstrate that although these approaches are equivalent under Mendelian expression, this equivalence is lost when genomic imprinting is acting. Imprinting introduces both parent-of-origin dependent and generation dependent effects that result in differences in the way additive and dominance effects are defined for the various approaches. Further, imprinting creates a covariance between additive and dominance terms absent under Mendelian expression, but the expression for this covariance cannot be derived using a number of the standard approaches for defining additive and dominance terms.

Introduction

A gene is imprinted when its level of expression is dependent on the sex of the parent from which it was inherited. For example, insulin-like growth factor 2 (Igf2) is expressed only from the paternal allele in most fetal tissues of eutherian and marsupial mammals, while the maternally inherited allele is inactivated [DeChiara et al., 1991; O'Neill et al., 2000]. Complex processes of epigenetic regulation are necessary for the repression of one allele while the other is expressed. These processes include allele-specific modifications such as differential DNA methylation, chromatin structure and histone packing, and differences in replication timing of the maternally and paternally inherited genomes [Rand and Cedar, 2003]. More generally, imprinting results in non-equivalence of reciprocal heterozygotes, where inheriting an A1 allele from one’s
mother and an $A_2$ allele from one’s father gives a different phenotype, on average, than the reverse inheritance pattern.

Approximately 83 imprinted genes have been identified in mammals, including 41 in humans, and many of these genes are thought to be involved in traits such as growth and development [Morison et al., 2005]. Recent years have seen an increasing number of statistical methods developed that aim to identify imprinting in quantitative traits. Using QTL mapping, for example, imprinting has been suggested for quantitative traits as diverse as carcass composition, growth, coat colour and reproductive traits [Knott et al., 1998; de Koning et al., 2000; Rattink et al., 2000; de Koning et al., 2001; Hirooka et al., 2002; Milan et al., 2002; Quintanilla et al., 2002; Lee et al., 2003], while general mixed models have demonstrated the involvement of imprinting in traits such as milk yield, litter size and growth [Schaeffer et al., 1989; Tier and Solkner, 1993; de Vries et al., 1994; Kaiser et al., 1998; Engellandt and Tier, 2002; Essl and Voith, 2002; Stella et al., 2003].

The inclusion of imprinting to these genetic methods highlights both the importance of imprinting to a range of economically important livestock production traits and to human health and disease, and the importance of understanding the effect imprinting may have on traditional approaches to modeling quantitative genetic traits. Quantitative genetic models aim to describe aspects such as the mean and variation of continuous traits in a population. Quantitative traits may be influenced by many genes, the environment and any number of interactions between them, and models for these traits are correspondingly complex. Nevertheless, we here employ a one-locus, two-allele quantitative genetic model to demonstrate the differences in a number of standard approaches for theoretically defining breeding values, genotypic variance and covariances between relatives. In doing so we show that genomic imprinting may have a large effect on the assumptions made in these most minimal models, and is therefore likely to also influence more complex models involving many alleles and multiple genetic loci.

**The Model**

We here present an overview of a number of approaches for deriving quantitative genetic models for imprinting at one locus. Such models are the basis for many quantitative genetic approaches for dissecting genetic and environmental effects.
in quantitative traits. Following the approach of Spencer [2002], consider an autosomal diallelic locus subject to imprinting, with alleles $A_1$ and $A_2$ at frequency $p_1$ and $p_2 = 1 - p_1$ respectively in the population. Note that the population under consideration is static, without selection, migration or mutation operating. Assume that on some suitable scale, the genotypic value of $A_1A_1$ homozygotes is 0 and $A_2A_2$ homozygotes is $2a$. Assuming no maternal effects, writing the maternally inherited allele first, $A_2A_1$ heterozygotes have genotypic value $a(1+k_1)$ and $A_1A_2$ heterozygotes have value $a(1+k_2)$ (Figure 1).

**Figure 1: Genotypic values for genotypes under genomic imprinting**

<table>
<thead>
<tr>
<th></th>
<th>$A_1A_1$</th>
<th>$A_2A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>0</td>
<td>$a(1+k_1)$</td>
<td>$a(1+k_2)$</td>
<td>$2a$</td>
</tr>
</tbody>
</table>

In general, imprinting is thought of as complete inactivation of one allele dependent on parental origin, corresponding to $k_1 = -1$ and $k_2 = 1$ (complete silencing of the maternal allele), or $k_1 = 1$ and $k_2 = -1$ (complete silencing of the paternal allele). More recently, however, imprinting has been treated as a quantitative trait, which implies that maternal or paternal alleles may only be partially inactivated [see, e.g., Sandovici et al., 2003; Naumova and Croteau, 2004; Sandovici et al., 2005], so that and $k_1$ and $k_2$ may take any real values. Biologically it seems likely that the $k$ coefficients would usually lie in the range [-1,1] so that partial inactivation does not result in a more extreme phenotype than either of the homozygotes, but we do not make this assumption in the following derivations.

With the help of Figure 1, the mean genotypic value over the population is

$$
\mu = p_1^2(0) + p_2p_1(a(1+k_1)) + p_1p_2(a(1+k_2)) + p_2^2(2a)
$$

$$
= a p_2 (2 + p_1(k_1 + k_2)).
$$

We follow a number of approaches in calculating breeding values, components of variance and covariances between relatives. Doing so illustrates that various assumptions made in these approaches are not valid in the presence of imprinting and maternal effects.
Approach 1

Using our notation, we follow the approach of Falconer and Mackay [1996] and Spencer [2002], using genotypic values of parents and offspring to calculate genotypic deviations, population breeding values and dominance deviations, components of variance and covariances between relatives.

The genotypic deviation of a genotype is the difference between its genotypic value and the population mean. The breeding value is defined as twice the difference between the mean genotypic value of the class’s offspring and the population mean [Falconer and Mackay, 1996]. Average values of progeny for females and males are shown in Table 1.

The dominance deviation for a genotypic class is the difference between the genotypic deviation and the breeding value [Falconer and Mackay, 1996]. Genotypic deviations, breeding values and dominance deviations are shown in Table 1.

Genetic variance components

As shown by Spencer [2002], the genetic variance of the population is the variance of the genotypic deviations:

\[ \sigma_{G(1)}^2 = p_1 p_2 (\alpha_f^2 + \alpha_m^2 + a^2 p_1 p_2 (k_1 + k_2)^2) \]

(1)

where

\[ \alpha_f = a(1 + k_1 p_1 - k_2 p_2) \]

and

\[ \alpha_m = a(1 + k_2 p_1 - k_1 p_2). \]

Note that throughout the chapter the bracketed number in the variance (and covariance) subscripts indicates the Approach used (here \((1)\) for Approach 1).

Female \( (\sigma_{Af(1)}^2) \) and male \( (\sigma_{Am(1)}^2) \) additive genetic variances are the respective variances of their breeding values:

\[ \sigma_{Af(1)}^2 = 2 p_1 p_2 \alpha_f^2 \]

(2)

and

\[ \sigma_{Am(1)}^2 = 2 p_1 p_2 \alpha_m^2, \]

(3)
with a population mean (assuming equal numbers of males and females) of
\[
\sigma^2_{A(1)} = \frac{1}{2}(\sigma^2_{Af(1)} + \sigma^2_{Am(1)})
\]
\[
= p_1 p_2 (\alpha_f^2 + \alpha_m^2),
\]
(4)

This population additive variance also appears in Dai and Weeks [2006]. The dominance genetic variance is the variance of the dominance deviations, and is the same for both females \((\sigma^2_{Df(1)})\) and males \((\sigma^2_{Dm(1)})\):
\[
\sigma^2_{Df(1)} = \sigma^2_{Dm(1)} = \sigma^2_{D(1)} = \alpha^2 p_1 p_2 ((k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2).
\]
(5)

The covariances between dominance deviations and breeding values can be shown to be
\[
\sigma_{ADf(1)} = a p_1 p_2 \alpha_f (k_2 - k_1)
\]
(6)
and
\[
\sigma_{ADm(1)} = a p_1 p_2 \alpha_m (k_1 - k_2)
\]
(7)
with an average value of
\[
\sigma_{AD(1)} = -a p_1 p_2 (k_1 - k_2)^2
\]
(8)
and it can be easily shown that
\[
\sigma^2_{G(1)} = \sigma^2_{Af(1)} + \sigma^2_{Df(1)} + 2\sigma_{ADf(1)} = \sigma^2_{Am(1)} + \sigma^2_{Dm(1)} + 2\sigma_{ADm(1)}.
\]
(9)

Resemblance between relatives
Again following the approach of Spencer [2002], we can see that the covariance between mothers and offspring is
\[
\sigma_{OPf(1)} = \frac{1}{4}(\sigma^2_{Af(1)} + \sigma_{ADf(1)})
\]
\[
= \frac{1}{4}(2 p_1 p_2 \alpha_f^2 + a p_1 p_2 \alpha_f (k_2 - k_1))
\]
\[
= \frac{1}{2} p_1 p_2 \alpha_f (\alpha_f + \alpha_m)
\]
(10)
while the covariance between fathers and offspring is
\[
\sigma_{OPm(1)} = \frac{1}{2}(\sigma^2_{Am(1)} + \sigma_{ADm(1)})
\]
\[
= \frac{1}{2}(2 p_1 p_2 \alpha_m^2 + a p_1 p_2 \alpha_m (k_1 - k_2))
\]
\[
= \frac{1}{2} p_1 p_2 \alpha_m (\alpha_f + \alpha_m).
\]
(11)
with a mean offspring-parent covariance of

\[ \sigma_{OP(1)} = \frac{1}{2} (\sigma_{OPf(1)} + \sigma_{OPm(1)}) \]

\[ = \frac{1}{2} p_1 p_2 (\alpha_f + \alpha_m)^2. \]

(12)

The covariance between half sibs sharing a mother is

\[ \sigma_{HSf(1)} = \frac{1}{4} \sigma_{Af(1)} \]

\[ = \frac{1}{4} p_1 p_2 \alpha_f^2 \]

and half sibs sharing a father is

\[ \sigma_{HSm(1)} = \frac{1}{4} \sigma_{Am(1)} \]

\[ = \frac{1}{4} p_1 p_2 \alpha_m^2 \]

(13)

(14)

[Spencer, 2002]. The mean half-sib covariance is

\[ \sigma_{HS(1)} = \frac{1}{4} (\sigma_{HSf(1)} + \sigma_{HSm(1)}) \]

\[ = \frac{1}{2} p_1 p_2 (\alpha_f^2 + \alpha_m^2) \]

(15)

Finally, we may also calculate the covariance of full sibs with the aid of Table 2:

\[ \sigma_{FS(1)} = \frac{1}{4} p_1 p_2 (2(\alpha_f^2 + \alpha_m^2) + \alpha^2 p_1 p_2 (k_1 + k_2)^2) \]

\[ = \frac{1}{2} (\sigma_{A(1)} + \sigma_{AD(1)}(1) + \sigma_{D(1)}) \]

(16)

Dai and Weeks [2006] extended a general framework for computing covariances between relatives using alleles shared identical by descent. Their derivations confirm the parent-offspring and half sib covariances described above from Spencer [2002] and expression (16) for the full sib covariance.

**Approach 2**

An alternative method to that described above is to follow a regression approach to calculate population dominance deviations, breeding values, components of variance and covariances between relatives. We may express the genotypic value \( G_{ij} \) of the \( A_iA_j \) genotype using least squares regression [Fisher, 1918]: based on the relationship between the number of copies of the \( A_2 \) allele in the genotype and the genotypic value, we may define \( G_{ij} \) as the sum of a predicted regression value \( \hat{G}_j \) and a residual error corresponding to a dominance deviation \( \lambda_j \). The predicted regression value may be further decomposed into the mean of the genotypes \( \mu_G \)
plus additive effects \( (\varepsilon) \), where additive effects are linear terms dependent on the number of \( A_1 \) and \( A_2 \) alleles in the genotype \((N_1 \text{ and } N_2 \text{ respectively})\), so that

\[
G_{ij} = \hat{G}_{ij} + \lambda_j
= \mu_G + \varepsilon_i N_1 + \varepsilon_2 N_2 + \lambda_j
\]

[Lynch and Walsh, 1998].

Noting that for the two allele case \( N_1 = 2 - N_2 \), we have

\[
G_{ij} = \mu_G + \varepsilon_i (2 - N_2) + \varepsilon_2 N_2 + \lambda_j
= t + N_2 (\varepsilon_2 - \varepsilon_i) + \lambda_j,
\]

where \( t = \mu_G + 2\varepsilon_i \) [Lynch and Walsh, 1998].

Now the genotypic values predicted by the regression are

\[
\hat{G}_{ij} = \mu_G + \varepsilon_i + \varepsilon_j = \begin{cases} 
\mu_G + 2\varepsilon_i & \text{for } \hat{G}_{i1} \\
\mu_G + \varepsilon_i + \varepsilon_2 & \text{for } \hat{G}_{21} \text{ and } \hat{G}_{22} \\
\mu_G + 2\varepsilon_2 & \text{for } \hat{G}_{22}
\end{cases}
\]

where \( \varepsilon_i = -ap_2(1 + \frac{1}{2}(k_1 + k_2)(p_1 - p_2)) \) and \( \varepsilon_2 = ap_1(1 + \frac{1}{2}(k_1 + k_2)(p_1 - p_2)) \).

We find that the slope of the regression is

\[
\varepsilon = a(1 + \frac{1}{2}(k_1 + k_2)(p_1 - p_2))
= \frac{1}{2}(\alpha_f + \alpha_m)
\]

(where \( \alpha_f \) and \( \alpha_m \) are defined as in Approach 1), and the intercept is

\[
t = \mu_G + 2\varepsilon_i
= ap_2(2 + p_1(k_1 + k_2)) - 2p_2\varepsilon
= ap_2^2(k_1 + k_2).
\]
Using Table 3, we can then derive the following properties for a single diallelic locus under imprinting:

\[ \mu_N = 2p_2 \]

\[ \text{E}[N^2] = 2p_2(1 + p_2) \]

\[ \mu_G = \mu = ap_2(2 + p_1(k_1 + k_2)) \]

\[ \text{E}[GN] = ap_2(p_1(2 + k_1 + k_2) + 4p_2) \]

\[ \sigma(G, N) = ap_1p_2(2 + (k_1 + k_2)(p_1 - p_2)) \]

\[ \sigma^2_N = 2p_1p_2 \]

\[ \mu_A = 1 + 2p_2\epsilon \]

\[ \mu_\lambda = 0 \]

\[ \text{E}[\hat{G}^2] = \lambda^2 + 4p_2\epsilon t + 2p_2\epsilon^2(1 + p_2) \]

\[ \text{E}[\hat{\lambda}^2] = \frac{1}{2}a^2p_1p_2((k_1 - k_2)^2 + 2(k_1 + k_2)^2p_1p_2) \]

The dominance deviations in Table 3 are equivalent to the mean of female and male dominance deviations from Approach 1.

The breeding value is defined as twice the difference between the mean genotypic value of the class’s offspring and the population mean [Falconer and Mackay, 1996]. When breeding values are equivalent for males and females, the breeding value of a genotypic class is also the sum of the additive effects of its genes:

\[ \text{BV}_{(i)}(A_1A_1) = 2\epsilon_1 \]

\[ \text{BV}_{(i)}(A_2A_1) = \text{BV}_{(i)}(A_1A_2) = \epsilon_1 + \epsilon_2 \]

\[ \text{BV}_{(i)}(A_2A_2) = 2\epsilon_2 \]

For an imprinted locus, however, breeding values are different for males and females. Nevertheless, it can be seen that the average of the male and female breeding values derived in Approach 1 is equivalent to the sum of the additive effects of the
genes for each genotypic class described above:

\[ BV_{(i)}(A_1A_1) = \frac{1}{2} (-2p_f\alpha_f - 2p_m\alpha_m) \]

\[ = 2\epsilon_i = BV_{(2)}(A_1A_1) \]

\[ BV_{(i)}(A_2A_2) = BV_{(i)}(A_1A_2) = \frac{1}{2} (\alpha_f(p_1 - p_2) + \alpha_m(p_1 - p_2)) \]

\[ = \epsilon_1 + \epsilon_2 = BV_{(2)}(A_2A_2) = BV_{(2)}(A_1A_2) \]

\[ BV_{(i)}(A_2A_2) = \frac{1}{2} (2p_f\alpha_f + 2p_m\alpha_m) \]

\[ = 2\epsilon_2 = BV_{(2)}(A_2A_2). \]

**Genetic variance components**

The additive genetic variation is the variance associated with the average additive effects of alleles and can be shown to be

\[ \sigma^2_{A(2)} = E(\hat{G}^2) - \mu^2_G \]

\[ = 2p_f p_m \epsilon^2 \]

\[ = \frac{1}{2} p_f p_m (\alpha_f + \alpha_m)^2 \]

Recalling that the average of the female and male additive variances derived in Approach 1 is

\[ \sigma^2_{A(1)} = p_f p_m (\alpha_f^2 + \alpha_m^2) \]

we see that \( \sigma^2_{A(2)} \) differs from \( \sigma^2_{A(1)} \) by the subtraction of \( \frac{1}{2} a^2 p_f p_m (k_1 - k_2)^2 \). Although this difference is surprising given that our breeding values are equivalent to the mean of female and male breeding values from Approach 1, this disparity arises because the variance of a sum of two correlated variables is not equivalent to the sum of the variances:

\[ \sigma^2_{(BV_f + BV_m)} \neq \sigma^2_{(BV_f)} + \sigma^2_{(BV_m)}. \]

Under Mendelian expression, male and female breeding values are the same and hence have a correlation of 1. Even under genomic imprinting, however, male and female breeding values are correlated.
The dominance genetic variance is the genetic variance associated with dominance effects:

\[
\sigma_{D(2)}^2 = E(\lambda^2) - \mu^2_{\lambda} = \frac{1}{4} a^2 p_1 p_2 ((k_1 - k_2)^2) + 2 p_1 p_2 (k_1 + k_2)^2.
\]  

(20)

Again \( \sigma_{D(2)}^2 \) differs from \( \sigma_{D(1)}^2 \) by a term of \( \frac{1}{2} a^2 p_1 p_2 (k_1 - k_2)^2 \).

We find that the covariance between the dominance deviations and breeding values (\( \sigma_{AD(2)} \)) is zero. For the additive by dominance covariance then, \( \sigma_{AD(2)} \) differs from the average of the male and female covariances from Approach 1 by a term of \( \frac{1}{2} a^2 p_1 p_2 (k_1 - k_2)^2 \).

Therefore

\[
\sigma_{G(2)}^2 = \sigma_{A(2)}^2 + \sigma_{D(2)}^2
\]

(21)

which is equivalent to the total variance (1) found in Approach 1.

**Resemblance between relatives**

Following Fisher [1918] the covariance between parents and offspring is

\[
\sigma_{OP(2)} = \frac{1}{2} \sigma_{A(2)}^2 = p_1 p_2 e^2.
\]

(22)

This offspring parent covariance corresponds to the mean of the female (10) and male (11) offspring-parent covariances from Approach 1:

\[
p_1 p_2 e^2 = \frac{1}{4} p_1 p_2 (\alpha_f^2 + \alpha_m^2)
\]

(23)

The covariance between half sibs is defined as

\[
\sigma_{HS(2)} = \frac{1}{2} \sigma_{A(2)}^2 = \frac{1}{2} p_1 p_2 e^2
\]

(24)

while the covariance between full sibs is

\[
\sigma_{FS(2)} = \frac{1}{2} \sigma_{A(2)}^2 + \frac{1}{4} \sigma_{D(2)}^2 = p_1 p_2 e^2 + \frac{1}{2} a^2 p_1 p_2 ((k_1 - k_2)^2) + 2 p_1 p_2 (k_1 + k_2)^2
\]
In contrast to the offspring-parent covariance above, the mean of the female and male half sib covariances (15) and the full sib covariance (16) do not correspond to equations (23) and (24) respectively above.

**Approach 3a**

We now follow a more general least squares approach to calculate population breeding values, dominance deviations, components of variance and covariances between relatives [Lynch and Walsh, 1998].

We write the genotypic value $G_{ij}$ as the sum of the mean plus additive allelic effects ($\epsilon$) and dominance effects ($\lambda$):

$$G_{ij} = \mu + \epsilon_{i*} + \epsilon_{j*} + \lambda_{ij}$$  (25)

where $\mu = ap_2(2 + p_1(k_1 + k_2))$ as above, $\epsilon_{i*}$ is the average additive effect of inheriting an $A_i$ allele from the mother, $\epsilon_{j*}$ is the average effect of inheriting an $A_j$ allele from the father and $\lambda_{ij}$ is the remaining dominance term. Note that here “•” represents either of an $A_1$ or $A_2$ allele in that position. We note that Dai and Weeks [2006] follow the same approach to define additive and dominance effects under imprinting, although set the population mean to zero.

The additive effect of an allele is defined as the deviation of members of the population with the allele from the population mean. In the absence of imprinting, the parental origin of the allele has no effect. With imprinting however, we can calculate the additive effect of the allele separately under maternal and paternal inheritance. For example, the additive effect of an $A_1$ allele when inherited maternally is

$$\epsilon_{i*} = p_1(0) + ap_2(1 + k_2) - \mu$$

$$= -ap_2(1 + k_1p_1 - k_2p_2)$$

while the additive effect of an $A_1$ allele when inherited paternally is

$$\epsilon_{i*} = p_1(0) + ap_2(1 + k_1) - \mu$$

$$= -ap_2(1 + k_2p_1 - k_1p_2).$$
The maternal and paternal additive effects are thus

\[ \varepsilon_{1}\bullet = -p_{2}\alpha_{f} \]
\[ \varepsilon_{1} = -p_{2}\alpha_{m} \]
\[ \varepsilon_{2} \bullet = ap_{1}(1+k_{1}p_{1}-k_{2}p_{2}) = p_{1}\alpha_{f} \]
\[ \varepsilon_{2} = ap_{1}(1+k_{2}p_{1}-k_{1}p_{2}) = p_{1}\alpha_{m}. \]

Note that the mean of \( \varepsilon_{1}\bullet \) and \( \varepsilon_{\bullet 1} \) is equal to \( \varepsilon_{1} \) (from Approach 2), and the mean of \( \varepsilon_{2}\bullet \) and \( \varepsilon_{\bullet 2} \) is equal to \( \varepsilon_{2}. \)

The dominance effects are defined as

\[ \lambda_{ij} = G_{ij} - \mu_{G} - \varepsilon_{\bullet 1} - \varepsilon_{\bullet 1}. \]

For example,

\[ \lambda_{11} = G_{11} - \mu_{G} - \varepsilon_{\bullet 1} - \varepsilon_{\bullet 1} \]
\[ = -ap_{1}^{2}(k_{1} + k_{2}) \]

The remaining dominance effects are thus

\[ \lambda_{21} = \lambda_{21} = ap_{2}p_{1}(k_{1} + k_{2}) \]
\[ \lambda_{22} = -ap_{1}^{2}(k_{1} + k_{2}). \]

Note that these dominance effects differ from Approaches 1 and 2.

As in Approach 2, we may define breeding values as the sum of additive effects of alleles, so that

\[ \text{BV}_{(3a)}(A_{1}A_{1}) = \varepsilon_{\bullet 1} + \varepsilon_{1} \]
\[ = -p_{2}(\alpha_{f} + \alpha_{m}) = \text{BV}_{(1)}(A_{1}A_{1}) \]

\[ \text{BV}_{(3a)}(A_{1}A_{2}) = \varepsilon_{\bullet 1} + \varepsilon_{1} \]
\[ = p_{1}\alpha_{f} - p_{2}\alpha_{m} \]

\[ \text{BV}_{(3a)}(A_{2}A_{1}) = \varepsilon_{\bullet 1} + \varepsilon_{1} \]
\[ = -p_{2}\alpha_{f} + p_{1}\alpha_{m} \]

\[ \text{BV}_{(3a)}(A_{2}A_{2}) = \varepsilon_{\bullet 2} + \varepsilon_{2} \]
\[ = p_{1}(\alpha_{f} + \alpha_{m}) = \text{BV}_{(1)}(A_{2}A_{2}) \]

The homozygote breeding values are equivalent to the mean of female and male breeding values from Approach 1 (see Table 1). It is interesting to note that, unlike Approaches 1 and 2, breeding values are different for the two heterozygotes.
However, the mean of these heterozygote breeding values is equal to the (mean) 
breeding values for heterozygotes for Approaches 1 and 2:
\[
\frac{1}{2} (p_i \alpha_f - p_z \alpha_m - p_z \alpha_f + p_i \alpha_m) = \frac{1}{2} (p_i - p_z) (\alpha_f + \alpha_m)
\]
\[= BV_{(1)}(\text{heterozygotes}) = BV_{(2)}(\text{heterozygotes}).\]

**Genetic variance components**

The additive variance is the variance of the additive allelic effects and can be 
shown to be
\[
\sigma^2_{A(3a)} = \sum_{i=1}^{2} p_i (e^2_i + e^2_i)
\]
\[= p_i p_z (\alpha_f^2 + \alpha_m^2) = \sigma^2_{A(1)}.
\]
Using this Approach we have recovered the same additive variance found by 
averaging the female and male additive variances from Approach 1. The dominance 
variance is the variance of the dominance deviations:
\[
\sigma^2_{D(3a)} = \sum_{i,j=1}^{2} p_i p_j \lambda_{ij}^2
\]
\[= (ap_i p_z (k_i + k_z))^2,
\]
which is different from the total dominance variance derived in Approach 1. Dai and 
Weeks [2006] similarly define the dominance variance as the variance of the 
dominance effects. The covariance between additive allelic and dominance effects is 
defined as
\[
\sigma_{AD(3a)} = \sum_{i,j=1}^{2} p_i p_j (e_i \ast + e_j \ast) \lambda_{ij}
\]
\[= 0.
\]
Finally, as the covariance between additive allelic and dominance effects is zero, the 
total variance is the sum of the additive and dominance variances and can be seen to 
be
\[
\sigma^2_{G(3a)} = p_i p_z (\alpha_f^2 + \alpha_m^2 + a^2 p_i p_z (k_i + k_z)^2)
\]
which is again equivalent to the total genetic variance found in Approach 1 (1).
Resemblance between relatives

Again in the absence of separate female and male variances, we follow Fisher [1918] and define the covariance between parents and offspring as

\[
\sigma_{OP(3a)} = \frac{1}{2} \sigma_{A(3a)}^2 \\
= \frac{1}{2} p_i p_j (\alpha_f^2 + \alpha_m^2) 
\]

which is not equal to the mean of the female and male offspring-parent covariances from Approach 1 (12).

The covariance between half sibs is defined as

\[
\sigma_{HS(3a)} = \frac{1}{4} \sigma_{A(3a)}^2 \\
= \frac{1}{4} p_i p_j (\alpha_f^2 + \alpha_m^2) 
\]

and, in contrast to the parent-offspring covariance, is equal to the mean of female and male half sib covariances from Approach 1 (15). The covariance between full sibs is

\[
\sigma_{FS(3a)} = \frac{1}{2} \sigma_{A(3a)}^2 + \frac{1}{4} \sigma_{D(3a)}^2 \\
= \frac{1}{2} p_i p_j (2(\alpha_f^2 + \alpha_m^2) + a^2 p_i p_j (k_1 + k_2)^2) 
\]

which is the same as that found in Approach 1 (16).

**Approach 3b**

Approach 3a calculated total additive and dominance effects and did not allow separate calculation of female and male additive and dominance variances as was possible in Approach 1. Let us treat individuals as parents in terms of the alleles that they will pass onto offspring in the next generation. This mirrors Approach 1 where breeding values and dominance deviations are defined using offspring mean values in the following generation. We redefine the genotypic value of an individual as a sex-specific sum, different for males and females. Additive effects are defined in terms of the additive effects of alleles that offspring of these male and female parents will inherit. Dominance effects are defined as a remainder so that the genotypic value of an individual is the sum of additive effects inherited by its offspring, plus the population mean and a dominance deviation. In using these definitions we partition the additive and dominance terms into those specific to male and female inheritance.
Now let

\[ G_{ij} = \mu + \varepsilon'_{i} + \varepsilon'_{j} + \lambda_{ijf} \]

\[ = \mu + \varepsilon'_{i} + \varepsilon'_{j} + \lambda_{ijm} \] (33)

where the extra subscript on \( \lambda \) indicates female (f) and male (m) dominance effects, and the additive terms \( \varepsilon'_{i} \) and \( \varepsilon'_{j} \) include primes as they are additive effects passed onto the next generation. As our model has no selection or mutation acting, the sex-specific additive effect of inheriting an \( A_1 \) or \( A_2 \) allele is the same whether inherited from grandparent to parent (Approach 3a) or from parent to offspring (this Approach). Therefore, following this model, \( \varepsilon'_{i} = \varepsilon_{i} \) and \( \varepsilon'_{j} = \varepsilon_{j} \) and our additive terms are defined as in Approach 3a. Now female and male dominance effects are

\[ \lambda_{ijf} = G_{ij} - \mu - \varepsilon_{i} - \varepsilon_{j} \]

and

\[ \lambda_{ijm} = G_{ij} - \mu - \varepsilon_{i} - \varepsilon_{j} \]

so that

\[ \lambda_{11f} = ap_{2}(k_{i}p_{1} - k_{2}(1 + p_{2})) \]

\[ \lambda_{21f} = a(k_{i}(1 - p_{1}^2) - k_{2}p_{2}^2) \]

\[ \lambda_{12f} = a(-k_{i}p_{1}^2 + k_{2}(1 - p_{2}^2)) \]

\[ \lambda_{22f} = ap_{2}(-k_{i}(1 + p_{1}) + k_{2}p_{2}) \]

and

\[ \lambda_{11m} = ap_{2}(k_{2}p_{1} - k_{1}(1 + p_{2})) \]

\[ \lambda_{21m} = a(-k_{2}p_{1}^2 + k_{1}(1 - p_{2}^2)) \]

\[ \lambda_{12m} = a(k_{2}(1 - p_{1}^2) - k_{1}p_{2}^2) \]

\[ \lambda_{22m} = ap_{2}(-k_{2}(1 + p_{1}) + k_{1}p_{2}) \].

We may also calculate breeding values as in Approaches 2 and 3a, as the sum of additive effects. For females,

\[ BV_{f(3b)}(A_{1}A_{1}) = \varepsilon_{i} + \varepsilon_{j} = -2p_{1}\alpha_{f} \]

\[ BV_{f(3b)}(A_{1}A_{2}) = \varepsilon_{i} + \varepsilon_{j} = \alpha_{f}(p_{1} - p_{2}) \]

\[ BV_{f(3b)}(A_{1}A_{2}) = \varepsilon_{i} + \varepsilon_{j} = \alpha_{f}(p_{1} - p_{2}) \]

\[ BV_{f(3b)}(A_{2}A_{2}) = \varepsilon_{i} + \varepsilon_{j} = 2p_{1}\alpha_{f} \]
which are identical to those found in Approach 1. Similarly for males, breeding values defined as the sum of male additive effects are equivalent to breeding values derived from progeny means in Approach 1. We may also see that dominance deviations are equivalent between these two approaches.

**Genetic variance components**

We can now calculate additive genetic variances separately for males and females, so that

\[
\sigma^2_{A_f} = \sum_{i=1}^{2} 2 p_i \epsilon^2_i, \\
\sigma^2_{A_m} = \sum_{i=1}^{2} 2 p_i \epsilon^2_i,
\]

These values for male and female additive effects mirror those in Dai and Weeks [2006]. The dominance genetic variance is the variance of the dominance deviations, and is the same for both males and females.

\[
\sigma^2_{D_f} = \sigma^2_{D_m} = \sigma^2_D = a^2 p_1 p_2 ((k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2)
\]

Finally, the covariances between dominance deviations and breeding values can be shown to be

\[
\sigma_{A_D_f} = a p_1 p_2 \alpha_f (k_2 - k_1) = \sigma_{A_D_f}(1)
\]

\[
\sigma_{A_D_m} = a p_1 p_2 \alpha_m (k_1 - k_2) = \sigma_{A_D_m}(1)
\]

from which we may recover our total genetic variance:

\[
\sigma^2_G = \sigma^2_{A_f} + \sigma^2_{D_f} + 2\sigma_{A_D_f} + \sigma^2_{A_m} + \sigma^2_{D_m} + 2\sigma_{A_D_m}
\]

Using this novel approach to define separate male and female effects, we are able to recover the total, additive and dominance variances and the additive by dominance covariance from Approach 1. As a consequence, we may see that the covariances between relatives (defined as sums of additive, dominance and covariance terms following Spencer [2002]) are also identical to those found in Approach 1.
Approach 4

Finally, we may also follow a multiple regression approach to dissect the genotypic value into additive and dominance components. Using matrix notation, we can express the genotypic value as

\[ G_{ij} = X\beta + \delta \]  \hspace{1cm} (40)

where

\[
\begin{bmatrix}
G_{i1} \\
G_{i2} \\
G_{11} \\
G_{22}
\end{bmatrix} =
\begin{bmatrix}
0 \\
a(1+k_1) \\
a(1+k_2) \\
2a
\end{bmatrix}
\]

is the matrix of genotypic values,

\[
X =
\begin{bmatrix}
1 & 0 & 0 \\
1 & 1 & 0 \\
1 & 0 & 1 \\
1 & 1 & 1
\end{bmatrix}
\]

is an incidence matrix,

\[
\beta =
\begin{bmatrix}
\kappa \\
\tau_{female} \\
\tau_{male}
\end{bmatrix}
\]

is the vector of the intercept (\(\kappa\)) and the two parental partial regression coefficients (\(\tau_{female}\) and \(\tau_{male}\)) and

\[
\delta =
\begin{bmatrix}
\delta_{11} \\
\delta_{21} \\
\delta_{12} \\
\delta_{22}
\end{bmatrix}
\]

is the vector of dominance effects [Lynch and Walsh, 1998]. Multiplied out, this gives

\[
\begin{bmatrix}
G_{i1} \\
G_{i2} \\
G_{11} \\
G_{22}
\end{bmatrix} =
\begin{bmatrix}
\kappa + \delta_{11} \\
\kappa + \tau_{female} + \delta_{21} \\
\kappa + \tau_{male} + \delta_{12} \\
\kappa + \tau_{female} + \tau_{male} + \delta_{22}
\end{bmatrix}
\]

We may now estimate \(\kappa\), \(\tau_{female}\), and \(\tau_{male}\) using a generalized least squares approach, so that

\[
\hat{\beta} = (X^TX)^{-1}X^TG_{ij} ,
\]  \hspace{1cm} (41)
where
\[ R = \text{diag}(p_1^2, p_2, 1, p_1, p_2, 1^2) \]
is the matrix of genotypic frequencies.

Solving, we find
\[ \kappa = ap_2^2(k_1 + k_2) \]
\[ \tau_{\text{female}} = a(1 + k_1p_1 - k_2p_2) = \alpha_f \]
\[ \tau_{\text{male}} = a(1 + k_2p_1 - k_1p_2) = \alpha_m \]
and
\[ \delta_{11} = -ap_2^2(k_1 + k_2) \]
\[ \delta_{21} = ap_1p_2(k_1 + k_2) \]
\[ \delta_{12} = ap_1p_2(k_1 + k_2) \]
\[ \delta_{22} = -ap_1^2(k_1 + k_2). \]

It is interesting to note that these dominance deviations are identical to those found in Approach 3a, the intercept is the same as that from Approach 2, and our partial regression coefficients correspond to \( \alpha_f \) and \( \alpha_m \).

Recalling from Approach 2
\[ G_{ij} = \hat{\lambda}_{ij} + \hat{\lambda}_{ij} \]
\[ = \mu + \epsilon_{11}N_1 + \epsilon_{2}N_2 + \hat{\lambda}_{ij} \]
we may write
\[ G_{ij} = \hat{\lambda}_{ij} + \hat{\delta}_{ij} \]
\[ = \mu + \rho_{ij} + \delta_{ij} \]
and define additive effects \( \rho \) as
\[ \rho_{ij} = G_{ij} - \mu - \delta_{ij} \]
Defining breeding values as again equal to additive effects (and noting that male and female breeding values are equivalent for this model), we have

\[
\begin{align*}
BV_{(4)}(A_1A_1) &= \rho_{11} = G_{11} - \mu - \delta_{11} \\
&= -a p_2 (2 + (k_1 + k_2)(p_1 - p_2)) \\
&= -p_2 (\alpha_f + \alpha_m) = BV_{(1)}(A_1A_1) \\
BV_{(4)}(A_2A_1) &= \rho_{21} = G_{21} - \mu - \delta_{21} \\
&= a(p_1 - p_2 + k_1 - 2p_1p_2(k_1+k_2)) \\
BV_{(4)}(A_1A_2) &= \rho_{12} = G_{12} - \mu - \delta_{12} \\
&= a(p_1 - p_2 + k_2 - 2p_1p_2(k_1+k_2)) \\
BV_{(4)}(A_2A_2) &= \rho_{22} = G_{22} - \mu - \delta_{22} \\
&= ap_1(2 + (k_1 + k_2)(p_1 - p_2)) \\
&= p_1 (\alpha_f + \alpha_m) = BV_{(1)}(A_2A_2).
\end{align*}
\]

As with Approach 3a, homozygote (but not heterozygote) breeding values are equivalent to the average breeding values from Approach 1, and again the mean of these heterozygote breeding values is equal to the (mean) breeding values for heterozygotes for Approaches 1 and 2:

\[
\frac{1}{2}(BV_{(4)}(A_2A_1) + BV_{(4)}(A_1A_2)) = \frac{1}{2} a(p_1 - p_2)(\alpha_f + \alpha_m) \\
= BV_{(1)}(\text{heterozygotes}) = BV_{(2)}(\text{heterozygotes}).
\]

**Genetic variance components**

The additive variance is the variance of the breeding values:

\[
\sigma^2_{A(4)} = \sum_{i,j=1}^{2} p_i \rho^2_{ij} = p_1 p_2 (\alpha_f^2 + \alpha_m^2) = \sigma^2_{A(1)} = \sigma^2_{A(3a)}
\]  
\[
(43)
\]

while the dominance variance is the variance of dominance effects:

\[
\sigma^2_{D(4)} = \sum_{i,j=1}^{2} p_i \delta^2_{ij} = (ap_1p_2(k_1+k_2))^2 = \sigma^2_{D(3a)}
\]  
\[
(44)
\]
The calculated covariance between additive and dominance effects is zero, hence
\[ \sigma_{G(4)}^2 = \sigma_{A(4a)}^2 + \sigma_{D(4a)}^2 \]
\[ = p_1 p_2 (\alpha_1^2 + \alpha_m^2 + a^2 p_1 p_2 (k_1 + k_2)^2) = \sigma_{G(1)}^2 \]
and we once again recover our population total genetic variance (1). Note that covariances between relatives under this model are also identical to Approach 3a.

**Discussion**

We have demonstrated that a simple one-locus two-allele model of genomic imprinting produces large differences in predictions for additive and dominance terms from a number of standard approaches for partitioning the genotypic value of an individual. These approaches are equivalent in the absence of imprinting under standard Mendelian expression (where heterozygotes have equivalent genotypic values and hence \( k_1 = k_2 \)). Although all approaches give identical total genetic variance, there are differences in the partitioning of the genetic variance into additive, dominance and covariance terms. These differences arise because imprinting introduces both sex- and generation-dependent effects to the inheritance of alleles. For example, Approach 1 uses progeny means to calculate breeding values for individuals, introducing a generation-effect. In addition, Approaches 1 and 3b introduce a sex-dependent effect as they allow separate calculation of male and female breeding values. Breeding values from the other approaches are by definition equivalent for males and females.

The major differences in the four approaches arise due to differences in how breeding values and additive effects are defined. If we consider only values averaged over males and females for Approaches 1 and 3b, we can see that the breeding values are equivalent for Approaches 1, 2 and 3b, while dominance deviations are equivalent for Approaches 1, 2 and 3b and for Approaches 3a and 4 (Table 4). Note that further differences arise between Approaches 1 and 3b and Approach 2 when males and females are considered separately.

Consider how breeding values are calculated for the four approaches. Approach 1 defines breeding values in terms of allelic contribution to offspring, and breeding values are the same for reciprocal heterozygotes. Approach 2 regresses the number of \( A_2 \) alleles in the genotype on the genotypic value and so by construction
forces equivalence between heterozygotes. Genotypic values in Approach 3b are defined in terms of the male or female effect they pass on to offspring, and so include the same sex-specific generation effect as Approach 1. Breeding values are consequently equivalent for reciprocal heterozygotes.

In contrast, Approaches 3a and 4 define breeding values in terms of an individual’s own genotype and the parental origin of alleles in that genotype. As a consequence of imprinting, parental origin of these alleles has an effect on the genotypic value of individuals and hence reciprocal heterozygotes have different breeding values.

Under standard Mendelian expression, breeding values are expected to be equivalent whether defined as the sum of additive allelic effects (Approaches 2-4) or from the means of progeny (Approach 1). However, differences have been noted where alleles in the population are not in Hardy-Weinberg equilibrium [Ewens, 1979], in relation to populations with non-random mating and inbreeding [Falconer, 1985; Templeton, 1987], and as a result of population subdivision [Goodnight, 2000]. Genomic imprinting represents a distinct phenomenon causing differences in the definition of additive effects between the approaches we have investigated. In contrast to potentially transient properties of species such as inbreeding and population subdivision, imprinting is a fundamental aspect of allelic expression that causes unique differences in the definition of breeding values.

In addition, genomic imprinting introduces a covariance between breeding values and dominance deviations [Spencer, 2002]. A covariance between additive effects and homozygous dominance effects has been noted for two alleles and multiple alleles at a single locus when a population is inbred [Harris, 1964; Cockerham and Weir, 1984; Wright and Cockerham 1986]. This covariance is zero for a locus with two alleles at equal frequency in the population [Cockerham and Weir, 1984]. However, it should be noted that this relationship between additive effects and homozygous dominance effects differs from the covariance between additive and dominance terms, as it does not include dominance deviations for heterozygotes. In the absence of imprinting, the covariance between additive \((\epsilon)\) and dominance \((\lambda)\) effects across \(AA_i\) genotypes with a total of \(n\) alleles is

\[
\sigma_{AD} = \sum_{i,j=1}^{n} p_i p_j (\epsilon_i + \epsilon_j) \lambda_{ij}
\]
whereas the covariance between additive effects and homozygous dominance effects is

\[ \sigma_{AD} = \sum_{i=1}^{k} p_i \epsilon_i \lambda_{ji} \]

Further, although \( \sigma_{AD} \) is only zero for the case of two equally frequent alleles, it is straightforward to demonstrate that \( \sigma_{AD} \) is zero for any number of alleles.

In comparing these approaches we have assumed that Approach 1 gives us “correct” values for population parameters. Approach 1 is the most time intensive method for partitioning genetic variance because it requires derivation of mating tables to give progeny mean values. However this Approach does allow separate calculation of male and female variances and covariances, which is of great value when considering offspring-parent and halfsib covariances in real populations.

Approach 2 successfully recovered mean values from Approach 1 for male and female breeding values and dominance deviations for each genotype, but genetic variance components were different. It is interesting to see that this Approach partitioned the covariance between breeding values and dominance deviations evenly into the additive and dominance variance terms. Clearly a single regression approach with an “average” regression coefficient is not appropriate when we are in fact dealing with four, not three, genotypes, and by construction we were unable to recover the covariance between additive effects (the predicted regression value) and dominance (or residual) effects.

Approach 3a was able to retrieve the additive variance but the true additive by dominance covariance was included in the expression for the dominance variance. By defining additive terms specific to male and female inheritance we were able to “rescue” this method to include separate breeding values and dominance deviations, and their corresponding variances, for the two sexes (Approach 3b). Of particular note is that Approach 3b was the only able to recover the Approach 1 covariance between additive and dominance effects. Defining separate male and female dominance terms \( \lambda_{jf} = G_j - \mu - \epsilon_i - \epsilon_j \), and \( \lambda_{jm} = G_j - \mu - \epsilon_i - \epsilon_j \) includes a “generation” effect that is not accounted for in Approaches 3a and 4. Approach 1 is based on calculating breeding values and dominance deviations that relate to the following generation because we use progeny means in their calculation. The equivalence of Approach 1 with Approach 3b is a reassurance that defining separate male and female dominance
terms is an appropriate measure to include a sex and generation effect in this Approach. A closer investigation of Approaches 1 and 3b is presented for a model including maternal genetic effects and genomic imprinting [Santure and Spencer, in press].

Approach 4 was able to recover the additive variance in the population and, interestingly, the intercept for the regression was the same as that found in Approach 2. It is well known that parental effects may have a large effect on the phenotype of offspring. It is important for methods to include such effects, but it is not easy to imagine how linear regression models such as Approaches 2 and 4 could allow for parental effects such as imprinting and maternal genetic effects.

Finally, we note that Dai and Weeks [2006] defined genotypic values in terms of additive and dominance effects, as with Approaches 3a and 3b. Their approach is a hybrid between 3a and 3b because although separate male and female additive effects were defined, dominance terms were identical for males and females. Although following the approach of Spencer [2002] the dominance variance is the same for males and females, dominance deviations do differ for males and females. As a consequence, the approach of Dai and Weeks [2006] would not be able to determine separate male and female dominance deviations or breeding values as we were able to do in Approach 3b.

In future research it is intended that the identity-by-descent measures described by Dai and Weeks [2006], to enable calculation of the coefficients for population variance and covariances for the expressions of covariances between relatives, will be extended to predict heritability and response to selection where an imprinted locus is influencing a quantitative trait of interest.

It is interesting to assess how different the approaches are in their estimation of variance and covariance components. The numerical examples in Table 5 contrast genetic variance components and resemblances between relatives for the four approaches for two scenarios, one where alleles are paternally largely inactivated, and one where maternally inherited alleles are largely inactivated. We assume phenotypic (and hence genotypic) values range from 0 to 1 \( (a = \frac{1}{2}) \). We can see that, as one would expect, paternal inactivation increases the covariance between mothers and offspring and half sibs sharing a mother, relative to fathers and offspring and half sibs sharing a father respectively (and vice versa) (from the correct expressions using
Approaches 1 and 3b). Approach 2 underestimates the true (Approach 1) population additive and dominance variances, half sib and full sib covariances while Approaches 3a and 4 overestimate the true additive variance and parent-offspring covariance but underestimate the dominance variance. As discussed previously, Approaches 2, 3a and 4 are not able to calculate the covariance between additive and dominance effects. The sex-averaged covariance $\sigma_{AD}^{(1)}$ is negative and so will be overestimated using these approaches. This covariance between breeding values and dominance deviations is included in the expressions for resemblance between parents and offspring and full sibs (see Equations (10), (11) and (16)) and is likely to play a large role in identifying quantitative traits that are influenced by imprinted loci [Spencer, 2002].

A large range of methods is presently available for assessing the role of imprinting in complex and quantitative traits. These methods follow the broad spectrum of genetic approaches for dissecting complex traits, from general mixed models, use of covariances between relatives and identification of parent-of-origin effects in phenotype inheritance for traits without genotypic information available; to the marker-based approaches of linkage mapping, association studies and QTL mapping [reviewed in Santure, in prep.]. A number of these approaches utilize variance component estimation, resemblances between relatives or differences in the phenotypic values of heterozygotes; quantities discussed in this manuscript. Such approaches are invaluable in the dissection of quantitative traits, and researchers are encouraged to employ an approach that can successfully incorporate genomic imprinting into a model of the quantitative trait of interest.
References


Santure AW. In prep. Detecting Genomic Imprinting in Complex Traits: A Comparison of Statistical Approaches.
Table 1: Values of genotypes under genomic imprinting

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_2A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>$p_1p_1$</td>
<td>$p_1p_2$</td>
<td>$p_1p_2$</td>
<td>$p_2p_2$</td>
</tr>
<tr>
<td>Genotypic Value</td>
<td>0</td>
<td>$a(1+k_1)$</td>
<td>$a(1+k_2)$</td>
<td>2$a$</td>
</tr>
</tbody>
</table>

Deviations from mean:

<table>
<thead>
<tr>
<th>Genotypic deviation</th>
<th>$-ap_2 (2 + p_1(k_1 + k_2))$</th>
<th>$a(1+k_1)$</th>
<th>$a(1+k_2)$</th>
<th>$ap_1 (2 - p_2 (k_1 + k_2))$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$-p_2 (2 + p_1(k_1 + k_2))$</td>
<td>$-p_2 (2 + p_1(k_1 + k_2))$</td>
<td>$-p_2 (2 + p_1(k_1 + k_2))$</td>
<td></td>
</tr>
<tr>
<td>Average value of progeny: Maternal</td>
<td>$ap_2 (1+k_2)$</td>
<td>$\frac{1}{2}a (p_1(1+k_2) + p_2(3+k_2))$</td>
<td>$\frac{1}{2}a (p_1(1+k_2) + p_2(3+k_2))$</td>
<td>$a(p_1(1+k_2) + 2p_2)$</td>
</tr>
<tr>
<td>Average value of progeny: Paternal</td>
<td>$ap_2 (1+k_1)$</td>
<td>$\frac{1}{2}a (p_1(1+k_1) + p_2(3+k_1))$</td>
<td>$\frac{1}{2}a (p_1(1+k_1) + p_2(3+k_1))$</td>
<td>$a(p_1(1+k_2) + 2p_2)$</td>
</tr>
<tr>
<td>Female Breeding Value</td>
<td>$-2p_2\alpha_f$</td>
<td>$\alpha_f (p_1 - p_2)$</td>
<td>$\alpha_f (p_1 - p_2)$</td>
<td>$2p_2\alpha_f$</td>
</tr>
<tr>
<td>Male Breeding Value</td>
<td>$-2p_2\alpha_m$</td>
<td>$\alpha_m (p_1 - p_2)$</td>
<td>$\alpha_m (p_1 - p_2)$</td>
<td>$2p_2\alpha_m$</td>
</tr>
<tr>
<td>Mean of Breeding Values</td>
<td>$-p_2(\alpha_f + \alpha_m)$</td>
<td>$\frac{1}{2} (p_1 - p_2)(\alpha_f + \alpha_m)$</td>
<td>$\frac{1}{2} (p_1 - p_2)(\alpha_f + \alpha_m)$</td>
<td>$-p_1(\alpha_f + \alpha_m)$</td>
</tr>
<tr>
<td>Female dominance deviation</td>
<td>$ap_2 (k_1p_1 - k_2(1 + p_2))$</td>
<td>$a(k_1(1 - p_1^2) - k_2 p_2^2)$</td>
<td>$a(-k_1 p_1^2 + k_2 (1 - p_2^2))$</td>
<td>$ap_1 (-k_1 (1 + p_1) + k_2 p_2)$</td>
</tr>
<tr>
<td>Male dominance deviation</td>
<td>$ap_2 (k_2p_1 - k_1(1 + p_2))$</td>
<td>$a(-k_2 p_1^2 + k_1 (1 - p_2^2))$</td>
<td>$a(k_2(1 - p_1^2) - k_1 p_2^2)$</td>
<td>$ap_1 (-k_2 (1 + p_1) + k_1 p_2)$</td>
</tr>
<tr>
<td>Mean of dominance deviations</td>
<td>$-ap_{2}^{2}(k_{1} + k_{2})$</td>
<td>$\frac{1}{2}a(k_{1}(1 + 2p_{1}p_{2}) - k_{2}(1 - 2p_{1}p_{2}))$</td>
<td>$\frac{1}{2}a(-k_{1}(1 - 2p_{1}p_{2}) + k_{2}(1 + 2p_{1}p_{2}))$</td>
<td>$-ap_{1}^{2}(k_{1} + k_{2})$</td>
</tr>
</tbody>
</table>

where $\alpha_{f} = a(1 + k_{1}p_{1} - k_{2}p_{2})$ and $\alpha_{m} = a(1 + k_{2}p_{1} - k_{1}p_{2})$
Table 2: Sibling combinations

<table>
<thead>
<tr>
<th>Mother</th>
<th>Father</th>
<th>Offspring mean combinations [proportion]</th>
<th>Frequency of mating</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1$</td>
<td>$A_1A_1$</td>
<td>0, 0 [1]</td>
<td>$p_1^4$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>0, 0 [$\frac{1}{4}$] 0, $a(1 + k_2)$ [$\frac{1}{2}$] 2$a(1 + k_2)$, $a(1 + k_2)$ [$\frac{1}{4}$]</td>
<td>$2p_1^3p_2$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1 + k_2)$, $a(1 + k_2)$ [1]</td>
<td>$p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$A_1A_1$</td>
<td>0, 0 [$\frac{1}{4}$] 0, $a(1 + k_i)$ [$\frac{1}{2}$] $a(1 + k_i)$, $a(1 + k_i)$ [$\frac{1}{4}$]</td>
<td>$2p_1^3p_2$</td>
</tr>
<tr>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>0, 0 [$\frac{1}{16}$] 0, $a(1 + k_i)$ [$\frac{1}{8}$] 0, $a(1 + k_2)$ [$\frac{1}{8}$] 0, 2$a$ [$\frac{1}{8}$] $a(1 + k_i)$, $a(1 + k_i)$ [$\frac{1}{16}$] $a(1 + k_i)$, $a(1 + k_2)$ [$\frac{1}{8}$] $a(1 + k_2)$, $2a$ [$\frac{1}{8}$] $a(1 + k_2)$, $a(1 + k_2)$ [$\frac{1}{16}$] $a(1 + k_2)$, $2a$ [$\frac{1}{8}$] 2$a$, 2$a$ [$\frac{1}{8}$]</td>
<td>$4p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$A_2A_2$</td>
<td>$a(1 + k_2)$, $a(1 + k_2)$ [$\frac{1}{4}$]</td>
<td>$2p_1p_2^3$</td>
</tr>
<tr>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$A_1A_1$</td>
<td>$a(1 + k_i)$, $a(1 + k_i)$ [1]</td>
<td>$p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$a(1+k_1), a(1+k_1) \left[ \frac{1}{2} \right]$</td>
<td>$a(1+k_1), 2a \left[ \frac{1}{2} \right]$</td>
</tr>
</tbody>
</table>
Table 3: Genotypic values under least squares regression model

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_2A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Content $N$</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Genotypic Value $G$</td>
<td>0</td>
<td>$a(1+k_1)$</td>
<td>$a(1+k_2)$</td>
<td>$2a$</td>
</tr>
<tr>
<td>Frequency $p_1p_1$</td>
<td>$t$</td>
<td>$t + \epsilon$</td>
<td>$t - \epsilon$</td>
<td>$t + 2\epsilon$</td>
</tr>
<tr>
<td>$G \cdot N$</td>
<td>0</td>
<td>$a(1+k_1)$</td>
<td>$a(1+k_2)$</td>
<td>$4a$</td>
</tr>
<tr>
<td>$N^2$</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Regression Value $\hat{G}$</td>
<td>$t$</td>
<td>$t + \epsilon$</td>
<td>$t - \epsilon$</td>
<td>$t + 2\epsilon$</td>
</tr>
<tr>
<td>Dominance deviation $\lambda = G - \hat{G}$</td>
<td>$-t$</td>
<td>$a(1+k_1) - t - \epsilon$</td>
<td>$a(1+k_2) - t - \epsilon$</td>
<td>$2a - t - 2\epsilon$</td>
</tr>
</tbody>
</table>

where $\alpha_f = a(1+k_1p_1-k_2p_2)$ and $\alpha_m = a(1+k_2p_1-k_1p_2)$
Table 4: Summary of breeding values for all approaches

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_1$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach 1 (mean), 2 and 3b (mean)</td>
<td>$-p_2(\alpha_j + \alpha_m)$</td>
<td>$\frac{1}{2}(p_1 - p_2)(\alpha_j + \alpha_m)$</td>
<td>$\frac{1}{2}(p_1 - p_2)(\alpha_j + \alpha_m)$</td>
<td>$p_1(\alpha_j + \alpha_m)$</td>
</tr>
<tr>
<td>Approach 3a</td>
<td>$-p_2(\alpha_j + \alpha_m)$</td>
<td>$p_1\alpha_j - p_2\alpha_m$</td>
<td>$-p_2\alpha_j + p_1\alpha_m$</td>
<td>$p_1(\alpha_j + \alpha_m)$</td>
</tr>
<tr>
<td>Approach 4</td>
<td>$-p_2(\alpha_j + \alpha_m)$</td>
<td>$a(p_1 - p_2 + k_1)$</td>
<td>$a(p_1 - p_2 + k_2)$</td>
<td>$p_1(\alpha_j + \alpha_m)$</td>
</tr>
</tbody>
</table>

where $\alpha_j = a(1 + k_1p_1 - k_2p_2)$ and $\alpha_m = a(1 + k_2p_1 - k_1p_2)$
Table 5: Values of variances and covariances for all approaches given paternal and maternal inactivation

<table>
<thead>
<tr>
<th></th>
<th>Paternal inactivation</th>
<th></th>
<th>Maternal inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p_1 = \frac{1}{2}$, $p_2 = \frac{1}{2}$, $a = \frac{1}{2}$, $k_1 = \frac{9}{10}$, $k_2 = -\frac{8}{10}$</td>
<td></td>
<td>$p_1 = \frac{1}{3}$, $p_2 = \frac{2}{3}$, $a = \frac{1}{2}$, $k_1 = -\frac{7}{10}$, $k_2 = \frac{95}{100}$</td>
</tr>
<tr>
<td><strong>Variance and covariance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Approaches 1 and 3b</td>
<td>Approach 2</td>
<td>Approaches 3a and 4</td>
</tr>
<tr>
<td></td>
<td>Approaches 1 and 3b</td>
<td>Approach 2</td>
<td>Approaches 3a and 4</td>
</tr>
<tr>
<td><strong>Additive Variance</strong></td>
<td>$\sigma_{Af}^2 = 0.4278$</td>
<td>$\sigma_{Am}^2 = 0.0028$</td>
<td>$\sigma_{Af}^2 = 0.0020$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{Am}^2 = 0.2153$</td>
<td>$\sigma_{Am}^2 = 0.1250$</td>
<td>$\sigma_{Am}^2 = 0.3534$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{Af}^2 = 0.1250$</td>
<td>$\sigma_{Af}^2 = 0.2153$</td>
<td>$\sigma_{Am}^2 = 0.1777$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{Am}^2 = 0.2153$</td>
<td>$\sigma_{Am}^2 = 0.3534$</td>
<td>$\sigma_{Am}^2 = 0.1777$</td>
</tr>
<tr>
<td><strong>Dominance Variance</strong></td>
<td>$\sigma_D^2 = 0.0905$</td>
<td>$\sigma_D^2 = 0.0905$</td>
<td>$\sigma_D^2 = 0.0905$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_D^2 = 0.0905$</td>
<td>$\sigma_D^2 = 0.0002$</td>
<td>$\sigma_D^2 = 0.0905$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_D^2 = 0.1520$</td>
<td>$\sigma_D^2 = 0.0905$</td>
<td>$\sigma_D^2 = 0.0905$</td>
</tr>
<tr>
<td><strong>Additive by dominance Covariance</strong></td>
<td>$\sigma_{ADf} = -0.1966$</td>
<td>$\sigma_{ADf} = 0.0122$</td>
<td>$\sigma_{ADf} = 0.0122$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{ADm} = 0.0159$</td>
<td>$\sigma_{ADm} = -0.1635$</td>
<td>$\sigma_{ADm} = -0.1635$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{ADf} = -0.0903$</td>
<td>$\sigma_{ADf} = -0.0756$</td>
<td>$\sigma_{ADf} = -0.0756$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{AD} = 0$</td>
<td>$\sigma_{AD} = 0$</td>
<td>$\sigma_{AD} = 0$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{OP_f}$</td>
<td>$\sigma_{OP_m}$</td>
<td>$\sigma_{OP}$</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>Offspring-Parent</strong></td>
<td>0.1156</td>
<td>0.0094</td>
<td>0.0625</td>
</tr>
<tr>
<td><strong>Covariance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1077</td>
<td>0.0007</td>
<td>0.0538</td>
</tr>
<tr>
<td><strong>Half-sib Covariance</strong></td>
<td>0.1070</td>
<td>0.0007</td>
<td>0.0313</td>
</tr>
<tr>
<td></td>
<td>0.1077</td>
<td>0.0007</td>
<td>0.0538</td>
</tr>
<tr>
<td><strong>Full-sib Covariance</strong></td>
<td>0.1077</td>
<td>0.0007</td>
<td>0.0538</td>
</tr>
<tr>
<td></td>
<td>0.1077</td>
<td>0.0007</td>
<td>0.0538</td>
</tr>
</tbody>
</table>
4. A Two Locus Quantitative Genetic Model
Incorporating Genomic Imprinting

Abstract

Genomic imprinting refers to the parent-of-origin dependent expression of alleles at a locus. Alleles may be completely inactivated when inherited from one parent, and as a consequence reciprocal heterozygotes can have very different mean phenotypic values for a trait of interest. We here present an overview of a quantitative genetic model for imprinting at two loci, including interactions between the loci. Such a model incorporates cases where both loci may or may not be imprinted, and alleles may be maternally or paternally inactivated. We demonstrate that epistasis may mask the effect of imprinting on population variances and covariances between relatives. Further, although we show that a number of signatures of imprinting are maintained with epistatic interactions between loci, the absence of these signatures does not confirm that imprinting is also absent. This work adds to current quantitative genetic models incorporating imprinting, and highlights the importance of full knowledge of the genetic architecture of a quantitative trait when assessing population characteristics.

Introduction

Expression of an imprinted gene is dependent on the sex of the parent from which it was inherited. Maternally (or paternally) derived alleles may be preferentially expressed while the other allele is inactivated. However, differential expression of maternal and paternal alleles may be confined to a particular developmental stage or a specific tissue type. A more general definition for imprinting, therefore, is that reciprocal heterozygotes do not exhibit the same phenotype; an individual with a maternally inherited $A_1$ allele and a paternally inherited $A_2$ allele has a different phenotype, on average, than individuals with the reverse inheritance pattern. 83 transcriptional units are imprinted in mammals, representing a small but significant portion of the genome, with organogenesis, cell cycle regulation and cell growth among the functions represented [Morison, Ramsay and Spencer, 2005].
By their definition, quantitative traits are influenced by many loci and by the environment, and interactions between loci or between a locus and the environment may have significant impact on the characteristics of individuals [Mackay, 2001]. Interactions between loci, termed epistasis, or epistatic interactions, arise when the expected phenotype of an individual cannot be predicted from knowledge of effects of loci separately. Thus the genotypic value of an individual is the sum of genotypic values for each locus separately, plus terms representing interaction between alleles at each locus [Fisher, 1918]. Although quantitative genetic models incorporating epistasis are extensive, evaluation of epistatic effects is restricted by low power to detect interactions in small samples or limited crosses, and the increased complexity of genetic models requiring greater computational effort [Carlborg and Haley, 2004]. However, significant epistatic interactions have been detected, for example in extensive mapping studies of model organisms such as *Drosophila*, mouse and *C. elegans* (reviewed in Mackay [2001]).

We here present a simple two locus model incorporating epistatic interactions between alleles and genomic imprinting, and develop expressions for population variances and resemblances between relatives. This approach adds to our understanding of the effect imprinting has on quantitative traits.

**The Model**

Following previous notation, consider two loci, denoted $A$ and $B$, subject to imprinting, with alleles $A_1$ and $A_2$ at locus $A$ at frequency $p_{A1}$ and $p_{A2}$ respectively in the population, and alleles $B_1$ and $B_2$ at locus $B$ at frequency $p_{B1}$ and $p_{B2}$. We write the two-locus genotype of an individual as $A_iA_jB_kB_l$, and designate $A_i$ and $B_k$ alleles to be maternally inherited while $A_j$ and $B_l$ alleles are paternally inherited.

Table 1 shows the mean phenotype (the genotypic value) of each combination of alleles at and between the loci. Note that the genotypic values for \{$A_1A_1$, $A_2A_1$, $A_1A_2$, $A_2A_2$\} are

\begin{align*}
G_{11A} &= 0, \quad G_{21A} = a_A(1 + k_{1A}), \quad G_{12A} = a_A(1 + k_{2A}), \quad G_{22A} = 2a_A \\
\end{align*}

while genotypic values for \{$B_1B_1$, $B_2B_1$, $B_1B_2$, $B_2B_2$\} are

\begin{align*}
G_{11B} &= 0, \quad G_{21B} = a_B(1 + k_{1B}), \quad G_{12B} = a_B(1 + k_{2B}), \quad G_{22B} = 2a_B \\
\end{align*}
The genotypic value $G_{ijkl}$ of an individual with genotype $A_iA_jB_kB_l$ is the sum of genotypic values at each locus separately, plus an interaction term that may be unique for each two locus genotype:

$$G_{ijkl} = G_{ia} + G_{ib} + G_{ij} + G_{ijkl}$$

For example, the genotypic value of an individual with genotype $A_1A_2B_2B_1$ is

$$G_{121} = G_{12} + G_{11} + G_{21} + G_{1221} = a_A (1 + k_2B) + a_B (1 + k_1B) + \epsilon_{121}.$$

Genomic imprinting is incorporated by setting different genotypic values for the two heterozygotes (Table 1), and consequently there are sixteen genotypic values. By confining the genotypic value of $A_1A_1B_1B_1$ individuals to be 0, we require 15 parameters to fully specify the model. Noting that each individual locus has three parameters ($a$, $k_1$ and $k_2$), we require nine epistatic interactions between the one locus genotypes (Table 1). In the absence of imprinting, reciprocal heterozygotes have equivalent genotypic values, there are only three genotypic classes at each locus and consequently $\epsilon_{212} = \epsilon_{211} = \epsilon_{121}$, $\epsilon_{222} = \epsilon_{221}$ and $\epsilon_{2122} = \epsilon_{1222}$.

The mean population genotypic value can be found by a matrix multiplication:

$$\mu = P_A \times G_{A} \times P_B$$

$$= p_A(a_A(2 + p_A((1 + k_{1A}) + p_B(a_B(2 + p_B(k_{1B} + k_{2B})) + p_A(a_B(2 + p_B(k_{1B} + k_{2B}) + p_A(a_B(2 + p_B(k_{1B} + k_{2B}) + P_AE_{AB}P_B$$

where

$$P_A = \begin{bmatrix} p_{1A} & p_{2A} & p_{1A} & p_{2A} \\ p_{2A} & p_{1A} & p_{1A} & p_{2A} \end{bmatrix}$$

represents genotype frequencies at locus $A$. 

4.3
is a matrix of genotypic values

\[ G_{AB} = \begin{bmatrix} 0 & (1 + k_{1B})a_B & (1 + k_{2B})a_B & 2a_B \\ (1 + k_{1A})a_A & (1 + k_{1A})a_A & (1 + k_{1A})a_A & +e_{2121} \\ (1 + k_{2A})a_A & +e_{2112} & +e_{2122} & \vdots \\ 2a_A & +e_{2221} & +e_{2212} & +e_{2222} \end{bmatrix} \]

is a matrix of epistatic interactions and

\[ E_{AB} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & e_{2121} & e_{2112} & e_{2122} \\ 0 & e_{1221} & e_{1212} & e_{1222} \\ 0 & e_{2221} & e_{2212} & e_{2222} \end{bmatrix} \]

represents genotype frequencies at locus B. We note that in the absence of epistatic interactions \((e_{ijkl} = 0)\), the population mean is

\[ \mu = p_{2A}a_A(2 + p_{1A}(k_{1A} + k_{2A})) + p_{2B}a_B(2 + p_{1B}(k_{1B} + k_{2B})) \]

which is equivalent to the sum of mean genotypic values from each locus separately (recalling from Chapter 3 that the mean of a single locus with imprinting is \(\mu = p_a(2 + p_i(k_i + k_j))\)).

We now calculate genotypic deviations, breeding values and dominance deviations following the approach of Falconer and Mackay [1996]. Genotypic deviations are defined as the difference between the genotypic value and the population mean \((G_{ijkl} - \mu)\). Breeding values for each genotype are calculated as twice the difference between the mean value of progeny from that genotype and the
population mean [Falconer and Mackay, 1996]. Breeding values differ for males and females as a consequence of imprinting [Spencer, 2002]. Let us consider a one-locus example for simplicity. Recall that an individual with genotype $A_iA_j$ has a maternally inherited $A_i$ allele and a paternally inherited $A_j$ allele. An $A_iA_1$ mother may have offspring with genotype $A_1A_1$ or $A_1A_2$, and her progeny mean will be

$$p_{iA}(0) + p_{2A}(a_A(1+k_{2A})) = a_A p_{2A}(1+k_{2A}).$$

In contrast, an $A_1A_1$ father may have $A_1A_1$ or $A_2A_1$ offspring, and his progeny mean will be

$$p_{iA}(0) + p_{2A}(a_A(1+k_{1A})) = a_A p_{2A}(1+k_{1A}).$$

Thus progeny means and hence breeding values differ for males and females sharing the same genotype.

Dominance deviations are defined as the difference between the genotypic deviation and the breeding value of a genotypic class. Because of the epistatic interactions between the loci, properties such as genotypic deviations, breeding values and dominance deviations can be shown to be the sum of these properties for each locus separately, plus an additional expression involving the epistatic terms.

Genotypic deviations are shown in Table 2, breeding values for females and males in Tables 3 and 4, and dominance deviations for females and males in Tables 5 and 6.

**Genetic variance components**

The genetic variance of the population is the variance of the genotypic deviations, and is equal to:

$$\sigma_G^2 = \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl} - \mu)^2$$

$$= \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl})^2 - 2 \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl} \times \mu) + \sum_{ijkl} p_i p_j p_k p_l (\mu^2)$$

$$= \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl})^2 - 2 \mu \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl}) + \mu^2 \sum_{ijkl} p_i p_j p_k p_l$$

$$= \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl})^2 - 2 \mu (\mu) + \mu^2 (1)$$

$$= \sum_{ijkl} p_i p_j p_k p_l (G_{ijkl})^2 - \mu^2$$
We may express this in matrix notation as

\[
\sigma_G^2 = P_A N_{AB} P_B - \mu^2
\]

where \(N_{AB}\) is a 4x4 matrix with values equal to the square of values in the genotypic value matrix \(G_{AB}\). Expanded, this gives

\[
\sigma_G^2 = p_{1A} p_{2A} [\alpha_{fA}^2 + \alpha_{mA}^2 + a_A^2 p_{1A} p_{2A} (k_{1A} + k_{2A})^2] \\
+ p_{1B} p_{2B} [\alpha_{fB}^2 + \alpha_{mB}^2 + a_B^2 p_{1B} p_{2B} (k_{1B} + k_{2B})^2] \\
+ 2 p_{1A} p_{2A} a_A \left[ \begin{array}{cccc}
- p_{1A} (2) & 1 + k_{1A} & 1 + k_{2A} & p_{2A} (2) \\
+ p_{1A} (k_{1A}) & - p_{2A} (2) & - p_{2A} (2) & - p_{2A} (k_{1A}) \\
+ p_{1A} (k_{2A}) & + p_{1A} (k_{1A}) & + p_{1A} (k_{2A}) & + p_{1A} (k_{2A}) \\
+ k_{2A} & + k_{2A} & + k_{2A} & + k_{2A} \\
\end{array} \right] E_{AB} P_B \\
+ 2 p_{1B} p_{2B} a_B P_A E_{AB} \left[ \begin{array}{cccc}
- p_{1B} (2 + p_{1B} (k_{1B} + k_{2B})) & 1 + k_{1B} - p_{2B} (2 + p_{1B} (k_{1B} + k_{2B})) & 1 + k_{2B} - p_{2B} (2 + p_{1B} (k_{1B} + k_{2B})) & p_{2B} (2 - p_{2B} (k_{1B} + k_{2B})) \\
0 & 0 & 0 & 0 \\
0 & \varepsilon_{2121} & \varepsilon_{2112} & \varepsilon_{2122} \\
0 & \varepsilon_{2121} & \varepsilon_{2112} & \varepsilon_{2122} \\
0 & \varepsilon_{2121} & \varepsilon_{2112} & \varepsilon_{2122} \\
\end{array} \right] P_B - (P_A E_{AB} P_B)^2
\]

where we use the abbreviations

\[
\alpha_{fA} = a_A (1 + k_{1A} p_{1A} - k_{2A} p_{2A}), \\
\alpha_{fB} = a_B (1 + k_{1B} p_{1B} - k_{2B} p_{2B}), \\
\alpha_{mA} = a_A (1 + k_{2A} p_{1A} - k_{1A} p_{2A})
\]

and

\[
\alpha_{mB} = a_B (1 + k_{2B} p_{1B} - k_{1B} p_{2B}).
\]

In the absence of epistatic interactions, the genetic variance reduces to

\[
\sigma_G^2 = p_{1A} p_{2A} [\alpha_{fA}^2 + \alpha_{mA}^2 + a_A^2 p_{1A} p_{2A} (k_{1A} + k_{2A})^2] \\
+ p_{1B} p_{2B} [\alpha_{fB}^2 + \alpha_{mB}^2 + a_B^2 p_{1B} p_{2B} (k_{1B} + k_{2B})^2].
\]
The additive genetic variances for females and males are the respective variances of their breeding values:

$$\sigma^2_A = \sum_{ijkl} p_i p_j p_k p_l (\text{breeding value})^2.$$ 

In the absence of epistatic interactions ($\epsilon_{ijkl} = 0$), female ($\sigma^2_{Af}$) and male ($\sigma^2_{Am}$) additive variances are

$$\sigma^2_{Af} = 2p_{1A}p_{2A}\alpha^2_{fA} + 2p_{1B}p_{2B}\alpha^2_{fB}$$

and

$$\sigma^2_{Am} = 2p_{1A}p_{2A}\alpha^2_{mA} + 2p_{1B}p_{2B}\alpha^2_{mB}.$$ 

Including epistasis between loci, additive genetic variances also include first ($\sigma^2_A(\epsilon_{ijkl})$) and second order ($\sigma^2_A(\epsilon_{ijkl} \times \epsilon_{ijkl})$) terms in $\epsilon_{ijkl}$. Second order terms are shown in Appendix A, and first order terms are

$$\sigma^2_{Af}(\epsilon_{ijkl}) = 2p_{1A}p_{2A}\alpha_{fA} \left[ -2p_{1A} (p_{1A} - p_{2A}) + 2p_{2A} \right] E_{AB}^2 p_B$$

$$+ 2p_{1B}p_{2B}\alpha_{fB} \left[ p_{1B} - p_{2B} \right] E_{AB}^2 p_B$$

for females and

$$\sigma^2_{Am}(\epsilon_{ijkl}) = 2p_{1A}p_{2A}\alpha_{mA} \left[ -2p_{1A} (p_{1A} - p_{2A}) + 2p_{2A} \right] E_{AB}^2 p_B$$

$$+ 2p_{1B}p_{2B}\alpha_{mB} \left[ p_{1B} - p_{2B} \right] E_{AB}^2 p_B$$

for males.

The dominance genetic variance is the variance of the dominance deviations

$$\sigma^2_D = \sum_{ijkl} p_i p_j p_k p_l (\text{dominance deviation})^2.$$ 

This variance is the same for both males and females in the absence of epistatic interactions:

$$\sigma^2_{Df} = \sigma^2_{Dm} = \sigma^2_D$$

$$= p_{1A}p_{2A}\alpha^2_{fA} (p_{1A} - k_{1A})^2 + (k_{1A} - k_{2A})^2$$

$$+ p_{1B}p_{2B}\alpha^2_{fB} (p_{1B} - k_{1B})^2 + (k_{1B} - k_{2B})^2$$
Similarly, female and male first order epistatic terms are identical:

\[ \sigma^2_{Df}(e_{ijkl}) = \sigma^2_{Dm}(e_{ijkl}) = \sigma^2_{D}(e_{ijkl}) \]

\[ = 2e_{2121}p_{1A}p_{1B}p_{2A}p_{2B}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] + a_B(k_{1B} - k_{2B}) + p_{1B}p_{2B}(k_{1B} + k_{2AB})] + 2e_{2112}p_{1A}p_{1B}p_{2A}p_{2B}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] + a_B(k_{1B} - k_{2B}) + p_{1B}p_{2B}(k_{1B} + k_{2AB})] + 2e_{2122}p_{1A}p_{2A}p_{2A}p_{2B}^{2}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] - a_Bp_{1B}^{2}(k_{1B} + k_{2B})] + 2e_{2211}p_{1A}p_{1B}p_{2A}p_{2B}^{2}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] + a_B(k_{1B} - k_{2B}) + p_{1B}p_{2B}(k_{1B} + k_{2AB})] + 2e_{2112}p_{1A}p_{1B}p_{2A}p_{2B}^{2}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] + a_B(k_{1B} - k_{2B}) + p_{1B}p_{2B}(k_{1B} + k_{2AB})] + 2e_{2212}p_{1A}p_{1B}p_{2B}^{2}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] - a_Bp_{1B}^{2}(k_{1B} + k_{2B})] + 2e_{2221}p_{1A}p_{1B}p_{2B}^{2}[a_A(k_{1A} - k_{2A}) + \epsilon_A(k_{1A} + k_{2A})] - a_Bp_{1B}^{2}(k_{1B} + k_{2B})]

Second order epistatic terms are shown in Appendix A, and interestingly differ for males and females.

The covariance between dominance deviations and breeding values is defined as

\[ \sigma_{AD} = \sum_{ijkl} p_ip_jp_\lambda p_i'(breeding\ value)(dominance\ deviation) \]

and in the absence of epistatic interactions is

\[ \sigma_{AD} = p_{1A}p_{2A}a_{\lambda A}(k_{2A} - k_{1A}) + p_{1B}p_{2B}a_{\lambda B}(k_{2B} - k_{1B}) \]

for females and

\[ \sigma_{AD} = p_{1A}p_{2A}a_{\lambda A}(k_{1A} - k_{2A}) + p_{1B}p_{2B}a_{\lambda B}(k_{1B} - k_{2B}) \]

for males. First order covariances for females (\( \sigma_{AD}(e_{ijkl}) \)) and males (\( \sigma_{AD}(e_{ijkl}) \)) are

\[ \sigma_{AD}(e_{ijkl}) = e_{2121}p_{1A}p_{1B}p_{2A}p_{2B}[a_A(-1 - 2k_{1A}p_{1A} + k_{2A}) + a_B(-1 - 2k_{1B}p_{1B} + k_{2B})] + e_{2112}p_{1A}p_{1B}p_{2A}p_{2B}[a_A(-1 - 2k_{1A}p_{1A} + k_{2A}) + a_B(1 + k_{1B} - 2k_{2B}p_{2B})] + e_{2122}p_{1A}p_{2A}p_{2B}^{2}[a_A(-1 - 2k_{1A}p_{1A} + k_{2A}) - a_Bp_{1B}(k_{1B} - k_{2B})] + e_{2211}p_{1A}p_{1B}p_{2A}p_{2B}[a_A(1 + k_{1A} - 2k_{2A}p_{2A}) + a_B(-1 - 2k_{1B}p_{1B} + k_{2B})] + e_{2112}p_{1A}p_{2A}p_{2B}^{2}[a_A(1 + k_{1A} - 2k_{2A}p_{2A}) + a_B(1 + k_{1B} - 2k_{2B}p_{2B})] + e_{2122}p_{1A}p_{2B}^{2}[a_A(1 + k_{1A} - 2k_{2A}p_{2A}) - a_Bp_{1B}(k_{1B} - k_{2B})] + e_{2221}p_{2A}p_{1B}p_{2B}[a_A(-1 - 2k_{1A}p_{1A} + k_{2A}) + a_B(-1 - 2k_{1B}p_{1B} + k_{2B})] + e_{2212}p_{2A}p_{1B}p_{2B}[a_A(-1 - 2k_{1A}p_{1A} + k_{2A}) + a_B(1 + k_{1B} - 2k_{2B}p_{2B})] + e_{2222}p_{2A}p_{2B}^{2}[a_A(-1 - 2k_{1A}p_{1A} + k_{2A}) - a_Bp_{1B}(k_{1B} - k_{2B})] \]
and

\[
\sigma_{ADm}(\varepsilon_{ijkl}) = \varepsilon_{2121} p_{1A} p_{2A} p_{1B} p_{2B} [a_A (1 - 2k_{1A} p_{2A} + k_{2A}) + a_B (1 - 2k_{1B} p_{2B} + k_{2B})] + \\
+ \varepsilon_{1122} p_{1A} p_{2A} p_{1B} p_{2B} [a_A (1 - 2k_{1A} p_{2A} + k_{2A}) + a_B (1 + k_{1B} - 2k_{2B} p_{1B})] + \\
+ \varepsilon_{2122} p_{1A} p_{2A} p_{2B}^2 [a_A (1 - 2k_{1A} p_{2A} + k_{2A}) + a_B p_{2B} (k_{1B} - k_{2B})] + \\
+ \varepsilon_{1221} p_{1A} p_{2A} p_{1B} p_{2B} [a_A (-1 + k_{1A} - 2k_{2A} p_{1A}) + a_B (1 - 2k_{1B} p_{2B} + k_{2B})] + \\
+ \varepsilon_{1212} p_{1A} p_{2A} p_{1B} p_{2B} [a_A (1 + k_{1A} - 2k_{2A} p_{1A}) + a_B (-1 + k_{1B} - 2k_{2B} p_{1B})] + \\
+ \varepsilon_{1222} p_{1A} p_{2A} p_{2B}^2 [a_A (-1 + k_{1A} - 2k_{2A} p_{1A}) + a_B p_{2B} (k_{1B} - k_{2B})] + \\
+ \varepsilon_{2221} p_{1A} p_{2A} p_{1B} p_{2B} [a_A p_{2A} (k_{1A} - k_{2A}) + a_B (1 - 2k_{1B} p_{2B} + k_{2B})] + \\
+ \varepsilon_{2212} p_{1A} p_{2A} p_{1B} p_{2B} [a_A p_{2A} (k_{1A} - k_{2A}) + a_B (-1 + k_{1B} - 2k_{2B} p_{1B})] + \\
+ \varepsilon_{2222} p_{1A} p_{2A} p_{2B}^2 [a_A p_{2A} (k_{1A} - k_{2A}) + a_B p_{2B} (k_{1B} - k_{2B})].
\]

Second order epistatic terms for the covariance between breeding values and dominance deviations are shown in Appendix A.

Finally, it can be easily shown that

\[
\sigma_G^2 = \sigma_A^2 + \sigma_D^2 + 2\sigma_{AD}
\]

both when first and second order epistatic interactions are and are not included.

Recalling that the total genetic variance is the variance of the genotypic deviations \((G_{ijkl} - \mu)\), and that

\[
G_{ijkl} = G_{ijA} + G_{ijkl} + \varepsilon_{ijkl}
\]

we may write

\[
\sigma_G^2 = \text{var}[G_{ijkl} + G_{ijkl} + \varepsilon_{ijkl} - \mu].
\]

Expressing \(\mu\) as

\[
\mu = \mu_A + \mu_B + \mu_\epsilon,
\]

we may alternatively express the genetic variance as

\[
\sigma_G^2 = \text{var}[G_{ijA} - \mu_A + G_{ijkl} - \mu_B + \varepsilon_{ijkl} - \mu_\epsilon] + \text{var}[\varepsilon_{ijkl} - \mu_\epsilon] + 2\text{cov}((G_{ijA} - \mu_A + G_{ijkl} - \mu_B)(\varepsilon_{ijkl} - \mu_\epsilon)).
\]

It can be shown that

\[
\text{cov}((G_{ijA} - \mu_A)(G_{ijkl} - \mu_B)) = 0
\]

and hence

\[
\sigma_G^2 = \text{var}[G_{ijA} - \mu_A] + \text{var}[G_{ijkl} - \mu_B] + \text{var}[\varepsilon_{ijkl} - \mu_\epsilon] + 2\text{cov}((G_{ijA} - \mu_A + G_{ijkl} - \mu_B)(\varepsilon_{ijkl} - \mu_\epsilon)).
\]
Referring above to our full expression for total genetic variance (the variance of the genotypic deviations) we can relate each term to a term above; variances expected for each locus separately:

\[
\text{var}[G_{ijA} - \mu_A] = p_{1A}p_{2A}(\alpha_{ijA}^2 + \alpha_{mA}^2 + a_{ijA}^2p_{1A}p_{2A}(k_{iA} + k_{2A})^2)
\]

\[
\text{var}[G_{ijB} - \mu_B] = p_{1B}p_{2B}(\alpha_{ijB}^2 + \alpha_{mB}^2 + a_{ijB}^2p_{1B}p_{2B}(k_{iB} + k_{2B})^2)
\]

variation in epistatic terms only:

\[
\text{var}[e_{ijkl} - \mu_e] = P_A \begin{bmatrix}
0 & 0 & 0 & 0 \\
0 & e_{2121} & e_{2112} & e_{2122} \\
0 & e_{1221} & e_{1212} & e_{1222} \\
0 & e_{2221} & e_{2212} & e_{2222}
\end{bmatrix}
\quad P_B - (P_AE_{AB}P_B)^2
\]

and a covariance between epistatic terms and genotypic values without epistasis:

\[
\text{cov}[(G_{ijA} - \mu_A + G_{ijB} - \mu_B)(e_{ijkl} - \mu_e)]
\]

\[
= p_{1A}p_{2A}a_A \begin{bmatrix}
-1 + k_{iA} & 1 + k_{2A} & a_{ijA}p_{2A}(2) & -p_{2A}(2) & p_{2A}(2) \\
+ p_{1A}(k_{iA} + k_{2A}) & + p_{1A}(k_{iA} + k_{2A}) & + p_{1A}(k_{iA} + k_{2A}) & -p_{2A}(k_{iA} + k_{2A}) & -p_{2A}(k_{iA} + k_{2A})
\end{bmatrix}
\]

\[
+ p_{1B}p_{2B}a_B P_A E_{AB} \begin{bmatrix}
-1 + k_{iB} & -p_{1B}(2 + p_{1B}(k_{iB} + k_{2B})) & -p_{1B}(2 + p_{1B}(k_{iB} + k_{2B})) & -p_{1B}(2 + p_{1B}(k_{iB} + k_{2B})) \\
+ k_{iB} & + k_{iB} & + k_{iB} & + k_{iB}
\end{bmatrix}
\]

Note that, following the treatment of Cheverud and Routman [1995], these dissections of the genetic variance do not include additive by additive, additive by dominance and dominance by dominance variances, which are effectively partitioned into the covariance between epistatic terms and genotypic values without epistasis. These cross terms between loci could be defined following a general least squares approach of successively partitioning the genotypic value [Lynch and Walsh, 1998]. However, as demonstrated in Approach 3a, Chapter 3, such a method would require incorporation of both sex and generation-dependent terms to account for the inclusion of imprinting.

Covariances between relatives

We now follow the approach of Kempthorne [1957] to calculate covariances between parents and their offspring. As a consequence of imprinting, the covariance between mothers and offspring differs from the covariance between fathers and
offspring [Spencer, 2002]. Similarly, the covariance between half sibs sharing a mother is different to the covariance of half sibs sharing a father.

The covariance between Offspring and Parent is 

\[ \sigma_{OP} = \sum_{ijkl} p_i p_j p_k p_1 (G_{ijkl} - \mu)(A_i A_j A_k A_1 \text{ progeny mean} - \mu) \]

and, when simplified, is equivalent to 

\[ \sigma_{OPf} = \frac{1}{2} (\sigma_{Af}^2 + \sigma_{Adf}^2) \]

for offspring and female parents and 

\[ \sigma_{OPm} = \frac{1}{2} (\sigma_{Am}^2 + \sigma_{Adm}^2) \]

for offspring and male parents.

Following Spencer [2002], the covariances between half sibs sharing a mother (female parent) and father (male parent) are

\[ \sigma_{HSf} = \frac{1}{4} \sigma_{Af}^2 \]

and 

\[ \sigma_{HSm} = \frac{1}{4} \sigma_{Am}^2. \]

Finally, we may consider the covariance between full sibs. In the absence of imprinting, and considering only one locus, the general expression for the covariance between full sibs is

\[ \sigma_{FS} = \frac{1}{2} \sigma_{A}^2 + \frac{1}{4} \sigma_D^2 \]

[Fisher, 1918]. For a one-locus case with imprinting, the full sib covariance becomes

\[ \sigma_{FS} = \frac{1}{4} (\sigma_{Af}^2 + \sigma_{Am}^2) + \frac{1}{4} \sigma_D^2 + \frac{1}{4} (\sigma_{Adf} + \sigma_{Adm}) \]

with the introduction of a covariance between breeding values and dominance deviations to total variance components [Spencer, 2002]. Noting that the variances for male and female dominance deviations differ if epistasis is included, our expression for the covariance between full sibs now becomes

\[ \sigma_{FS} = \frac{1}{4} (\sigma_{Af}^2 + \sigma_{Am}^2 + \sigma_{Adf}^2 + \sigma_{Adm}^2) + \sigma_{Adf} + \sigma_{Adm}. \]

**Discussion**

Derivation of a two locus quantitative genetic model including epistatic interactions between loci is somewhat complicated by the inclusion of imprinting to the model, with the definition of 15 parameters needed to fully specify the model. Exhaustive investigation of combinations of each of these parameters across their
expected ranges would be unfeasible, so we here examine a number of interesting scenarios in order to make some broad conclusions about the effect that two loci, imprinting and interactions between loci might have on population variances and covariances between relatives.

We begin by taking a number of simple examples with no imprinting or epistasis, epistasis only and imprinting only, and calculate population genotypic values, genetic variances and covariances, and covariances between relatives (Tables 7 and 8). We generally assume equal allele frequencies at both loci, with $p_{1A} = p_{1B} = \frac{1}{2}$ (and hence $p_{2A} = p_{2B} = \frac{1}{2}$). Recall that in the absence of imprinting, reciprocal heterozygotes have equivalent genotypic values. Examples 1.1 and 1.4 represent populations with no imprinting or epistasis acting. For example 1.1, alleles at each locus act (almost) additively, so that the heterozygotes fall around the middle of the range of the two homozygotes. Example 1.4 represents allele $B_1$ acting with partial dominance at locus $B$, while $A_2$ is partially dominant at locus $A$. These two examples share additive variances, but differ in total and dominance variances (Table 7). The difference in dominance variation is reflected in the relationship between full sibs for these populations (Table 8).

**Epistatic interactions only**

Examples 1.2 and 1.3 add epistatic interactions to the genotypic values from example 1.1. For example 1.2, the presence of either or both alleles $A_2$ and $B_2$ results in a genotypic value of 1. This increases total, additive and dominance variances relative to example 1.1 (Table 7), and correspondingly covariances between relatives increase (Table 8). For example 1.3, genotypic values for individuals with genotype $A_1A_1B_2B_2$, $A_1A_2B_2B_1$, $A_2A_2B_2B_1$ and $A_2A_1B_1B_2$ are 1, while $A_2A_2B_2B_2$ individuals have genotypic value 1.5. As expected, total, additive and dominance genetic variance increase relative to example 1.1 (Table 7). Most interesting is the appearance of a covariance between additive and dominance effects. As discussed above, this covariance could be further partitioned into additive by additive, additive by dominance and dominance by dominance covariances between the loci. For a one-locus case, a covariance between additive and dominance terms arises in the presence of imprinting or maternal effects (see chapter 3 and the following chapters 5 and 6) and is generally zero otherwise.
Example 1.5 is based on example 1.4 but has quite a different population structure with locus $B$ dominant to locus $A$ (except for individuals with a $B_1B_1$ genotype). Additive and total variances decrease and there is a marked decrease in the covariances expected between relatives, as expected when one locus has almost no effect on genotypic values. Note that there is again a non zero covariance between breeding values and dominance deviations for this example. Example 1.6 introduces a perhaps extraordinary relationship between the loci where heterozygotes at both loci interact to give a genotypic value of 1; what is most interesting in this case is the large dominance variance and absence of a covariance term.

**Imprinting only**

Example 1.7 introduces imprinting (with no epistasis) to the two-locus model, with reciprocal heterozygotes taking very different genotypic values. Both loci are strongly paternally inactivated. We can see from Table 7 that additive variances differ for males and females, as do covariances between breeding values and dominance deviations. The much larger additive variances in females compared to males is reflected in the strong relationship between mothers and offspring and between half sibs sharing a mother. The covariance between full sibs is less than that between mothers and offspring; an occurrence that is in general only true of populations with imprinting acting (refer chapter 3 and following chapters 5 and 6). Also interesting, and another characteristic of imprinting, is that the covariance between half sibs sharing a mother is similar to the covariance between mother and offspring (Table 8) as a consequence of the negative relationship between female breeding values and dominance deviations (Table 7). In previous examples without imprinting acting (examples 1.1-1.6), the covariance between half sibs is around half of that between mother and offspring.

Example 1.8 represents a different imprinting scenario: alleles at locus $A$ are paternally inactivated while alleles at locus $B$ are maternally inactivated. Because the loci are equally weighted ($a_a = a_b = \frac{1}{2}$) and the strength of imprinting is identical, (although in opposite direction), variance components are the same for males and females (Table 7). This equivalence is reflected in the identity of covariances between relatives for males and females (Table 8). Further, the covariance between full sibs exceeds the resemblance between parents and offspring. In this circumstance,
although imprinting is clearly affecting genetic values, it is not apparent by consideration of population variances and covariances. Note however that if there is any difference in the allele frequencies at the two loci (such that \( p_{1A} \neq p_{1B} \)), population variances and covariances will no longer be the same for males and females and hence imprinting will be detectable.

Example 1.9 is characterised by imprinting (paternal inactivation) at only one locus. Although the difference is not as strong as with both loci imprinted (refer example 1.7), male and female additive variances differ (Table 7), as do father-offspring and mother-offspring covariances and resemblances between half sibs sharing a mother or sharing a father (Table 8).

Finally, loci are not equally weighted in example 1.10, with the \( B \) locus contributing three times more towards genotypic values. The \( A \) locus is strongly paternally inactivated while the \( B \) locus is partially maternally inactivated. Although genotypic values of reciprocal heterozygotes from the \( B \) locus are similar, the \( B \) locus outweighs the strong effect of paternal inactivation from the \( A \) locus and male exceed female additive variances (Table 7). Consequently the relationship between father and offspring exceeds that between mother and offspring (and similarly for half sibs sharing a father compared to mother) (Table 8). As we saw in example 1.8, exactly opposite imprinting status at two loci may mask signatures of imprinting in variance and covariances. However, although for this example the covariance between full sibs is greatest, the contribution of imprinting is still apparent in the differences between maternal and paternal offspring and half sib covariances.

Combining imprinting and epistatic interactions

We now extend our exploration to a number of cases where both imprinting and epistatic interactions are acting. We again assume \( p_{1A} = p_{1B} = \frac{1}{2} \). Examples 2.1-2.5 are based upon the imprinting scenario in example 1.7 (paternal inactivation), examples 2.6 & 2.7 based upon example 1.8 (contrasting maternal and paternal inactivation), and examples 2.8-2.10 are based upon the imprinting structure in example 1.10 (unequal contribution of loci).

**Paternal inactivation**

Example 2.1 sets the genotypic values \( G_{1121} = G_{2112} = G_{2122} = G_{2221} \) and \( A_1A_1B_1B_2 = A_1A_2B_1B_1 = A_2A_1B_2B_2 = A_2A_2B_1B_2 \). Compared to example 1.7, we may see
that the total variance has decreased (Table 9). Most significantly, the full sib covariance and covariance between half sibs sharing a mother now greatly exceed the covariance between mother and offspring (Table 10). Interestingly, choice of allele frequencies in this example may have a significant effect on expected signatures of imprinting; for the same genotypic values but allele frequencies of $p_{1A} = \frac{1}{10}$ and $p_{1B} = \frac{1}{3}$, the female and male additive variances are $\sigma_{Af}^2 = 0.0245$ and $\sigma_{Am}^2 = 0.0367$; consequently the father offspring covariance exceeds the mother offspring covariance and the covariance between half sibs sharing a father exceeds that between half sibs sharing a mother.

Examining example 2.2, we see that the choice of epistatic interactions has enhanced the influence of maternal genotype, and as a consequence we have increased the difference between female and male additive variances relative to example 1.7 (Table 9). There is also an increase in total genetic variance, and a slight difference in male and female dominance variances. Female and full sib covariances have increased while the covariance between fathers and offspring and half sibs sharing a father has decreased (Table 10). The covariance between females and their offspring exceeds that between full sibs.

Example 2.3, again sharing the same underlying genotypic values as example 1.7, also mirrors example 1.6 where genotypic values of all double heterozygotes are equal to 1. As with example 1.6, we can see that the dominance variance is a more significant contributor to total variance than the additive variances. Example 2.4 is a somewhat extreme example of interactions between loci creating a shared genotypic value of 1 for nine different genotypes (as with example 1.2). This composition decreases the impact of paternal inactivation of alleles and consequently decreases the difference between female and male additive variances relative to example 1.7 (Table 9), and covariances between females and males and their offspring (Table 10).

A final derivation based on example 1.7, example 2.5 follows example 1.3 by setting $G_{2122} = G_{1222} = G_{2221} = G_{2212} = 1$ and $G_{2222} = 1.5$. This largest range in genotypic values is reflected in the total genetic variance of 0.1848 (Table 9). Male additive variance is enhanced relative to example 1.7, while the covariance between mothers and offspring is maintained as the largest of the resemblances between relatives.
Contrasting maternal and paternal inactivation

Example 2.6 shares features with both examples 1.8 (discordant imprinting at the two loci) and 1.4 \( (G_{2122} = G_{1222} \) and \( G_{2221} = G_{2212} \) \). Worthy of note is that the choice of epistatic interactions has created a difference in the female and male additive variances (Table 9) and consequently differences in covariances between relatives (Table 10). Although the full sib covariance is largest, the inequality of male and female parent-offspring covariances and half sib relationships do indicate the influence of imprinting on the trait. Interestingly, for example 2.7, setting genotypic values almost completely dependent upon the genotype at the \( B \) locus (as in example 1.5), the maternal contribution has been swamped and additive variances are indicative of maternal inactivation (Table 9). The covariance between half sibs sharing a father exceeds the covariance between fathers and offspring (an occurrence otherwise only seen in example 2.1). Note again however that differences in the allele frequencies at the two loci may reverse these patterns, and the maternal contribution may no longer be swamped by locus \( B \).

Unequal contribution of loci

Example 2.8, based on the imprinting structure of example 1.10, represents an interaction between heterozygotes masking the influence of imprinting. Compared to example 1.10, the suggestion of maternal inactivation is reversed and additive variances and covariances between relatives suggest instead very weak paternal inactivation (Tables 9 and 10), although this feature is dependent on our choice of allele frequencies at the two loci. As with many other examples, the full sib covariance exceeds that between mother and offspring. Example 2.9 reverses the arrangement of example 1.5, with locus \( A \) having most effect on the phenotype of individuals, regardless of the genotype at locus \( B \). Consequently, variances and covariances strengthen the patterns from example 2.8, suggesting moderate paternal inactivation.

The final example, 2.10, sets nine of the genotypic values to 1, as we have seen in examples 1.2 and 2.4. Unexpectedly, the female additive variance is greater than the male additive variance, despite the influence of the dominant \( B \) locus. Examining allelic values, we can see that average values for reciprocal heterozygotes at the \( B \) locus differ by 0.0281 \( (\text{Average}(B_2B_1) = \frac{1}{4}(0.3+1+1+1) = 0.825; \)
\[ \text{Average}(B_1B_2) = \frac{1}{4}(0.4125+1+1+1) = 0.8531 \) \). In contrast, average values for
reciprocal heterozygotes at the A locus differ by 0.0531
(Average($A_1A_1$) = $\frac{1}{4}(0.225 + 1 + 1) = 0.8063$;

Average($A_2A_2$) = $\frac{1}{4}(0.0125 + 1 + 1) = 0.7531$). This greater difference between
average values of reciprocal heterozygotes means that heterozygote genetic values are
more closely correlated with the homozygote corresponding to the maternally
inherited allele. As a consequence, the female additive variance is slightly higher than
the male, the covariance between mothers and offspring exceeds the covariance
between fathers and offspring, and the covariance between half sibs sharing a female
parent exceeds that between half sibs sharing a male parent.

From these examples we may make a number of conclusions. First, and most
importantly, observations of differences in female and male additive variances, and
differences in male and female parent-offspring and half sib resemblances, indicate
that imprinting is acting in a population (if it can be assumed that there are no
maternal effects). Imprinting may be present in a population if this signature is not
present only if two non-interacting, oppositely-imprinted loci with identical allele
frequencies are affecting the trait of interest. Even slight epistatic interactions between
loci in this case will result in a difference between male and female variance
components and hence covariances between relatives.

Two other signatures may suggest imprinting is affecting one or both loci,
although unfortunately it is not possible to conclude that imprinting is absent if these
signatures are not present. Imprinting is present where the covariance between
offspring and one parent exceeds the covariance between full sibs. Further, if we
assume no imprinting, the covariance between breeding values and dominance
deviations is the same for males and females and is equal to

$$\sigma_{AD} = p_{1A}p_{2A}p_{1B}p_{2B}(p_{2B}(e_{1222}(p_{1A} - p_{2A}) + e_{2222}p_{2A})
+ e_{1212}(p_{1A} - p_{2A})(p_{1B} - p_{2B}) + e_{2212}p_{2A}(p_{1B} - p_{2B}))^2
> 0$$

Therefore only in the presence of imprinting can this covariance become negative.

Recalling that

$$\sigma_{OPF} = \frac{1}{2}(\sigma_f^2 + \sigma_{Mf})$$

and

$$\sigma_{HSf} = \frac{1}{4} \sigma_f^3$$
(and similarly for male covariances) we can see that if twice the male or female half sib covariance exceeds the covariance between offspring and the corresponding parent, the trait must be influenced by imprinting.

Although not fully considered above, many examples could be constructed such that underlying imprinting at one or both loci is masked by epistatic interactions, perhaps even reversing the prediction of the direction of imprinting. Resolving this complexity for quantitative traits will not be straightforward. For example, there is strong evidence for a quantitative trait locus (QTL) for bipolar affective disorder mapping to chromosome 18q. However, there is conflicting evidence about whether this locus is imprinted – Stine et al. [1995], McMahon et al. [2001], McInnis et al. [2003] and Schulze et al. [2003] all report strong evidence for a paternally expressed susceptibility locus on 18q, while McMahon et al. [1997] reported both maternal and paternal parent-of-origin effects and Lambert and Gill [2002] presented evidence for maternal expression on 18q, although this signal diminished with addition of more families. This lack of reproducibility may certainly be due to general restrictions in mapping human complex disease (such as incomplete penetrance, locus heterogeneity, impact of environmental factors, or low statistical power; see for example Lander and Schork [1994]) or even variation in imprinting status between individuals [Pastinen et al., 2003; Sandovici et al., 2003; Naumova and Croteau, 2004]. However, it is worth considering also that epistatic interaction between an imprinted locus on chromosome 18 and a secondary locus may indeed mask imprinted phenotypes in populations fixed for certain alleles. With the increasing density of marker maps, evaluation of epistatic interactions when one or more loci affecting a trait are imprinted is an exciting challenge for the future.
References


Appendix A: Second order epistatic interaction terms

Female additive variance

\[ \sigma_A^2 (e_{ij}, e_{ij}) \]  
\[ = p_{2A}p_{2B}[2e_{1212}^2e_{2212}p_{1A}p_{1B}p_{2A}(-2+3p_{2A})p_{2B} \]
\[ + e_{1212}^2p_{1A}p_{1B}p_{2A}p_{2B}(2p_{2B}+p_{2A}(2-3p_{2B})) \]
\[ -2e_{1212}e_{1222}p_{1A}p_{2A}(2-5p_{2A}+3p_{2A}^2)p_{2B} \]
\[ -2p_{1A}p_{2A}p_{2B}(2-5p_{2B}+3p_{2B}^2)(e_{1212}e_{2112}p_{1A}+e_{1212}e_{2212}p_{2A}) \]
\[ +2e_{1222}e_{2222}p_{1A}p_{1B}p_{2A}p_{2B}(1-3p_{2B}) \]
\[ +p_{2A}p_{2B}(1+p_{2A}+p_{2B}-3p_{2A}p_{2B})(2e_{2112}e_{2222}p_{1A}p_{1B}+e_{2222}e_{2222}p_{2A}p_{2B}) \]
\[ -6p_{1A}p_{1B}p_{2A}p_{2B}(p_{1A}p_{1B}(e_{1212}e_{2112}+e_{1212}e_{2212})+p_{1B}p_{2A}(e_{1212}e_{2112}+e_{1212}e_{2212}) \]
\[ +p_{1A}p_{2B}(e_{1222}e_{2112}+e_{1212}e_{2212})+p_{2A}p_{2B}(e_{1222}e_{2112}+e_{1212}e_{2212})) \]
\[ +2p_{2B}(1-3p_{2A})[(p_{1B}^2p_{2A}(e_{2112}e_{2212}p_{1A}+e_{2212}e_{2212}p_{2A})+p_{1B}p_{2B}(e_{2112}e_{2112}p_{1A}^2+e_{2212}e_{2212}p_{2A}^2) \]
\[ +p_{1A}p_{2B}(e_{1222}e_{2112}+e_{1212}e_{2212})+p_{1A}p_{2A}p_{2B}(e_{1222}e_{2112}p_{1A}+e_{1212}e_{2212}p_{2A})] \]
\[ +2(1-4p_{2B}+3p_{2B}^2)(e_{1222}e_{2222}p_{1A}^2p_{2A}p_{2B}+p_{1B}^2p_{2B}(e_{2112}e_{2112}p_{1A}+e_{2112}e_{2212}p_{2A}) \]
\[ +p_{1A}p_{2B}(e_{1212}e_{2112}p_{1A}+e_{1212}e_{2212}p_{2A})+p_{1A}p_{2A}p_{2B}(e_{2112}e_{2212}p_{1A}+e_{2112}e_{2212}p_{2A}) \]
\[ +p_{1B}p_{2B}(2-2p_{2B}+p_{2A}(-2+3p_{2B}))(e_{2112}^2p_{1A}^2+2e_{2112}e_{2212}p_{1A}p_{2A}+e_{2212}^2p_{2A}^2) \]
\[ +e_{2122}e_{2212}p_{1B}p_{2B}(e_{2112}e_{2212}p_{1A}+e_{2112}e_{2222}p_{2B}) \]
\[ +(1+p_{2A}+p_{2A}(1-3p_{2B}))(p_{1A}p_{2B}(e_{2121}e_{2112}+e_{2112}e_{2212}p_{2B}) \]
\[ +p_{1B}p_{2A}(e_{2212}e_{2212}p_{2A}+2e_{2112}e_{2212}p_{1A}p_{2B})+p_{1A}p_{2B}(e_{2212}p_{1A}+2e_{2112}e_{2222}p_{2A}) \]
\[ +2p_{1B}p_{2A}(e_{2112}e_{2222}p_{1A}p_{1B}+e_{2212}e_{2222}p_{2A}p_{2B})] \]
Male additive variance

\[ \sigma^2_{Am}(e_{ijk} \times e_{ijk}) = p_{2A}p_{2B} [2e_{2124}p_{1A}p_{1B}p_{2A}^2 (2 + 3p_{2A} + p_{2B})] \\
+ e_{2124}^2 p_{1A}p_{1B}p_{2A}p_{2B} (2p_{2B} + p_{2A} (2 - 3p_{2B})) \\
- 2e_{2124}e_{2122}p_{1A}p_{2A} (2 - 5p_{2A} + 3p_{2B}^2) \\
- 2p_{1A}p_{2A}p_{2B} (2 - 5p_{2B} + 3p_{2A}^2) (e_{1221}^2 e_{1221} p_{1A} + e_{1221} e_{2221} p_{2A}) \\
+ 2e_{2112} e_{2222} p_{1A} p_{1B} p_{2A}^2 p_{2B} (1 - 3p_{2B}) \\
+ p_{2A}p_{2B} (1 + p_{2A} + p_{2B} - 3p_{2A}p_{2B}) (2e_{1212} e_{2222} p_{1A} p_{1B} + e_{2222} p_{2A} p_{2B}) \\
- 6p_{1A}p_{1B}p_{2A}p_{2B} [p_{1B}^2 p_{2A} (e_{1212} e_{2212} + e_{2112} e_{2221}) + p_{1A} p_{2B} (e_{1222} e_{2121} + e_{2121} e_{2122})] \\
+ p_{2A}p_{2B} (e_{2122} e_{2221} + e_{2121} e_{2222}) + p_{1A} p_{1B} (e_{1221} e_{2112} + e_{1212} e_{2121})] \\
+ 2p_{2B} (1 - 3p_{2A}) [p_{1B} p_{2B} (e_{1212} e_{2222} p_{1A}^2 + e_{2222} e_{2222} p_{2A}^2) + p_{1B}^2 p_{2A} (e_{1212} e_{2222} p_{1A} + e_{2212} e_{2222} p_{2A})] \\
+ p_{1A} p_{1B} p_{2A} (e_{1222} e_{2212} + e_{2212} e_{2222}) + p_{1A} p_{1B} p_{2B} (e_{1222} e_{2122} + e_{2122} e_{2222} p_{2A})] \\
+ 2(1 - 4p_{2A} + 3p_{2A}^2) [p_{2A} p_{1B} p_{2B}^2 (e_{1222} e_{2222} + e_{2222} e_{2222}) + p_{2B}^2 p_{2A} (e_{1212} e_{2222} p_{1A} + e_{2212} e_{2222} p_{2A})] \\
+ p_{1A} p_{2A} (e_{2122} e_{2122} p_{1A} + e_{2112} e_{2212} p_{2A} + e_{2122} e_{2212} p_{2A})] \\
+ p_{1A} p_{2B} (2 - 2p_{2B} + p_{2A} (-2 + 3p_{2B})) (e_{2121}^2 p_{1A}^2 + 2e_{1221} e_{2221} p_{1A} p_{2A} + e_{2211}^2 p_{2A}^2) \\
+ p_{1A} p_{2A} (2 - 2p_{2B} + p_{2A} (-1 + 3p_{2B})) (e_{2112}^2 p_{1A}^2 + 2e_{2112} e_{2122} p_{1B} p_{2B} + e_{2212}^2 p_{2B}^2) \\
+ (1 + p_{2B} + p_{2A} (1 - 3p_{2B})) [p_{1A} p_{1B} (e_{2121}^2 p_{1B} + 2e_{1212} e_{2212} p_{2B}) \\
+ p_{1A}^2 (e_{2212}^2 p_{1B}^2 + 2e_{2222} e_{2222} p_{1B} p_{2B}) + p_{2B}^2 (e_{1222}^2 p_{1A}^2 + 2e_{1222} e_{2222} p_{1A} p_{2A})] \\
+ 2p_{1A} p_{1B} p_{2A} (e_{1222} e_{2212} p_{1B} + e_{1212} e_{2222} p_{1B})]]
Female dominance variance

$$\sigma^2_f (e_{ijl} \times e_{ijkl})$$

$$= p_{A} P_{B} (-p_{A} P_{B} [ e_{1212} e_{2221} P_{1A} P_{2A} + e_{1212} e_{2122} P_{1A} P_{2B} + e_{1212} e_{2122} P_{1A} P_{2B} ] + p_{A} P_{B} [ e_{1212} e_{2212} P_{1A} P_{2A} + e_{1212} e_{2212} P_{1A} P_{2B} + e_{1212} e_{2122} P_{1A} P_{2B} ])$$

$$= -2 p_{A} P_{B} [ e_{1212} e_{2221} P_{1A} P_{2A} + e_{1212} e_{2221} P_{1A} P_{2B} ] + p_{A} P_{B} [ e_{1212} e_{2212} P_{1A} P_{2A} + e_{1212} e_{2212} P_{1A} P_{2B} ]$$

$$+ 2 p_{A} P_{B} (-2 + p_{A} + p_{B}) [ e_{1212} e_{2221} P_{1A} P_{2A} + e_{1212} e_{2221} P_{1A} P_{2B} ]$$

$$= -p_{A} P_{B} (1 - 2 p_{A} + 2 p_{B}^2) [ e_{1212} e_{2212} P_{1A} P_{2A} + e_{1212} e_{2212} P_{1A} P_{2B} ]$$

$$+ p_{A} P_{B} (-1 + 2 p_{A} + 2 p_{B}^2) [ e_{1212} e_{2212} P_{1A} P_{2A} + e_{1212} e_{2212} P_{1A} P_{2B} ]$$

$$- p_{A} P_{B} (1 - 3 p_{A} + 2 p_{B}^2) [ e_{1212} e_{2122} P_{1A} + e_{2112} e_{2222} P_{2A} ]$$

$$+ e_{2112} e_{2222} P_{1A} P_{2A} P_{2B} (1 + 2 p_{A} - 2 p_{B}) + e_{2112} e_{2222} P_{1A} P_{2A} P_{2B} (1 - 2 p_{A} + 2 p_{B})$$

$$- e_{2122} e_{2112} P_{1A} P_{2A} (p_{2B} + 2 p_{2B}) - e_{2122} e_{2112} P_{1A} P_{2A} (p_{2B} - 2 p_{2B})$$

$$+ e_{2222} P_{1A} P_{2A} (1 - p_{2B}^2 + p_{A}^2) + e_{2122} P_{1A} P_{2B} (1 - p_{A}^2 + p_{B}^2)$$

$$+ 2 e_{2222} e_{2112} P_{1A} P_{2B} (-2 - p_{A}^2 + p_{B}^2) + 2 e_{2112} e_{2222} P_{1A} P_{2B} (-2 + 5 p_{A} - 5 p_{B}^2 + 2 p_{A}^2)$$

$$+ e_{2122} e_{2112} P_{1A} P_{2A} P_{2B} (-2 + 5 p_{A} - 5 p_{B}^2 + 2 p_{A}^2) + e_{2112} e_{2212} P_{1A} P_{2A} (-2 + 5 p_{B} - 5 p_{A}^2 + 2 p_{B}^2)$$

$$- e_{2212} e_{2212} P_{1A} P_{2A} P_{2B} (-2 + 5 p_{A} - 5 p_{B}^2 + 2 p_{A}^2) + e_{2212} e_{2212} P_{1A} P_{2A} (-2 + 5 p_{B} - 5 p_{A}^2 + 2 p_{B}^2)$$

$$- e_{2122} e_{2112} P_{1A} P_{2A} P_{2B} (-2 + 5 p_{A} - 5 p_{B}^2 + 2 p_{A}^2) + e_{2122} e_{2112} P_{1A} P_{2A} (-2 + 5 p_{B} - 5 p_{A}^2 + 2 p_{B}^2)$$

$$+ e_{2212} e_{2212} P_{1A} P_{2A} P_{2B} (-2 + 5 p_{A} - 5 p_{B}^2 + 2 p_{A}^2) + e_{2212} e_{2212} P_{1A} P_{2A} (-2 + 5 p_{B} - 5 p_{A}^2 + 2 p_{B}^2)$$

$$- e_{2212} e_{2212} P_{1A} P_{2A} P_{2B} (-2 + 5 p_{A} - 5 p_{B}^2 + 2 p_{A}^2) + e_{2212} e_{2212} P_{1A} P_{2A} (-2 + 5 p_{B} - 5 p_{A}^2 + 2 p_{B}^2)$$

$$+ e_{2122} e_{2112} P_{1A} P_{2A} P_{2B} (1 + 2 p_{A} + 2 p_{B}^2) + e_{2122} e_{2112} P_{1A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2)$$

$$- e_{2122} e_{2112} P_{1A} P_{2A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2) + e_{2122} e_{2112} P_{1A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2)$$

$$+ e_{2122} e_{2112} P_{1A} P_{2A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2) + e_{2122} e_{2112} P_{1A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2)$$

$$+ e_{2212} e_{2212} P_{1A} P_{2A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2) + e_{2212} e_{2212} P_{1A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2)$$

$$+ e_{2122} e_{2112} P_{1A} P_{2A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2) + e_{2122} e_{2112} P_{1A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2)$$

$$+ e_{2212} e_{2212} P_{1A} P_{2A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2) + e_{2212} e_{2212} P_{1A} P_{2B} (1 - 2 p_{A} + 2 p_{B}^2)$$
Male dominance variance

\[ \sigma_{Dm}^2 (e_{ijkl} \times e_{ijkl}) \]

\[ = p_{2A} p_{2B} [ - p_{1A} p_{1B} (e_{2121} e_{2121} p_{1A} p_{2B} + e_{2122} e_{2121} p_{1A} p_{2B}) + p_{2A} p_{2B} (e_{2121} e_{2122} + e_{2121} e_{2221} + e_{2121} e_{2222}) ] \]

\[ - 2 p_{2A} p_{2B} (p_{1A} p_{1B} (e_{2122} e_{2122} p_{1A} + e_{2122} e_{2221} p_{1A})) + e_{2122} e_{2222} p_{1A} p_{2B} + e_{2121} e_{2222} p_{1A} p_{2B} ] \]

\[ + 2 p_{2A} p_{2B} (-2 + p_{2A} + p_{2B}) (e_{2122} e_{2222} p_{1A} p_{2B} + e_{2122} e_{2222} p_{1A} p_{2B}) \]

\[ - p_{1A} (1 - 2 p_{2A} + 2 p_{2A}^2) (e_{2121} e_{2121} p_{2B} + e_{2121} e_{2121} p_{2B}) + p_{1A} p_{1B} (-1 + 2 p_{2A} + 2 p_{2B}) (e_{2121} e_{2122} p_{1A} p_{2B} + e_{2121} e_{2222} p_{1A} p_{2B}) \]

\[ - p_{1B} p_{2A} (1 - 3 p_{2A} + 2 p_{2A}^2) (e_{2121} e_{2222} p_{2B} + e_{2121} e_{2222} p_{2B} + e_{2121} e_{2222} p_{2B}) \]

\[ + e_{2121} e_{2122} p_{1A} p_{1B} p_{2A} p_{2B} (1 - 2 p_{2A} + 2 p_{2B}) + e_{2122} e_{2221} p_{1A} p_{1B} p_{2A} p_{2B} (1 + 2 p_{2A} - 2 p_{2B}) \]

\[ + e_{2122} e_{2121} p_{1A} p_{1B} (-p_{1A} + p_{2B} - 2 p_{2A} p_{2B}) - e_{2121} e_{2121} p_{1A} p_{1B} p_{2A} p_{2B} (1 + 2 p_{2A} - 2 p_{2B}) \]

\[ + e_{2121} e_{2121} p_{1A} p_{1B} (-1 + 2 p_{2B} - 2 p_{2B}^2 + 2 p_{2B}^3) + e_{2122} e_{2122} p_{2B} (1 - 2 p_{2A} + 2 p_{2A}^2 + p_{2A}^3) \]

\[ + e_{2222} e_{2122} p_{1A} p_{1B} (1 + p_{2B} (1 - p_{2A} p_{1B})) + e_{2121} e_{2122} p_{1A} p_{1B} (1 + p_{2A} (1 - p_{2B} p_{1B}) - p_{1B} p_{2B}) \]

\[ + e_{2121} e_{2122} p_{1A} p_{1B} (1 - p_{2B} p_{2A} + p_{2B} p_{2A}^2) + e_{2122} e_{2121} p_{1A} p_{1B} (1 - p_{2B} p_{2A} + p_{2B} p_{2A}^2) \]

\[ + e_{2222} e_{2122} (-1 + 2 p_{2B} - 2 p_{2B}^2 + 2 p_{2B}^3) + e_{2122} e_{2121} p_{1A} p_{1B} p_{2A} (-2 + 3 p_{2B} - 2 p_{2B}^3) \]

\[ + 2 e_{2122} e_{2222} p_{1A} p_{1B} p_{2B} p_{2B} (-1 + 2 p_{2B}) \]

\[ + e_{2121} e_{2122} p_{1A} p_{1B} p_{2A} p_{2B} (-3 + 2 p_{2A} + 2 p_{2B}) \]

\[ + e_{2222} p_{2A} p_{2B} (1 + p_{2A} p_{2B} + p_{2A} p_{2B} (-3 + p_{2B})) \]

\[ - e_{2121} e_{2121} p_{1A} p_{1B} (-1 + p_{2A} p_{2B} + p_{2A} p_{2B} (-2 + p_{2B})) \]

\[ + e_{2122} p_{1A} p_{1B} (1 + p_{2B} p_{2A} - p_{2B} p_{2A}^2 + p_{2B} - p_{2B}^2) \]

\[ - e_{2121} e_{2121} p_{1A} p_{2A} p_{2B} (1 - 3 p_{2A} + 2 p_{2A}^2) \]

\[ - e_{2121} e_{2121} p_{1A} p_{2B} (1 - 2 p_{2B} + 2 p_{2B}^2) \]

\[ - e_{2222} e_{2122} p_{1A} p_{2A} (1 - p_{2B} + 2 p_{2B}^2) \]

\[ + e_{2122} e_{2122} p_{2B} (-1 + 2 p_{2A} - 3 p_{2A}^2 + 2 p_{2A}^3) + e_{2122} e_{2121} p_{1A} p_{2B} (-1 + 3 p_{2B} - 4 p_{2B}^2 + 2 p_{2B}^3)] \]
Female covariance between breeding values and dominance deviations

\[ \sigma_{AB}^2 (\epsilon_{ijkl} \times \epsilon_{ijkl}) \]

\[ = \frac{1}{2} p_{1A} p_{1B} p_{2A}^2 p_{2B}^2 \]

\[ [2 p_{1A} p_{1B} p_{2A}^2 p_{2B}^2 [e_{2222}^2 + 2e_{2222} e_{2212}] \]

\[ + 2 p_{1A} p_{1B} p_{2A} p_{2B} (1 - 2 p_{1A} p_{2B}) [e_{2212} e_{2212} p_{1A} + e_{2212} e_{2222} p_{2A}] \]

\[ + 2 p_{1A} p_{1B} p_{2A}^2 (1 - 2 p_{1B} p_{2A}) [e_{2222} e_{2222} + e_{2222} e_{2222} p_{2B}] \]

\[ + p_{1A} p_{1B} p_{2A} (1 - 4 p_{1B} p_{2A}) [e_{2122} e_{2222} p_{1B} + e_{2122} e_{2222} p_{2B}] \]

\[ + p_{1A} p_{1B} p_{2B} (1 - 4 p_{1A} p_{2B}) [e_{2122} e_{2122} p_{1A} + e_{2122} e_{2222} p_{2A}] \]

\[ + p_{1A} p_{1B} p_{2A}^2 p_{2B} (1 - 4 p_{1A} p_{2B}) [e_{2122} e_{2222} + e_{2122} e_{2212}] \]

\[ + p_{1A} p_{1B} (1 + 4 p_{1A} p_{2B}) [e_{1212} e_{2222} p_{1B} + e_{1212} e_{2222} p_{1A} p_{2B} + e_{1212} e_{2222} p_{2A} p_{2B}] \]

\[ + 2 p_{1A} p_{1B} p_{2A} (1 - 2 p_{1A} p_{2A}) [e_{2222} e_{2222} p_{1B} + e_{2222} e_{2222} p_{1A} + e_{2222} e_{2222} p_{2A}] \]

\[ + p_{1A} p_{1B} p_{2B} (1 - 2 p_{1B} p_{2A}) [e_{2222} e_{2222} p_{1B} + e_{2222} e_{2222} p_{1A} + e_{2222} e_{2222} p_{2A}] \]

\[ + p_{1A} p_{1B} (1 + 4 p_{1B} p_{2A}) [e_{2222} e_{2222} p_{1B} + e_{2222} e_{2222} p_{1A} + e_{2222} e_{2222} p_{2A}] \]

\[ + e_{2122} e_{2212} p_{1A} p_{1B} p_{2A} (1 - 4 p_{1A} p_{2A} p_{2B}) + e_{2122} e_{2122} p_{1A} p_{1B} p_{2B} (1 + 4 p_{1A} p_{2A} p_{2B}) \]

\[ + e_{2122} e_{2212} p_{1B} p_{2A} (1 - 4 p_{1A} p_{2A} p_{2B}) + e_{2122} e_{2122} p_{1B} p_{2B} (1 + 4 p_{1A} p_{2A} p_{2B}) \]

\[ + e_{2122} e_{2212} p_{1A} p_{1B} p_{2A}^2 (3 - 2 p_{1B} p_{2A}) + e_{2122} e_{2212} p_{1A} p_{1B} p_{2B}^2 (-3 + 2 p_{1A} p_{2B}) \]

\[ + 2 e_{2222} e_{2222} p_{1A} p_{2A}^2 (1 - 2 p_{1A} p_{1B} p_{2B}) + 2 e_{2222} e_{2222} p_{1A} p_{2B}^2 (1 - 2 p_{1A} p_{1B} p_{2A}) \]

\[ + 2 e_{2222} p_{1A} p_{2A}^2 (1 - 1 + p_{1A} p_{2A}) + 2 e_{2222} p_{1A} p_{2B}^2 (1 + p_{1A} p_{2B}) \]

\[ + e_{2122} e_{2222} p_{1A} p_{1B} p_{2A} (2 + p_{2B} (5 - 4 p_{2A}) + 4 p_{1A} p_{2B}^2) \]

\[ + e_{2222} e_{2222} p_{1A} p_{1B} p_{2B} (2 + p_{2B} (5 - 4 p_{2A}) + 4 p_{1B} p_{2A}^2) \]

\[ + e_{2122} e_{2122} p_{1A} p_{1B} p_{2A} (1 + p_{2B} (3 - 4 p_{2A}) + 4 p_{1A} p_{2B}^2) \]

\[ + e_{2222} e_{2222} p_{1A} p_{1B} p_{2B} (1 + p_{2A} (3 - 4 p_{2A}) + 4 p_{1B} p_{2A}^2) \]

\[ + e_{2122} e_{2222} p_{1A} p_{1B} p_{2A} (5 - 4 p_{1B} p_{2A}) + e_{2122} e_{2222} p_{1A} p_{1B} p_{2B} (5 - 4 p_{1A} p_{2B}) \]

\[ - 4 p_{1A} p_{2B}^2 (p_{1B} p_{2A} + p_{2B}) \]

\[ + e_{2122} e_{2222} p_{1A} p_{1B} p_{2B} (1 - 4 p_{1B} p_{2A} + 4 p_{2B}) \]

\[ - e_{2122} p_{1A} p_{2B}^2 (1 + 2 p_{1B} p_{2A} + 2 p_{2B}) \]

\[ + e_{1212} p_{1A} p_{1B} p_{2A} p_{2B}^2 (3 + 2 p_{2A} p_{2B}) \]

\[ + e_{2212} p_{1A} p_{2A} (p_{1A} + p_{2B} - 6 p_{2A} p_{2B} + 4 p_{1B} p_{2B}^2 + 4 p_{2A} p_{2B}^2) \]

\[ - e_{1212} p_{1A} p_{1B} (-p_{1A} + p_{2B} - 6 p_{2A} p_{2B} + 4 p_{1B} p_{2B}^2 + 4 p_{2A} p_{2B}^2)) \]

4.25
Male covariance between breeding values and dominance deviations

\[ \sigma_{ADm}^2 (e_{bi}^2 \times e_{bi}^2) \]

\[ = \frac{1}{4} p_{2A} p_{2B} \]

\[ + 2 p_{1A} p_{1B} p_{2A} p_{2B}^2 [\varepsilon_{2222}^2 + 2 \varepsilon_{2122} \varepsilon_{2221}] \]

\[ + 2 p_{1B} p_{2A} p_{2B} (1 - 2 p_{1A} p_{2B}) [\varepsilon_{2122} \varepsilon_{2221} p_{1A} + \varepsilon_{2221} \varepsilon_{2222} p_{2A}] \]

\[ + 2 p_{1A} p_{2A} p_{2B} (1 - 2 p_{1B} p_{2A}) [\varepsilon_{2122} \varepsilon_{2212} p_{1B} + \varepsilon_{2122} \varepsilon_{2222} p_{2B}] \]

\[ + p_{1A} p_{1B} p_{2A} (1 - 4 p_{1B} p_{2A}) [\varepsilon_{2112} \varepsilon_{2212} p_{1B} + \varepsilon_{2112} \varepsilon_{2222} p_{2A}] \]

\[ + p_{1A} p_{1B} p_{2A} (1 - 4 p_{1B} p_{2A})^2 [\varepsilon_{2121} \varepsilon_{2212} p_{1A} + \varepsilon_{2121} \varepsilon_{2222} p_{1B}] \]

\[ + p_{1A} p_{1B} (1 + 4 p_{2A} p_{2B}) [\varepsilon_{2121} \varepsilon_{2212} p_{1A} + \varepsilon_{2121} \varepsilon_{2222} p_{1B} + \varepsilon_{2121} \varepsilon_{2222} p_{2A}] \]

\[ - 2 (p_{1A} p_{2A} + p_{2B}) [\varepsilon_{2122} \varepsilon_{2212} p_{1B} + \varepsilon_{2221} \varepsilon_{2222} p_{2B}] \]

\[ + 2 p_{1B} p_{2B} (1 - 2 p_{1B} p_{2A} - 2 p_{2B}) [\varepsilon_{2122} \varepsilon_{2222} p_{1B} + \varepsilon_{2222} \varepsilon_{2222} p_{1A}] \]

\[ - p_{1A} p_{1B} (1 + 4 p_{1B} p_{2A} + 4 p_{2B}) [\varepsilon_{2121} \varepsilon_{2212} p_{1B} + \varepsilon_{2121} \varepsilon_{2222} p_{1B}] \]

\[ + \varepsilon_{2121} \varepsilon_{2212} p_{1A} p_{1B} (1 - 4 p_{1A} p_{1B} p_{2A}) + \varepsilon_{2121} \varepsilon_{2212} p_{1A} p_{1B} (1 - 4 p_{1A} p_{1B} p_{2A}) \]

\[ + \varepsilon_{2112} \varepsilon_{2212} p_{1A} p_{1B} p_{2B} (1 - 4 p_{1A} p_{1B} p_{2A}) + \varepsilon_{2112} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} (1 - 4 p_{1A} p_{1B} p_{2B}) \]

\[ + \varepsilon_{2112} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} (1 + 4 p_{1B} p_{2A}) + \varepsilon_{2112} \varepsilon_{2212} p_{1A} p_{1B} p_{2B} (1 + 4 p_{1A} p_{2B}) \]

\[ + \varepsilon_{2112} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} (3 + 2 p_{1B} p_{2A}) + \varepsilon_{2112} \varepsilon_{2212} p_{1A} p_{1B} p_{2B} (3 + 2 p_{1A} p_{2B}) \]

\[ + 2 \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B}^2 (1 - 2 p_{1A} p_{1B} p_{2A}) + 2 \varepsilon_{2122} \varepsilon_{2222} p_{1A} p_{1B}^2 (1 - 2 p_{1A} p_{1B} p_{2B}) \]

\[ + 2 \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B}^2 (1 + p_{1A} p_{2A}) + 2 \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B}^2 (1 + p_{1A} p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (2 + p_{2B} (-5 + 4 p_{2A}) + 4 p_{1A} p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (2 + p_{2B} (-5 + 4 p_{2A}) + 4 p_{1A} p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (1 + p_{2B} (-3 + 4 p_{2A}) + 4 p_{1A} p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (1 + p_{2B} (-3 + 4 p_{2B}) + 4 p_{1B} p_{2A}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (-5 + 4 p_{1B} p_{2A}) + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} p_{2B} (-5 + 4 p_{1A} p_{2B}) \]

\[ - 4 \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} p_{2B} (p_{1B} p_{2A} + p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} p_{2B} (1 - 4 p_{1B} p_{2A} - 4 p_{2B}) \]

\[ - \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} p_{2B} (1 + 2 p_{1B} p_{2A} + 2 p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} p_{2A} p_{2B} (-3 + 2 p_{2A} p_{2B}) \]

\[ + \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (p_{2A} + 2 p_{2B} - 4 p_{1B} p_{2A} p_{2B} - 4 p_{2A} p_{2B}) \]

\[ - \varepsilon_{2122} \varepsilon_{2212} p_{1A} p_{1B} (-p_{1A} + 2 p_{2A} - 6 p_{2A} p_{2B} + 4 p_{1B} p_{2A} p_{2B} + 4 p_{2A} p_{2B}) \]
Table 1: Genotypic values under imprinting and epistatic interactions for two loci

<table>
<thead>
<tr>
<th>A locus genotype</th>
<th>B locus genotype</th>
<th>B&lt;sub&gt;1&lt;/sub&gt;B&lt;sub&gt;1&lt;/sub&gt;</th>
<th>B&lt;sub&gt;2&lt;/sub&gt;B&lt;sub&gt;1&lt;/sub&gt;</th>
<th>B&lt;sub&gt;1&lt;/sub&gt;B&lt;sub&gt;2&lt;/sub&gt;</th>
<th>B&lt;sub&gt;2&lt;/sub&gt;B&lt;sub&gt;2&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0</td>
<td>( a_B (1 + k_{1B}) )</td>
<td>( a_B (1 + k_{2B}) )</td>
<td>( 2a_B )</td>
<td></td>
</tr>
<tr>
<td>A&lt;sub&gt;2&lt;/sub&gt;A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>( a_A (1 + k_{1A}) ) + ( a_B (1 + k_{1B}) ) + ( \epsilon_{2121} )</td>
<td>( a_A (1 + k_{2A}) ) + ( a_B (1 + k_{1B}) ) + ( \epsilon_{2121} )</td>
<td>( a_A (1 + k_{2A}) ) + ( a_B (1 + k_{2B}) ) + ( \epsilon_{2112} )</td>
<td>( a_A (1 + k_{1A}) ) + ( 2a_B ) + ( \epsilon_{2122} )</td>
<td></td>
</tr>
<tr>
<td>A&lt;sub&gt;1&lt;/sub&gt;A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>( a_A (1 + k_{2A}) ) + ( a_B (1 + k_{1B}) ) + ( \epsilon_{1221} )</td>
<td>( a_A (1 + k_{2A}) ) + ( a_B (1 + k_{1B}) ) + ( \epsilon_{1221} )</td>
<td>( a_A (1 + k_{2A}) ) + ( a_B (1 + k_{2B}) ) + ( \epsilon_{1212} )</td>
<td>( a_A (1 + k_{1A}) ) + ( 2a_B ) + ( \epsilon_{1222} )</td>
<td></td>
</tr>
<tr>
<td>A&lt;sub&gt;2&lt;/sub&gt;A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2( a_A ) + ( a_B (1 + k_{1B}) ) + ( \epsilon_{2221} )</td>
<td>2( a_A ) + ( a_B (1 + k_{1B}) ) + ( \epsilon_{2221} )</td>
<td>2( a_A ) + ( a_B (1 + k_{2B}) ) + ( \epsilon_{2212} )</td>
<td>2( a_A ) + ( 2a_B ) + ( \epsilon_{2222} )</td>
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</table>
Table 2: Genotypic deviations for two-locus genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotypic deviation</th>
</tr>
</thead>
</table>
| $A_1A_1B_1B_1$ | $-p_{2A}a_A(2 + p_{1A}(k_{1A} + k_{2A}))$  
|            | $-p_{2B}a_B(2 + p_{1B}(k_{1B} + k_{2B}))$  
|            | $-(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
|            | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$  
|            | $+ p_{2A}p_{1B}p_{2B}e_{2211} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})$  
| $A_1A_1B_2B_1$ | $-p_{2A}a_A(2 + p_{1A}(k_{1A} + k_{2A}))$  
|            | $+a_B(1 + k_{1B})$  
|            | $-p_{2B}(2 + p_{1B}(k_{1B} + k_{2B})))$  
|            | $-(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
|            | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$  
|            | $+ p_{2A}p_{1B}p_{2B}e_{2211} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})$  
| $A_1A_1B_2B_2$ | $-p_{2A}a_A(2 + p_{1A}(k_{1A} + k_{2A}))$  
|            | $+p_{1B}a_B(2 - p_{2B}(k_{1B} + k_{2B}))$  
|            | $-(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
|            | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$  
|            | $+ p_{2A}p_{1B}p_{2B}e_{2211} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})$  
| $A_1A_2B_1B_1$ | $a_A((1 + k_{1A})$  
|            | $-p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))$  
|            | $-p_{2B}a_B(2 + p_{1B}(k_{1B} + k_{2B}))$  
|            | $-(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
|            | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$  
|            | $+ p_{2A}p_{1B}p_{2B}e_{2211} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})$  
| $A_2A_1B_1B_1$ | $a_A((1 + k_{1A})$  
|            | $-p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))$  
|            | $-p_{2B}a_B(2 + p_{1B}(k_{1B} + k_{2B}))$  
|            | $-(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
|            | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$  
|            | $+ p_{2A}p_{1B}p_{2B}e_{2211} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})$  

4.28
\[
\begin{align*}
A_{2}A_{1}B_{2}B_{1} & : \quad a_{A}((1 + k_{1A}) \nonumber \\
& - p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))) \nonumber \\
& + a_{B}((1 + k_{1B}) \nonumber \\
& - p_{2B}(2 + p_{1B}(k_{1B} + k_{2B}))) \nonumber \\
& - ((p_{1A}p_{2A}p_{1B}p_{2B} - 1)\epsilon_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{2122} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{1212} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{1222} + p_{2A}p_{1B}p_{2B}\epsilon_{2221} + p_{2A}p_{1B}p_{2B}\epsilon_{2212} + p_{2A}p_{2B}^{2}\epsilon_{2222})
\end{align*}
\]

\[
\begin{align*}
A_{2}A_{1}B_{2} & : \quad a_{A}((1 + k_{1A}) \nonumber \\
& - p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))) \nonumber \\
& + a_{B}((1 + k_{2B}) \nonumber \\
& - p_{2B}(2 + p_{1B}(k_{1B} + k_{2B}))) \nonumber \\
& - ((p_{1A}p_{2A}p_{1B}p_{2B} - 1)\epsilon_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{2122} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{1212} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{1222} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2221} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2212} + p_{2A}p_{2B}^{2}\epsilon_{2222})
\end{align*}
\]

\[
\begin{align*}
A_{3}A_{1}B_{2} & : \quad a_{A}((1 + k_{1A}) \nonumber \\
& - p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))) \nonumber \\
& + p_{1B}a_{B}(2 - p_{2B}(k_{1B} + k_{2B})) \nonumber \\
& - ((p_{1A}p_{2A}p_{1B}p_{2B} - 1)\epsilon_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{2122} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{1212} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{1222} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2221} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2212} + p_{2A}p_{2B}^{2}\epsilon_{2222})
\end{align*}
\]

\[
\begin{align*}
A_{1}A_{2}B_{1} & : \quad a_{A}((1 + k_{1A}) \nonumber \\
& - p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))) \nonumber \\
& - p_{2B}a_{B}(2 + p_{1B}(k_{1B} + k_{2B})) \nonumber \\
& - ((p_{1A}p_{2A}p_{1B}p_{2B} - 1)\epsilon_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{2122} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{1212} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{1222} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2221} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2212} + p_{2A}p_{2B}^{2}\epsilon_{2222})
\end{align*}
\]

\[
\begin{align*}
A_{1}A_{2}B_{2} & : \quad a_{A}((1 + k_{2A}) \nonumber \\
& - p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))) \nonumber \\
& + a_{B}((1 + k_{1B}) \nonumber \\
& - p_{2B}(2 + p_{1B}(k_{1B} + k_{2B}))) \nonumber \\
& - ((p_{1A}p_{2A}p_{1B}p_{2B} - 1)\epsilon_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{2122} + (p_{1A}p_{2A}p_{1B}p_{2B} - 1)\epsilon_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2A}p_{2B}^{2}\epsilon_{2122} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2221} + p_{2A}p_{1B}p_{2B}^{2}\epsilon_{2212} + p_{2A}p_{2B}^{2}\epsilon_{2222})
\end{align*}
\]
| $A_1 A_2 B_1 B_2$ | $a_A((1 + k_{2A})$
| | $- p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))$
| | $+ a_B((1 + k_{2B})$
| | $- p_{2B}(2 + p_{1B}(k_{1B} + k_{2B}))$
| | $- (p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + p_{1A} p_{2A} p_{2B} p^2_{2B} e_{2122})$
| | $+ p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + (p_{1A} p_{2A} p_{1B} p_{2B} - 1)e_{2122} + p_{1A} p_{2A} p_{2B} e_{2122}$
| | $+ p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{2B} e_{2222})$
| $A_1 A_2 B_2 B_2$ | $a_A((1 + k_{2A})$
| | $- p_{2A}(2 + p_{1A}(k_{1A} + k_{2A}))$
| | $+ p_{1B} a_B((2 + p_{2B}(k_{1B} + k_{2B})$
| | $- (p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + p_{1A} p_{2A} p_{2B} e_{2122})$
| | $+ p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + (p_{1A} p_{2A} p_{2B} - 1)e_{2122}$
| | $+ p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{2B} e_{2222})$
| $A_2 A_2 B_1 B_1$ | $p_{1A} a_A((2 - p_{2A}(k_{1A} + k_{2A})$
| | $- p_{2A} a_B((2 + p_{1B}(k_{1B} + k_{2B})$
| | $- (p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + p_{1A} p_{2A} p_{2B} e_{2122})$
| | $+ p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + (p_{1A} p_{2A} p_{2B} - 1)e_{2122}$
| | $+ p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{2B} e_{2222})$
| $A_2 A_2 B_1 B_2$ | $p_{1A} a_A((2 - p_{2A}(k_{1A} + k_{2A})$
| | $+ a_B((1 + k_{2B})$
| | $- p_{2B}(2 + p_{1B}(k_{1B} + k_{2B}))$
| | $- (p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + p_{1A} p_{2A} p_{2B} e_{2122})$
| | $+ p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B} e_{2122} + (p_{1A} p_{2A} p_{2B} - 1)e_{2122}$
| | $+ p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{1B} p_{2B} e_{2211} + p_{2A} p_{2B} e_{2222})$
| $A_2A_2B_2B_2$ | $p_{1A} a_A (2 - p_{2A} (k_{1A} + k_{2A}))$
$+ p_{1B} a_B (2 - p_{2B} (k_{1B} + k_{2B}))$
$- (p_{1A} p_{2A} p_{1B} p_{2B} \varepsilon_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} \varepsilon_{2112} + p_{1A} p_{2A} p_{2B}^2 \varepsilon_{2122}$
$+ p_{1A} p_{2A} p_{1B} p_{2B} \varepsilon_{1221} + p_{1A} p_{2A} p_{1B} p_{2B} \varepsilon_{1212} + p_{1A} p_{2A} p_{2B}^2 \varepsilon_{1222}$
$+ p_{2A}^2 p_{1B} p_{2B} \varepsilon_{2221} + p_{2A}^2 p_{1B} p_{2B} \varepsilon_{2212} + (p_{2A} p_{2B}^2 - 1) \varepsilon_{2222}$ |
Table 3: Female breeding values for two-locus genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Female BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1B_1B_1$</td>
<td>$-2p_{2a}\alpha_{fa} - 2p_{2b}\alpha_{fb} + \frac{1}{2}(p_{1a}p_{2a}p_{1b}p_{2b}e_{2121} + p_{1a}p_{2a}p_{1b}p_{2b}e_{2112} + p_{1a}p_{2a}p_{2b}^2e_{2122} + p_{1a}p_{2a}p_{1b}p_{2b}e_{1221} + p_{1a}p_{2a}p_{1b}p_{2b}e_{1212} + p_{1a}p_{2a}p_{2b}^2e_{1222} + 2p_{2a}p_{1b}p_{2b}e_{2221} + 2p_{2a}p_{1b}p_{2b}e_{2212} + p_{2a}p_{2b}^2e_{2222})$</td>
</tr>
<tr>
<td>$A_1A_1B_2B_1$</td>
<td>$-2p_{2a}\alpha_{fa} + (p_{1b} - p_{2b})\alpha_{fb} - \frac{1}{2}(2(p_{1a}p_{2a}p_{1b}p_{2b}e_{2121} + p_{1a}p_{2a}p_{1b}p_{2b}e_{2112} + p_{1a}p_{2a}p_{2b}^2e_{2122} + 2p_{2a}p_{1b}p_{2b}e_{2221} + 2p_{2a}p_{1b}p_{2b}e_{2212} + p_{2a}p_{2b}^2e_{2222})$</td>
</tr>
<tr>
<td>$A_1A_1B_2B_2$</td>
<td>$-2p_{2a}\alpha_{fa} + (p_{1b} - p_{2b})\alpha_{fb} - \frac{1}{2}(2(p_{1a}p_{2a}p_{1b}p_{2b}e_{2121} + p_{1a}p_{2a}p_{1b}p_{2b}e_{2112} + p_{1a}p_{2a}p_{2b}^2e_{2122} + 2p_{2a}p_{1b}p_{2b}e_{2221} + 2p_{2a}p_{1b}p_{2b}e_{2212} + p_{2a}p_{2b}^2e_{2222})$</td>
</tr>
<tr>
<td>$A_1A_2B_1B_2$</td>
<td>$-2p_{2a}\alpha_{fa} + 2p_{1b}\alpha_{fb} - \frac{1}{2}(2(p_{1a}p_{2a}p_{1b}p_{2b}e_{2121} + p_{1a}p_{2a}p_{1b}p_{2b}e_{2112} + p_{1a}p_{2a}p_{2b}^2e_{2122} + 2p_{2a}p_{1b}p_{2b}e_{2221} + 2p_{2a}p_{1b}p_{2b}e_{2212} + p_{2a}p_{2b}^2e_{2222})$</td>
</tr>
<tr>
<td>$A_2A_1B_1B_1$</td>
<td>$(p_{1A} - p_{2A})\alpha_{fA} - 2p_{2B}\alpha_{fB}$</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>$-(2p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2B}(2p_{2A}p_{1B} - 1)e_{2112} + 2p_{1A}p_{2A}p_{2B}^2e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ 2p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)e_{1212} + 2p_{1A}p_{2A}p_{2B}^2e_{1222}$</td>
</tr>
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<td>$+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{2B}(2p_{2A}p_{1B} - 1)e_{2212} + 2p_{2A}p_{2B}^2e_{2222}$)</td>
</tr>
<tr>
<td>$A_2A_1B_2B_1$</td>
<td>$(p_{1A} - p_{2A})\alpha_{fA} + (p_{1B} - p_{2B})\alpha_{fB}$</td>
</tr>
<tr>
<td></td>
<td>$-\frac{1}{2}(p_{1A}p_{1B}(4p_{2A}p_{2B} - 1)e_{2121} + p_{1A}p_{2B}(4p_{2A}p_{1B} - 1)e_{2112} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)e_{2122}$</td>
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<tr>
<td></td>
<td>$+ p_{2A}p_{1B}(4p_{1A}p_{2B} - 1)e_{1221} + p_{2A}p_{2B}(4p_{1A}p_{1B} - 1)e_{1212} + p_{2A}p_{2B}(4p_{1A}p_{2B} - 1)e_{1222}$</td>
</tr>
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<td></td>
<td>$+ p_{2A}p_{1B}(4p_{2A}p_{2B} - 1)e_{2221} + p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)e_{2212} + p_{2A}p_{2B}(4p_{2A}p_{2B} - 1)e_{2222}$)</td>
</tr>
<tr>
<td>$A_2A_1B_2B_2$</td>
<td>$(p_{1A} - p_{2A})\alpha_{fA} + 2p_{1B}\alpha_{fB}$</td>
</tr>
<tr>
<td></td>
<td>$-(p_{1A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2121} + 2p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2122}$</td>
</tr>
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<td></td>
<td>$+ p_{2A}p_{1B}(2p_{2A}p_{1B} - 1)e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{2A}p_{2B}(2p_{1A}p_{2B} - 1)e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2221} + 2p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2222}$)</td>
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4.33
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<tr>
<th>$A_1A_2B_1B_2$</th>
<th>$(p_{1A} - p_{2A})\alpha_{fA} - 2p_{2B}\alpha_{fB}$</th>
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<tbody>
<tr>
<td></td>
<td>$-(2p_{1A}p_{2A}p_{1B}p_{2B}\varepsilon_{2121} + p_{1A}p_{2B}(2p_{2A}p_{1B} - 1)\varepsilon_{2112} + 2p_{1A}p_{2A}p_{2B}^2\varepsilon_{2122}$</td>
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<td></td>
<td>$+2p_{1A}p_{2A}p_{1B}p_{2B}\varepsilon_{2221} + p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)\varepsilon_{2112} + 2p_{1A}p_{2A}p_{2B}^2\varepsilon_{2222}$</td>
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<td></td>
<td>$+2p_{2A}^2p_{1B}p_{2B}\varepsilon_{2222} + p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)\varepsilon_{2212} + 2p_{2A}^2p_{2B}^2\varepsilon_{2222}$</td>
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<table>
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<tr>
<th>$A_1A_2B_1B_2$</th>
<th>$-(p_{1A} - p_{2A})\alpha_{fA} - (p_{1B} - p_{2B})\alpha_{fB}$</th>
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<tr>
<td></td>
<td>$-rac{1}{2}(p_{1A}p_{1B}(4p_{2A}p_{2B} - 1)\varepsilon_{2121} + p_{1A}p_{2B}(4p_{2A}p_{1B} - 1)\varepsilon_{2112} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\varepsilon_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+p_{2A}p_{1B}(4p_{1A}p_{2B} - 1)\varepsilon_{2221} + p_{2A}p_{2B}(4p_{1A}p_{1B} - 1)\varepsilon_{2112} + p_{2A}p_{2B}(4p_{1A}p_{2B} - 1)\varepsilon_{2222}$</td>
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<td></td>
<td>$+p_{2A}p_{1B}(4p_{2A}p_{2B} - 1)\varepsilon_{2221} + p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)\varepsilon_{2212} + p_{2A}p_{2B}(4p_{2A}p_{2B} - 1)\varepsilon_{2222}$</td>
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<table>
<thead>
<tr>
<th>$A_1A_2B_1B_2$</th>
<th>$(p_{1A} - p_{2A})\alpha_{fA} + (p_{1B} - p_{2B})\alpha_{fB}$</th>
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<tr>
<td></td>
<td>$-(p_{1A}p_{1B}(4p_{2A}p_{2B} - 1)\varepsilon_{2121} + p_{1A}p_{2B}(4p_{2A}p_{1B} - 1)\varepsilon_{2112} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\varepsilon_{2122}$</td>
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<td></td>
<td>$+p_{2A}p_{1B}(4p_{1A}p_{2B} - 1)\varepsilon_{2221} + p_{2A}p_{2B}(4p_{1A}p_{1B} - 1)\varepsilon_{2112} + p_{2A}p_{2B}(4p_{1A}p_{2B} - 1)\varepsilon_{2222}$</td>
</tr>
<tr>
<td></td>
<td>$+p_{2A}p_{1B}(4p_{2A}p_{2B} - 1)\varepsilon_{2221} + p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)\varepsilon_{2212} + p_{2A}p_{2B}(4p_{2A}p_{2B} - 1)\varepsilon_{2222}$</td>
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<table>
<thead>
<tr>
<th>$A_1A_2B_1B_2$</th>
<th>$(p_{1A} - p_{2A})\alpha_{fA} + 2p_{1B}\alpha_{fB}$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$-(p_{1A}p_{1B}(2p_{2A}p_{2B} - 1)\varepsilon_{2121} + 2p_{1A}p_{2A}p_{1B}p_{2B}\varepsilon_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)\varepsilon_{2112}$</td>
</tr>
<tr>
<td></td>
<td>$+p_{2A}p_{1B}(2p_{1A}p_{2B} - 1)\varepsilon_{2221} + 2p_{1A}p_{2A}p_{1B}p_{2B}\varepsilon_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B} - 1)\varepsilon_{2222}$</td>
</tr>
<tr>
<td></td>
<td>$+p_{2A}p_{1B}(2p_{2A}p_{2B} - 1)\varepsilon_{2221} + 2p_{2A}^2p_{1B}p_{2B}\varepsilon_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B} - 1)\varepsilon_{2222}$</td>
</tr>
</tbody>
</table>
\[
\begin{array}{|c|c|}
\hline
A_2 A_3 B_1 A_1 & 2 p_{1A} \alpha_{A} - 2 p_{2B} \alpha_{B} + \\
& -2(p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2B}(p_{2A} p_{1B} - 1) e_{2112} + p_{1A} p_{2A} p_{2B}^2 e_{2122} + p_{2A} p_{1B} p_{2B} e_{2221} + p_{2A} p_{1B}(p_{2A} p_{1B} - 1) e_{2212} + p_{2A} p_{2B}^2 e_{2222}) \\
\hline
A_2 A_3 B_1 B_1 & 2 p_{1A} \alpha_{A} + (p_{1B} - p_{2B}) \alpha_{B} + \\
& -(p_{1A} p_{1B}(2 p_{2A} p_{2B} - 1) e_{2121} + p_{1A} p_{2B}(2 p_{2A} p_{1B} - 1) e_{2112} + p_{1A} p_{2B}(2 p_{2A} p_{2B} - 1) e_{2122} + 2(p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B}^2 e_{2122}) + p_{2A} p_{1B}(2 p_{2A} p_{2B} - 1) e_{2221} + p_{2A} p_{2B}(2 p_{2A} p_{1B} - 1) e_{2212} + p_{2A} p_{2B}(2 p_{2A} p_{2B} - 1) e_{2222}) \\
\hline
A_2 A_3 B_1 B_2 & 2 p_{1A} \alpha_{A} + (p_{1B} - p_{2B}) \alpha_{B} + \\
& -(p_{1A} p_{1B}(2 p_{2A} p_{2B} - 1) e_{2121} + p_{1A} p_{2B}(2 p_{2A} p_{1B} - 1) e_{2112} + p_{1A} p_{2B}(2 p_{2A} p_{2B} - 1) e_{2122} + 2(p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} p_{2B}^2 e_{2122}) + p_{2A} p_{1B}(2 p_{2A} p_{2B} - 1) e_{2221} + p_{2A} p_{2B}(2 p_{2A} p_{1B} - 1) e_{2212} + p_{2A} p_{2B}(2 p_{2A} p_{2B} - 1) e_{2222}) \\
\hline
A_2 A_3 B_2 B_2 & 2 p_{1A} \alpha_{A} + 2 p_{1B} \alpha_{B} + \\
& -2(p_{1A} p_{1B}(2 p_{2A} p_{2B} - 1) e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2B}(2 p_{2A} p_{2B} - 1) e_{2122} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2121} + p_{1A} p_{2A} p_{2B}^2 e_{2122} + p_{2A} p_{1B}(2 p_{2A} p_{2B} - 1) e_{2221} + p_{2A} p_{2B}(2 p_{2A} p_{2B} - 1) e_{2222}) \\
\hline
\end{array}
\]

where \( \alpha_{A} = a_{A}(1 + k_{1A} p_{1A} - k_{2A} p_{2A}) \), \( \alpha_{B} = a_{B}(1 + k_{1B} p_{1B} - k_{2B} p_{2B}) \), \( \alpha_{mA} = a_{A}(1 + k_{2A} p_{1A} - k_{1A} p_{2A}) \), and \( \alpha_{mB} = a_{B}(1 + k_{2B} p_{1B} - k_{1B} p_{2B}) \)
Table 4: Male breeding values for two-locus genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Male BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1B_1$</td>
<td>$-2p_{2A}\alpha_{mA} - 2p_{2B}\alpha_{mB}$</td>
</tr>
<tr>
<td></td>
<td>$-2(p_{2A}p_{2B}(p_{1A}p_{1B} - 1)e_{2111} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$</td>
</tr>
</tbody>
</table>
|          | $+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$ |}

| $A_1A_2B_1$ | $-2p_{2A}\alpha_{mA} + (p_{1B} - p_{2B})\alpha_{mB}$                  |
|             | $-(p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)e_{2111} + p_{2A}p_{1B}(2p_{1A}p_{2B} - 1)e_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B} - 1)e_{2122}$ |
|             | $+ 2(p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$ |
|             | $+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$ |}

| $A_1A_1B_2$ | $-2p_{2A}\alpha_{mA} + (p_{1B} - p_{2B})\alpha_{mB}$                  |
|             | $-(p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)e_{2111} + p_{2A}p_{1B}(2p_{1A}p_{2B} - 1)e_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B} - 1)e_{2122}$ |
|             | $+ 2(p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$ |
|             | $+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$ |}

<p>| $A_1A_2B_2$ | $-2p_{2A}\alpha_{mA} + 2p_{1B}\alpha_{mB}$                           |
|             | $-2(p_{1A}p_{2A}p_{1B}p_{2B}e_{2111} + p_{2A}p_{1B}(p_{1A}p_{2B} - 1)e_{2112} + p_{2A}p_{2B}(p_{1A}p_{2B} - 1)e_{2122}$ |
|             | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222}$ |
|             | $+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$ |</p>
<table>
<thead>
<tr>
<th>Case</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
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<td>$A_2A_1B_1B_1$</td>
<td>$(p_{1A} - p_{2A}) \alpha_{mA} - 2p_{2B} \alpha_{mB} - (p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)\epsilon_{2121} + 2p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + 2p_{1A}p_{2A}p_{2B}^2\epsilon_{2122} + p_{1A}p_{2B}(2p_{2A}p_{1B} - 1)\epsilon_{1221} + 2p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{1212} + 2p_{1A}p_{2A}p_{2B}^2\epsilon_{1222})$</td>
</tr>
<tr>
<td>$A_2A_1B_2B_1$</td>
<td>$(p_{1A} - p_{2A}) \alpha_{mA} + (p_{1B} - p_{2B}) \alpha_{mB} - \frac{1}{2}(p_{2A}p_{2B}(4p_{1A}p_{1B} - 1)\epsilon_{2121} + p_{2A}p_{1B}(4p_{1A}p_{2B} - 1)\epsilon_{2112} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{2212} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{2222} + p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)\epsilon_{1221} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{1212} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{1222})$</td>
</tr>
<tr>
<td>$A_2A_1B_1B_2$</td>
<td>$(p_{1A} - p_{2A}) \alpha_{mA} + (p_{1B} - p_{2B}) \alpha_{mB} - \frac{1}{2}(p_{2A}p_{2B}(4p_{1A}p_{1B} - 1)\epsilon_{2121} + p_{2A}p_{1B}(4p_{1A}p_{2B} - 1)\epsilon_{2112} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{2212} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{2222} + p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)\epsilon_{1221} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{1212} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)\epsilon_{1222})$</td>
</tr>
<tr>
<td>$A_2A_1B_2B_2$</td>
<td>$(p_{1A} - p_{2A}) \alpha_{mA} + 2p_{2B} \alpha_{mB} - (2p_{1A}p_{2B}p_{1B}p_{2B}\epsilon_{2212} + 2p_{1A}p_{2B}p_{2B}\epsilon_{2112} + p_{1A}p_{2B}(2p_{1A}p_{2B} - 1)\epsilon_{2122} + 2p_{1A}p_{2A}p_{2B}p_{1B}p_{2B}\epsilon_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)\epsilon_{2122} + 2p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)\epsilon_{1222} + 2p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)\epsilon_{1222} + 2p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)\epsilon_{1222})$</td>
</tr>
<tr>
<td>$A_1A_2B_1B_1$</td>
<td>$(p_{1A} - p_{2A}) \alpha_{mA} - 2p_{2B} \alpha_{mB} - (p_{2A}p_{2B}(2p_{1A}p_{1B} - 1)\epsilon_{2121} + 2p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{2112} + 2p_{1A}p_{2A}p_{2B}^2\epsilon_{2122} + p_{1A}p_{2B}(2p_{2A}p_{1B} - 1)\epsilon_{1221} + 2p_{1A}p_{2A}p_{1B}p_{2B}\epsilon_{1212} + 2p_{1A}p_{2A}p_{2B}^2\epsilon_{1222})$</td>
</tr>
<tr>
<td>$A_1A_2B_2B_1$</td>
<td>$(p_{1A} - p_{2A})\alpha_{mA} + (p_{1B} - p_{2B})\alpha_{mB}$</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
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<td>$- \frac{1}{2}(p_{2A} - p_{2A})(4p_{1A}p_{1B} - 1)e_{2121} + p_{2A}p_{1B}(4p_{1A} - 1)e_{2112} + p_{2A}p_{2B}(4p_{1A}p_{2B} - 1)e_{2122}$</td>
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<td></td>
<td>$+ p_{2A}p_{1B}(4p_{2A}p_{1B} - 1)e_{1221} + p_{1A}p_{1B}(4p_{2A}p_{2B} - 1)e_{1212} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)e_{1222}$</td>
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<tr>
<td></td>
<td>$+ p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)e_{2221} + p_{2A}p_{1B}(4p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(4p_{2A}p_{2B} - 1)e_{2222}$</td>
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</table>

<table>
<thead>
<tr>
<th>$A_1A_2B_1B_2$</th>
<th>$(p_{1A} - p_{2A})\alpha_{mA} + (p_{1B} - p_{2B})\alpha_{mB}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$- \frac{1}{2}(p_{2A} - p_{2A})(4p_{1A}p_{1B} - 1)e_{2121} + p_{2A}p_{1B}(4p_{1A} - 1)e_{2112} + p_{2A}p_{2B}(4p_{1A}p_{2B} - 1)e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}(4p_{2A}p_{1B} - 1)e_{1221} + p_{1A}p_{1B}(4p_{2A}p_{2B} - 1)e_{1212} + p_{1A}p_{2B}(4p_{2A}p_{2B} - 1)e_{1222}$</td>
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<tr>
<td></td>
<td>$+ p_{2A}p_{2B}(4p_{2A}p_{1B} - 1)e_{2221} + p_{2A}p_{1B}(4p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(4p_{2A}p_{2B} - 1)e_{2222}$</td>
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<tr>
<th>$A_1A_2B_2B_2$</th>
<th>$(p_{1A} - p_{2A})\alpha_{mA} + 2p_{1B}\alpha_{mB}$</th>
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<td></td>
<td>$- 2p_1A p_{2A}p_{1B}P_{2B}e_{2121} + p_1A p_{1B}(2p_1A p_{2B} - 1)e_{2112} + p_2A P_{1B}(2p_1A p_{2B} - 1)e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ 2p_1A P_{2A} p_{1B}P_{2B}e_{2121} + p_1A p_{1B}(2p_2A P_{2B} - 1)e_{1212} + p_1A P_{2B}(2p_2A P_{2B} - 1)e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ 2p_2A P_{2B} p_{1B}P_{2B}e_{2221} + p_2A P_{2B}(2p_2A P_{2B} - 1)e_{2212} + p_2A P_{2B}(2p_2A P_{2B} - 1)e_{2222}$</td>
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<tr>
<th>$A_2A_2B_1B_1$</th>
<th>$2p_{1A}\alpha_{mA} - 2p_{2B}\alpha_{mB}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$- 2(p_{1A} p_{2A} p_{1B} P_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} P_{2B}^{2} e_{2122})$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A} p_{2B}(2p_{2A} p_{1B} - 1)e_{1221} + p_{1A} p_{2A} p_{1B} p_{2B} e_{1212} + p_{1A} p_{2A} p_{2B}^{2} e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A} p_{2B}(2p_{2A} p_{1B} - 1)e_{2221} + p_{2A} p_{1B} p_{2B}^{2} e_{2212} + p_{2A} p_{2B}^{2} e_{2222}$</td>
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<tr>
<th>$A_2A_2B_2B_1$</th>
<th>$2p_{1A}\alpha_{mA} + (p_{1B} - p_{2B})\alpha_{mB}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$-(2p_{1A} p_{2A} p_{1B} P_{2B} e_{2121} + p_{1A} p_{2A} p_{1B} p_{2B} e_{2112} + p_{1A} p_{2A} P_{2B}^{2} e_{2122})$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A} p_{2B}(2p_{2A} p_{1B} - 1)e_{1221} + p_{1A} p_{2A} p_{1B} p_{2B} e_{1212} + p_{1A} p_{2A} p_{2B}^{2} e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A} p_{2B}(2p_{2A} p_{1B} - 1)e_{2221} + p_{2A} p_{1B} p_{2B}^{2} e_{2212} + p_{2A} p_{2B}^{2} e_{2222}$</td>
</tr>
</tbody>
</table>
\[2p_1A\alpha_{mA} + (p_1B - p_2B)\alpha_{mB} \]

\[-(2(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122})
+ p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)e_{1211} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)e_{1212} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)e_{1222}
+ p_{2A}p_{2B}(2p_{2A}p_{1B} - 1)e_{2221} + p_{2A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2222})\]

\[2p_1A\alpha_{mA} + 2p_1B\alpha_{mB} \]

\[-2(p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}
+ p_{1A}p_{2A}p_{1B}p_{2B}^2e_{2122} + p_{1A}p_{2A}p_{1B}(p_{2A}p_{2B} - 1)e_{1212} + p_{1A}p_{2B}(p_{2A}p_{2B} - 1)e_{1222}
+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}(p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(p_{2A}p_{2B} - 1)e_{2222})\]

where \(\alpha_{fA} = a_A(1 + k_{1A}p_{1A} - k_{2A}p_{2A})\), \(\alpha_{fB} = a_B(1 + k_{1B}p_{1B} - k_{2B}p_{2B})\), \(\alpha_{mA} = a_A(1 + k_{1A}p_{1A} - k_{1A}p_{2A})\) and \(\alpha_{mB} = a_B(1 + k_{2B}p_{1B} - k_{1B}p_{2B})\)
Table 5: Female dominance deviations for two-locus genotypes

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<th>Genotype</th>
<th>Female dom dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1B_1B_1$</td>
<td>$p_{2A}a_A(k_{1A}p_{1A} - k_{2A}(1 + p_{2A})) + p_{2A}b(k_{1B}p_{1B} - k_{2B}(1 + p_{2B}))$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{2B}^2e_{2222}$</td>
</tr>
<tr>
<td>$A_1A_1B_2B_1$</td>
<td>$p_{2A}a_A(k_{1A}p_{1A} - k_{2A}(1 + p_{2A})) + a_B(k_{1B}p_{1B} - k_{2B}p_{2B}^2)$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}p_{2B}(p_{1A}p_{1B} - 1)e_{1221} + p_{2A}p_{2B}(p_{1A}p_{1B} - 1)e_{1212} + p_{2A}p_{2B}(p_{1A}p_{2B} - 1)e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$</td>
</tr>
<tr>
<td>$A_1A_1B_1B_2$</td>
<td>$p_{2A}a_A(k_{1A}p_{1A} - k_{2A}(1 + p_{2A})) + a_B(-k_{1B}p_{1B} + k_{2B}(1 - p_{2B}^2))$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}(p_{1A}p_{2B} - 1)e_{1221} + p_{2A}p_{2B}(p_{1A}p_{1B} - 1)e_{1212} + p_{2A}p_{2B}(p_{1A}p_{2B} - 1)e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$</td>
</tr>
<tr>
<td>$A_1A_1B_2B_2$</td>
<td>$p_{2A}a_A(k_{1A}p_{1A} - k_{2A}(1 + p_{2A})) + p_{1B}a_B(k_{1B}(1 + p_{1B}) + k_{2B}p_{2B})$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}(p_{1A}p_{2B} - 2)e_{1221} + p_{1A}p_{2A}p_{2B}^2e_{1212} + p_{2A}p_{2B}(p_{1A}p_{2B} - 2)e_{1222}$</td>
</tr>
<tr>
<td></td>
<td>$+ p_{2A}p_{1B}p_{2B}^2e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222}$</td>
</tr>
</tbody>
</table>
| $A_2A_1B_1$ | $A_A(k_1(1-p_{11}^2)-k_{1A}p_{1A}^2)+p_{2B}a_B(k_{1B}p_{1B}-k_{2B}(1+p_{2B}))$
| | $+p_{1A}P_{2A}P_{1B}P_{2B}e_{2121}+p_{1A}P_{2B}(p_{2A}P_{1B}-1)e_{2122}+p_{1A}P_{2A}P_{2B}^2e_{2122}$
| | $+p_{1A}P_{2A}P_{1B}P_{2B}e_{1221}+p_{2A}P_{2B}(p_{1A}P_{1B}-1)e_{1221}+p_{1A}P_{2A}P_{2B}^2e_{1222}$
| | $+p_{2A}P_{1B}p_{2B}e_{2221}+p_{2A}P_{2B}(p_{2A}P_{1B}-1)e_{2212}+p_{2A}P_{2B}^2e_{2222}$
| $A_2A_1B_2$ | $A_A(k_1(1-p_{11}^2)-k_{1A}p_{1A}^2)+a_B(k_{1B}(1-p_{11}^2)-k_{2B}p_{2B}^2)$
| | $+\frac{1}{2}(2+p_{1A}P_{1B}(2p_{2A}P_{2B}+1))e_{2121}+p_{1A}P_{2B}(2p_{2A}P_{1B}-1)e_{2121}+p_{1A}P_{2B}(2p_{2A}P_{2B}-1)e_{2122}$
| | $+p_{2A}P_{1B}(2p_{1A}P_{2B}-1)e_{1221}+p_{2A}P_{2B}(2p_{1A}P_{1B}-1)e_{1221}+p_{1A}P_{2B}(2p_{1A}P_{2B}-1)e_{1222}$
| | $+p_{2A}P_{1B}(2p_{2A}P_{2B}-1)e_{2221}+p_{2A}P_{2B}(2p_{2A}P_{1B}-1)e_{2212}+p_{2A}P_{2B}(2p_{2A}P_{2B}^1-1)e_{2222}$
| $A_2A_1B_2$ | $A_A(k_1(1-p_{11}^2)-k_{1A}p_{1A}^2)+a_B(-k_{1B}P_{1B}^1+k_{2B}(1-p_{2B}^2))$
| | $+\frac{1}{2}(p_{1A}P_{1B}(2p_{2A}P_{2B}-1))e_{2121}+(2+p_{1A}P_{2B}(2p_{2A}P_{1B}-1))e_{2121}+p_{1A}P_{2B}(2p_{2A}P_{2B}^1-1)e_{2122}$
| | $+p_{2A}P_{1B}(2p_{1A}P_{2B}-1)e_{1221}+p_{2A}P_{2B}(2p_{1A}P_{1B}-1)e_{1221}+p_{1A}P_{2B}(2p_{1A}P_{2B}^1-1)e_{1222}$
| | $+p_{2A}P_{1B}(2p_{2A}P_{2B}-1)e_{2221}+p_{2A}P_{2B}(2p_{2A}P_{1B}-1)e_{2212}+p_{2A}P_{2B}(2p_{2A}P_{2B}^1-1)e_{2222}$
| $A_2A_1B_2$ | $A_A(k_1(1-p_{11}^2)-k_{1A}p_{1A}^2)+p_{1B}a_B(-k_{1B}(1+p_{1B})+k_{2B}P_{2B}^1)$
| | $+p_{1A}P_{1B}(p_{2A}P_{2B}-1)e_{2121}+p_{1A}P_{2A}P_{1B}P_{2B}^1e_{2112}+(1+p_{1A}P_{2B}(p_{2A}P_{2B}-1))e_{2122}$
| | $+p_{2A}P_{1B}(p_{1A}P_{2B}-1)e_{2212}+p_{1A}P_{2A}P_{1B}P_{2B}^2e_{1212}+p_{2A}P_{2B}(p_{1A}P_{2B}-1)e_{1222}$
| | $+p_{2A}P_{1B}(p_{2A}P_{2B}-1)e_{2221}+p_{2A}P_{2B}(p_{2A}P_{2B}^1-1)e_{2212}+p_{2A}P_{2B}(p_{2A}P_{2B}^1-1)e_{2222}$

4.41
| $A_1A_2B_1$ | $a_A(-k_{1A}a_{1A}^2 + k_{2A}(1 - p_{2A})) + p_{2A}a_b(k_{1B}p_{1B} - k_{2B}(1 + p_{2B}))$  

$+ p_{1A}p_{2A}p_{1B}P_{2B}e_{212} + p_{1A}p_{2B}(p_{2A}p_{1B} - 1)e_{2112} + p_{1A}p_{2B}P_{2B}e_{2121}$  

$+ p_{1A}p_{2A}p_{1B}P_{2B}e_{2122} + p_{1A}p_{2B}(p_{2A}p_{1B} - 1)e_{2121} + p_{1A}p_{2B}P_{2B}e_{2212}$  

$+ p_{2A}^2p_{1B}P_{2B}e_{2221} + p_{2A}p_{2B}(p_{2A}p_{1B} - 1)e_{2121} + p_{2A}P_{2B}e_{2222}$ |
| $A_1A_2B_2$ | $a_A(-k_{1A}a_{1A}^2 + k_{2A}(1 - p_{2A})) + a_b(k_{1B}(1 - P_{1B}^2) - k_{2B}P_{2B}^2)$  

$+ \frac{1}{2}(p_{1A}p_{1B}(2p_{2A}P_{2B} - 1)e_{2121} + p_{1A}P_{2B}(2p_{2A}p_{1B} - 1)e_{2112} + p_{1A}p_{2B}(2p_{2A}P_{2B} - 1)e_{2122}$  

$+(2 + p_{2A}p_{1B}(2p_{1A}P_{1B} - 1)e_{2212} + p_{2A}P_{2B}(2p_{1A}P_{1B} - 1)e_{2211} + p_{2A}p_{2B}(2p_{1A}P_{1B} - 1)e_{2222}$  

$+ p_{2A}p_{2B}(2p_{2A}P_{2B} - 1)e_{2222} + p_{2A}P_{2B}(2p_{2A}P_{2B} - 1)e_{2222} + p_{2A}P_{2B}(2p_{2A}P_{2B} - 1)e_{2222}$ |
| $A_1A_2B_1$ | $a_A(-k_{1A}a_{1A}^2 + k_{2A}(1 - p_{2A})) + a_b(-k_{1B}p_{1B}^2 + k_{2B}(1 - p_{2B}^2))$  

$+ \frac{1}{2}(p_{1A}p_{1B}(2p_{2B}P_{2B} - 1)e_{2121} + p_{1A}P_{2B}(2p_{2B}p_{1B} - 1)e_{2112} + p_{1A}p_{2B}(2p_{2B}P_{2B} - 1)e_{2122}$  

$+(2 + p_{2A}P_{1B}(2p_{1B}p_{1B} - 1)e_{2212} + p_{2A}P_{2B}(2p_{1B}P_{1B} - 1)e_{2211} + p_{2A}p_{2B}(2p_{1B}P_{1B} - 1)e_{2222}$  

$+ p_{2A}p_{2B}(2p_{2B}P_{2B} - 1)e_{2222} + p_{2A}P_{2B}(2p_{2B}P_{2B} - 1)e_{2222} + p_{2A}P_{2B}(2p_{2B}P_{2B} - 1)e_{2222}$ |
| $A_1A_2B_2$ | $a_A(-k_{1A}a_{1A}^2 + k_{2A}(1 - p_{2A})) + p_{1B}a_b(-k_{1B}(1 + P_{1B}) + k_{2B}P_{2B})$  

$+ p_{1A}P_{1B}(2p_{2A}P_{2B} - 1)e_{2122} + p_{1A}P_{2B}(2p_{2A}p_{1B} - 1)e_{2122} + p_{1A}P_{2B}(2p_{2A}P_{2B} - 1)e_{2122}$  

$+ p_{2A}P_{1B}(2p_{1B}p_{1B} - 1)e_{2212} + p_{2A}P_{2B}(2p_{1B}P_{1B} - 1)e_{2212} + (1 + P_{2A}P_{2B}(p_{1A}P_{1B} - 1))e_{2222}$  

$+ p_{2A}P_{2B}(2p_{2B}P_{2B} - 1)e_{2222} + p_{2A}P_{2B}(2p_{2B}P_{2B} - 1)e_{2222} + p_{2A}P_{2B}(2p_{2B}P_{2B} - 1)e_{2222}$ |
| $A_2A_2B_1$ | $p_{1A}a_A(-k_{1A}(1 + P_{1A}) + k_{2A}P_{2A}) + p_{2B}a_b(k_{1B}P_{1B} - k_{2B}(1 + P_{2B}))$  

$+ p_{1A}P_{1B}(2p_{2B}P_{2B} - 2)e_{2122} + p_{1A}P_{2B}(2p_{2B}P_{2B} - 2)e_{2122}$  

$+ p_{1A}P_{2B}(2p_{2B}P_{2B} - 2)e_{2112} + p_{1A}P_{2B}(2p_{2B}P_{2B} - 2)e_{2122}$  

$+ p_{2A}P_{1B}(2p_{2B}P_{2B} - 2)e_{2212} + p_{2A}P_{2B}(2p_{2B}P_{2B} - 2)e_{2212}$  

$+ p_{2A}P_{2B}(2p_{2B}P_{2B} - 2)e_{2212} + p_{2A}P_{2B}(2p_{2B}P_{2B} - 2)e_{2212}$

\[4.42\]
| \( A_2A_2B_2B_1 \) | \( p_{1A}a_A(-k_{1A}(1+p_{1A})+k_{2A}p_{2A})+a_B(-k_{1B}p_{1B}^2+k_{2B}p_{2B}^2) 
+ p_{1A}p_{1B}(p_{2A}p_{2B}-1)e_{2121} + p_{1A}p_{2B}(p_{2A}p_{1B}-1)e_{2112} + p_{1A}p_{2B}(p_{2A}p_{2B}-1)e_{2122} 
+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{2B}^2e_{1222} 
+ (1+p_{2A}p_{1B}(p_{2A}p_{2B}-1))e_{2221} + p_{2A}p_{2B}(p_{2A}p_{1B}-1)e_{2112} + p_{2A}p_{2B}(p_{2A}p_{2B}-1)e_{2222} \) |
| \( A_2A_2B_1B_2 \) | \( p_{1A}a_A(-k_{1A}(1+p_{1A})+k_{2A}p_{2A})+a_B(-k_{1B}p_{1B}^2+k_{2B}p_{2B}^2) 
+ p_{1A}p_{1B}(p_{2A}p_{2B}-1)e_{2121} + p_{1A}p_{2B}(p_{2A}p_{1B}-1)e_{2112} + p_{1A}p_{2B}(p_{2A}p_{2B}-1)e_{2122} 
+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{2B}^2e_{1222} 
+ p_{2A}p_{1B}(p_{2A}p_{2B}-1)e_{2221} + (1+p_{2A}p_{2B}(p_{2A}p_{1B}-1))e_{2112} + p_{2A}p_{2B}(p_{2A}p_{2B}-1)e_{2222} \) |
| \( A_2A_2B_2B_2 \) | \( p_{1A}a_A(-k_{1A}(1+p_{1A})+k_{2A}p_{2A})+p_{1B}a_B(-k_{1B}(1+p_{1B})+k_{2B}p_{2B}) 
+ p_{1A}p_{1B}(p_{2A}p_{2B}-2)e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2B}(p_{2A}p_{2B}-2)e_{2122} 
+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{1222} 
+ p_{2A}p_{1B}(p_{2A}p_{2B}-2)e_{2221} + p_{2A}^2p_{1B}p_{2B}e_{2212} + (p_{2A}p_{2B}-1)^2e_{2222} \) |
Table 6: Male dominance deviations for two-locus genotypes

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<th>Genotype</th>
<th>Male dom dev</th>
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</thead>
<tbody>
<tr>
<td>(A_1A_1B_1B_1)</td>
<td>(p_{2A}a_A(k_{2A}p_{1A} - k_{1A}(1 + p_{2A})) + p_{2B}a_B(k_{2B}p_{1B} - k_{1B}(1 + p_{2B})))</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{2B}(p_{1A}p_{1B} - 2)e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})</td>
</tr>
<tr>
<td>(A_1A_1B_2B_1)</td>
<td>(p_{2A}a_A(k_{2A}p_{1A} - k_{1A}(1 + p_{2A})) + a_B(k_{1B}(1 - p_{2B}^2) - k_{2B}p_{1B}^2))</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{2B}(p_{1A}p_{1B} - 1)e_{2121} + p_{2A}p_{1B}(p_{1A}p_{1B} - 1)e_{2112} + p_{2A}p_{2B}(p_{1A}p_{2B} - 1)e_{2122})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})</td>
</tr>
<tr>
<td>(A_1A_1B_1B_2)</td>
<td>(p_{2A}a_A(k_{2A}p_{1A} - k_{1A}(1 + p_{2A})) + a_B(-k_{1B}p_{2B}^2 + k_{2B}(1 - p_{1B}^2)))</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{2B}(p_{1A}p_{1B} - 1)e_{2121} + p_{2A}p_{1B}(p_{1A}p_{1B} - 1)e_{2112} + p_{2A}p_{2B}(p_{1A}p_{2B} - 1)e_{2122})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})</td>
</tr>
<tr>
<td>(A_1A_1B_2B_2)</td>
<td>(p_{2A}a_A(k_{2A}p_{1A} - k_{1A}(1 + p_{2A})) + p_{1B}a_B(-k_{2B}(1 + p_{1B}) + k_{1B}p_{2B}))</td>
</tr>
<tr>
<td></td>
<td>(+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{2A}p_{1B}(p_{1A}p_{2B} - 2)e_{2112} + p_{2A}p_{2B}(p_{1A}p_{2B} - 2)e_{2122})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{1A}p_{2A}p_{1B}p_{2B}e_{1221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{1212} + p_{1A}p_{2A}p_{2B}^2e_{1222})</td>
</tr>
<tr>
<td></td>
<td>(+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}p_{2B}e_{2212} + p_{2A}p_{2B}^2e_{2222})</td>
</tr>
</tbody>
</table>
| $A_2A_1B_1$ | $a_A(k_{1A}(1-p_{2A}^2)-k_{2A}p_{1A}^2) + p_{2A}a_B(k_{2B}p_{1B} - k_{1B}(1+p_{2B}))$
| | $+ p_{2A}p_{2B}(p_{1A}p_{1B}-1)e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$
| | $+ p_{1A}p_{2B}(p_{2A}p_{1B}-1)e_{2221} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2222}$
| | $+ p_{2A}p_{2B}(p_{2A}p_{1B}-1)e_{2221} + p_{2A}p_{2B}p_{2B}e_{2112} + p_{2A}p_{2B}^2e_{2222}$
| $A_2A_1B_2$ | $a_A(k_{1A}(1-p_{2A}^2)-k_{2A}p_{1A}^2) + a_B(k_{1B}(1-p_{2B}^2)-k_{2B}p_{1B}^2)$
| | $+ \frac{1}{2}((2+p_{2A}p_{2B}(2p_{1A}p_{1B}-1))e_{2121} + p_{2A}p_{1B}(2p_{1A}p_{2B}-1)e_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B}-1)e_{2122}$
| | $+ p_{1A}p_{2B}(2p_{2A}p_{1B}-1)e_{2221} + p_{1A}p_{1B}(2p_{2A}p_{2B}-1)e_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B}-1)e_{2222}$
| | $+ p_{2A}p_{2B}(2p_{2A}p_{1B}-1)e_{2221} + p_{2A}p_{1B}(2p_{2A}p_{2B}-1)e_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B}-1)e_{2222}$
| $A_2A_1B_2$ | $a_A(k_{1A}(1-p_{2A}^2)-k_{2A}p_{1A}^2) + a_B(-k_{1B}p_{2B}^2 + k_{2B}(1-p_{2B}^2))$
| | $+ \frac{1}{2}((2+p_{2A}p_{2B}(2p_{1A}p_{1B}-1))e_{2121} + (2+p_{2A}p_{1B}(2p_{1A}p_{2B}-1))e_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B}-1)e_{2122}$
| | $+ p_{1A}p_{2B}(2p_{2A}p_{1B}-1)e_{2221} + p_{1A}p_{1B}(2p_{2A}p_{2B}-1)e_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B}-1)e_{2222}$
| | $+ p_{2A}p_{2B}(2p_{2A}p_{1B}-1)e_{2221} + p_{2A}p_{1B}(2p_{2A}p_{2B}-1)e_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B}-1)e_{2222}$
| $A_2A_1B_2$ | $a_A(k_{1A}(1-p_{2A}^2)-k_{2A}p_{1A}^2) + p_{1B}a_B(-k_{2B}(1+p_{1B}) + k_{1B}p_{2B})$
| | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{2A}p_{1B}(p_{1A}p_{2B}-1)e_{2112} + (1+p_{2A}p_{2B}(p_{1A}p_{2B}-1))e_{2122}$
| | $+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{1B}(p_{2A}p_{2B}-1)e_{2112} + p_{1A}p_{2B}(p_{2A}p_{2B}-1)e_{2122}$
| | $+ p_{2A}p_{1B}p_{2B}^2e_{2221} + p_{2A}p_{1B}(p_{2A}p_{2B}-1)e_{2212} + p_{2A}p_{2B}(p_{2A}p_{2B}-1)e_{2222}$
| $A_1A_2B_1B_1$ | $\alpha_a(-k_{1A}p_{2A}^2 + k_{2A}(1 - p_{1A}^2)) + p_{2A}a_b(k_{2B}p_{1B} - k_{1B}(1 + p_{2B}))$  
$+ p_{2A}^2p_{2B}(p_{1A}p_{1B} - 1)e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}^2p_{2B}e_{2122}$  
$+ p_{1A}p_{2A}(p_{2A}^2p_{1B} - 1)e_{2211} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}^2p_{2B}e_{2222}$  
$+ p_{2A}^2p_{2B}(p_{2A}p_{1B} - 1)e_{2221} + p_{2A}^2p_{2B}p_{2B}e_{2212} + p_{2A}^2p_{2B}^2e_{2222}$ |
| $A_1A_2B_2B_1$ | $\alpha_a(-k_{1A}p_{2A}^2 + k_{2A}(1 - p_{1A}^2)) + a_b(k_{1B}(1 - p_{2B}^2) - k_{2B}p_{1B}^2)$  
$+ \frac{1}{2}(p_{2A}^2p_{2B}(2p_{1A}p_{1B} - 1)e_{2121} + p_{2A}p_{1B}(2p_{1A}p_{2B} - 1)e_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B} - 1)e_{2122}$  
$+(2 + p_{1A}p_{2B}(2p_{2A}p_{1B} - 1)e_{2211} + p_{1A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2222}$  
$+ p_{2A}^2p_{2B}(2p_{2A}p_{1B} - 1)e_{2221} + p_{2A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2222}$ |
| $A_1A_2B_2B_2$ | $\alpha_a(-k_{1A}p_{2A}^2 + k_{2A}(1 - p_{1A}^2)) + a_b(-k_{1B}p_{2B}^2 + k_{2B}(1 - p_{1B}^2))$  
$+ \frac{1}{2}(p_{2A}^2p_{2B}(2p_{1A}p_{1B} - 1)e_{2121} + p_{2A}p_{1B}(2p_{1A}p_{2B} - 1)e_{2112} + p_{2A}p_{2B}(2p_{1A}p_{2B} - 1)e_{2122}$  
$+ p_{1A}p_{2B}(2p_{2A}p_{1B} - 1)e_{2211} + (2 + p_{1A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2112} + p_{1A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2222}$  
$+ p_{2A}^2p_{2B}(2p_{2A}p_{1B} - 1)e_{2221} + p_{2A}p_{1B}(2p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(2p_{2A}p_{2B} - 1)e_{2222}$ |
| $A_2A_2B_2B_2$ | $\alpha_a(-k_{1A}p_{2A}^2 + k_{2A}(1 - p_{1A}^2)) + p_{1A}a_b(-k_{2B}(1 + p_{1B}) + k_{1B}p_{2B})$  
$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{2A}p_{1B}(p_{1A}p_{2B} - 1)e_{2112} + p_{2A}p_{2B}(p_{1A}p_{2B} - 1)e_{2122}$  
$+ p_{1A}p_{2A}p_{2B}(p_{2A}p_{1B} - 1)e_{2121} + (1 + p_{1A}p_{2B}(p_{2A}p_{2B} - 1))e_{2112}$  
$+ p_{2A}^2p_{2B}p_{2B}e_{2221} + p_{2A}p_{1B}(p_{2A}p_{2B} - 1)e_{2212} + p_{2A}p_{2B}(p_{2A}p_{2B} - 1)e_{2222}$ |
| $A_2A_2B_1B_1$ | $p_{1A}a_a(-k_{2A}(1 + p_{1A}) + k_{1A}p_{2A}) + p_{2A}a_b(k_{2B}p_{1B} - k_{1B}(1 + p_{2B}))$  
$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
$+ p_{1A}p_{2B}(p_{2A}p_{1B} - 2)e_{2212} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2222}$  
$+ p_{2A}^2p_{2B}(p_{2A}p_{1B} - 2)e_{2221} + p_{2A}^2p_{2B}^2e_{2212} + p_{2A}^2p_{2B}^2e_{2222}$ |
| $A_2A_2B_2B_1$ | $p_{1A}a_A(-k_{2A}(1+p_{1A})+k_{1A}p_{2A}) + a_B(k_{1B}(1-p_{2B})^2-k_{2B}p_{1B}^2)$  
$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
$+ p_{1A}p_{2B}(p_{2A}p_{1B}-1)e_{2221} + p_{1A}p_{1B}(p_{2A}p_{2B}-1)e_{2121} + p_{1A}p_{2B}(p_{2A}p_{2B}-1)e_{2222}$  
$+(1+ p_{2A}p_{2B}(p_{2A}p_{1B}-1))e_{2221} + p_{2A}p_{1B}(p_{2A}p_{2B}-1)e_{2212} + p_{2A}p_{2B}(p_{2A}p_{2B}-1)e_{2222}$ |
| $A_2A_2B_1B_2$ | $p_{1A}a_A(-k_{2A}(1+p_{1A})+k_{1A}p_{2A}) + a_B(-k_{1B}p_{2B}^2+k_{2B}(1-p_{1B}^2))$  
$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
$+ p_{1A}p_{2B}(p_{2A}p_{1B}-1)e_{2221} + p_{1A}p_{1B}(p_{2A}p_{2B}-1)e_{2121} + p_{1A}p_{2B}(p_{2A}p_{2B}-1)e_{2222}$  
$+ p_{2A}p_{2B}(p_{2A}p_{1B}-1)e_{2221} + (1+ p_{2A}p_{1B}(p_{2A}p_{2B}-1))e_{2212} + p_{2A}p_{2B}(p_{2A}p_{2B}-1)e_{2222}$ |
| $A_2A_2B_2B_2$ | $p_{1A}a_A(-k_{2A}(1+p_{1A})+k_{1A}p_{2A}) + p_{1B}a_B(-k_{2B}(1+p_{1B})+k_{1B}p_{2B})$  
$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{2A}p_{1B}p_{2B}e_{2112} + p_{1A}p_{2A}p_{2B}^2e_{2122}$  
$+ p_{1A}p_{2A}p_{1B}p_{2B}e_{2121} + p_{1A}p_{1B}(p_{2A}p_{2B}-2)e_{2121} + p_{1A}p_{2B}(p_{2A}p_{2B}-2)e_{2222}$  
$+ p_{2A}p_{1B}p_{2B}e_{2221} + p_{2A}p_{1B}(p_{2A}p_{2B}-2)e_{2212} + (p_{2A}p_{2B}-1)^2e_{2222}$ |
Table 7: Genetic variances for populations with no imprinting and no epistasis; epistasis only and imprinting only

<table>
<thead>
<tr>
<th>Condition</th>
<th>( G_{AB} )</th>
<th>( \sigma_G^2 ) (total genetic)</th>
<th>( \sigma_A^2 ) (additive genetic)</th>
<th>( \sigma_D^2 ) (dominance genetic)</th>
<th>( \sigma_{AD} ) (additive by dominance covariance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all:</td>
<td>( P_{1A} = P_{1B} = \frac{1}{2} )</td>
<td>( \begin{bmatrix} 0 &amp; 0.2375 &amp; 0.2375 &amp; 0.5 \ 0.2375 &amp; 0.475 &amp; 0.475 &amp; 0.7375 \ 0.2375 &amp; 0.475 &amp; 0.475 &amp; 0.7375 \ 0.5 &amp; 0.7375 &amp; 0.7375 &amp; 1 \end{bmatrix} )</td>
<td>0.0626</td>
<td>0.0625</td>
<td>0.0001</td>
</tr>
<tr>
<td>(1.1) No imprinting or epistasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( a_A = a_B = \frac{1}{4} ), ( k_{1A} = k_{2A} = \frac{1}{20} ), ( k_{1B} = k_{2B} = \frac{1}{20} ), ( \epsilon_{ijkl} = 0 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.2) No imprinting</td>
<td>( a_A = a_B = \frac{1}{4} ), ( k_{1A} = k_{2A} = \frac{1}{20} ), ( k_{1B} = k_{2B} = \frac{1}{20} ), ( \epsilon_{2121} = \epsilon_{2112} = \epsilon_{1212} = \epsilon_{2121} = \frac{21}{60} ), ( \epsilon_{2122} = \epsilon_{1222} = \epsilon_{2221} = \epsilon_{2212} = \frac{21}{60} )</td>
<td>( \begin{bmatrix} 0 &amp; 0.2375 &amp; 0.2375 &amp; 0.5 \ 0.2375 &amp; 1 &amp; 1 &amp; 1 \ 0.2375 &amp; 1 &amp; 1 &amp; 1 \ 0.5 &amp; 1 &amp; 1 &amp; 1 \end{bmatrix} )</td>
<td>0.1395</td>
<td>0.0996</td>
<td>0.0399</td>
</tr>
</tbody>
</table>
| (1.3) No imprinting | \[
\begin{align*}
  a_A &= a_B = \frac{1}{4}, \quad k_{1A} &= k_{2A} = \frac{4}{20}, \\
  k_{1B} &= k_{2B} = \frac{1}{20}, \\
  \epsilon_{2122} &= \epsilon_{1222} = \epsilon_{2221} = \epsilon_{2212} = \frac{21}{80}, \\
  \epsilon_{2222} &= \frac{1}{2},
\end{align*}
\] |
| \[
\begin{bmatrix}
  0 & 0.2375 & 0.2375 & 0.5 \\
  0.2375 & 0.475 & 0.475 & 1 \\
  0.2375 & 0.475 & 0.475 & 1 \\
  0.5 & 1 & 1 & 1.5 \\
\end{bmatrix}
\] | 0.1509 | 0.1440 | 0.0050 | 0.0010 |
| (1.4) No imprinting or epistasis | \[
\begin{align*}
  a_A &= a_B = \frac{1}{4}, \quad k_{1A} &= k_{2A} = \frac{17}{20}, \\
  k_{1B} &= k_{2B} = \frac{9}{10}, \quad \epsilon_{ijkl} = 0
\end{align*}
\] |
| \[
\begin{bmatrix}
  0 & 0.025 & 0.025 & 0.5 \\
  0.4625 & 0.4875 & 0.4875 & 0.9625 \\
  0.4625 & 0.4875 & 0.4875 & 0.9625 \\
  0.5 & 0.525 & 0.525 & 1 \\
\end{bmatrix}
\] | 0.0864 | 0.0625 | 0.0239 | 0 |
| (1.5) No imprinting | \[
\begin{align*}
  a_A &= a_B = \frac{1}{4}, \quad k_{1A} &= k_{2A} = \frac{17}{20}, \\
  k_{1B} &= k_{2B} = \frac{9}{10}, \\
  \epsilon_{2122} &= \epsilon_{1221} = \epsilon_{1212} = \epsilon_{2112} = \frac{37}{80}, \\
  \epsilon_{2221} &= \epsilon_{2212} = \epsilon_{2222} = \frac{1}{2}
\end{align*}
\] |
| \[
\begin{bmatrix}
  0 & 0.025 & 0.025 & 0.5 \\
  0.4625 & 0.025 & 0.025 & 0.5 \\
  0.4625 & 0.025 & 0.025 & 0.5 \\
  0.5 & 0.025 & 0.025 & 0.5 \\
\end{bmatrix}
\] | 0.0538 | 0.0055 | 0.0464 | 0.0010 |
| (1.6) No imprinting | \[
\begin{align*}
  a_A &= a_B = \frac{1}{4}, \quad k_{1A} &= k_{2A} = \frac{4}{20}, \\
  k_{1B} &= k_{2B} = \frac{1}{20}, \\
  \epsilon_{2122} &= \epsilon_{1222} = \epsilon_{2212} = \epsilon_{2221} = \frac{37}{80}
\end{align*}
\] |
| \[
\begin{bmatrix}
  0 & 0.2375 & 0.2375 & 0.5 \\
  0.4625 & 1 & 1 & 0.4625 \\
  0.4625 & 1 & 1 & 0.4625 \\
  0.5 & 0.525 & 0.525 & 1 \\
\end{bmatrix}
\] | 0.1189 | 0.0391 | 0.0798 | 0 |
\[ a_A = a_B = \frac{1}{4}, \ k_{1A} = k_{2A} = \frac{17}{20}, \]
\[ k_{1B} = k_{2B} = \frac{9}{10}, \]
\[ \varepsilon_{2121} = \varepsilon_{2112} = \varepsilon_{1221} = \varepsilon_{1212} = \frac{41}{80}, \]
\[ \varepsilon_{2122} = \varepsilon_{1222} = \frac{1}{2} \]

| (1.7) No epistasis | \[ \begin{bmatrix} 0 & 0.45 & 0.025 & 0.5 \\ 0.45 & 0.9 & 0.475 & 0.95 \\ 0.025 & 0.475 & 0.05 & 0.525 \\ 0.5 & 0.95 & 0.525 & 1 \end{bmatrix} \] | 0.1077 | \[ \sigma_{Af}^2 = 0.2139 \]
| | | | \[ \sigma_{Am}^2 = 0.0014 \]
| | | | \[ \sigma_{ADf} = -0.0983 \]
| | | | \[ \sigma_{ADm} = 0.0080 \]

| (1.8) No epistasis | \[ \begin{bmatrix} 0 & 0.025 & 0.45 & 0.5 \\ 0.45 & 0.475 & 0.9 & 0.95 \\ 0.025 & 0.05 & 0.475 & 0.525 \\ 0.5 & 0.525 & 0.95 & 1 \end{bmatrix} \] | 0.1077 | \[ \sigma_{Af}^2 = 0.1077 \]
| | | | \[ \sigma_{Am}^2 = 0.0177 \]
| | | | \[ \sigma_{ADf} = -0.0452 \]
| | | | \[ \sigma_{ADm} = -0.0452 \]

| (1.9) No epistasis, imprinting at one locus only | \[ \begin{bmatrix} 0 & 0.2375 & 0.2375 & 0.5 \\ 0.45 & 0.6875 & 0.6875 & 0.95 \\ 0.025 & 0.2625 & 0.2625 & 0.525 \\ 0.5 & 0.7375 & 0.7375 & 1 \end{bmatrix} \] | 0.0852 | \[ \sigma_{Af}^2 = 0.1382 \]
| | | | \[ \sigma_{Am}^2 = 0.0320 \]
| | | | \[ \sigma_{ADf} = -0.0491 \]
| | | | \[ \sigma_{ADm} = 0.0040 \]
(1.10) No epistasis, contribution of loci not equally weighted

\[ \begin{align*}
  a_A &= \frac{1}{8}, \quad a_B = \frac{5}{8}, \\
  k_{1A} &= \frac{4}{5}, \quad k_{2A} = \frac{9}{10}, \\
  k_{1B} &= \frac{4}{5}, \quad k_{2B} = \frac{1}{10} \\
  \epsilon_{ijkl} &= 0
\end{align*} \]

\[
\begin{pmatrix}
  0 & 0.3 & 0.4125 & 0.75 \\
  0.225 & 0.525 & 0.6375 & 0.975 \\
  0.0125 & 0.3125 & 0.425 & 0.7625 \\
  0.25 & 0.55 & 0.6625 & 1
\end{pmatrix}
\]

| \( \sigma^2_{Af} \) | 0.0775 |
| \( \sigma^2_{Am} \) | 0.0932 |
| \( \sigma_{Adj} \) | 0.0146 |
| \( \sigma_{Adj} \) | -0.0033 |
| \( \sigma_{Adj} \) | -0.0111 |

4.51
Table 8: Resemblances between relatives for populations with no imprinting and no epistasis; epistasis only and imprinting only

<table>
<thead>
<tr>
<th>Condition</th>
<th>Covariances</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all:</td>
<td>( G_{AB} )</td>
</tr>
</tbody>
</table>
| \( p_{1A} = p_{1B} = \frac{1}{2} \)                                      | \[
\begin{pmatrix}
0 & 0.2375 & 0.2375 & 0.5 \\
0.2375 & 0.475 & 0.475 & 0.7375 \\
0.2375 & 0.475 & 0.475 & 0.7375 \\
0.5 & 0.7375 & 0.7375 & 1
\end{pmatrix}
\] | 0.03125 | 0.0156 | 0.03127 |
| (1.1) No imprinting or epistasis                                          | \[ a_A = a_B = \frac{1}{4}, \ k_{1A} = k_{2A} = \frac{1}{20}, \]
| \( k_{1B} = k_{2B} = \frac{1}{20}, \ \varepsilon_{ijkl} = 0 \)            | \[
\begin{pmatrix}
0 & 0.2375 & 0.2375 & 0.5 \\
0.2375 & 1 & 1 & 1 \\
0.2375 & 1 & 1 & 1 \\
0.5 & 1 & 1 & 1
\end{pmatrix}
\] | 0.0498 | 0.0249 | 0.0598 |
| (1.2) No imprinting                                                        | \[ a_A = a_B = \frac{1}{4}, \ k_{1A} = k_{2A} = \frac{1}{20}, \]
| \( k_{1B} = k_{2B} = \frac{1}{20}, \ \varepsilon_{2121} = \varepsilon_{2112} = \varepsilon_{1212} = \frac{21}{40}, \]
| \( \varepsilon_{2122} = \varepsilon_{1222} = \varepsilon_{2221} = \varepsilon_{2212} = \frac{21}{80} \) | \[
\begin{pmatrix}
0 & 0.2375 & 0.2375 & 0.5 \\
0.2375 & 0.475 & 0.475 & 1 \\
0.2375 & 0.475 & 0.475 & 1 \\
0.5 & 1 & 1 & 1.5
\end{pmatrix}
\] | 0.0725 | 0.0360 | 0.0737 |
| (1.3) No imprinting                                                        | \[ a_A = a_B = \frac{1}{4}, \ k_{1A} = k_{2A} = \frac{1}{20}, \]
| \( k_{1B} = k_{2B} = \frac{1}{20}, \ \varepsilon_{ijkl} = 0 \)            | \[
\begin{pmatrix}
0 & 0.2375 & 0.2375 & 0.5 \\
0.2375 & 0.475 & 0.475 & 1 \\
0.2375 & 0.475 & 0.475 & 1 \\
0.5 & 1 & 1 & 1.5
\end{pmatrix}
\] | 0.0725 | 0.0360 | 0.0737 |
<table>
<thead>
<tr>
<th>( a_A = a_B = \frac{1}{4}, ) ( k_{1A} = k_{2A} = \frac{1}{20}, )</th>
<th>( k_{1B} = k_{2B} = \frac{1}{20}, )</th>
<th>( \varepsilon_{2122} = \varepsilon_{1222} = \varepsilon_{2221} = \varepsilon_{2212} = \frac{21}{80} )</th>
<th>( \varepsilon_{2222} = \frac{1}{2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 0 )</td>
<td>0.025</td>
<td>0.025</td>
<td>0.5</td>
</tr>
<tr>
<td>0.4625</td>
<td>0.4875</td>
<td>0.4875</td>
<td>0.9625</td>
</tr>
<tr>
<td>0.4625</td>
<td>0.4875</td>
<td>0.4875</td>
<td>0.9625</td>
</tr>
<tr>
<td>0.5</td>
<td>0.525</td>
<td>0.525</td>
<td>1</td>
</tr>
<tr>
<td>0.03125</td>
<td>0.0156</td>
<td>0.0372</td>
<td></td>
</tr>
</tbody>
</table>

(1.4) No imprinting or epistasis

\[ a_A = a_B = \frac{1}{4}, \quad k_{1A} = k_{2A} = \frac{17}{30}, \]
\[ k_{1B} = k_{2B} = \frac{9}{10}, \quad \varepsilon_{ijkl} = 0 \]

\[ \begin{bmatrix} 0 & 0.025 & 0.025 & 0.5 \\ 0.4625 & 0.4875 & 0.4875 & 0.9625 \\ 0.4625 & 0.4875 & 0.4875 & 0.9625 \\ 0.5 & 0.525 & 0.525 & 1 \end{bmatrix} \]

0.03125 0.0156 0.0372

(1.5) No imprinting

\[ a_A = a_B = \frac{1}{4}, \quad k_{1A} = k_{2A} = \frac{17}{20}, \]
\[ k_{1B} = k_{2B} = \frac{9}{10}, \quad \varepsilon_{2121} = \varepsilon_{2112} = \varepsilon_{1221} = \varepsilon_{1212} = \varepsilon_{2212} = \varepsilon_{1222} = \frac{37}{80} \]

\[ \begin{bmatrix} 0 & 0.025 & 0.025 & 0.5 \\ 0.4625 & 0.025 & 0.025 & 0.5 \\ 0.4625 & 0.025 & 0.025 & 0.5 \\ 0.5 & 0.025 & 0.025 & 0.5 \end{bmatrix} \]

0.0032 0.0014 0.0148

(1.6) No imprinting

\[ a_A = a_B = \frac{1}{4}, \quad k_{1A} = k_{2A} = \frac{17}{20}, \]
\[ k_{1B} = k_{2B} = \frac{9}{10}, \quad \varepsilon_{2121} = \varepsilon_{2112} = \varepsilon_{1221} = \varepsilon_{1212} = \varepsilon_{2212} = \varepsilon_{1222} = \frac{1}{2} \]

\[ \begin{bmatrix} 0 & 0.025 & 0.025 & 0.5 \\ 0.4625 & 1 & 1 & 0.4625 \\ 0.4625 & 1 & 1 & 0.4625 \\ 0.5 & 0.525 & 0.525 & 1 \end{bmatrix} \]

0.0195 0.0098 0.0395
| (1.7) No epistasis | \[
\begin{bmatrix}
0 & 0.45 & 0.025 & 0.5 \\
0.45 & 0.9 & 0.475 & 0.95 \\
0.025 & 0.475 & 0.05 & 0.525 \\
0.5 & 0.95 & 0.525 & 1 \\
\end{bmatrix}
\] | \[
\begin{align*}
\sigma_{OPf} & = 0.0578 \\
\sigma_{OPm} & = 0.0047 \\
\sigma_{HSf} & = 0.0535 \\
\sigma_{HSm} & = 0.0004 \\
\end{align*}
\] | 0.0538 |
|---|---|---|---|
| (1.8) No epistasis | \[
\begin{bmatrix}
0 & 0.025 & 0.45 & 0.5 \\
0.45 & 0.9 & 0.475 & 0.95 \\
0.025 & 0.05 & 0.475 & 0.525 \\
0.5 & 0.525 & 0.95 & 1 \\
\end{bmatrix}
\] | \[
\begin{align*}
\sigma_{OPf} & = 0.0313 \\
\sigma_{OPm} & = 0.0313 \\
\sigma_{HSf} & = 0.0269 \\
\sigma_{HSm} & = 0.0269 \\
\end{align*}
\] | 0.0538 |
| (1.9) No epistasis, imprinting at one locus only | \[
\begin{bmatrix}
0 & 0.2375 & 0.2375 & 0.5 \\
0.45 & 0.6875 & 0.6875 & 0.95 \\
0.025 & 0.2625 & 0.2625 & 0.525 \\
0.5 & 0.7375 & 0.7375 & 1 \\
\end{bmatrix}
\] | \[
\begin{align*}
\sigma_{OPf} & = 0.0445 \\
\sigma_{OPm} & = 0.0180 \\
\sigma_{HSf} & = 0.0346 \\
\sigma_{HSm} & = 0.0080 \\
\end{align*}
\] | 0.0426 |
| (1.10) No epistasis, contribution of loci not equally weighted | \[
\begin{bmatrix}
0 & 0.3 & 0.4125 & 0.75 \\
0.225 & 0.525 & 0.6375 & 0.975 \\
0.0125 & 0.3125 & 0.425 & 0.7625 \\
0.25 & 0.55 & 0.6625 & 1 \\
\end{bmatrix}
\] | \[
\begin{align*}
\sigma_{OPf} & = 0.0371 \\
\sigma_{OPm} & = 0.0410 \\
\sigma_{HSf} & = 0.0194 \\
\sigma_{HSm} & = 0.0233 \\
\end{align*}
\] | 0.0427 |
\[
\begin{align*}
\alpha_A &= \frac{1}{8}, \quad \alpha_B = \frac{1}{8}, \\
\kappa_{1A} &= \frac{4}{5}, \quad \kappa_{2A} = \frac{9}{10}, \\
\kappa_{1B} &= \frac{1}{5}, \quad \kappa_{2B} = \frac{1}{10} \\
\epsilon_{ijkl} &= 0
\end{align*}
\]
Table 9: Variance components for populations with epistasis and imprinting

<table>
<thead>
<tr>
<th>Condition</th>
<th>Variances</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all:</td>
<td>$G_{AB}$</td>
</tr>
<tr>
<td>$p_{1A} = p_{1B} = \frac{1}{2}$, $\epsilon_{ijkl} = 0$ unless otherwise specified</td>
<td></td>
</tr>
<tr>
<td>(2.1)</td>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{1}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\epsilon_{2122} = \epsilon_{2222} = \epsilon_{2221}$</td>
</tr>
<tr>
<td>(2.2)</td>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{1}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\epsilon_{2121} = \frac{1}{20}$, $\epsilon_{2122} = \frac{1}{20}$, $\epsilon_{2212} = \epsilon_{1221} = \epsilon_{2222}$</td>
</tr>
</tbody>
</table>
\begin{align*}
(2.3) \\
a_A &= a_B = \frac{1}{3}, \quad k_{1A} = k_{1B} = \frac{2}{3}, \\
k_{2A} &= k_{2B} = \frac{9}{10}, \\
e_{2121} &= \frac{1}{10}, \quad e_{1212} = \frac{19}{20}, \\
e_{2112} &= e_{1211} = \frac{21}{40},
\end{align*}

\[
\begin{bmatrix}
0 & 0.45 & 0.025 & 0.5 \\
0.45 & 1 & 1 & 0.95 \\
0.025 & 1 & 1 & 0.525 \\
0.5 & 0.95 & 0.525 & 1
\end{bmatrix}
\]

\begin{align*}
\sigma_{Af}^2 &= 0.1269, \\
\sigma_{Df}^2 &= 0.3395, \\
\sigma_{Am}^2 &= 0.0207, \\
\sigma_{Dm}^2 &= 0.3395, \\
\sigma_{Adf} &= -0.0379, \\
\sigma_{Adm} &= 0.0153.
\end{align*}

\begin{align*}
(2.4) \\
a_A &= a_B = \frac{1}{4}, \quad k_{1A} = k_{1B} = \frac{2}{3}, \\
k_{2A} &= k_{2B} = \frac{9}{10}, \\
e_{2121} &= \frac{1}{10}, \quad e_{2112} = e_{1211} = \frac{21}{40}, \\
e_{2112} &= e_{2212} = \frac{1}{2}, \quad e_{1212} = \frac{10}{20}, \\
e_{2212} &= e_{2222} = \frac{19}{40},
\end{align*}

\[
\begin{bmatrix}
0 & 0.45 & 0.025 & 0.5 \\
0.45 & 1 & 1 & 1 \\
0.025 & 1 & 1 & 1 \\
0.5 & 1 & 1 & 1
\end{bmatrix}
\]

\begin{align*}
\sigma_{Af}^2 &= 0.1388, \\
\sigma_{Df}^2 &= 0.0568, \\
\sigma_{Am}^2 &= 0.0717, \\
\sigma_{Dm}^2 &= 0.0568, \\
\sigma_{Adf} &= -0.0224, \\
\sigma_{Adm} &= 0.0111.
\end{align*}

\begin{align*}
(2.5) \\
a_A &= a_B = \frac{1}{4}, \quad k_{1A} = k_{1B} = \frac{2}{3}, \\
k_{2A} &= k_{2B} = \frac{9}{10}, \\
e_{2122} &= e_{2222} = \frac{1}{10}, \\
e_{1212} &= e_{1222} = \frac{19}{40}, \\
e_{2212} &= e_{2222} = \frac{1}{2},
\end{align*}

\[
\begin{bmatrix}
0 & 0.45 & 0.025 & 0.5 \\
0.45 & 0.9 & 0.475 & 1 \\
0.025 & 0.475 & 0.05 & 1 \\
0.5 & 1 & 1 & 1.5
\end{bmatrix}
\]

\begin{align*}
\sigma_{Af}^2 &= 0.2894, \\
\sigma_{Df}^2 &= 0.0704, \\
\sigma_{Am}^2 &= 0.0550, \\
\sigma_{Dm}^2 &= 0.0638, \\
\sigma_{Adf} &= -0.0875, \\
\sigma_{Adm} &= 0.0330.
\end{align*}

\begin{align*}
(2.6) \\
a_A &= a_B = \frac{1}{4}, \quad k_{1A} = k_{2B} = \frac{2}{3}, \\
k_{2A} &= k_{1B} = \frac{9}{10}, \\
e_{2122} &= \frac{17}{40}, \quad e_{2222} = \frac{17}{40},
\end{align*}

\[
\begin{bmatrix}
0 & 0.025 & 0.45 & 0.5 \\
0.45 & 0.475 & 0.9 & 0.525 \\
0.025 & 0.05 & 0.475 & 0.525 \\
0.5 & 0.95 & 0.95 & 1
\end{bmatrix}
\]

\begin{align*}
\sigma_{Af}^2 &= 0.1077, \\
\sigma_{Df}^2 &= 0.0678, \\
\sigma_{Am}^2 &= 0.0738, \\
\sigma_{Dm}^2 &= 0.0678, \\
\sigma_{Adf} &= -0.0339, \\
\sigma_{Adm} &= -0.0169.
\end{align*}

4.57
(2.7)\[ a_A = a_B = \frac{1}{4}, \quad k_{1A} = k_{2B} = \frac{1}{4}, \]
\[ k_{2A} = k_{1B} = \frac{\phi}{10}, \]
\[ e_{2121} = e_{2112} = e_{2122} = \frac{\phi}{20}, \]
\[ e_{1221} = e_{1212} = e_{1222} = \frac{\phi}{40}, \]
\[ e_{2221} = e_{2212} = e_{2222} = \frac{1}{2}, \]
\[
\begin{bmatrix}
0 & 0.025 & 0.45 & 0.5 \\
0.45 & 0.025 & 0.45 & 0.5 \\
0.025 & 0.025 & 0.45 & 0.5 \\
0.5 & 0.025 & 0.45 & 0.5 \\
\end{bmatrix}
\]
\[
\sigma^2_{Af} = 0.0136, \quad \sigma^2_{Am} = 0.0581, \quad \sigma^2_{Df} = 0.0587, \quad \sigma^2_{Dm} = 0.0620, \quad \sigma_{Adj} = -0.0118, \quad \sigma_{Adm} = -0.0357
\]

(2.8)\[ a_A = \frac{1}{8}, \quad a_B = \frac{3}{8}, \]
\[ k_{1A} = \frac{2}{3}, \quad k_{2A} = \frac{3}{2}, \]
\[ k_{1B} = \frac{1}{3}, \quad k_{2B} = \frac{1}{2}, \]
\[ e_{2121} = \frac{\phi}{30}, \quad e_{2112} = \frac{7}{80}, \]
\[ e_{1221} = \frac{1}{10}, \quad e_{2112} = \frac{1}{80}, \]
\[
\begin{bmatrix}
0 & 0.3 & 0.4125 & 0.75 \\
0.225 & 0.55 & 0.55 & 0.975 \\
0.0125 & 0.4125 & 0.4125 & 0.7625 \\
0.25 & 0.55 & 0.6625 & 1 \\
\end{bmatrix}
\]
\[
\sigma^2_{Af} = 0.0827, \quad \sigma^2_{Am} = 0.0820, \quad \sigma^2_{Df} = 0.0091, \quad \sigma^2_{Dm} = 0.0091, \quad \sigma_{Adj} = -0.0044, \quad \sigma_{Adm} = -0.0040
\]

(2.9)\[ a_A = \frac{1}{8}, \quad a_B = \frac{3}{8}, \]
\[ k_{1A} = \frac{2}{3}, \quad k_{2A} = \frac{3}{2}, \]
\[ k_{1B} = \frac{1}{3}, \quad k_{2B} = \frac{1}{2}, \]
\[ e_{2121} = e_{1221} = e_{2221} = \frac{\phi}{20}, \]
\[ e_{2112} = e_{1212} = e_{2212} = \frac{27}{80}, \]
\[
\begin{bmatrix}
0 & 0.3 & 0.4125 & 0.75 \\
0.225 & 0.975 & 0.975 & 0.975 \\
0.0125 & 0.7625 & 0.7625 & 0.7625 \\
0.25 & 1 & 1 & 1 \\
\end{bmatrix}
\]
\[
\sigma^2_{Af} = 0.1195, \quad \sigma^2_{Am} = 0.0826, \quad \sigma^2_{Df} = 0.0403, \quad \sigma^2_{Dm} = 0.0403, \quad \sigma_{Adj} = -0.0150, \quad \sigma_{Adm} = 0.0034
\]
\begin{align*}
\text{(2.10)} \\
a_A &= \frac{4}{5}, \quad a_B = \frac{3}{5}, \\
k_{1A} &= \frac{4}{5}, \quad k_{2A} = \frac{6}{10}, \\
k_{1B} &= \frac{1}{5}, \quad k_{2B} = \frac{4}{10}, \\
\epsilon_{2121} &= \frac{19}{80}, \quad \epsilon_{2112} = \frac{29}{80}, \quad \epsilon_{2122} = \frac{1}{40}, \\
\epsilon_{1221} &= \frac{55}{80}, \quad \epsilon_{1212} = \frac{23}{80}, \quad \epsilon_{1222} = \frac{19}{80}, \\
\epsilon_{2221} &= \frac{9}{20}, \quad \epsilon_{2212} = \frac{27}{80}, \\
\end{align*}

\begin{bmatrix}
0 & 0.3 & 0.4125 & 0.75 \\
0.225 & 1 & 1 & 1 \\
0.0125 & 1 & 1 & 1 \\
0.25 & 1 & 1 & 1 \\
\end{bmatrix}

\begin{align*}
\sigma_{Af}^2 &= 0.1088 \\
\sigma_{Am}^2 &= 0.1084 \\
\sigma_{Df}^2 &= 0.045 \\
\sigma_{Dm}^2 &= 0.045 \\
\sigma_{ADF} &= -0.0006 \\
\sigma_{ADM} &= -0.0004 \\
\end{align*}

4.59
Table 10: Resemblances between relatives for populations with epistasis and imprinting

<table>
<thead>
<tr>
<th>Condition</th>
<th>Covariances</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>For all:</td>
<td>$G_{AB}$</td>
<td>$\sigma_{OP}$</td>
<td>$\sigma_{HS}$</td>
<td>$\sigma_{FS}$</td>
</tr>
<tr>
<td>$p_{1A} = p_{1B} = \frac{1}{2}$, $\epsilon_{ijkl} = 0$ unless otherwise specified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{4}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\epsilon_{2122} = \epsilon_{1222} = \epsilon_{2221}$</td>
<td>$\begin{bmatrix} 0 &amp; 0.45 &amp; 0.25 &amp; 0.5 \ 0.45 &amp; 0.9 &amp; 0.45 &amp; 0.5 \ 0.025 &amp; 0.475 &amp; 0.05 &amp; 0.025 \ 0.5 &amp; 0.45 &amp; 0.025 &amp; 0.5 \end{bmatrix}$</td>
<td>$\sigma_{OPf} = 0.0096$</td>
<td>$\sigma_{OPm} = -0.0037$</td>
<td>$\sigma_{HSf} = 0.0192$</td>
</tr>
<tr>
<td>(2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{4}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\epsilon_{2121} = \epsilon_{1212} = \epsilon_{2112} = \epsilon_{2212} = \epsilon_{1221}$</td>
<td>$\begin{bmatrix} 0 &amp; 0.45 &amp; 0.25 &amp; 0.5 \ 0.45 &amp; 1 &amp; 0.45 &amp; 0.95 \ 0.025 &amp; 0.45 &amp; 0 &amp; 0.5 \ 0.5 &amp; 0.95 &amp; 0.5 &amp; 1 \end{bmatrix}$</td>
<td>$\sigma_{OPf} = 0.0594$</td>
<td>$\sigma_{OPm} = 0.0015$</td>
<td>$\sigma_{HSf} = 0.0579$</td>
</tr>
<tr>
<td>Equation</td>
<td>Parameters</td>
<td>Values</td>
<td>OPf</td>
<td>OPm</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>--------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>(2.3)</td>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{4}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\varepsilon_{2121} = \frac{1}{10}$, $\varepsilon_{1212} = \frac{19}{20}$, $\varepsilon_{2112} = \varepsilon_{1221} = \frac{21}{40}$</td>
<td>$\begin{bmatrix} 0 &amp; 0.45 &amp; 0.025 &amp; 0.5 \ 0.45 &amp; 1 &amp; 1 &amp; 0.95 \ 0.025 &amp; 1 &amp; 1 &amp; 0.525 \ 0.5 &amp; 0.95 &amp; 0.525 &amp; 1 \end{bmatrix}$</td>
<td>$\sigma_{OPf} = 0.0445$</td>
<td>$\sigma_{OPm} = 0.0180$</td>
</tr>
<tr>
<td>(2.4)</td>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{4}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\varepsilon_{2121} = \frac{1}{10}$, $\varepsilon_{2112} = \varepsilon_{1221} = \frac{21}{40}$, $\varepsilon_{2122} = \varepsilon_{2221} = \frac{1}{20}$, $\varepsilon_{1212} = \varepsilon_{1212} = \frac{19}{20}$, $\varepsilon_{2212} = \varepsilon_{1222} = \frac{19}{40}$</td>
<td>$\begin{bmatrix} 0 &amp; 0.45 &amp; 0.025 &amp; 0.5 \ 0.45 &amp; 1 &amp; 1 &amp; 1 \ 0.025 &amp; 1 &amp; 1 &amp; 1 \ 0.5 &amp; 1 &amp; 1 &amp; 1 \end{bmatrix}$</td>
<td>$\sigma_{OPf} = 0.0582$</td>
<td>$\sigma_{OPm} = 0.0414$</td>
</tr>
<tr>
<td>(2.5)</td>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{4}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\varepsilon_{2121} = \varepsilon_{2221} = \frac{1}{10}$, $\varepsilon_{1212} = \varepsilon_{1212} = \frac{19}{20}$, $\varepsilon_{1222} = \varepsilon_{2212} = \frac{19}{40}$, $\varepsilon_{2222} = \frac{17}{20}$</td>
<td>$\begin{bmatrix} 0 &amp; 0.45 &amp; 0.025 &amp; 0.5 \ 0.45 &amp; 0.9 &amp; 0.475 &amp; 1 \ 0.025 &amp; 0.475 &amp; 0.05 &amp; 1 \ 0.5 &amp; 1 &amp; 1 &amp; 1.5 \end{bmatrix}$</td>
<td>$\sigma_{OPf} = 0.1009$</td>
<td>$\sigma_{OPm} = 0.0440$</td>
</tr>
<tr>
<td>(2.6)</td>
<td>$a_A = a_B = \frac{1}{4}$, $k_{1A} = k_{1B} = \frac{4}{5}$, $k_{2A} = k_{2B} = \frac{9}{10}$, $\varepsilon_{2122} = \varepsilon_{2212} = \frac{17}{40}$, $\varepsilon_{2222} = \frac{17}{40}$</td>
<td>$\begin{bmatrix} 0 &amp; 0.025 &amp; 0.45 &amp; 0.5 \ 0.45 &amp; 0.475 &amp; 0.9 &amp; 0.525 \ 0.025 &amp; 0.05 &amp; 0.475 &amp; 0.525 \ 0.5 &amp; 0.95 &amp; 0.95 &amp; 1 \end{bmatrix}$</td>
<td>$\sigma_{OPf} = 0.0369$</td>
<td>$\sigma_{OPm} = 0.0284$</td>
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\[(2.7)\]
\[a_A = a_B = \frac{4}{5}, \quad k_{1A} = k_{2B} = \frac{4}{5},\]
\[k_{2A} = k_{1B} = \frac{9}{10},\]
\[\mathbf{e}_{2121} = \mathbf{e}_{1121} = \mathbf{e}_{2122} = \frac{9}{20},\]
\[\mathbf{e}_{1221} = \mathbf{e}_{1212} = \mathbf{e}_{2222} = \frac{9}{40},\]
\[\mathbf{e}_{2221} = \mathbf{e}_{2212} = \mathbf{e}_{2222} = \frac{9}{30}\]

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<th>\sigma_{OPm}</th>
<th>\sigma_{HSm}</th>
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\[(2.8)\]
\[a_A = \frac{1}{5}, \quad a_B = \frac{3}{5},\]
\[k_{1A} = \frac{4}{5}, \quad k_{2A} = \frac{9}{10},\]
\[k_{1B} = \frac{4}{5}, \quad k_{2B} = \frac{1}{10},\]
\[\mathbf{e}_{2121} = \frac{1}{40}, \quad \mathbf{e}_{2112} = \frac{7}{80},\]
\[\mathbf{e}_{1221} = \frac{1}{10}, \quad \mathbf{e}_{1212} = \frac{1}{80}\]

\[(2.9)\]
\[a_A = \frac{1}{5}, \quad a_B = \frac{3}{5},\]
\[k_{1A} = \frac{4}{5}, \quad k_{2A} = \frac{9}{10},\]
\[k_{1B} = \frac{4}{5}, \quad k_{2B} = \frac{1}{10},\]
\[\mathbf{e}_{2121} = \mathbf{e}_{1221} = \mathbf{e}_{2221} = \frac{9}{20},\]
\[\mathbf{e}_{2112} = \mathbf{e}_{1212} = \mathbf{e}_{2212} = \frac{22}{80}\]

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4.62
\[(2.10)\]

\[a_A = \frac{4}{5}, \quad a_B = \frac{3}{5},\]

\[k_{1A} = \frac{4}{5}, \quad k_{2A} = \frac{9}{10},\]

\[k_{1B} = \frac{4}{5}, \quad k_{2B} = \frac{1}{10}\]

\[\varepsilon_{2121} = \frac{19}{40}, \quad \varepsilon_{2122} = \frac{1}{40}, \quad \varepsilon_{2122} = \frac{1}{40},\]

\[\varepsilon_{1221} = \frac{55}{40}, \quad \varepsilon_{1222} = \frac{23}{40}, \quad \varepsilon_{1222} = \frac{19}{40},\]

\[\varepsilon_{2221} = \frac{9}{20}, \quad \varepsilon_{2221} = \frac{9}{20}\]

\[
\begin{bmatrix}
0 & 0.3 & 0.4125 & 0.75 \\
0.225 & 1 & 1 & 1 \\
0.0125 & 1 & 1 & 1 \\
0.25 & 1 & 1 & 1
\end{bmatrix}
\]

\[\sigma_{OPF} = 0.0541, \quad \sigma_{OPm} = 0.0540, \quad \sigma_{HSF} = 0.0272, \quad \sigma_{HSim} = 0.0271, \quad 0.0653\]

4.63
5. A Quantitative Genetic Model incorporating Genomic Imprinting and Environmental Effects

Abstract

A gene is imprinted when its level of expression is dependent on the sex of the parent it was inherited from. As a consequence, reciprocal heterozygotes in a population may display different mean phenotypic values for traits of interest. We here incorporate environmental effects into a standard quantitative genetic model with genomic imprinting acting. Environmental effects impact significantly on quantitative traits and may equally affect the phenotype of all individuals in a population, or may influence individuals with different genotypes uniquely via an interaction between genotype and environment. We here demonstrate that for a population residing in two environments, the latter of these two influences may have significant effect on variances in a population and covariances between relatives. Further, signatures in variance and covariance components that are expected as a consequence of imprinting may be masked by interactions between genotype and environment.

Introduction

The level of expression of an imprinted gene is dependent on the sex of the parent it was inherited from. Typically, both the maternally and paternally inherited alleles of an autosomal gene are expressed equally and regulated in concert. For imprinted genes, however, an allele inherited from one parent may be inactivated while the other is expressed. For example, insulin-like growth factor 2 (Igf2) is expressed only from the paternal allele in most fetal tissues of eutherian and marsupial mammals, while the maternally inherited allele is inactivated [DeChiara et al., 1991; O'Neill et al., 2000]. Differential expression of alleles of an imprinted gene may be dependent on the developmental stage of the organism or the specific tissue type. More generally, therefore, imprinting results in non-equivalence of reciprocal heterozygotes, where inheriting an $A_1$ allele from one’s mother and an $A_2$ allele from one’s father gives a different phenotype, on average, than the reverse inheritance pattern. Around 83 unique transcriptional units are imprinted in mammals, although imprinting status may be variable across species [Morison et al., 2005]. Interestingly,
imprinting status may also vary between individuals and within an individual over time [Pastinen et al., 2003; Sandovici et al., 2003; Naumova and Croteau, 2004].

Environmental effects are well known to influence the phenotype of individuals. For example, differences in maternal licking and grooming during nursing have a significant effect on behavioural response to stress in rat offspring [Liu et al., 1997; Caldji et al., 1998]. The maternal care given to female offspring correlates with the care she gives to her own offspring, but is a learned behaviour rather than a genomically inherited trait [Francis et al., 1999]. Such environmental effects may influence all individuals in a population or group equally, regardless of genotype. However, particular environments can also affect individuals with certain genotypes differently. Such influences are termed genotype by environment interactions [Lynch and Walsh, 1998]. For example, consider a single locus with two alleles, \( A_1 \) and \( A_2 \). A genotype by environment interaction would arise if \( A_1 \) alleles were repressed while \( A_2 \) alleles were expressed normally in a particular environment, as the environment would only affect the phenotype of individuals carrying an \( A_1 \) allele.

Quantitative genetic models aim to describe properties of populations for a trait of interest, such as the population mean value, variation in the population and resemblances between relatives. Typically, such models incorporate multiple loci as many genes, the environment and interaction between genotype and environment influence the quantitative phenotype. However we here develop a simple one locus quantitative genetic model with environmental effects to explore the influence genomic imprinting has on the expressions for population variance and resemblances between relatives. Such a model will form a basis for more complex analyses investigating the influence of multiple loci, environmental effects and genomic imprinting on quantitative traits.

**The Model**

Following the approach of Spencer [2002], consider a locus subject to imprinting, with alleles \( A_1 \) and \( A_2 \) at frequency \( p_1 \) and \( p_2 (=1 – p_1) \) respectively in the population. Assume that on some suitable scale, the genotypic value \( G \) of \( A_1A_1 \) homozygotes is \( G_{11} = 0 \) and of \( A_2A_2 \) homozygotes is \( G_{22} = 2a \). We incorporate imprinting by setting different values for the reciprocal heterozygotes. Writing the
maternally inherited allele first, \( A_2A_1 \) heterozygotes have genotypic value \( G_{21} = a(1+k_1) \) and \( A_1A_2 \) heterozygotes have value \( G_{12} = a(1+k_2) \) (Figure 1). In the absence of imprinting, \( k_1 = k_2 \) and reciprocal heterozygotes have equivalent genotypic values.

**Figure 1: Genotypic values for genotypes under genomic imprinting**

<table>
<thead>
<tr>
<th></th>
<th>( A_1A_1 )</th>
<th>( A_2A_1 )</th>
<th>( A_1A_2 )</th>
<th>( A_2A_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>( a(1+k_1) )</td>
<td>( a(1+k_2) )</td>
<td>( 2a )</td>
</tr>
</tbody>
</table>

Note that important parameters and notation introduced in this text are also summarized in Table 1.

The mean genotypic value over the population is

\[
\mu = \sum_{i,j=1}^{2} p_i p_j G_{ij} = a p_y (2 + p_y (k_1 + k_2)).
\]

We now add environmental effects to our model of imprinting. We define the phenotype \( z \) of an \( A_iA_j \) individual in environment \( h \) as

\[
z_{ij} = G_{ij} + I_{ij} + E_h
\]

Here \( E_h \) represents the constant effect environment \( h \) has on all individuals in the population, regardless of genotype. \( I_{ij} \) are genotype-environment interactions that differ for each genotype. This means that, in contrast to \( E_h \), the environment does not have the same effect on individuals with different genotypes.

We define two environments and assume that half of the population resides in environment \( Y \) (equivalently subpopulation \( Y \)), and the other half in environment \( Z \) (subpopulation \( Z \)), so that

\[
z_{yi} = G_{yi} + I_{yi} + E_Y
\]

for individuals in environment \( Y \) and

\[
z_{zi} = G_{zi} + I_{zi} + E_Z
\]

for individuals in environment \( Z \) [Lynch and Walsh, 1998]. Given that we are concerned only with two environments, we may further simplify the phenotypic expressions for individuals in environments \( Y \) and \( Z \) [Lynch and Walsh, 1998]. We assume that \( E_Z = -E_Y \), and hence \( E_Z = -E \) and \( E_Y = E \).
Now for each genotype, the average phenotype in the two environments must be equal to the genotypic value for that genotype, that is:

\[ G_y = \frac{1}{2} [z_{yij} + z_{zij}] \]
\[ = \frac{1}{2} [G_y + I_{yij} + E + G_y + I_{zij} - E] \]
\[ = G_y + \frac{1}{2} [I_{yij} + I_{zij}]. \]

Similarly, therefore, \( I_{zij} = -I_{yij} \), and we may term \( I_{zij} = -I_y \) and \( I_{yij} = I_y \). We therefore rewrite our phenotypic expressions as

\[ z_{yij} = G_y + I_y + E \]
for individuals in environment \( Y \) and
\[ z_{zij} = G_y - I_y - E \]
for individuals in environment \( Z \). Here we define the sum of \( G \) and \( I \) as the genetic effect for the individual, with \( E \) the remaining environmental effect. Phenotypic values for each genotype in the two environments are shown in Table 2 along with the mean phenotypic value of individuals in environments \( Y (\mu_Y) \) and \( Z (\mu_Z) \), assuming that \( p_Y = p_Z \). Note that the overall population mean \( \mu \) is equivalent to the mean genotypic value for a population with imprinting but no environmental effects defined above (refer Chapter 3).

We can now follow the approach of Falconer and Mackay [1996] and calculate genotypic deviations (\( gd \)), progeny means, breeding values (\( bv \)) and dominance deviations (\( dd \)) for each environment separately. Genotypic deviations (\( gd \)) for each genotype are the difference between the phenotypic value (\( z \)) and the mean for the environment, and are displayed in Table 4.

\[ gd_{yij} = z_{yij} - \mu_h; \]
\[ gd_{yij} = G_y + I_y + E - \mu_Y \]
\[ gd_{zij} = G_y - I_y - E - \mu_Z \]

We next calculate the average phenotypic value of progeny of mothers and fathers with genotype \( A_iA_j \). For example, a heterozygous mother contributes equal numbers of \( A_1 \) and \( A_2 \) alleles to offspring. Fathers contribute \( A_1 \) alleles at frequency \( p_1 \) and \( A_2 \) alleles at frequency \( p_2 \). Hence the average phenotypic value of progeny of a heterozygous mother in environment \( h \) is

\[ \frac{1}{2} p_1 [z_{h11} + z_{h21}] + \frac{1}{2} p_2 [z_{h12} + z_{h22}]. \]
In contrast, the average value of progeny of a heterozygous father is
\[ \frac{1}{2} p_1 z_{a11} + z_{a12} + \frac{1}{2} p_2 z_{a21} + z_{a22}. \]

Average phenotypic values of progeny are displayed in Table 3 for environments Y and Z. When progeny means from each environment are combined we retrieve an overall population progeny mean that is equivalent to a population without environmental effects acting (refer Chapter 3).

Breeding values for each genotype are defined as twice the difference between the progeny mean and the subpopulation mean. For example, the breeding value for \(A_2A_2\) females in environment \(Z\) is
\[
\text{bv}_{Zj_{22}} = 2[a(p_1(1+k_1)+2p_2) - I_{21}p_1 - I_{22}p_2 - E - \mu_Z]
\]
\[
= 2p_1[a(1+k_1)p_1 - k_2p_2) + p_1(I_{11} - I_{21}) + p_2(I_{12} - I_{22})].
\]

Finally, we may calculate the dominance for each genotype in each environment, the difference between the genotypic deviation and the breeding value. Genotypic deviations, breeding values and dominance deviations are displayed in Table 4. Note that we use the terms \(\alpha_f\) and \(\alpha_m\) to abbreviate expressions, where
\[
\alpha_f = a(1+k_1p_1 - k_2p_2) \quad \text{and} \quad \alpha_m = a(1+k_2p_1 - k_1p_2).
\]

**Genetic variance components**

The total genetic effect variance in each subpopulation (\(\sigma_{Gh}^2\)) is the variance of the genotypic deviations:
\[
\sigma_{Gy}^2 = \sum p_jp_j g \sigma_{yij}^2
\]
\[
= p_1 p_2 (\alpha_f^2 + \alpha_m^2 + a^2 p_1 p_2 (k_1 + k_2)^2)
\]
\[
+ I_{11}^2 p_1^2 + I_{21}^2 p_1 p_2 + I_{12}^2 p_1 p_2 + I_{22}^2 p_2^2 - (I_{11} p_1^2 + I_{21} p_1 p_2 + I_{12} p_1 p_2 + I_{22} p_2^2)^2
\]
\[
- 2a p_1 p_2 [I_{11} p_1 (2 + p_1(k_1 + k_2)) - I_{21} (p_1 - p_2 - p_1p_2k_2 + k_4 (1-p_1p_2))]
\]
\[
- I_{12} (p_1 - p_2 - p_1p_2 k_1 + k_2 (1-p_1p_2)) + I_{22} p_2^2 (2 + p_2 (k_1 + k_2))]
\]
and
\[
\sigma_{GZ}^2 = \sum_{ij} p_i p_j g d_{zij}
\]
\[
= p_i p_j (\alpha_f^2 + \alpha_m^2 + \alpha^2 p_1 p_2 (k_1 + k_2)^2)
\]
\[+ I_{11i}^2 p_i^2 + I_{21i}^2 p_i p_2 + I_{22i}^2 p_2^2 - (I_{11i} p_i^2 + I_{21i} p_i p_2 + I_{22i} p_2^2)^2
\]
\[+ 2a p_i p_j I_{11} p_2 (2 + p_i (k_1 + k_2)) - I_{21} (p_i - p_2 - p_i p_2 k_2 + k_2 (1 - p_i p_2))
\]
\[- I_{22} (p_i - p_2 - p_i p_2 k_1 + k_1 (1 - p_i p_2)) + I_{22} p_2 (2 + p_2 (k_1 + k_2)).
\]

Recalling
\[
\mu_Y = a p_i (2 + p_i (k_1 + k_2)) + E + I_{11} p_i^2 + p_i p_2 (I_{21} + I_{12}) + I_{22} p_2^2
\]
\[
\mu_Y = a p_i (2 + p_i (k_1 + k_2)) - E - I_{11} p_i^2 - p_i p_2 (I_{21} + I_{12}) - I_{22} p_2^2
\]

and that
\[
gd_{yi} = G_y + I_i + E - \mu_Y
\]
\[
gd_{zi} = G_y - I_i - E - \mu_Z
\]

we can see that the total genetic effect variances for each environment do not involve terms in \(E\), as expected. Hence we can write the expressions for total variance as
\[
\sigma_{Gh}^2 = \text{var}(\tilde{G} + \tilde{I}_h) = \sigma_G^2 + \sigma_I^2 + 2\sigma_{G,I}
\]

where \(\tilde{G}\) and \(\tilde{I}\) represent genetic and interaction terms less the mean for each environment. Further, given we are concerned only with two environments, we may write
\[
\sigma_{GV}^2 = \text{Var}(\tilde{G} + \tilde{I}) = \sigma_G^2 + \sigma_I^2 + 2\sigma_{G,I}
\] and
\[
\sigma_{GZ}^2 = \text{Var}(\tilde{G} - \tilde{I}) = \sigma_G^2 + \sigma_I^2 - 2\sigma_{G,I}
\]

where, from above,
\[
\sigma_G^2 = p_i p_j (\alpha_f^2 + \alpha_m^2 + \alpha^2 p_1 p_2 (k_1 + k_2)^2)
\]
\[
\sigma_I^2 = I_{11i}^2 p_i^2 + I_{21i}^2 p_i p_2 + I_{22i}^2 p_2^2 - (I_{11i} p_i^2 + I_{21i} p_i p_2 + I_{22i} p_2^2)^2
\]

and
\[
\sigma_{G,I} = a p_i p_j [I_{11i} p_2 (2 + p_i (k_1 + k_2)) - I_{21i} (p_i - p_2 - p_i p_2 k_2 + k_2 (1 - p_i p_2))
\]
\[- I_{22i} (p_i - p_2 - p_i p_2 k_1 + k_1 (1 - p_i p_2)) + I_{22i} p_2 (2 + p_2 (k_1 + k_2)].
\]

[Lynch and Walsh, 1998].
We may also calculate the covariance in genetic effects between the two environments:

\[
\sigma_{GYZ} = \sum_{ij} p_ip_j gd_{i1} gd_{2j} \\
= p_1p_2(\alpha_f^2 + \alpha_m^2 + 2^{p_1p_2}(k_1 + k_2)^2) \\
- [I_{11}p_1^2 + I_{21}p_1p_2 + I_{12}^2p_1p_2 + I_{22}^2p_2^2 - (I_{11}p_1^2 + I_{21}p_1p_2 + I_{12}^2p_1p_2 + I_{22}^2p_2^2)^2].
\]

As above, this may be written as

\[
\sigma_{GYZ} = \text{cov}[(\hat{G} + \hat{I})(\hat{G} - \hat{I})] \\
= \sigma_G^2 - \sigma_I^2
\]

[Lynch and Walsh, 1998].

Finally, following Lynch and Walsh [1998], the variance in genetic terms, variance in interaction terms and covariance between these terms may be dissected from the expressions for the total genetic effect variances and covariances between environments:

\[
\sigma_G^2 = \frac{1}{4}(\sigma_{GV}^2 + \sigma_{GZ}^2) + \frac{1}{4}\sigma_{GYZ} \\
\sigma_I^2 = \frac{1}{4}(\sigma_{GV}^2 + \sigma_{GZ}^2) - \frac{1}{4}\sigma_{GYZ} \\
\sigma_{G,I} = \frac{1}{4}(\sigma_{GV}^2 - \sigma_{GZ}^2).
\]

The additive genetic variances for females and males are the respective variances of their breeding values:

\[
\sigma_{AY}^2 = \sum_{ij} p_ip_j b_{Yij}^2 \\
= 2p_1p_2[\alpha_f - p_1(I_{11} - I_{21})] + 2p_1p_2[I_{11}I_{21} - I_{12}I_{22}] \\
\sigma_{AYm}^2 = \sum_{ij} p_ip_j b_{Ymij}^2 \\
= 2p_1p_2[\alpha_m - p_1(I_{11} - I_{12})] + 2p_1p_2[I_{11}I_{12} - I_{12}I_{22}] \\
\sigma_{AZf}^2 = \sum_{ij} p_ip_j b_{Zij}^2 \\
= 2p_1p_2[\alpha_f + p_1(I_{11} - I_{21}) + p_2(I_{12} - I_{22})]^2
\]

and

\[
\sigma_{AZm}^2 = \sum_{ij} p_ip_j b_{Zmij}^2 \\
= 2p_1p_2[\alpha_m + p_1(I_{11} - I_{12}) + p_2(I_{12} - I_{22})]^2.
\]
The dominance genetic variance is the variance of the dominance deviations, and is the same for both males and females.

\[ \sigma_{DY}^2 = \sum_{ij} p_i p_j d^2_{ij} = \sum_{ij} p_i p_j d^2_{mij} \]

\[ = a^2 + p_1 p_2 [(k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2] + p_1 p_2 (I_{21} - I_{12}) (I_{11} p_1 - I_{22} p_2) \]

\[ + p_1^2 p_2^2 (I_{11} - I_{21} - I_{12} + I_{22}) (I_{11} p_1 - I_{22} p_2 - 2a(k_1 + k_2)) \]

\[ \sigma_{DZ}^2 = \sum_{ij} p_i p_j d^2_{zij} = \sum_{ij} p_i p_j d^2_{zmi} \]

\[ = a^2 + p_1 p_2 [(k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2] + p_1 p_2 (I_{21} - I_{12}) (I_{11} p_1 - I_{22} p_2) \]

\[ + p_1^2 p_2^2 (I_{11} - I_{21} - I_{12} + I_{22}) (I_{11} p_1 - I_{22} p_2 + 2a(k_1 + k_2)) \]

The covariances between dominance deviations and breeding values can be shown to be

\[ \sigma_{ADf} = \sum_{ij} p_i p_j b_{v_{ij}} d_{ij} dd_{ij} \]

\[ = ap_1 p_2 \alpha_f (k_2 - k_1) \]

\[ + p_1 p_2 [I_{21} p_1 - I_{12} p_2 + I_{21} I_{12} - (I_{21} - I_{12})(I_{11} p_1 - I_{22} p_2)] \]

\[ + a (I_{21} (1 - k_2 + 2k_2 p_2) + I_{12} (1 + k_1 - 2k_2 p_2) + (k_1 - k_2)(I_{11} p_1 - I_{22} p_2)) \]

\[ \sigma_{ADm} = \sum_{ij} p_i p_j b_{v_{mij}} d_{mij} dd_{mij} \]

\[ = ap_1 p_2 \alpha_m (k_1 - k_2) \]

\[ + p_1 p_2 [I_{12} p_1 - I_{21} p_2 + I_{21} I_{12} - (I_{21} - I_{12})(I_{11} p_1 - I_{22} p_2)] \]

\[ - a (I_{21} (1 + k_2 - 2k_1 p_2) + I_{12} (1 - k_1 + 2k_1 p_2) + (k_1 - k_2)(I_{11} p_1 - I_{22} p_2)) \]

\[ \sigma_{ADf} = \sum_{ij} p_i p_j b_{v_{df}} d_{df} dd_{df} \]

\[ = ap_1 p_2 \alpha_f (k_2 - k_1) \]

\[ + p_1 p_2 [I_{21} p_1 - I_{12} p_2 + I_{21} I_{12} - (I_{21} - I_{12})(I_{11} p_1 - I_{22} p_2)] \]

\[ - a (I_{21} (1 - k_2 + 2k_2 p_2) + I_{12} (1 + k_1 - 2k_2 p_2) + (k_1 - k_2)(I_{11} p_1 - I_{22} p_2)) \]

\[ \sigma_{ADm} = \sum_{ij} p_i p_j b_{v_{dm}} d_{dm} dd_{dm} \]

\[ = ap_1 p_2 \alpha_m (k_1 - k_2) \]

\[ + p_1 p_2 [I_{12} p_1 - I_{21} p_2 + I_{21} I_{12} - (I_{21} - I_{12})(I_{11} p_1 - I_{22} p_2)] \]

\[ + a (I_{21} (1 + k_2 - 2k_1 p_2) + I_{12} (1 - k_1 + 2k_1 p_2) + (k_1 - k_2)(I_{11} p_1 - I_{22} p_2)) \]

and it can be easily shown that

\[ \sigma_{GY}^2 = \sigma_{AY}^2 + \sigma_{DY}^2 + 2 \sigma_{ADf} \]

\[ = \sigma_{AY}^2 + \sigma_{DY}^2 + 2 \sigma_{ADm} \]
and
\[
\sigma^2_{GZ} = \sigma^2_{AZ} + \sigma^2_{DZ} + 2\sigma_{ADZ} \\
= \sigma^2_{AZm} + \sigma^2_{DZ} + 2\sigma_{ADZm}.
\]

Covariances between relatives

We now follow the approach of Kempthorne [1957] to calculate covariances between relatives. Using Table 5 we may calculate the covariance between mothers and offspring (\(\sigma_{OPm}\), covariance between Offspring and female Parent) and fathers and offspring (\(\sigma_{OPf}\), covariance between Offspring and male Parent). Now

\[
\sigma_{OPm} = \sum_j p_i p_j (\mu_j - \mu_i)(A_{mi}A_{hj} \text{ progeny mean } - \mu_i);
\]

\[
\sigma_{OPf} = \frac{1}{2} p_i p_j [\alpha_f (a(k_i - k_j) + 2\alpha_f) \\
-4\alpha_f (p_i (I_{11} - I_{21}) + p_j (I_{12} - I_{22})) \\
+ a(-I_{21}(1-k_j + 2k_j p_j) + I_{12}(1-k_i + 2k_i p_i) + (k_i - k_j)(I_{11}p_i - I_{22}p_j)) \\
+ 2(p_i (I_{11} - I_{21}) + p_j (I_{12} - I_{22}))^2 \\
- I_{21}^2p_i - I_{22}^2p_j + I_{21}I_{22} + (I_{11} - I_{12})(I_{11}p_i - I_{22}p_j)]
\]

\[
\sigma_{OPm} = \frac{1}{2} p_i p_j [\alpha_m (a(k_i - k_j) + 2\alpha_m) \\
-4\alpha_m (p_i (I_{11} - I_{12}) + p_j (I_{21} - I_{22})) \\
- a(-I_{21}(1-k_j + 2k_j p_j) + I_{12}(1-k_i + 2k_i p_i) + (k_i - k_j)(I_{11}p_i - I_{22}p_j)) \\
+ 2(p_i (I_{11} - I_{12}) + p_j (I_{21} - I_{22}))^2 \\
- I_{12}^2p_i - I_{11}^2p_j + I_{12}I_{11} + (I_{21} - I_{22})(I_{11}p_i - I_{22}p_j)]
\]

\[
\sigma_{OPf} = \frac{1}{2} p_i p_j [\alpha_f (a(k_i - k_j) + 2\alpha_f) \\
+ 4\alpha_f (p_i (I_{11} - I_{21}) + p_j (I_{22} - I_{21})) \\
- a(-I_{21}(1-k_j + 2k_j p_j) + I_{12}(1-k_i + 2k_i p_i) + (k_i - k_j)(I_{21}p_i - I_{22}p_j)) \\
+ 2(p_i (I_{11} - I_{21}) + p_j (I_{22} - I_{21}))^2 \\
- I_{21}^2p_i - I_{22}^2p_j + I_{21}I_{22} + (I_{21} - I_{22})(I_{21}p_i - I_{22}p_j)]
\]

\[
\sigma_{OPm} = \frac{1}{2} p_i p_j [\alpha_m (a(k_i - k_j) + 2\alpha_m) \\
+ 4\alpha_m (p_i (I_{11} - I_{12}) + p_j (I_{12} - I_{22})) \\
+ a(-I_{21}(1-k_j + 2k_j p_j) + I_{22}(1-k_i + 2k_i p_i) + (k_i - k_j)(I_{11}p_i - I_{22}p_j)) \\
+ 2(p_i (I_{11} - I_{12}) + p_j (I_{12} - I_{22}))^2 \\
- I_{12}^2p_i - I_{11}^2p_j + I_{12}I_{11} + (I_{11} - I_{12})(I_{11}p_i - I_{22}p_j)]
\]
The expressions for these covariances can be simplified as

\[ \sigma_{\text{OPY}} = \frac{1}{2} (\sigma_{AY}^2 + \sigma_{ADY}^2) \]
\[ \sigma_{\text{OPn}} = \frac{1}{2} (\sigma_{An}^2 + \sigma_{ADYn}^2) \]
\[ \sigma_{\text{OPm}} = \frac{1}{2} (\sigma_{Am}^2 + \sigma_{ADYm}^2) \]

and

\[ \sigma_{\text{OPZ}} = \frac{1}{2} (\sigma_{AZ}^2 + \sigma_{ADZ}^2) \]

following Spencer [2002]. The full-sib covariance for environment Y may be calculated with the aid of Table 6. Now

\[ \sigma_{FSY} = \sum_{\text{offspring pairs}} fr(\text{offspring } z_{ij} - \mu_i)(\text{offspring } z_{ij} - \mu_i) \]

\[ = \frac{1}{4} p_1 p_2 (a^2 p_1 p_2 (k_1 + k_2)^2 + 2(\alpha_f^2 + \alpha_m^2)) + 2d((k_1 + k_2)(3p_1 p_2 (I_{11} - I_{12} - I_{21} + I_{22}) - 2(I_{11} p_1 + I_{22} p_2)) + 2(I_{21} k_1 + I_{12} k_2 - 2I_{11} p_1 + (I_{21} + I_{12})(p_1 - p_2) + 2I_{22} p_2)] + 3[I_{11} p_1^2 - p_1 p_2 (I_{11}^2 + I_{12}^2) + I_{22} p_2^2 - 2I_{21} I_{12} p_1 p_2 - I_{11} p_1 (2p_1 (I_{21} + I_{12}) + I_{22} p_2) - I_{22} p_2 (2p_1 (I_{21} + I_{12}) + I_{11} p_1)] + I_{11} p_1 + 2(I_{21} + I_{12}) + I_{22} p_2 + 2(I_{21} + I_{12})(I_{11} p_1 + I_{22} p_2)], \]

and similarly

\[ \sigma_{FSZ} = \frac{1}{4} p_1 p_2 (a^2 p_1 p_2 (k_1 + k_2)^2 + 2(\alpha_f^2 + \alpha_m^2)) \]

\[ = -2d((k_1 + k_2)(3p_1 p_2 (I_{11} - I_{12} - I_{21} + I_{22}) - 2(I_{11} p_1 + I_{22} p_2)) + 2(I_{21} k_1 + I_{12} k_2 - 2I_{11} p_1 + (I_{21} + I_{12})(p_1 - p_2) + 2I_{22} p_2)] + 3[I_{11} p_1^2 - p_1 p_2 (I_{11}^2 + I_{12}^2) + I_{22} p_2^2 - 2I_{21} I_{12} p_1 p_2 - I_{11} p_1 (2p_1 (I_{21} + I_{12}) + I_{22} p_2) - I_{22} p_2 (2p_1 (I_{21} + I_{12}) + I_{11} p_1)] + I_{11} p_1 + 2(I_{21} + I_{12}) + I_{22} p_2 + 2(I_{21} + I_{12})(I_{11} p_1 + I_{22} p_2)], \]

which simplifies to

\[ \sigma_{FSY} = \frac{1}{4} (\sigma_{AY}^2 + \sigma_{AYm}^2 + \sigma_{DY}^2 + \sigma_{ADY}^2 + \sigma_{ADYm}^2). \]

Interestingly, this may also be written as

\[ \sigma_{FSY} = \frac{1}{2} \sigma_{AY}^2 + \frac{1}{4} \sigma_{DY}^2 + \frac{1}{2} \sigma_{ADY} + \frac{1}{4} \sigma_{ADYm} \]

\[ = \frac{1}{2} \sigma_{AYm}^2 + \frac{1}{4} \sigma_{DY}^2 + \frac{1}{2} \sigma_{ADY} + \frac{1}{4} \sigma_{ADYm}. \]

Similarly, for environment Z,

\[ \sigma_{FSZ} = \frac{1}{4} (\sigma_{AZ}^2 + \sigma_{AZm}^2 + \sigma_{DZ}^2 + \sigma_{ADZ}^2 + \sigma_{ADZm}). \]
or equivalently
\[
\sigma_{FSZ} = \frac{1}{2} \sigma_{ADZ}^2 + \frac{1}{2} \sigma_{DZ}^2 + \frac{1}{2} \sigma_{ADZf} - \frac{1}{4} \sigma_{ADZm} \\
= \frac{1}{2} \sigma_{ADZm} + \frac{1}{2} \sigma_{DZ}^2 + \frac{1}{4} \sigma_{ADZf} - \frac{1}{4} \sigma_{ADZm}.
\]

Finally, we may also calculate the covariance between offspring who share a mother or a father. Following Spencer [2002], the covariance of half siblings who share a mother is
\[
\sigma_{HSf} = \frac{1}{4} \sigma_{AF}^2;
\]
\[
\sigma_{HSYf} = \frac{1}{4} \sigma_{AY}^2
\]
\[
= \frac{1}{2} p_1 p_2 [\alpha_f - p_1 (I_{11} - I_{21}) - p_2 (I_{12} - I_{22})]^2
\]
\[
\sigma_{HSf} = \frac{1}{4} \sigma_{AF}^2
\]
\[
= \frac{1}{2} p_1 p_2 [\alpha_f + p_1 (I_{11} - I_{21}) + p_2 (I_{12} - I_{22})]^2
\]
and the covariance of half sibs sharing a father is
\[
\sigma_{HSm} = \frac{1}{4} \sigma_{Am}^2;
\]
\[
\sigma_{HSm} = \frac{1}{4} \sigma_{Am}^2
\]
\[
= \frac{1}{2} p_1 p_2 [\alpha_m - p_1 (I_{11} - I_{12}) - p_2 (I_{21} - I_{22})]^2
\]
\[
\sigma_{HSm} = \frac{1}{4} \sigma_{Am}^2
\]
\[
= \frac{1}{2} p_1 p_2 [\alpha_m + p_1 (I_{11} - I_{12}) + p_2 (I_{21} - I_{22})]^2.
\]

**Discussion**

In developing this quantitative genetic model incorporating environmental effects and imprinting, it is of most interest to investigate the effect these influences will have on population characteristics and resemblances between relatives. Specifically, we wish to assess whether genotype by environment interactions are likely to mask the effect of imprinting on a quantitative trait of interest. We therefore use illustrative examples to investigate the environmental influence on an imprinted trait.

**Standard model: no environmental effects or imprinting**

We begin by investigating the effect that imprinting and environmental effects have separately on our expressions for population variances and resemblances between relatives. Let us first assume that neither imprinting nor environmental
effects are acting in the population. We set all genotype-environment interactions and environmental effects to zero, that is $I_{hi} = 0$ and $E = 0$. Following Chapter 3, we may assume that no imprinting is acting in the population by setting the values of reciprocal heterozygotes equal such that $k_i = k_2 = k$. We now assume that the range of genotypic values lies between 0 and 1 so that $a = \frac{1}{2}$, and set $k = \frac{1}{20}$, corresponding to genotypic values of 0, $\frac{9}{20}$, and 1 for $A_1A_1$, $A_1A_2$ (=$A_2A_1$) and $A_2A_2$ genotypes respectively. Let $p_1 = p_2 = \frac{1}{2}$. Total, additive and dominance variances for the population may be seen in Row 1 of Table 7. Note that, as expected in the absence of imprinting, the covariance between additive and dominance effects is zero (Row 1, Column 5). Table 8, Row 1, calculates covariances between relatives for the population without imprinting or environmental effects acting.

**Effect of imprinting only**

We now add imprinting to our model. Recall that an $A_iA_j$ individual has a maternally inherited $A_i$ allele and a paternally inherited $A_j$ allele. Let us assume that for all individuals, the paternally inherited $A_j$ allele is almost completely inactivated. We set $k_i = \frac{8}{10}$ and $k_2 = \frac{9}{10}$ and note that genotypic values are now 0, $\frac{1}{10}$, $\frac{9}{10}$ and 1 for $A_1A_1$, $A_1A_2$, $A_2A_1$ and $A_2A_2$ genotypes respectively. From Table 7 (Row 2), we can see that under imprinting, the additive variances and additive by dominance covariances are different for males and females [Spencer, 2002]. Because paternal alleles are almost silenced, the additive variance in females is much larger than that in males (Row 2, Column 3). We may also see that including imprinting to the model increases the total variance of the population, as would be expected by adding another genotypic value to the model. In addition, the dominance variance is much larger than in a population with no imprinting acting (Row 2, Column 4). Table 8 shows resemblances between relatives, and as would be expected from paternal inactivation, the covariances between mothers and offspring and between half sibs sharing a mother greatly exceed the covariances between fathers and offspring and half sibs sharing a father respectively. Finally of note, we can see that in the absence of imprinting the greatest covariance between relatives is between full sibs, with $\sigma_{fs} = 0.06254$. In contrast, in a population with paternal inactivation of alleles, the covariance between mothers and offspring is largest; $\sigma_{opf} = 0.1156$. 

5.12
Effect of genotype-environment interactions

Let us now add environmental effects, but not imprinting, to our model. We again set $k_1 = k_2 = k = \frac{1}{2}$ and $a = \frac{1}{2}$. Tables 7 and 8 show subpopulation variance and covariance terms, and resemblances between relatives, for four cases of genotype by environment interaction: where the interaction between genotype and environment is zero for homozygotes but $\frac{1}{2}$ (row 3, Tables 7 and 8) or $\frac{1}{10}$ (row 4) for heterozygotes, and where the interaction is zero for heterozygotes but $\frac{1}{2}$ (row 5) or $\frac{1}{10}$ (row 6) for homozygotes. These four cases correspond to phenotypic values of $\{0, \frac{36}{40}, 1\}$, $\{0, \frac{23}{40}, 1\}$, $\{\frac{1}{2}, \frac{10}{20}, \frac{3}{2}\}$ and $\{\frac{1}{10}, \frac{10}{20}, \frac{11}{10}\}$ for $\{A_1A_1, A_1A_2 (=A_2A_1), A_2A_2\}$ in environment $Y$ and $\{0, \frac{36}{40}, 1\}$, $\{0, \frac{23}{40}, 1\}$, $\{\frac{1}{2}, \frac{10}{20}, \frac{3}{2}\}$ and $\{\frac{1}{10}, \frac{10}{20}, \frac{9}{10}\}$ in environment $Z$.

The first observation of note from the models including environmental effects is that regardless of the values for interaction terms, the additive by dominance covariance is always zero, as expected in the absence of imprinting. Further, the additive variance in both environments is always 0.1250 and is in this case unaffected by the magnitude of the interaction between genotype and environment. Also of interest is that when interaction terms are small ($\frac{1}{10}$), the total variance in genetic effects in each of the environments is similar to that in a single population without imprinting, as expected. We may moreover see that the same variances appear in subpopulations $Y$ and $Z$ through the table: for instance, $\sigma_{G_Y}^2 = 0.1814$ in Row 3, Column 1 and $\sigma_{G_Z}^2 = 0.1814$ in Row 5, Column 1. This is not surprising when we see that phenotypic values for these two situations are $\{0, \frac{36}{40}, 1\}$ (environment $Y$) and $\{\frac{1}{2}, \frac{10}{20}, \frac{3}{2}\}$ (environment $Z$) – the distribution of these values across the genotypes are identical although the subpopulation means are different. This symmetry is repeated for all situations: Column 3, environment $Z =$ Column 5, environment $Y$, Column 4, environment $Y =$ Column 6, environment $Z$ and Column 4, environment $Z =$ Column 6, environment $Y$, and dominance variances for the subpopulations follow an identical pattern.

In terms of covariances between relatives, we can see that relatedness between offspring and parents and between half sibs sharing a mother or father are identical regardless of the magnitude (compare Rows 3 & 5 and Rows 4 & 6) or direction (compare environment $Y$ to $Z$ each Row) of interactions. However, we can see slight
differences between the covariances between full sibs between environments and
different strengths of interaction. The greatest covariance between full sibs may be
seen to correspond to the subpopulation with the largest genetic variance (Table 7) –
for example, for row 3, $\sigma_{GZ}^2 > \sigma_{GY}^2$ and hence $\sigma_{FSZ}^2 > \sigma_{FSY}^2$.

**Effect of genotype-environment interactions and imprinting**

With these results in mind, we may now examine the relationships between
variances and covariances across the two environments for a population where
imprinting is acting. Table 9 details the population genetic variances, additive and
dominance variances and covariances between environments and between additive
and dominance effects for subpopulations with environmental effects and imprinting
acting. Table 10 shows resemblances between relatives including covariances
between offspring and male and female parents, between fullsibs and between halfsibs
sharing a female or male parent for the two environments.

Figures 2.1-2.6 illustrate the conditions we have placed on the interactions
between genotype and environment. We note that these figures and tables do not
include a general environmental effect $E$ because, as discussed above, terms involving
$E$ do not appear in expressions for variances or covariances. This makes sense
because such a general environmental effect is shared by all members of a
subpopulation and so will not increase or decrease variance or covariance terms when
considering that subpopulation.

Figures 2.1-2.6 explore a number of possibilities for genotype by environment
interactions. Figure 2.1 sets genotype by environment interactions identical for
genotypes most similar in genotypic value; that is, $A_1A_1$ & $A_1A_2$, and $A_2A_1$ & $A_2A_2$
share identical interaction terms. Figure 2.2 sets interaction terms for homozygotes
equal and heterozygotes equal while Figure 2.3 sets the interaction between genotype
and environment equivalent for $A_1A_1$ & $A_2A_1$. Note that in these figures, the genotype
by environment interactions are positive for environment $Y$ and negative for
environment $Z$. Figures 2.4-2.6 represent cases where one genotype has a positive
genotype by environment interaction while another has a negative interaction of the
same magnitude. For Figure 2.4, in environment $Y A_1A_1$ has a positive interaction
while $A_1A_2$ has a negative interaction (and vice versa for environment $Z$). Figures 2.5a
and 2.5b represent a positive and negative interaction for $A_1A_1$ & $A_2A_2$ genotypes and
$A_1A_2$ & $A_2A_1$ genotypes respectively in environment $Y$. Finally, Figure 2.6 represents a positive interaction for $A_1A_1$ and a negative interaction for $A_2A_1$ in environment $Y$. These conditions are specified in the Figure legends and also in Tables 9 and 10. Note that we follow the examples in Tables 7 and 8 by choosing the magnitude of interactions to be both weak ($=\frac{1}{10}$) and strong ($=\frac{1}{2}$) for each of the conditions.

**Figure 2.1: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{12}, I_{21} = I_{22} = 0$**

![Figure 2.1: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{12}, I_{21} = I_{22} = 0$](image1)

**Figure 2.2: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{22}, I_{12} = I_{21} = 0$**

![Figure 2.2: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{22}, I_{12} = I_{21} = 0$](image2)

**Figure 2.3: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{21}, I_{12} = I_{22} = 0$**

![Figure 2.3: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{21}, I_{12} = I_{22} = 0$](image3)
Figure 2.4: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{21}, I_{22} = 0$

Figure 2.5a: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{22}, I_{12} = I_{21} = 0$

Figure 2.5b: Interaction terms for Environments $Y$ and $Z$; $I_{11} = I_{22} = 0, I_{12} = -I_{21}$

Figure 2.6: Interaction terms for Environments $Y$ and $Z$; $I_{11} = -I_{21}, I_{12} = I_{22} = 0$
It is expected that for many of the above situations, the interaction terms will mirror the effect of imprinting, where heterozygotes are relatively different in their expected phenotypic values and are most similar in value to the homozygote corresponding to their maternally inherited allele. Therefore, patterns in variances, covariances and resemblances in each subpopulation are likely to be similar to those seen under imprinting alone. However, if heterozygotes in one environment are grouped closely together as a consequence of the interaction terms, we can expect that the effect of imprinting may be masked for that subpopulation.

**Environment and imprinting effects: population variances**

Considering total population genetic variances (Table 9, Column 1), we can see that the smallest subpopulation variance is \( \sigma_{GY}^2 = 0.0467 \) (Row 1, Column 1), corresponding to the population with the smallest range in phenotypic values of \( \frac{1}{2} \) (Figure 2.1 with \( I_{11} = I_{12} = \frac{1}{2} \) giving phenotypic values of \( \{ \frac{1}{2}, \frac{1}{10}, \frac{1}{10}, 1 \} \) for \( \{A_1A_1, A_1A_2, A_2A_1, A_2A_2\} \) in environment \( Y \)). The largest total population variance is \( \sigma_{GZ}^2 = 0.5905 \) (Row 9, Column 1) corresponding to the largest range in phenotypic values of 2 (Figure 2.5a with \( I_{11} = \frac{1}{2} \) and \( I_{22} = \frac{3}{2} \) giving phenotypic values of \( \{\frac{1}{2}, \frac{1}{10}, \frac{9}{10}, \frac{3}{2}\} \) for \( \{A_1A_1, A_1A_2, A_2A_1, A_2A_2\} \) in environment \( Z \)). The variance in environment \( Y \) for this situation (phenotypic values \( \{\frac{1}{2}, \frac{1}{10}, \frac{9}{10}, \frac{1}{2}\} \); range \( \frac{9}{10} - \frac{1}{10} = \frac{8}{10} \) ) is \( \sigma_{GY}^2 = 0.0905 \), and the difference in variances between environments is also largest for this situation at \( \sigma_{GZ}^2 - \sigma_{GY}^2 = 0.5000 \), corresponding to the largest difference between the ranges of phenotypic values for the two environments. The total variance in environment \( Z \) exceeds that in environment \( Y \) except for Figure 2.2, Rows 3 and 4, the only situations where the range in phenotypic values is largest for environment \( Y \). As expected, the majority of population variances are above what would be expected for populations with imprinting or environmental effects alone (from Table 7), as both of these effects increase variation in phenotypic values for individuals in a population.

The covariances between environments \( Y \) and \( Z \) appear not to be dependent upon the nature of genotype by environment interaction but do differ according to the magnitude of these interactions, with \( \sigma_{GYZ} = 0.1530 \) when \( I = \pm \frac{1}{2} \) and \( \sigma_{GYZ} = 0.2130 \) when \( I = \pm \frac{1}{10} \). These covariances are larger than what is expected under environmental effects alone, without imprinting acting (Table 7).
Additive genetic variances show a number of interesting patterns. As expected under imprinting, additive variances differ for males and females. In general $\sigma^2_{Af} > \sigma^2_{Am}$ for both environments. However, where the value of both homozygotes is identical (Row 9, Column 3; phenotypic values for environment $Y$ \{\(\frac{1}{10}, \frac{9}{10}\), \(\frac{1}{7}\)\}), we see that $\sigma^2_{AfY} = \sigma^2_{Afm} = 0.0903$. Further, where the value of $A_1A_2$ exceeds the phenotypic value of $A_2A_1$ (Row 11, Column 3; phenotypic values for environment $Y$ \{0, \(\frac{11}{20}\), \(\frac{8}{20}\), ]\}), the male additive variance exceeds the female additive variance $(\sigma^2_{Af} = 0.0903; \sigma^2_{Am} = 0.1653)$. For this situation we can see that in environment $Z$, the female additive variance far exceeds the male additive variance. Thus, in one environment this signature of imprinting is reinforced, while in the other it appears that maternal, not paternal, alleles have been inactivated.

There is an interesting relationship between the additive genetic variances of a number of the situations: Rows 1 & 13, 2 & 14, 5 & 7 and 6 & 8 share identical additive variances for environments $Y$ and $Z$ and for males and females, as do Rows 3 & 4 (Column 3, Table 9). Although phenotypic ranges for these situations differ, it is worthy of note that situations sharing identical additive variances also share identical differences between the phenotypic values of homozygotes and of heterozygotes. For example, Rows 1 and 13 represent a phenotypic difference of $\frac{1}{7}$ between homozygotes and $\frac{7}{20}$ between heterozygotes in environment $Y$, and differences of $\frac{3}{7}$ between homozygotes and $\frac{37}{20}$ between heterozygotes in environment $Z$.

Rows 9 and 10 share identical dominance variances while variances for rows 1 & 5 and 2 & 6 are swapped for environments $Y$ and $Z$. The largest $(\sigma^2_{Dy} = 0.8558)$ (Row 11, Column 3) and smallest $(\sigma^2_{Dy} = 0.0058)$ (Row 11, Column 3) dominance variances correspond to the largest and smallest differences between reciprocal heterozygotes in the respective populations.

Finally, we may see that as expected with imprinting acting, the covariances between additive and dominance effects are non zero for all situations, and male and female covariances are not equal. Female covariances are all negative except environment $Y$, Row 11, representing the smallest difference between the values of reciprocal heterozygotes and the only situation where the value of $A_1A_2$ exceeds $A_2A_1$. As with additive variances, the values of covariances across environments and for the
sexes are identical for Rows 1 & 13, 2 & 14, 5 & 7, 6 & 8 and 3 & 4 (Table 9, Column 5).

**Environment and imprinting effects: resemblances between relatives**

Considering now the values for resemblances between relatives, we may make a number of observations. As expected under imprinting, the covariance between offspring and female parents is much larger than that between offspring and male parents for all but two cases. For Row 9, environment $Y$, homozygotes have identical phenotypic values and there is no relationship between the phenotypic values of parents and offspring. For Row 11, environment $Y$, the phenotypic value of $A_1A_2$ exceeds $A_2A_1$ and as a consequence the covariance between fathers and offspring is greatest because it appears that maternal, not paternal, alleles are inactivated. The same trend is apparent when considering covariances between half sibs sharing a female or male parent.

The largest covariance between full sibs ($\sigma_{FSZ} = 0.2952$; Row 9, Column 2) corresponds to the subpopulation with greatest genetic variance. We may see that covariances are again not equal for environments $Y$ and $Z$. The full sib covariance in environment $Z$ exceeds that in environment $Y$ except for Rows 3 and 4, corresponding to the two situations where the total genetic variance in environment $Y$ is greater than that in environment $Z$ due to a larger range of phenotypic values in environment $Y$.

An indication that a population has imprinting acting is that the largest covariance between relatives is between offspring and one parent, whereas in the absence of imprinting it is expected that the covariance between full sibs is greatest (refer Table 8). Examining Table 10 we may see that this signature of imprinting is masked in many of the populations. In some cases the covariance between full sibs exceeds that between offspring and (typically female) parent only in one subpopulation. However, for Figure 2.2 with $I_{11} = I_{22} = \frac{1}{2}$ (Row 3) and Figure 2.6 with to $I_{11} = I_{22} = \frac{1}{2}$ (Row 13), the full sib covariance is largest for both environments. Also of interest is that in general we would expect the covariance between offspring and their mothers to exceed that between half sibs sharing a mother (refer Table 8). The combined effect of imprinting and environmental effects means that covariances between half sibs are largest for environment $Y$ in Figures 2.3, 2.4 and 2.5a and for environment $Z$ in Figure 2.5b.
The differences in phenotypic predictions across the different situations and between environments often give conflicting indications of whether environmental effects or imprinting are acting in a subpopulation or population. Figure 2.5b represents an extreme situation where in one environment, paternally inherited alleles appear to be inactivated while in the other, variance and covariance estimates indicate that maternal alleles are inactivated. The strength of genotype by environment interaction needs to be large in this case to produce such an effect, but a number of other situations may give conflicting indications of whether or not imprinting is acting at all. These results suggest that even if only one environment carries signatures of imprinting, such as larger additive variances in one sex, larger covariances between offspring and one parent, or covariances between offspring and one parent exceeding the covariance between full sibs, we may conclude that an imprinted locus is indeed influencing the trait of interest. Further, these results highlight the importance of assessing genotype by environment interactions, and the strength of these interactions, when making predictions about subpopulation variances and covariances.

There is a vast literature of quantitative trait models, beginning with Fisher’s decomposition of the genetic variance into additive and dominance terms, and derivation of expressions for resemblances between relatives [Fisher, 1918]. This model adds in particular to investigation of sex differences in quantitative traits, including models of sex-linked inheritance [Bohidar, 1964; James, 1973; Grossman and Eisen, 1989], sex-dependent expression [Grossman and Eisen, 1989] and genomic imprinting [Hill and Keightley, 1989; Spencer 2002].

Polymorphic imprinting, imprinting of alleles in one individual but normal expression of both maternal and paternal alleles in another, has been observed for a number of genes, including Igf2 and Igf2R [Pastinen et al., 2003; Sandovici et al., 2003; Naumova and Croteau, 2004]. DNA methylation is known to influence expression of genes [see Bird, 2002], and loss of inactivation of imprinted alleles is associated with changes in DNA methylation. Sandovici et al. [2003] sampled relative methylation of maternal and paternal alleles in individuals at two time points up to nine years apart, and found that although methylation is relatively stable over time for Igf2, methylation patterns of Igf2r changed dramatically for some individuals. Although the mechanism causing change over time is unclear, such variation in imprinting status is likely to be affected by genetic and environmental factors, and interactions between them.
An additional example of the interaction between genetic and environmental factors causing changes in DNA methylation is the agouti locus in mice. “Agouti” is a grey-tan colouration in mice resulting from alternate black and yellow pigment along individual hair follicles. Mice heterozygous for the viable yellow allele (A<sup>vy</sup>) and a recessive allele (a) (which does not produce yellow pigment) of the agouti gene display variegated agouti coat colour patterns on a yellow background. The degree of variegation ranges continuously from all yellow to all agouti (with mice appearing “normal”) and is dependent upon the level of gene expression of A<sup>vy</sup>, in turn correlated with the level of DNA methylation of the viable yellow allele [Cooney et al., 2002]. The proportion of heterozygous offspring developing a “normal” agouti phenotype is dependent upon the sex of the parent transmitting the A<sup>vy</sup> allele, with paternal A<sup>vy</sup> alleles more likely to be silenced, providing evidence for imprinting at this locus [Wolff et al., 1998]. Interestingly, methylation (and hence repression) of the A<sup>vy</sup> allele in offspring is increased when mothers are fed dietary methyl supplements during pregnancy [Cooney et al., 2002]. Thus expression of A<sup>vy</sup> at this locus is dependent both on the sex of the transmitting parent, and the influence of methyl levels in the fetal environment. Assessing such interactions between genomic imprinting and environmental effects is an exciting challenge for future research.
**References**


Table 1: Definition of parameters and notation used in text

<table>
<thead>
<tr>
<th>Parameter or term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_iA_j$</td>
<td>Individual with maternally inherited $A_i$ allele and paternally inherited $A_j$ allele.</td>
</tr>
<tr>
<td>$G_{ij}$</td>
<td>Genotypic value of $A_iA_j$.</td>
</tr>
<tr>
<td>$z_{hij}$</td>
<td>Phenotype of an $A_iA_j$ individual in environment $h$.</td>
</tr>
<tr>
<td>$I_{hij}$</td>
<td>Effect environment $h$ has on individual with genotype $A_iA_j$.</td>
</tr>
<tr>
<td>$E_h$</td>
<td>Constant effect on all individuals in environment $h$.</td>
</tr>
<tr>
<td>$gd_{hij}$</td>
<td>Genotypic deviation for $A_i$ in environment $h$, the difference between the phenotypic value ($z_{hij}$) and the mean value of individuals in the environment ($\mu_i$).</td>
</tr>
<tr>
<td>$bv_{hij}$; $bv_{hmij}$</td>
<td>Breeding value of female $A_iA_j$ genotype in environment $h$; breeding value of male $A_iA_j$ genotype in environment $h$.</td>
</tr>
<tr>
<td>$dd_{hij}$; $dd_{hmij}$</td>
<td>Dominance deviation for female $A_i$ in environment $h$; male $A_i$ in environment $h$.</td>
</tr>
<tr>
<td>$\sigma^2_{Gh}$</td>
<td>Total variance in genetic effects for environment $h$.</td>
</tr>
<tr>
<td>$\sigma_{GYZ}$</td>
<td>Covariance between genetic effects between environments $Y$ and $Z$.</td>
</tr>
<tr>
<td>$\sigma^2_{Ahf}$; $\sigma^2_{Ahm}$</td>
<td>Additive genetic variance for females in environment $h$; additive genetic variance for males in environment $h$.</td>
</tr>
<tr>
<td>$\sigma^2_{Dhf}$; $\sigma^2_{Dhm}$</td>
<td>Dominance genetic variance for females in environment $h$; dominance genetic variance for males in environment $h$.</td>
</tr>
<tr>
<td>$\sigma_{ADhf}$; $\sigma_{ADhm}$</td>
<td>Covariance between breeding values (additive effects) and dominance deviations for females; males in environment $h$.</td>
</tr>
<tr>
<td>$\sigma_{OPhf}$; $\sigma_{OPhm}$</td>
<td>Covariance between offspring and mother (female parent) genotypic values in environment $h$; covariance between offspring and father (male parent) genotypic values in environment $h$.</td>
</tr>
<tr>
<td>$\sigma_{FSh}$</td>
<td>Covariance between full sib genotypic values in environment $h$.</td>
</tr>
<tr>
<td>$\sigma_{HShf}$; $\sigma_{HShm}$</td>
<td>Covariance between genotypic values of half sibs sharing a female parent; male parent in environment $h$.</td>
</tr>
</tbody>
</table>
Table 2: Phenotypic values for individuals in environments Y and Z

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Genotype</th>
<th>Mean Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_1$</td>
<td>$A_1A_1$</td>
<td>$\mu_y = ap_1(2$ $+ p_1(k_1 + k_2))$ $+ E + I_{11}p_1^2$ $+$ $p_1p_2(I_{21} + I_{12})$ $+ I_{22}p_2^2$</td>
</tr>
<tr>
<td>$p_1p_2$</td>
<td>$A_1A_2$</td>
<td>$z_{y11} = 0$ $a(1 + k_1)$ $- I_{11} - E$ $2a$ $a(1 + k_2)$ $- I_{22} - E$ $2a$ $\mu$ $= \frac{1}{2} [\mu_y + \mu_z]$ $= ap_1(2$ $+ p_1(k_1 + k_2))$</td>
</tr>
<tr>
<td>$p_1$</td>
<td>$A_2A_1$</td>
<td>$z_{y21} = a(1 + k_1)$ $+ I_{21} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $\mu$ $= \frac{1}{2} [\mu_y + \mu_z]$ $= ap_1(2$ $+ p_1(k_1 + k_2))$</td>
</tr>
<tr>
<td>$p_2$</td>
<td>$A_2A_2$</td>
<td>$z_{y22} = a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $a(1 + k_2)$ $+ I_{22} + E$ $2a$ $\mu$ $= \frac{1}{2} [\mu_y + \mu_z]$ $= ap_1(2$ $+ p_1(k_1 + k_2))$</td>
</tr>
</tbody>
</table>

Phenotypic value: environment Y ($z_Y$)

Phenotypic value: environment Z ($z_Z$)

Mean across Y and Z

5.25
Table 3: Average values of maternal and paternal progeny for environments Y and Z

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_2A_1=A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y</strong></td>
<td>$ap_2(1+k_2)$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) + p_1(I_{11} + I_{21}) + p_2(I_{12} + I_{22})]$</td>
<td>$a(p_1(1+k_1) + 2p_2) + I_{21}p_1 + I_{22}p_2 + E$</td>
</tr>
<tr>
<td></td>
<td>$+ I_{11}p_1 + I_{12}p_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$+ E$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>$ap_2(1+k_2)$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) + p_1(I_{11} + I_{21}) - p_2(I_{12} + I_{22})]$</td>
<td>$a(p_1(1+k_1) + 2p_2) - I_{21}p_1 - I_{22}p_2 - E$</td>
</tr>
<tr>
<td></td>
<td>$- I_{11}p_1 - I_{12}p_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$- E$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Y &amp; Z</strong></td>
<td>$ap_2(1+k_2)$</td>
<td>$\frac{a}{2}(p_1(1+k_1) + p_2(3+k_2))$</td>
<td>$a(p_1(1+k_1) + 2p_2)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Average value of progeny: maternal**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_2A_1=A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y</strong></td>
<td>$ap_2(1+k_1)$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) + p_1(I_{11} + I_{12}) + p_2(I_{21} + I_{22})]$</td>
<td>$a(p_1(1+k_1) + 2p_2) + I_{12}p_1 + I_{22}p_2 + E$</td>
</tr>
<tr>
<td></td>
<td>$+ I_{11}p_1 + I_{21}p_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$+ E$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>$ap_2(1+k_1)$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) + p_1(I_{11} + I_{12}) - p_2(I_{21} + I_{22})]$</td>
<td>$a(p_1(1+k_1) + 2p_2) - I_{12}p_1 - I_{22}p_2 - E$</td>
</tr>
<tr>
<td></td>
<td>$- I_{11}p_1 - I_{21}p_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$- E$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Y &amp; Z</strong></td>
<td>$ap_2(1+k_1)$</td>
<td>$\frac{a}{2}(p_1(1+k_1) + p_2(3+k_2))$</td>
<td>$a(p_1(1+k_1) + 2p_2)$</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

**Average value of progeny: paternal**

5.26
Table 4: Genotypic deviations, breeding values and dominance deviations for males and females in environments Y and Z

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_2A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>$p_1^2$</td>
<td>$p_1p_2$</td>
<td>$p_1p_2$</td>
<td>$p_2^2$</td>
</tr>
<tr>
<td>Genetic effect Y</td>
<td>$z_{y11} = I_{11} + E$</td>
<td>$z_{y21} = a(1+k_1) + I_{12} + E$</td>
<td>$z_{y12} = a(1+k_2) + I_{12}$</td>
<td>$z_{y22} = 2a + I_{22} + E$</td>
</tr>
<tr>
<td>Genetic effect Z</td>
<td>$z_{z11} = -I_{11} - E$</td>
<td>$z_{z21} = a(1+k_1) - I_{21} - E$</td>
<td>$z_{z12} = a(1+k_2) - I_{12} - E$</td>
<td>$z_{z22} = 2a - I_{22} - E$</td>
</tr>
<tr>
<td>Genotypic Value Y &amp; Z</td>
<td>0</td>
<td>$a(1+k_1)$</td>
<td>$a(1+k_2)$</td>
<td>2a</td>
</tr>
<tr>
<td>Deviations from mean:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypic deviation Y</td>
<td>$gd_{y11} = -ap_2(2 + p_1(k_1 + k_2)) + I_{11} - I_{11}P_1^2 - I_{22}P_2^2 - p_1p_2(I_{21} + I_{12})$</td>
<td>$gd_{y21} = a(1+k_1 - p_2(2 + p_1(k_1 + k_2)) + I_{21} - I_{11}P_1^2 - I_{22}P_2^2 - p_1p_2(I_{21} + I_{12})$</td>
<td>$gd_{y12} = a(1+k_2 - p_2(2 + p_1(k_1 + k_2)) + I_{12} - I_{11}P_1^2 - I_{22}P_2^2 - p_1p_2(I_{21} + I_{12})$</td>
<td>$gd_{y22} = ap_1(2 - p_2(k_1 + k_2)) + I_{22} - I_{11}P_1^2 - I_{22}P_2^2 - p_1p_2(I_{21} + I_{12})$</td>
</tr>
<tr>
<td>Genotypic deviation ( Z )</td>
<td>( gd_{Z11} = )</td>
<td>( gd_{Z21} = )</td>
<td>( gd_{Z12} = )</td>
<td>( gd_{Z22} = )</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>(-ap_2(2 + p_1(k_1 + k_2)) - I_{11})</td>
<td>(a(1 + k_1 - p_2(2 + p_1(k_1 + k_2))) - I_{21})</td>
<td>(a(1 + k_2 - p_2(2 + p_1(k_1 + k_2))) - I_{12})</td>
<td>(ap_2(2 - p_2(k_1 + k_2)) - I_{22})</td>
<td></td>
</tr>
<tr>
<td>(+I_{11}p_1^2 + I_{22}p_2^2 + p_1p_2(I_{21} + I_{12}))</td>
<td>(+I_{11}p_1^2 + I_{22}p_2^2 + p_1p_2(I_{21} + I_{12}))</td>
<td>(+I_{11}p_1^2 + I_{22}p_2^2 + p_1p_2(I_{21} + I_{12}))</td>
<td>(+I_{11}p_1^2 + I_{22}p_2^2 + p_1p_2(I_{21} + I_{12}))</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female breeding value ( Y )</th>
<th>(bv_{Y11} = )</th>
<th>(bv_{Y21} = )</th>
<th>(bv_{Y12} = )</th>
<th>(bv_{Y22} = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-2p_2[\alpha_f] + p_1(I_{21} - I_{11}) + p_2(I_{22} - I_{12}))</td>
<td>((p_1 - p_2)[\alpha_f] + p_1(I_{21} - I_{11}) + p_2(I_{22} - I_{12}))</td>
<td>((p_1 - p_2)[\alpha_f] + p_1(I_{21} - I_{11}) + p_2(I_{22} - I_{12}))</td>
<td>((p_1 - p_2)[\alpha_f] + p_1(I_{21} - I_{11}) + p_2(I_{22} - I_{12}))</td>
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</table>

<table>
<thead>
<tr>
<th>Female breeding value ( Z )</th>
<th>(bv_{Z11} = )</th>
<th>(bv_{Z21} = )</th>
<th>(bv_{Z12} = )</th>
<th>(bv_{Z22} = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-2p_2[\alpha_f] - p_1(I_{21} - I_{11}) - p_2(I_{22} - I_{12}))</td>
<td>((p_1 - p_2)[\alpha_f] - p_1(I_{21} - I_{11}) - p_2(I_{22} - I_{12}))</td>
<td>((p_1 - p_2)[\alpha_f] - p_1(I_{21} - I_{11}) - p_2(I_{22} - I_{12}))</td>
<td>((p_1 - p_2)[\alpha_f] - p_1(I_{21} - I_{11}) - p_2(I_{22} - I_{12}))</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Male breeding value ( Y )</th>
<th>(bv_{Y11} = )</th>
<th>(bv_{Y21} = )</th>
<th>(bv_{Y12} = )</th>
<th>(bv_{Y22} = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-2p_2[\alpha_m] + p_1(I_{12} - I_{11}) + p_2(I_{22} - I_{21}))</td>
<td>((p_1 - p_2)[\alpha_m] + p_1(I_{12} - I_{11}) + p_2(I_{22} - I_{21}))</td>
<td>((p_1 - p_2)[\alpha_m] + p_1(I_{12} - I_{11}) + p_2(I_{22} - I_{21}))</td>
<td>((p_1 - p_2)[\alpha_m] + p_1(I_{12} - I_{11}) + p_2(I_{22} - I_{21}))</td>
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</table>

<table>
<thead>
<tr>
<th>Male breeding value ( Z )</th>
<th>(bv_{Z11} = )</th>
<th>(bv_{Z21} = )</th>
<th>(bv_{Z12} = )</th>
<th>(bv_{Z22} = )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-2p_2[\alpha_m] - p_1(I_{12} - I_{11}) - p_2(I_{22} - I_{21}))</td>
<td>((p_1 - p_2)[\alpha_m] - p_1(I_{12} - I_{11}) - p_2(I_{22} - I_{21}))</td>
<td>((p_1 - p_2)[\alpha_m] - p_1(I_{12} - I_{11}) - p_2(I_{22} - I_{21}))</td>
<td>((p_1 - p_2)[\alpha_m] - p_1(I_{12} - I_{11}) - p_2(I_{22} - I_{21}))</td>
<td></td>
</tr>
</tbody>
</table>

5.28
<table>
<thead>
<tr>
<th>Female dominance deviation</th>
<th>$dd_{Y11} = p_2[a(k_i p_1 - k_z (1 + p_z)) + I_{21} p_i - I_{12} (1 + p_2) + p_z (I_{11} + I_{22})]$</th>
<th>$dd_{Y21} = a(k_i (1 - p_1^2) - k_z p_z^2) - p_z p_z (I_{11} + I_{22}) + I_{21} (1 - p_1^2) - I_{12} p_z^2$</th>
<th>$dd_{Y12} = a(-k_i p_1^2 - k_z (1 - p_z^2)) - p_z p_z (I_{11} + I_{22}) + I_{21} p_1^2 + I_{12} (1 - p_z^2)$</th>
<th>$dd_{Y22} = p_1[a(-k_i (1 + p_i) + k_z p_z) - I_{21} (1 + p_1) + I_{12} p_z + p_z (I_{11} + I_{22})]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female dominance deviation</td>
<td>$dd_{Z11} = p_2[a(k_i p_1 - k_z (1 + p_z)) - I_{21} p_i + I_{12} (1 + p_2) - p_z (I_{11} + I_{22})]$</td>
<td>$dd_{Z21} = a(k_i (1 - p_1^2) - k_z p_z^2) + p_z p_z (I_{11} + I_{22}) - I_{21} (1 - p_1^2) + I_{12} p_z^2$</td>
<td>$dd_{Z12} = a(-k_i p_1^2 + k_z (1 - p_z^2)) + p_z p_z (I_{11} + I_{22}) - I_{21} p_1^2 - I_{12} (1 - p_z^2)$</td>
<td>$dd_{Z22} = p_1[a(-k_i (1 + p_i) + k_z p_z) + I_{21} (1 + p_1) - I_{12} p_z - p_z (I_{11} + I_{22})]$</td>
</tr>
<tr>
<td>Male dominance deviation</td>
<td>$dd_{Y11} = p_2[a(k_2 p_1 - k_i (1 + p_1)) + I_{12} p_i - I_{21} (1 + p_2) + p_z (I_{11} + I_{22})]$</td>
<td>$dd_{Y21} = a(-k_2 p_1^2 + k_i (1 - p_2^2)) - p_1 p_z (I_{11} + I_{22}) - I_{21} p_1^2 + I_{12} (1 - p_2^2)$</td>
<td>$dd_{Y12} = a(k_2 (1 - p_1^2) - k_i p_2^2) - p_1 p_z (I_{11} + I_{22}) + I_{21} p_1^2 - I_{12} p_2^2$</td>
<td>$dd_{Y22} = p_1[a(-k_2 (1 + p_1) + k_i p_2) - I_{21} (1 + p_1) + I_{12} p_2 + p_z (I_{11} + I_{22})]$</td>
</tr>
<tr>
<td>Male dominance deviation</td>
<td>$dd_{Z11} = p_2[a(k_2 p_1 - k_i (1 + p_1)) - I_{12} p_i + I_{21} (1 + p_2) - p_z (I_{11} + I_{22})]$</td>
<td>$dd_{Z21} = a(-k_2 p_1^2 + k_i (1 - p_2^2)) + p_1 p_z (I_{11} + I_{22}) - I_{21} p_1^2 - I_{12} p_2^2$</td>
<td>$dd_{Z12} = a(k_2 (1 - p_1^2) - k_i p_2^2) + p_1 p_z (I_{11} + I_{22}) + I_{21} p_1^2 + I_{12} p_2^2$</td>
<td>$dd_{Z22} = p_1[a(-k_2 (1 + p_1) + k_i p_2) + I_{21} (1 + p_1) - I_{12} p_2 - p_z (I_{11} + I_{22})]$</td>
</tr>
</tbody>
</table>
Table 5: Genotypic values and progeny means for mother-offspring and father-offspring pairs for environments Y and Z

<table>
<thead>
<tr>
<th>Parent genotype</th>
<th>Phenotypic Value</th>
<th>Progeny mean of females</th>
<th>Progeny mean of males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Environment Y</td>
<td></td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$z_{y11} = I_{11} + E$</td>
<td>$ap_2(1+k_2) + I_{11}p_1 + I_{12}p_2 + E$</td>
<td>$ap_2(1+k_1) + I_{11}p_1 + I_{21}p_2 + E$</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>$z_{y21} = a(1+k_1) + I_{21} + E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) + p_1(I_{11} + I_{21}) + p_2(I_{12} + I_{22})] + E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_2) + p_2(3+k_1)) + p_1(I_{11} + I_{12}) + p_2(I_{21} + I_{22})] + E$</td>
</tr>
<tr>
<td>$A_1A_2$</td>
<td>$z_{y12} = a(1+k_2) + I_{12} + E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) + p_1(I_{11} + I_{21}) + p_2(I_{12} + I_{22})] + E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_2) + p_2(3+k_1)) + p_1(I_{11} + I_{12}) + p_2(I_{21} + I_{22})] + E$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$z_{y22} = 2a + I_{22} + E$</td>
<td>$a(p_1(1+k_1) + 2p_2) + I_{21}p_1 + I_{22}p_2 + E$</td>
<td>$a(p_1(1+k_2) + 2p_2) + I_{12}p_1 + I_{22}p_2 + E$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Environment Z</td>
<td></td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$z_{y11} = -I_{11} - E$</td>
<td>$ap_2(1+k_2) - I_{11}p_1 - I_{12}p_2 - E$</td>
<td>$ap_2(1+k_1) - I_{11}p_1 - I_{21}p_2 - E$</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>$z_{y21} = a(1+k_1) - I_{21} - E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) - p_1(I_{11} + I_{21}) - p_2(I_{12} + I_{22})] - E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_2) + p_2(3+k_1)) - p_1(I_{11} + I_{12}) - p_2(I_{21} + I_{22})] - E$</td>
</tr>
<tr>
<td>$A_1A_2$</td>
<td>$z_{y12} = a(1+k_2) - I_{12} - E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_1) + p_2(3+k_2)) - p_1(I_{11} + I_{21}) - p_2(I_{12} + I_{22})] - E$</td>
<td>$\frac{1}{2}[a(p_1(1+k_2) + p_2(3+k_1)) - p_1(I_{11} + I_{12}) - p_2(I_{21} + I_{22})] - E$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$z_{y22} = 2a - I_{22} - E$</td>
<td>$a(p_1(1+k_1) + 2p_2) - I_{21}p_1 - I_{22}p_2 - E$</td>
<td>$a(p_1(1+k_2) + 2p_2) - I_{12}p_1 - I_{22}p_2 - E$</td>
</tr>
</tbody>
</table>
Table 6: Phenotypic values for fullsib offspring pairs from mating combinations for environment $Y$

<table>
<thead>
<tr>
<th>Mother</th>
<th>Father</th>
<th>Offspring pair genotypic values [proportion of total offspring of mating class]</th>
<th>Frequency of mating class</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1$</td>
<td>$A_1A_1$</td>
<td>$I_{11} + E, I_{11} + E \left[ \frac{1}{4} \right]$</td>
<td>$p_1^4$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$I_{11} + E, I_{11} + E \left[ \frac{1}{4} \right] \quad I_{11} + E, a(1+k_2) + I_{12} + E \left[ \frac{1}{4} \right] \quad a(1+k_2) + I_{12} + E, a(1+k_2) + I_{12} + E \left[ \frac{1}{4} \right]$</td>
<td>$2p_1^3p_2$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1+k_2) + I_{12} + E, a(1+k_2) + I_{12} + E \left[ 1 \right]$</td>
<td>$p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$I_{11} + E, I_{11} + E \left[ \frac{1}{16} \right] \quad I_{11} + E, a(1+k_1) + I_{21} + E \left[ \frac{1}{4} \right] \quad I_{11} + E, a(1+k_1) + I_{12} + E \left[ \frac{1}{4} \right] \quad I_{11} + E, 2a + I_{22} + E \left[ \frac{1}{4} \right] \quad a(1+k_1) + I_{21} + E, a(1+k_1) + I_{21} + E \left[ \frac{1}{16} \right] \quad a(1+k_1) + I_{21} + E, a(1+k_1) + I_{12} + E \left[ \frac{1}{16} \right] \quad a(1+k_1) + I_{21} + E, 2a + I_{22} + E \left[ \frac{1}{16} \right] \quad a(1+k_1) + I_{12} + E, 2a + I_{22} + E \left[ \frac{1}{16} \right] \quad a(1+k_1) + I_{12} + E, 2a + I_{22} + E \left[ \frac{1}{16} \right] \quad a(1+k_1) + I_{12} + E, 2a + I_{22} + E \left[ \frac{1}{16} \right]$</td>
<td>$4p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$A_2A_2$</td>
<td>$a(1+k_2) + I_{12} + E, a(1+k_2) + I_{12} + E \left[ \frac{1}{4} \right] \quad a(1+k_2) + I_{12} + E, 2a + I_{22} + E \left[ \frac{1}{4} \right] \quad 2a + I_{22} + E, 2a + I_{22} + E \left[ \frac{1}{4} \right]$</td>
<td>$2p_1^3$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$A_1A_1$</td>
<td>$a(1+k_1) + I_{21} + E, a(1+k_1) + I_{21} + E \left[ 1 \right]$</td>
<td>$p_1^4p_2^2$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$A_2A_1$ and $A_1A_2$</td>
<td>$a(1+k_1) + I_{21} + E, a(1+k_1) + I_{21} + E \left[ \frac{1}{4} \right] \quad a(1+k_1) + I_{21} + E, 2a + I_{22} + E \left[ \frac{1}{4} \right] \quad 2a + I_{22} + E, 2a + I_{22} + E \left[ \frac{1}{4} \right]$</td>
<td>$2p_1^3p_2^2$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$A_2A_2$</td>
<td>$2a + I_{22} + E, 2a + I_{22} + E \left[ 1 \right]$</td>
<td>$p_2^4$</td>
</tr>
</tbody>
</table>
Table 7: Genetic variances for populations with no imprinting or environmental effects; imprinting only and environmental effects only

<table>
<thead>
<tr>
<th>Condition</th>
<th>Column:</th>
<th>Variance component</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all: $a = \frac{1}{2}$, $p_1 = p_2 = \frac{1}{2}$</td>
<td>1</td>
<td>$\sigma^2_G$</td>
</tr>
<tr>
<td>No imprinting or environmental effects</td>
<td>2</td>
<td>0.1252</td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{a}{2a}$, $I_{ij} = 0$</td>
<td>3</td>
<td>$\sigma^2_{GY} = 0.1814$</td>
</tr>
<tr>
<td>Imprinting only $k_1 = \frac{a}{2a}$, $k_2 = \frac{-a}{2a}$, $I_{ij} = 0$</td>
<td>4</td>
<td>$\sigma^2_{GY} = 0.1264$</td>
</tr>
<tr>
<td>Environmental effects only $k_1 = \frac{a}{2a}$, $I_{11} = I_{22} = 0$, $I_{12} = I_{21} = \frac{1}{2}$</td>
<td>5</td>
<td>$\sigma^2_{GY} = 0.1289$</td>
</tr>
</tbody>
</table>

5.32
<table>
<thead>
<tr>
<th>$k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = 0$, $I_{12} = I_{21} = \frac{1}{10}$</th>
<th>Environmental effects only $k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = \frac{1}{2}$, $I_{12} = I_{21} = 0$</th>
<th>Environmental effects only $k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = \frac{1}{2}$, $I_{12} = I_{21} = 0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_{G_Y}^2 = 0.1939$ $\sigma_{G_Z}^2 = 0.1814$</td>
<td>$\sigma_{A_Y}^2 = 0.1250$ $\sigma_{A_Z}^2 = 0.1250$ $\sigma_{D_Y}^2 = 0.0689$ $\sigma_{D_Z}^2 = 0.0564$</td>
<td>$\sigma_{A_Y}^2 = 0.1289$ $\sigma_{A_Z}^2 = 0.1264$ $\sigma_{D_Y}^2 = 0.0039$ $\sigma_{D_Z}^2 = 0.0014$</td>
</tr>
<tr>
<td>5</td>
<td>0.0627</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 8: Resemblances between relatives for populations with no imprinting or environmental effects; imprinting only and environmental effects only

<table>
<thead>
<tr>
<th>Condition</th>
<th>Covariances between relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all: $a = \frac{1}{3}$, $p_1 = p_2 = \frac{1}{2}$</td>
<td>$\sigma_{op}$</td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{1}{20}$, $I_y = 0$</td>
<td>Column: 1</td>
</tr>
<tr>
<td>No imprinting or environmental effects</td>
<td></td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{1}{20}$, $I_y = 0$</td>
<td>Row: 1</td>
</tr>
<tr>
<td>Imprinting only</td>
<td></td>
</tr>
<tr>
<td>$k_1 = \frac{8}{10}$, $k_2 = \frac{9}{10}$, $I_y = 0$</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental effects only</td>
<td></td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = 0$, $I_{12} = I_{21} = \frac{1}{2}$</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental effects only</td>
<td></td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = 0$, $I_{12} = I_{21} = \frac{1}{10}$</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental effects only</td>
<td></td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = \frac{1}{2}$, $I_{12} = I_{21} = 0$</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental effects only</td>
<td></td>
</tr>
<tr>
<td>$k_1 = k_2 = \frac{1}{20}$, $I_{11} = I_{22} = 0$, $I_{12} = I_{21} = 0$</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
\[
\begin{align*}
k_1 &= k_2 = \frac{1}{20}, \\
I_{11} &= I_{22} = \frac{1}{10}, \\
I_{12} &= I_{21} = 0
\end{align*}
\]
Table 9: Variance components for populations with imprinting and environmental effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Variance component</th>
<th>( \sigma_G^2 )</th>
<th>( \sigma_{GY}^2 )</th>
<th>( \sigma_A^2 )</th>
<th>( \sigma_D^2 )</th>
<th>( \sigma_{AD} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all:</td>
<td>( a = \frac{1}{2} ), ( p_1 = p_2 = \frac{1}{2} ), ( k_1 = \frac{8}{10}, k_2 = \frac{2}{10} )</td>
<td>Column: 1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Figure 2.1: I_{11} = I_{12} = \frac{1}{2}, I_{21} = I_{22} = 0</td>
<td>( \sigma_{GY}^2 = 0.0467 ), ( \sigma_{GZ}^2 = 0.5092 )</td>
<td>0.1530</td>
<td>( \sigma_{AY}^2 = 0.0903 )</td>
<td>( \sigma_{AZ}^2 = 0.1015 )</td>
<td>( \sigma_{DZ}^2 = 0.4558 )</td>
<td>( \sigma_{ADY} = -0.0372 ), ( \sigma_{ADZ} = 0.0066 )</td>
</tr>
<tr>
<td>Figure 2.1: I_{11} = I_{12} = \frac{1}{10}, I_{21} = I_{22} = 0</td>
<td>( \sigma_{GY}^2 = 0.1717 ), ( \sigma_{GZ}^2 = 0.2642 )</td>
<td>0.2130</td>
<td>( \sigma_{AY}^2 = 0.3403 )</td>
<td>( \sigma_{AZ}^2 = 0.5253 )</td>
<td>( \sigma_{DZ}^2 = 0.2258 )</td>
<td>( \sigma_{ADY} = -0.1547 ), ( \sigma_{ADZ} = 0.0141 )</td>
</tr>
<tr>
<td>Figure 2.2: I_{11} = I_{22} = \frac{1}{2}, I_{12} = I_{21} = 0</td>
<td>( \sigma_{GY}^2 = 0.2842 ), ( \sigma_{GZ}^2 = 0.2717 )</td>
<td>0.1530</td>
<td>( \sigma_{AY}^2 = 0.4278 )</td>
<td>( \sigma_{AZ}^2 = 0.0028 )</td>
<td>( \sigma_{DZ}^2 = 0.2370 )</td>
<td>( \sigma_{ADY} = -0.1966 ), ( \sigma_{ADZ} = 0.0159 )</td>
</tr>
<tr>
<td>Figure</td>
<td>$I_{11} = I_{21}$</td>
<td>$I_{12} = I_{22}$</td>
<td>$\sigma_{GY}^2$</td>
<td>$\sigma_{GZ}^2$</td>
<td>$\sigma_{AJf}^2$</td>
<td>$\sigma_{AZm}^2$</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>2.2</td>
<td>$\frac{1}{10}$</td>
<td>0</td>
<td>0.2192</td>
<td>0.2167</td>
<td>0.4278</td>
<td>0.0028</td>
</tr>
<tr>
<td>2.3</td>
<td>$\frac{1}{7}$</td>
<td>0</td>
<td>0.2592</td>
<td>0.2967</td>
<td>0.4278</td>
<td>0.0028</td>
</tr>
<tr>
<td>2.3</td>
<td>$\frac{1}{10}$</td>
<td>0</td>
<td>0.2142</td>
<td>0.2217</td>
<td>0.4278</td>
<td>0.0028</td>
</tr>
<tr>
<td>2.4</td>
<td>$\frac{1}{2}$</td>
<td>$\frac{1}{2}$</td>
<td>0.3280</td>
<td>0.3530</td>
<td>0.4278</td>
<td>0.0028</td>
</tr>
<tr>
<td>Figure</td>
<td>Condition</td>
<td>( I_{11} )</td>
<td>( I_{12} )</td>
<td>( I_{21} )</td>
<td>( I_{22} )</td>
<td>( \sigma_{GY}^2 )</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Figure 2.4:</td>
<td>( I_{11} = \frac{1}{10}, \ I_{12} = \frac{1}{10}, \ I_{21} = I_{22} = 0 )</td>
<td>8</td>
<td>0.2105</td>
<td>0.2170</td>
<td>0.2230</td>
<td>( \sigma_{GZ}^2 = 0.2230 )</td>
</tr>
<tr>
<td>Figure 2.5a:</td>
<td>( I_{11} = \frac{1}{3}, \ I_{12} = \frac{1}{3}, \ I_{21} = I_{22} = 0 )</td>
<td>9</td>
<td>0.0905</td>
<td>0.0905</td>
<td>0.9095</td>
<td>( \sigma_{GZ}^2 = 0.5905 )</td>
</tr>
<tr>
<td>Figure 2.5a:</td>
<td>( I_{11} = \frac{1}{3}, \ I_{12} = \frac{1}{3}, \ I_{21} = I_{22} = 0 )</td>
<td>10</td>
<td>0.2105</td>
<td>0.1705</td>
<td>0.2705</td>
<td>( \sigma_{GZ}^2 = 0.2705 )</td>
</tr>
<tr>
<td>Figure 2.5b:</td>
<td>( I_{11} = I_{22} = 0, \ I_{12} = \frac{1}{2}, \ I_{21} = \frac{1}{2} )</td>
<td>11</td>
<td>0.0905</td>
<td>0.1280</td>
<td>0.5530</td>
<td>( \sigma_{GZ}^2 = 0.5530 )</td>
</tr>
<tr>
<td>Figure 2.5b:</td>
<td>( I_{11} = I_{22} = 0, \ I_{12} = \frac{1}{10}, \ I_{21} = \frac{1}{10} )</td>
<td>12</td>
<td>0.2105</td>
<td>0.1780</td>
<td>0.2630</td>
<td>( \sigma_{GZ}^2 = 0.2630 )</td>
</tr>
<tr>
<td>Figure 2.6:</td>
<td></td>
<td></td>
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<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$I_{11} = \frac{1}{2}$, $I_{21} = \frac{1}{2}$, $I_{12} = I_{22} = 0$</td>
<td>13</td>
<td>$\sigma_{GZ}^2 = 0.5655$</td>
<td>$\sigma_{GY}^2 = 0.1154$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma_{AZf}^2 = 0.0003$</td>
<td>$\sigma_{AZm}^2 = 0.5253$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma_{ADZf}^2 = -0.0066$</td>
<td>$\sigma_{ADZm}^2 = -0.2691$</td>
<td></td>
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</tr>
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</table>

<table>
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<tr>
<th>Figure 2.6:</th>
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</thead>
<tbody>
<tr>
<td>$I_{11} = \frac{1}{10}$, $I_{21} = \frac{1}{10}$, $I_{12} = I_{22} = 0$</td>
<td>14</td>
<td>$\sigma_{GZ}^2 = 0.2655$</td>
<td>$\sigma_{GY}^2 = 0.1755$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma_{AZf}^2 = 0.0028$</td>
<td>$\sigma_{AZm}^2 = 0.0283$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma_{ADZf}^2 = -0.4809$</td>
<td>$\sigma_{ADZm}^2 = 0.0178$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma_{ADYf}^2 = -0.2434$</td>
<td>$\sigma_{ADYm}^2 = 0.0141$</td>
</tr>
</tbody>
</table>
Table 10: Resemblances between relatives for populations with imprinting and environmental effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Covariances between relatives</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>For all:</td>
<td></td>
<td>Column: 1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \sigma_{OP} )</td>
<td>( \sigma_{FS} )</td>
</tr>
<tr>
<td>( a = \frac{1}{2} ), ( p_1 = p_2 = \frac{1}{2} ), ( k_1 = \frac{8}{10}, k_2 = \frac{2}{10} )</td>
<td>( \sigma_{OPij} = 0.0266 )</td>
<td>( \sigma_{OPij} = 0.0047 )</td>
<td>( \sigma_{FS} = 0.0233 )</td>
</tr>
<tr>
<td>( I_{11} = I_{12} = \frac{1}{2}, I_{21} = I_{22} = 0 )</td>
<td>( \sigma_{OPij} = 0.0928 )</td>
<td>( \sigma_{OPij} = 0.0084 )</td>
<td>( \sigma_{FS} = 0.0858 )</td>
</tr>
<tr>
<td>( I_{11} = I_{12} = \frac{3}{10}, I_{21} = I_{22} = 0 )</td>
<td>( \sigma_{OPij} = 0.1156 )</td>
<td>( \sigma_{OPij} = 0.0094 )</td>
<td>( \sigma_{FS} = 0.1249 )</td>
</tr>
<tr>
<td>( I_{11} = I_{12} = \frac{1}{2}, I_{12} = I_{21} = 0 )</td>
<td>( \sigma_{OPij} = 0.1156 )</td>
<td>( \sigma_{OPij} = 0.0094 )</td>
<td>( \sigma_{FS} = 0.1086 )</td>
</tr>
<tr>
<td>( I_{11} = I_{22} = \frac{3}{10}, I_{12} = I_{21} = 0 )</td>
<td>( \sigma_{OPij} = 0.0578 )</td>
<td>( \sigma_{OPij} = -0.0266 )</td>
<td>( \sigma_{FS} = 0.1296 )</td>
</tr>
</tbody>
</table>
| Figure 2.3: | \[ I_{11} = I_{21} = \frac{1}{10}, \]  
<p>| I_{12} = I_{22} = 0 | [ \sigma_{OPYf} = 0.1041, \sigma_{OPYm} = -0.0028, \sigma_{OPZf} = 0.1272, \sigma_{OPZm} = 0.0241 ] | [ \sigma_{FSY} = 0.1071, \sigma_{FSZ} = 0.1108 ] | [ \sigma_{HSYf} = 0.1070, \sigma_{HSYm} = 0.0001, \sigma_{HSZf} = 0.1070, \sigma_{HSZm} = 0.0038 ] |
| Figure 2.4: | [ I_{11} = \frac{1}{2}, I_{12} = \frac{1}{2}, I_{21} = I_{22} = 0 ] | [ \sigma_{OPYf} = 0.0578, \sigma_{OPYm} = -0.0266, \sigma_{OPZf} = 0.1734, \sigma_{OPZm} = 0.1078 ] | [ \sigma_{FSY} = 0.1468, \sigma_{FSZ} = 0.1624 ] | [ \sigma_{HSYf} = 0.1070, \sigma_{HSYm} = 0.0226, \sigma_{HSZf} = 0.1070, \sigma_{HSZm} = 0.0413 ] |
| Figure 2.4: | [ I_{11} = \frac{1}{10}, I_{12} = \frac{1}{10}, I_{21} = I_{22} = 0 ] | [ \sigma_{OPYf} = 0.1041, \sigma_{OPYm} = -0.0028, \sigma_{OPZf} = 0.1272, \sigma_{OPZm} = 0.0241 ] | [ \sigma_{FSY} = 0.1080, \sigma_{FSZ} = 0.1111 ] | [ \sigma_{HSYf} = 0.1070, \sigma_{HSYm} = 0.0001, \sigma_{HSZf} = 0.1070, \sigma_{HSZm} = 0.0038 ] |
| Figure 2.5a: | [ I_{11} = \frac{1}{2}, I_{22} = \frac{1}{2}, I_{12} = I_{21} = 0 ] | [ \sigma_{OPYf} = 0.0000, \sigma_{OPYm} = 0.0000, \sigma_{OPZf} = 0.3563, \sigma_{OPZm} = 0.1438 ] | [ \sigma_{FSY} = 0.0452, \sigma_{FSZ} = 0.2952 ] | [ \sigma_{HSYf} = 0.0226, \sigma_{HSYm} = 0.0226, \sigma_{HSZf} = 0.2538, \sigma_{HSZm} = 0.0413 ] |
| Figure 2.5a: | [ I_{11} = \frac{1}{10}, I_{22} = \frac{1}{10}, I_{12} = I_{21} = 0 ] | [ \sigma_{OPYf} = 0.0825, \sigma_{OPYm} = -0.0025, \sigma_{OPZf} = 0.1538, \sigma_{OPZm} = 0.0263 ] | [ \sigma_{FSY} = 0.0852, \sigma_{FSZ} = 0.1352 ] | [ \sigma_{HSYf} = 0.0851, \sigma_{HSYm} = 0.0001, \sigma_{HSZf} = 0.1313, \sigma_{HSZm} = 0.0038 ] |
| Figure 2.5b: | [ I_{11} = I_{22} = 0, I_{12} = \frac{1}{2}, I_{21} = \frac{1}{2} ] | [ \sigma_{OPYf} = 0.0531, \sigma_{OPYm} = 0.0719, \sigma_{OPZf} = 0.1781, \sigma_{OPZm} = -0.0531 ] | [ \sigma_{FSY} = 0.0639, \sigma_{FSZ} = 0.2764 ] | [ \sigma_{HSYf} = 0.0226, \sigma_{HSYm} = 0.0413, \sigma_{HSZf} = 0.2538, \sigma_{HSZm} = 0.0226 ] |
| Figure 2.5b: | [ I_{11} = I_{22} = 0, I_{12} = \frac{1}{10}, I_{21} = \frac{1}{10} ] | [ \sigma_{OPYf} = 0.1031, \sigma_{OPYm} = 0.0219, \sigma_{OPZf} = 0.1281, \sigma_{OPZm} = -0.0031 ] | [ \sigma_{FSY} = 0.0889, \sigma_{FSZ} = 0.1314 ] | [ \sigma_{HSYf} = 0.0851, \sigma_{HSYm} = 0.0038, \sigma_{HSZf} = 0.1313, \sigma_{HSZm} = 0.0001 ] |
| Figure 2.6: | [ I_{11} = \frac{1}{2}, I_{21} = \frac{1}{2}, I_{12} = I_{22} = 0 ] | [ \sigma_{OPYf} = 0.0266, \sigma_{OPYm} = 0.0047 ] | [ \sigma_{FSY} = 0.0405, \sigma_{FSZ} = 0.2686 ] | [ \sigma_{HSYf} = 0.0226, \sigma_{HSYm} = 0.0007 ] |</p>
<table>
<thead>
<tr>
<th></th>
<th>$\sigma_{OPZf}$</th>
<th>$\sigma_{OPZm}$</th>
<th>$\sigma_{HSZf}$</th>
<th>$\sigma_{HSZm}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Figure 2.6:</strong></td>
<td>$I_{11} = \frac{1}{10}$, $I_{21} = \frac{1}{10}$, $I_{12} = I_{22} = 0$</td>
<td>$\sigma_{OPYf} = 0.0928$</td>
<td>$\sigma_{OPYm} = 0.0084$</td>
<td>$\sigma_{FSYf} = 0.0868$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{OPZf} = 0.2672$</td>
<td>$\sigma_{OPZm} = 0.0140$</td>
<td>$\sigma_{HSZf} = 0.2538$</td>
<td>$\sigma_{HSZm} = 0.0007$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{OPZf} = 0.1409$</td>
<td>$\sigma_{OPZm} = 0.0103$</td>
<td>$\sigma_{FSZf} = 0.1324$</td>
<td>$\sigma_{FSZm} = 0.0007$</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{FSYf} = 0.0851$</td>
<td>$\sigma_{FSYm} = 0.0007$</td>
<td>$\sigma_{HSYf} = 0.1313$</td>
<td>$\sigma_{HSYm} = 0.0007$</td>
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</table>
6. Quantitative Genetic Models for Maternal Genetic Effects and Genomic Imprinting

Abstract

The expression of an imprinted gene is dependent on the sex of the parent it was inherited from, and as a result reciprocal heterozygotes may display different phenotypes. In contrast, maternal genetic terms arise when the phenotype of an offspring is influenced by the genotype of its mother beyond the direct inheritance of alleles. Both maternal effects and imprinting may contribute to resemblance between offspring of the same mother. We demonstrate that two standard quantitative genetic models for deriving breeding values, population variances and covariances between relatives are not equivalent when maternal genetic effects and imprinting are acting. Maternal and imprinting effects introduce both sex-dependent and generation-dependent effects that result in differences in the way additive and dominance effects are defined for the two approaches. We use a simple example to demonstrate that imprinting and maternal genetic effects both add extra terms to covariances between relatives, and that model misspecification may over- or under-estimate true covariances or lead to extremely variable parameter estimation. Thus, an understanding of various forms of parental effects is essential in correctly estimating quantitative genetic variance components.

Introduction

A gene is imprinted when its level of expression is dependent on the sex of the parent from which it was inherited. Imprinted loci are characterized by the reduced or absence of expression of either the paternally or maternally derived allele at a particular developmental stage or in a specific tissue type [Bartolomei and Tilghman, 1997]. Some 83 transcriptional units are currently known to be imprinted in mammals [Morison et al., 2005]. Complete inactivation of an imprinted gene results in functional haploidy, with only one of the two copies of a gene expressed. For example, insulin-like growth factor 2 (Igf2) is only expressed from the paternal allele in most fetal tissues of eutherian and marsupial mammals [DeChiara et al., 1991; O'Neill et al., 2000]. More generally, however, imprinting results in the functional
non-equivalence of reciprocal heterozygotes, where inheriting an $A_1$ allele from one’s mother and an $A_2$ allele from one’s father gives a different phenotype, on average, than the reverse inheritance pattern.

Maternal effects arise when the genetic and environmental characteristics of a mother influence the phenotype of her offspring, beyond the direct inheritance of alleles. These effects contribute to resemblance between offspring of the same mother, and between mothers and their offspring, and are extensively recognized in traits such as offspring growth, production and disease risk [Wade, 1998]. For example, significant maternal effects for early growth in mice were detected in a QTL mapping study [Wolf et al., 2002]. Maternal genetic effects contribute an extra term in addition to an offspring’s own genotypic value, dependent on the genotype of the mother [Lynch and Walsh, 1998]. This effect on offspring phenotype is also termed an indirect genetic effect, as the maternal phenotype (itself determined by genetic factors) acts as an environmental influence on offspring phenotype [Moore et al., 1998]. Such indirect genetic effects increase resemblances between mothers and offspring, and between siblings. Maternal effects may also arise independently of genetic factors. For example, Huck [1987] demonstrated that food restriction in the early life of golden hamsters, *Mesocricetus auratus*, leads to reduced numbers and female-biased sex ratios in litters borne later in life. Further, a non genetic influence need not be restricted to a maternal environmental effect – the father’s environmental conditions may also contribute to the characteristics of offspring [Shaw and Byers, 1998].

For quantitative traits, it may be difficult to distinguish maternal genetic effects from imprinting effects. For example, both maternal effects and genomic imprinting can increase the covariance between the genotypic values of mothers and their offspring [Kempthorne, 1957; Spencer, 2002]. It is therefore of interest to derive a quantitative genetic model to incorporate both imprinting and maternal genetic effects (hereafter termed maternal effects) to discover if these distinct causative processes lead to differences in population statistics.

**The Model**

We combine standard quantitative genetic models for additive maternal genetic effects [Kempthorne, 1957] and genomic imprinting [Spencer, 2002] to
calculate breeding values, genetic variances and covariances between relatives.
Following the approach of Spencer [2002], consider an autosomal two-allele locus
with alleles $A_1$ and $A_2$ at frequency $p_1$ and $p_2$ respectively in the population. We write
the maternally inherited allele first, such that $A_2A_1$ has a maternally inherited $A_2$
allele and a paternally inherited $A_1$ allele. Let $A_{ijkl}$ represent an $A_iA_j$ offspring with an $A_kA_l$
mother and $G_{ijkl}$ represent the genotypic value of $A_{ijkl}$. Note that important parameters
and notation introduced in this text are also summarized in Table 1.

Table 2 shows all possible genotypic values for offspring, given the genotype
of their mother. Here 0, $a(1+k_1)$, $a(1+k_2)$ and $2a$ represent genotypic contributions
from $A_1A_1$, $A_2A_1$, $A_1A_2$ and $A_2A_2$ offspring and 0, $b(1+m_1)$, $b(1+m_2)$ and $2b$ represent
genotypic contributions from $A_1A_1$, $A_2A_1$, $A_1A_2$ and $A_2A_2$ mothers. For example, an
$A_2A_1$ offspring with an $A_1A_2$ mother has a genotypic value $G_{2112} = a(1+k_1)+b(1+m_2)$,
with $a(1+k_1)$ representing the contribution from its own genotype and $b(1+m_2)$
representing the contribution to genotypic value from its mother’s genotype.
Following Spencer [2002], genomic imprinting is included in the model by assigning
separate genotypic contributions for the reciprocal heterozygotes $A_2A_1$ and $A_1A_2$ by
use of the parameters $k_1 \& k_2$, and $m_1 \& m_2$. Note that in the absence of imprinting $k_1$
= $k_2$ and $m_1 = m_2$, while in the absence of maternal effects $b = 0$ (and hence $m_1 = m_2 = 0$ also).

The classical definition for imprinting, complete inactivation of one allele,
corresponds to $k_1 = -1 \& k_2 = 1$ and $m_1 = -1 \& m_2 = 1$ (complete silencing of the
maternal allele), or $k_1 = 1 \& k_2 = -1$ and $m_1 = 1 \& m_2 = -1$ (complete silencing of the
paternal allele). More recently, however, imprinting has been treated as a quantitative
trait, which implies that maternal or paternal alleles may only be partially inactivated
[see, e.g., Sandovici et al., 2003; Naumova and Croteau, 2004; Sandovici et al., 2005],
and $k_1$, $k_2$, $m_1$ and $m_2$ may take any value in the range [-1,1].

Table 3 shows the complete array of offspring genotypes and their frequency
in the population from each possible parent mating combination. Returning to Tables
2 and 3, note that a number of mother-offspring combinations are not possible without
introducing mutation - for example it is not possible for an $A_1A_1$ mother to produce an
$A_2A_1$ offspring.
With the help of Table 3, the mean genotypic value over the population is

\[
\mu = \sum \text{genotypic value} \times \text{proportion} \times \text{frequency of mating}
\]

\[
= p_2(a(2 + p_1(k_1 + k_2)) + b(2 + p_1(m_1 + m_2))).
\]

When maternal effects are zero (that is, \(b = 0\)), the mean genotypic value is identical to that under imprinting alone [Spencer, 2002]. Similarly with no imprinting (\(k_1 = k_2 = k\) and \(m_1 = m_2 = m\)) the mean reduces to \(\mu = 2p_2(a(1+kp_1) + b(1+mp_1))\), the equivalent expression in Kempthorne’s [1957] model.

We follow a number of approaches in calculating breeding values, components of variance and covariances between relatives. Doing so illustrates that various assumptions made in these approaches are not valid in the presence of imprinting and maternal effects.

**Approach 1**

We first follow the approach of Falconer and Mackay [1996] and Kempthorne [1957], using genotypic values of parents and offspring to calculate population breeding values, dominance deviations, components of variance and covariances between relatives.

We begin by calculating the frequency, \(f_{ijkl}\), of each genotype, \(A_{ijkl}\) (Table 4), by summing over the product of mating frequencies and proportion of offspring for each \(A_{ijkl}\) from Table 3. For example (from Table 3),

\[
\begin{align*}
\hat{f}_{1221} &= \frac{1}{2}p_1^2p_2^3 + \frac{1}{2}p_2^2p_1^3 + \frac{1}{2}p_1p_2^4 \\
&= \frac{1}{2}p_1p_2^2.
\end{align*}
\]

We now calculate genotypic deviations \(gd_{ijkl}\) for each \(A_{ijkl}\), the difference between the genotypic value \(G_{ijkl}\) and the population mean; the values are shown in Table 4. Note that genotypic deviations are calculated separately for each \(A_{ijkl}\) and should not be averaged over mothers.

Breeding values for each \(AA_A_i\) genotype are defined as twice the difference between the mean genotypic value of that class’s offspring and the population mean [Falconer and Mackay, 1996]. Progeny means are included in Table 4. Unlike genotypic values and deviations, progeny means and breeding values need not be calculated separately for genotypes with different maternal genotypes (i.e. for all \(A_{ijkl}\), but do need to be calculated separately for males \((bv_{mij})\) and females \((bv_{fij})\).
values are different for males and females because all offspring of a dam share the same maternal effect while offspring of a sire have four different maternal contributions. Finally, male and female dominance deviations ($dd_{mijkl}$ and $dd_{fijkl}$), the difference between the genotypic deviation and the breeding value for each genotype, may be derived (Table 4).

**Genetic variance components**

The genetic variance of the population ($\sigma^2_G$) is the variance of the genotypic deviations:

$$\sigma^2_G = \sum_{ijkl} f_{ijkl} g d_{ijkl}^2$$

$$= p_1 p_2 [a^2 (k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2] + b^2 ((m_1 - m_2)^2 + p_1 p_2 (m_1 + m_2)^2) + 2\alpha f \alpha_m + 2\beta f \beta_m + \alpha f (\beta f + \beta_m)]$$

$$= p_1 p_2 [a^2 p_2 k_1 + k_2]^2 + b^2 p_1 p_2 (m_1 + m_2)^2$$

$$+ \alpha^2 f + \alpha^2 m + \beta^2 f + \beta^2 m + \alpha f (\beta f + \beta_m)]$$

where, for simplicity, we define the terms

$$\alpha f = a(1+k_1 p_1-k_2 p_2),$$

$$\alpha_m = a(1+k_2 p_1-k_1 p_2),$$

$$\beta f = b(1+m_1 p_1-m_2 p_2)$$

and

$$\beta_m = b(1+m_2 p_1-m_1 p_2).$$

In the absence of maternal effects ($b = 0$), the total variance is equivalent to that under imprinting alone [Spencer, 2002].

Note that when $k_1 = k_2 = k$ and $m_1 = m_2 = m$, so that imprinting is absent, equations (0) and (2) reduce to

$$\mu = 2 p_2 (a(1+k p_1)+b(1+mp_1))$$

and

$$\sigma^2_G = 2 p_1 p_2 [2 p_1 p_2 (a^2 k^2 + b^2 m^2 + \alpha^2 + \alpha \beta + \beta^2)],$$

where $\alpha = a(1+k(p_1 - p_2))$ and $\beta = b(1+m(p_1 - p_2))$. These are equivalent to the values of Kempthorne [1957] using our notation (see Table 5 for the mating table showing all possible offspring genotypes for maternal effects in the absence of imprinting, and Table 6 for genotypic values, breeding values and dominance deviations under maternal effects alone).
The additive genetic variances for females ($\sigma_{Af}^2$) and males ($\sigma_{Am}^2$) are the respective variances of their breeding values:

$$\sigma_{Af}^2 = \sum_{i,j=1}^{2} p_i p_j b v_{ij}^2$$

$$= 2p_i p_2 [b^2 (m_i - m_2)^2 + 2p_i p_2 (m_i + m_2)^2] + (\alpha_f + \beta_f + \beta_m)^2$$

and

$$\sigma_{Am}^2 = \sum_{i,j=1}^{2} p_i p_j b v_{mij}^2$$

$$= 2p_i p_2 \alpha_m^2.$$

The male additive variance is equivalent to that under imprinting alone [Spencer, 2002], and is therefore unaffected by the addition of maternal effects to the model. In contrast, the female additive genetic variance is equivalent to that under imprinting alone [Spencer, 2002] only when maternal effects are absent ($b = 0$). We may define progeny means and breeding values for maternal effects alone (i.e., in the absence of imprinting) (see Table 6) as described above and find that the additive genetic variances simplify to

$$\sigma_{Af}^2 = 2p_i p_2 [8b^2 m^2 p_1 p_2 + \alpha^2 + 4\alpha \beta + 4 \beta^2]$$

and

$$\sigma_{Am}^2 = 2p_i p_2 \alpha^2.$$

The dominance genetic variance is the variance of the dominance deviations, and is not the same for females ($\sigma_{Df}^2$) and males ($\sigma_{Dm}^2$):

$$\sigma_{Df}^2 = \sum_{ijkl} f_{ijkl} d d_{fijkl}$$

$$= p_i p_2 [a^2 ((k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2)$$

$$+ 4ab((k_1 - k_2)(1 + m_2) - 2k_1 p_2 (m_1 + m_2) + p_2^2 (k_1 + k_2) (m_1 + m_2))$$

$$+ b^2 (6 - 2m_1 m_2 + 4m_1 (p_1 - 2p_2) + 4m_2 (2p_1 - p_2)$$

$$- p_1 p_2 (m_1 + m_2)^2 + m_2^2 (3p_1 + 5p_2) + m_2^2 (5p_1 + 3p_2))]$$

and

$$\sigma_{Dm}^2 = \sum_{ijkl} f_{ijkl} d d_{mijkl}$$

$$= p_i p_2 [a^2 ((k_1 - k_2)^2 + p_1 p_2 (k_1 + k_2)^2) + a(k_1 - k_2)(\beta_j + \beta_m)$$

$$+ b^2 (2 + m_1^2 + m_2^2 + 2(m_1 + m_2)(p_1 - p_2) - p_1 p_2 (m_1 + m_2)^2)].$$
Under imprinting alone, dominance variances are equivalent for males and females [Spencer, 2002]. It is interesting to note that this equivalence is lost when maternal effects are included. Taking the variance of the dominance deviations for maternal effects alone (defined in Table 6), we find that

\[ \sigma_{Dm}^2 = 2p_1p_2[(2a_1^2 b^2 + 2b_1^2 m^2) + 3\beta^2] \]  

and

\[ \sigma_{Df}^2 = 2p_1p_2[b_1^2 m^2 + \beta^2]. \]  

The non-equivalence of dominance deviation variances under imprinting and maternal effects is therefore due to differences between male and female dominance variances under maternal effects alone.

The covariances between dominance deviations and breeding values are given by

\[ \sigma_{Adj} = \sum_{ijkl} f_{ijkl} b_{ij} d_{ijkl} \]

\[ = p_1p_2[-\frac{1}{2}ab(6 + k_1(10 - 6p_2 + 3m_1 + 7m_2) - k_2(4 + 6p_2 + 4m_2)) + (m_1 + m_2)(3(p_1 - p_2) + p_2(-17k_1 - 3k_2 + 10p_2(k_1 + k_2))))] \]  

\[ -b_1^2(6 + m_1(5 - 12p_2) + m_2(7 - 12p_2) - m_1m_2(1 + 4p_1p_2)) + m_1^2(3 + p_2 - 2p_1p_2) + m_2^2(3 + p_1 - 2p_1p_2) + a\alpha_f(k_2 - k_1)] \]  

and

\[ \sigma_{Adm} = \sum_{ijkl} f_{ijkl} b_{ij} \sigma_{mi} \sigma_{ijkl} \]

\[ = p_1p_2[\alpha_m\alpha_f(k_1 - k_2) + \frac{1}{2}(\beta_f + \beta_m)]. \]

Under maternal effects alone these simplify to

\[ \sigma_{Adm} = p_1p_2[8abkmp_1p_2 - 16b_1^2 m^2 p_1 p_2 - 3\beta(\alpha + 2\beta)] \]  

and

\[ \sigma_{Adm} = p_1p_2[\alpha \beta], \]  

and in the absence of both maternal effects and imprinting \((b = 0 \text{ and } k_1 = k_2)\), the covariances are zero and breeding values and dominance deviations are uncorrelated.

Finally, it can be easily shown that

\[ \sigma_G^2 = \sigma_A^2 + \sigma_D^2 + 2\sigma_{Ad} \]

\[ = \sigma_A^2 + \sigma_D^2 + 2\sigma_{Adm} \]

for both maternal effects and imprinting, and maternal effects alone.
It is reassuring to note that values for the population mean, variances and covariances under maternal effects alone are equivalent whether they are derived independently from Tables 5 and 6 or by substituting \(k = k_1 = k_2\) and \(m = m_1 = m_2\) into equations (0), (2), (6), (5), (10), (9), (14) and (13).

**Resemblance between relatives**

We now follow the approach of Kempthorne [1957] to calculate the mother-offspring covariance (\(\sigma_{opf}\), covariance between Offspring and female Parent) and father-offspring covariance (\(\sigma_{opm}\), covariance between Offspring and male Parent) using Table 7. Table 7 displays the genotypic values of parents and the mean value of offspring of these parents. Note that this Table covers all twelve possible parent genotypes, as it is important to not average over \(A_{kl}\) genotypes (the male or female parent’s own mother).

Then

\[
\sigma_{op} = \sum_{ijkl} fr_{ijkl} (G_{ijkl} - \mu_G)(A_{ij} \text{ progeny mean} - \mu_G);
\]

\[
\sigma_{opf} = \frac{1}{4} p_1 p_2 [5ab(-2 + k_1 m_1 + k_2 m_2) - 6ab p_1 p_2 (k_1 + k_2) (m_1 + m_2) + 2\alpha_f(\alpha_f + \alpha_m) + 2\beta_f (\beta_f + \beta_m) + a\beta_m (k_1 - k_2) + 5a(\beta_f + \beta_m) + 5b(\alpha_f + \alpha_m)]
\]

and

\[
\sigma_{opm} = \frac{1}{4} p_1 p_2 \alpha_m [2(\alpha_f + \alpha_m) + \beta_f + \beta_m].
\]

Note that, following Spencer [2002], these covariances are equivalent to

\[
\sigma_{opf} = \frac{1}{2}(\sigma_{Af}^2 + \sigma_{Adf}^2)
\]

and

\[
\sigma_{opm} = \frac{1}{2}(\sigma_{Am}^2 + \sigma_{Adm}^2)
\]

The full-sib covariance (\(\sigma_{fs}\)) can be calculated with the aid of Table 8, which displays all possible genotypic values and frequencies of pairs of siblings:

\[
\sigma_{fs} = \sum_{\text{offspring pairs}} fr(\text{offspring } G_{ijkl} - \mu_G)(\text{offspring } G_{ijkl} - \mu_G)
\]

\[
= p_1 p_2 [\frac{1}{2} a^2 p_1 p_2 (k_1 + k_2)^2 + \frac{1}{2}(\alpha_f^2 + \alpha_m^2) + b^2 p_1 p_2 (m_1 + m_2)^2 + \beta_f^2 + \beta_m^2 + \alpha_f (\beta_f + \beta_m)].
\]
In the absence of imprinting, setting $k = k_1 = k_2$ and $m = m_1 = m_2$, we find that

$$\sigma_{opf} = \frac{1}{2} p_1 p_2 [8 a b k m p_1 p_2 + 2 \alpha^2 + 2 \beta^2 + 5 \alpha \beta],$$

$$\sigma_{opm} = \frac{1}{2} p_1 p_2 \alpha [2 \alpha + \beta]$$

and

$$\sigma_{fs} = p_1 p_2 [a^2 k^2 p_1 p_2 + 4 b^2 m^2 p_1 p_2 + \alpha^2 + 2 \alpha \beta + 2 \beta^2].$$

These covariances are equivalent to the values of Kempthorne [1957] using our notation (note that his definitions for $\alpha$ and $\beta$ are not the same as ours). When imprinting is present in the absence of maternal effects ($b = 0$),

$$\sigma_{opf} = \frac{1}{2} p_1 p_2 \alpha_f [a (k_z - k_i) + 2 \alpha_f],$$

$$\sigma_{opm} = \frac{1}{2} p_1 p_2 \alpha_m [a (k_i - k_z) + 2 \alpha_m]$$

(also derived by Spencer [2002]) and

$$\sigma_{fs} = \frac{1}{2} p_1 p_2 [a^2 p_1 p_2 ((k_z + k_i)^2 + 2 p_1 (k_i - k_z) (2 - p_2 (k_z + k_i))) + 2 (\alpha_j^2 + \alpha_m^2)].$$

Finally, we may also calculate the covariance between offspring who share a mother or a father. Following Spencer [2002], the covariance of half siblings who share a mother is

$$\sigma_{hsf} = \frac{1}{4} \sigma_{sf}^2$$

$$= \frac{1}{2} p_1 p_2 [b^2 ((m_1 - m_2)^2 + 2 p_1 p_2 (m_1 + m_2)^2)$$

$$+ \alpha_j^2 + 2 \alpha_f (\beta_f + \beta_m) + (\beta_f + \beta_m)^2]$$

and the covariance of half sibs sharing a father is

$$\sigma_{hsm} = \frac{1}{4} \sigma_{sm}^2$$

$$= \frac{1}{2} p_1 p_2 \alpha_m^2.$$

These covariances reduce to

$$\sigma_{hsf} = \frac{1}{2} p_1 p_2 [8 b^2 m^2 p_1 p_2 + \alpha^2 + 4 \alpha \beta + 4 \beta^2]$$

and

$$\sigma_{hsm} = \frac{1}{2} p_1 p_2 \alpha^2$$

in the absence of imprinting, and

$$\sigma_{hsf} = \frac{1}{2} p_1 p_2 \alpha_j^2$$

and

$$\sigma_{hsm} = \frac{1}{2} p_1 p_2 \alpha_m^2$$

if we assume no maternal effects [Spencer, 2002].
**Approach 2a**

We now follow a general least squares approach [Lynch and Walsh, 1998] to calculate population breeding values, dominance deviations, components of variance and covariances between relatives.

We can write the genotypic value $G_{ijkl}$ as the sum of the mean plus the additive ($\varepsilon$ and $\omega$) and dominance ($\lambda$, $\theta$ and $\delta$) effects:

$$G_{ijkl} = \mu + (\varepsilon_{ij} + \varepsilon_{kl}) + (\lambda_j + \omega_{ik} + \omega_{lj}) + \theta_{kl} + \delta_{ijkl}$$

(24)

where $\mu = 2p_2(a(1+kp_i) + b(1+mp_i))$ as above, $\varepsilon_{ij}$ is the average additive effect of inheriting an $A_i$ allele from the mother, $\varepsilon_{kj}$ is the average additive effect of inheriting an $A_j$ allele from the father, $\omega_{ik}$ is the average additive effect of having a mother who received an $A_k$ allele from her own mother, and $\omega_{lj}$ is the average additive effect of having a mother who received an $A_l$ allele from her own father. The dominance effects $\lambda$, $\theta$ and $\delta$ are defined below. Note that here “••” represents either of an $A_1$ or $A_2$ allele in that position.

We first calculate the average genetic values $G_{ij••}$ of $A_iA_j$ genotypes using Table 3. For example, the average genotypic value of an $A_1A_1$ individual is

$$G_{11••} = \frac{1}{p_1^2}(0(p_1^3 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2) + b(1+m_1)(\frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + p_1^3p_2) + b(1+m_2)(\frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + \frac{1}{2}p_1^3p_2 + p_1^3p_2)] = \frac{1}{2}bp_2(2+m_1+m_2).$$

Similarly,

$$G_{21••} = a(1+k_1) + \frac{1}{2}b(p_1(2+m_1+m_2)+4p_2)$$
$$G_{12••} = a(1+k_2) + \frac{1}{2}bp_2(2+m_1+m_2)$$
$$G_{22••} = 2a + \frac{1}{2}b(p_1(2+m_1+m_2)+4p_2).$$

It can be noted that, as expected,

$$\mu = p_1^2G_{11••} + p_2p_1G_{21••} + p_1p_2G_{12••} + p_2^2G_{22••} = p_2(a(2+p_1(k_1+k_2)+b(2+p_1(m_1+m_2))).$$

The additive effect of an allele is the deviation of members of the population with the allele from the population mean. In the absence of imprinting, the parental origin of the allele has no effect. With imprinting however, we can calculate the additive effect of the allele separately under maternal and paternal inheritance. For
example, the average additive effect of an $A_1$ allele when inherited maternally is the average of the mean $A_1A_1$ and $A_1A_2$ genotypic values minus the population mean:

$$
\epsilon_{1*} = p_1G_{11} + p_2G_{12} - \mu
$$

$$
= -\frac{1}{2} p_2(2\alpha_f + \beta_f + \beta_m)
$$

while the additive effect of an $A_1$ allele when inherited paternally is

$$
\epsilon_{1*} = p_1G_{11} + p_2G_{12} - \mu
$$

$$
= -p_2\alpha_m.
$$

The other two additive effects are thus

$$
\epsilon_{2*} = -\frac{1}{2} p_1(2\alpha_f + \beta_f + \beta_m)$$

$$
\epsilon_{2*} = p_2\alpha_m.
$$

The dominance effects are defined as

$$
\lambda_{ij} = G_{ij} - \mu - \epsilon_{i*} - \epsilon_{j*},
$$

for example,

$$
\lambda_{11} = G_{11} - \mu - \epsilon_{1*} - \epsilon_{1*}
$$

$$
= -ap_1^2(k_1 + k_2).
$$

The other dominance effects are shown below:

$$
\lambda_{21} = \lambda_{12} = ap_1p_2(k_1 + k_2)
$$

$$
\lambda_{22} = -ap_2^2(k_1 + k_2).
$$

It is interesting to note that the dominance effects are the same for individuals with an $A_{12}$ genotype (regardless of mother) as they are for individuals with an $A_{21}$ genotype.

With the help of Table 3, we may now define average genetic values $G_{***}$ of individuals with an $A_kA_l$ mother. For example, the average genotypic value of an individual with an $A_1A_1$ mother is

$$
G_{11} = \frac{1}{2} p_1^2 \left[ p_1^4(0) + p_1^3p_2(0) + p_1^3p_2(a(1+k_2)) + p_1^2p_2^2(a(1+k_2)) \right]
$$

$$
= a(p_2 + k_2p_2).
$$

Similarly,

$$
G_{21} = \frac{1}{2} a(1+2p_2+k_1p_1+k_2p_2) + b(1+m_1)
$$

$$
G_{12} = \frac{1}{2} a(1+2p_2+k_1p_1+k_2p_2) + b(1+m_1)
$$

$$
G_{22} = a(p_1^2 + 2p_2 + k_1p_1) + 2b
$$

and again, as expected,

$$
\mu = p_1^2G_{11} + p_2p_1G_{21} + p_1p_2G_{12} + p_2^2G_{22}.
$$
The additive effects of maternal allele may now be calculated. For example, the average additive effect of a mother with a maternally inherited \(A_1\) allele is

\[
\omega_1 = p_1 G_{*11} + p_2 G_{*12} - \mu = -\frac{1}{2} \, p_2 (\alpha_f + 2 \beta_f)
\]

while the additive effect of a mother with a paternally inherited \(A_1\) allele is

\[
\omega_1 = p_1 G_{*11} + p_2 G_{*22} - \mu = -\frac{1}{2} \, p_2 (\alpha_f + 2 \beta_m).
\]

The other two additive maternal effects are similarly

\[
\begin{align*}
\omega_2 & = -\frac{1}{2} \, p_2 (\alpha_f + 2 \beta_f) \\
\omega_2 & = -\frac{1}{2} \, p_2 (\alpha_f + 2 \beta_m).
\end{align*}
\]

The maternal dominance effects are defined as

\[
\theta_1 = G_{*11} - \omega_1 - \omega_1,
\]

for example,

\[
\theta_1 = G_{*11} - \omega_1 - \omega_1 = -bp_2^2 (m_1 + m_2).
\]

The other maternal dominance effects are similarly

\[
\theta_2 = \theta_1 = bp_1 p_2 (m_1 + m_2)
\]

\[
\theta_2 = -bp_1^2 (m_1 + m_2).
\]

Finally, we calculate the combined offspring-mother genotype dominance deviations as

\[
\delta_{ijkl} = G_{ijkl} - \mu - e_i - e_j - \lambda_{ij} - \omega_1 - \omega_2 - \theta_{kl}
\]

The combined dominance effects are shown below:

\[
\begin{align*}
\delta_{111} & = \delta_{112} = \frac{1}{2} \, p_2 (2 \alpha_f + \beta_f + \beta_m) \\
\delta_{121} & = \delta_{122} = \delta_{211} = \delta_{212} = \frac{1}{2} (\alpha_f (p_2 - p_1) + p_2 (\beta_f + \beta_m)) \\
\delta_{221} & = \delta_{222} = \frac{1}{2} (\alpha_f (p_2 - p_1) - p_1 (\beta_f + \beta_m)) \\
\delta_{2122} & = \delta_{2222} = -\frac{1}{2} \, p_1 (2 \alpha_f + \beta_f + \beta_m).
\end{align*}
\]

In Approach 1, we followed the definition that the breeding value of an individual is twice the difference between the mean genotypic value of the class’s offspring and the population mean [Falconer and Mackay, 1996]. When breeding
values are equivalent for males and females, the breeding value of a genotypic class is also the sum of the additive effects of its genes [Lynch and Walsh, 1998]:

\[
\begin{align*}
\text{bv}_{11} &= e_{*} + e_{i} = -\frac{1}{2} p_{2} (2\alpha_{f} + \beta_{f} + \beta_{m}) - p_{2} \alpha_{m} \\
&= -p_{2} (\alpha_{f} + \alpha_{m} + \frac{1}{2} (\beta_{f} + \beta_{m})) \\
\text{bv}_{21} &= e_{*} + e_{i} \\
&= p_{1} \alpha_{f} - p_{2} \alpha_{m} + \frac{1}{2} p_{1} (\beta_{f} + \beta_{m}) \\
\text{bv}_{12} &= e_{*} + e_{i} \\
&= -p_{2} \alpha_{f} + p_{1} \alpha_{m} - \frac{1}{2} p_{2} (\beta_{f} + \beta_{m}) \\
\text{bv}_{22} &= e_{*} + e_{i} = \frac{1}{2} p_{1} (2\alpha_{f} + \beta_{f} + \beta_{m}) + p_{1} \alpha_{m} \\
&= p_{1} (\alpha_{f} + \alpha_{m} + \frac{1}{2} (\beta_{f} + \beta_{m}))
\end{align*}
\]

For a locus influenced by imprinting and maternal effects, however, breeding values are different for males and females. Taking the mean of female and male breeding values from Approach 1 (Table 4), we can see that

\[
\begin{align*}
\frac{1}{2} [\text{bv}_{f11} + \text{bv}_{m11}] &= -p_{2} (\alpha_{f} + \alpha_{m} + b(2 + p_{1}(m_{1} + m_{2}))) \\
\frac{1}{2} [\text{bv}_{f21} + \text{bv}_{m21}] &= \frac{1}{2} (\alpha_{f} + \alpha_{m})(p_{1} - p_{2}) + b(p_{1} - p_{2} + m_{1} - p_{1} p_{2}(m_{1} + m_{2})) \\
\frac{1}{2} [\text{bv}_{f12} + \text{bv}_{m12}] &= \frac{1}{2} (\alpha_{f} + \alpha_{m})(p_{1} - p_{2}) + b(p_{1} - p_{2} + m_{2} - p_{1} p_{2}(m_{1} + m_{2})) \\
\frac{1}{2} [\text{bv}_{f22} + \text{bv}_{m22}] &= p_{1} ((\alpha_{f} + \alpha_{m} + b(2 - p_{2}(m_{1} + m_{2})))
\end{align*}
\]

which are not equivalent to the combined female and male breeding values calculated above from the sum of additive effects.

**Genetic variance components**

We may now calculate variances associated with the population. The offspring genotype additive genetic variation is the variance associated with the average additive effects of alleles and can be shown to be

\[
\sigma_{A,\text{avg}}^{2} = \sum_{i=1}^{2} p_{i} (e_{*}^{2} + e_{i}^{2})
\]

\[
= \frac{1}{4} p_{1} p_{2} [4\alpha_{m}^{2} + (2\alpha_{f} + \beta_{f} + \beta_{m})^{2}]
\]

while the offspring genotype dominance genetic variance is the genetic variance associated with dominance effects:

\[
\sigma_{D,\text{avg}}^{2} = \sum_{i,j=1}^{2} p_{i} p_{j} \lambda_{ij}^{2}
\]

\[
= a^{2} p_{1}^{2} p_{2}^{2} (k_{1} + k_{2})^{2}.
\]
Similarly we calculate the variance in the maternal genotype additive effects as

\[ \sigma^2_{A(m)} = \sum_{k=1}^{2} p_k (\omega^2_k + \omega^2_{-k}) = \frac{1}{4} p_1 p_2 [b^2 (m_1 - m_2)^2 + (\alpha_f + \beta_f + \beta_m)^2] \]

and dominance variance for maternal genotype as

\[ \sigma^2_{D(m)} = \sum_{k=1}^{2} p_k p_{l} \theta^2_{kl} = b^2 p_1^2 p_2^2 (m_1 + m_2)^2. \]

The variance in combined dominance effects is

\[ \sigma^2_{D(\delta)} = \sum_{ijkl} f_{ijkl} \delta^2_{ijkl} = \frac{1}{4} p_1 p_2 [\alpha^2_f + (\alpha_f + \beta_f + \beta_m)^2]. \]

Recalling that we defined our genotypic effects as

\[ G_{ijkl} = \mu + (\varepsilon_0 + \varepsilon_i) + (\omega_0 + \omega_j) + \theta_{kl} + \delta_{ijkl}, \]

we may write

\[ gd_{ijkl} = (\varepsilon_0 + \varepsilon_i) + (\omega_0 + \omega_j) + \theta_{kl} + \delta_{ijkl} \]

and the total variance (var) in the population can be expressed as

\[ \text{var}(gd_{ijkl}) = \text{var}(\varepsilon_0 + \varepsilon_i) + \text{var}(\omega_0 + \omega_j) + \text{var}(\theta_{kl}) + \text{var}(\delta_{ijkl}) \]

\[ + 2 \text{cov}(\varepsilon_0 + \varepsilon_i, \omega_0 + \omega_j) + \text{cov}(\varepsilon_0 + \varepsilon_i, \theta_{kl}) + \text{cov}(\varepsilon_0 + \varepsilon_i, \delta_{ijkl}) + \text{cov}(\omega_0 + \omega_j, \theta_{kl}) + \text{cov}(\omega_0 + \omega_j, \delta_{ijkl}) + \text{cov}(\theta_{kl}, \delta_{ijkl}) \]

\[ \text{cov}(\delta_{ijkl})] = \sigma^2_{A(\varepsilon)} + \sigma^2_{D(\lambda)} + \sigma^2_{A(\omega)} + \sigma^2_{D(\theta)} + \sigma^2_{D(\delta)} + 2 \sigma_{A(\varepsilon)D(\lambda)} + \sigma_{A(\varepsilon)A(\omega)} + \sigma_{A(\varepsilon)D(\theta)} + \sigma_{A(\varepsilon)D(\delta)} + \sigma_{D(\lambda)A(\omega)} + \sigma_{D(\lambda)D(\theta)} + \sigma_{D(\lambda)D(\delta)} + \sigma_{A(\omega)D(\theta)} + \sigma_{A(\omega)D(\delta)} + \sigma_{D(\delta)D(\delta)} \]

The covariances (cov) of additive by additive and additive by dominance effects are

\[ \sigma_{A(\varepsilon)A(\omega)} = \frac{1}{4} p_1 p_2 [2\alpha_f^2 + 3\alpha_f (\beta_f + \beta_m) + (\beta_f + \beta_m)^2] \]

\[ \sigma_{A(\varepsilon)D(\delta)} = -\frac{1}{4} p_1 p_2 [2\alpha_f^2 + 3\alpha_f (\beta_f + \beta_m) + (\beta_f + \beta_m)^2] \]

\[ \sigma_{A(\omega)D(\delta)} = -\frac{1}{4} p_1 p_2 [2\alpha_f^2 + 3\alpha_f (\beta_f + \beta_m) + (\beta_f + \beta_m)^2] \]
Note that all other covariances are zero. As expected, the total variance in the population (2) may be recovered from equation (25).

**Approach 2b**

Approach 2a calculated total additive and dominance effects and did not allow separate calculation of female and male additive and dominance variances as were possible in Approach 1. Therefore let us redefine the additive allele effects as female and male effects, so that

\[
G_{ijkl} = \mu + (\epsilon_i + \epsilon_j) + \lambda_i + (\omega_i + \omega_j) + \theta_{kl} + \delta_{ijkl}
\]

\[
= \mu + (\epsilon_i + \epsilon_j) + \lambda_{ij} + (\omega_i + \omega_j) + \theta_{ij} + \delta_{ijkl}
\]

\[
= \mu + (\epsilon_i + \epsilon_j) + \delta_{ijkl}
\]

where the extra subscripts on \( \lambda \) and \( \delta \) indicate female \((f)\) and male \((m)\) effects. These definitions allow inclusion of a parental influence on the next generation into the model. For example, a \( G_{ijkl} \) mother will contribute \( \epsilon_i \) and \( \epsilon_j \) alleles to her offspring, plus a maternal component of \( \omega_i + \omega_j \) from her own genotype (plus dominance terms). In contrast, \( G_{ijkl} \) fathers will only contribute \( \epsilon_i \) and \( \epsilon_j \) alleles to offspring (plus a dominance term) and will not contribute a maternal term. In using these definitions we endeavor to partition the additive and dominance terms into those specific to male and female inheritance.

Following this model, \( \epsilon, \omega \) and \( \theta \) terms are defined as in Approach 2a. We define female offspring dominance effects as

\[
\hat{\lambda}_{ij} = G_{ij} - \mu - \epsilon_i - \epsilon_j.
\]

For example,

\[
\hat{\lambda}_{21} = G_{21} - \mu - \epsilon_2 - \epsilon_1.
\]

The other female offspring dominance effects are thus

\[
\hat{\lambda}_{11} = \frac{1}{2} p_2 (2a(k_1(p_1 + p_2) - k_2 p_2) + \beta_f + \beta_m)
\]

\[
\hat{\lambda}_{12} = -\frac{1}{2} p_1 (2a(k_1 p_1 - k_2 (p_1 + 2 p_2)) + \beta_f + \beta_m)
\]

\[
\hat{\lambda}_{22} = -\frac{1}{2} p_1 (2a(k_1 (2 p_1 + p_2) - k_2 p_2) + \beta_f + \beta_m).
\]

Note that dominance effects are no longer equivalent for \( A_{12} \) and \( A_{21} \) individuals. The mean female dominance deviation is zero.
We now calculate the combined offspring-mother genotype dominance deviations for females as

\[
\delta_{fijkl} = G_{ijkl} - \mu - \epsilon_i - \epsilon_j - \lambda_{ij} - \omega_i - \omega_j - \theta_g.
\]

The female combined dominance deviations are therefore

\[
\begin{align*}
\delta_{f1111} &= p_2 \alpha_j + \frac{1}{2} p_2 (\beta_j + \beta_m) \\
\delta_{f1121} &= \frac{1}{2} b (2 + 2 p_2 + m_1 (2 p_1 + p_2 + 2 p_1 p_2) + m_2 p_2 (p_1 - p_2)) + p_2 \alpha_j \\
\delta_{f1112} &= \frac{1}{2} b (2 + 2 p_2 + m_1 p_2 (p_1 - p_2) + m_2 (2 p_1 + p_2 + 2 p_1 p_2)) + p_2 \alpha_j \\
\delta_{f2121} &= \frac{1}{2} \alpha_j (p_2 - p_1) - \frac{1}{2} p_1 (\beta_f + \beta_m) \\
\delta_{f2112} &= \frac{1}{2} b (-2 p_1 + m_1 (-3 p_1 - 2 p_2 + 2 p_1 p_2) + m_2 (p_1 + 2 p_2 + 2 p_1 p_2)) + \frac{1}{2} \alpha_j (p_2 - p_1) \\
\delta_{f1221} &= \frac{1}{2} b (2 p_2 + m_1 (-3 p_1 - 2 p_2 + 2 p_1 p_2) + m_2 p_1 (p_2 - p_1)) + \frac{1}{2} \alpha_j (p_2 - p_1) \\
\delta_{f1211} &= \frac{1}{2} b (-2 p_1 + m_1 p_2 (p_2 - p_1) + m_2 (-2 p_1 - 3 p_2 + 2 p_1 p_2)) + \frac{1}{2} \alpha_j (p_2 - p_1) \\
\delta_{f1222} &= \frac{1}{2} b (2 p_2 + m_1 (2 p_1 + p_2 + 2 p_1 p_2) + m_2 (-2 p_1 - 3 p_2 + 2 p_1 p_2)) + \frac{1}{2} \alpha_j (p_2 - p_1) \\
\delta_{f2222} &= \frac{1}{2} \alpha_j (p_2 - p_1) + 1/2 p_1 (\beta_f + \beta_m) \\
\delta_{f2221} &= \frac{1}{2} b (-2 (2 p_1 + p_2) + m_1 (p_1 + 2 p_2 + 2 p_1 p_2) + m_2 p_1 (p_2 - p_1)) + p_1 \alpha_j \\
\delta_{f2221} &= \frac{1}{2} b (-2 (2 p_1 + p_2) + m_1 p_1 (p_2 - p_1) + m_2 (p_1 + 2 p_2 + 2 p_1 p_2)) + p_1 \alpha_j \\
\delta_{f2222} &= -p_1 \alpha_j - \frac{1}{2} p_1 (\beta_f + \beta_m).
\end{align*}
\]

The male offspring combined dominance deviations are calculated as

\[
\delta_{mijkl} = G_{ijkl} - \mu - \epsilon_i - \epsilon_j
\]
and are thus
\[
\delta_{m111} = \alpha_k (p_1 + 2p_2) - k_2 p_1 + bp_2 (-2 - p_1 (m_1 + m_2))
\]
\[
\delta_{m121} = \alpha_k (p_1 + 2p_2) - k_2 p_1 + b(p_1 - p_2 + m_1 (1-p_1 p_2) - m_2 p_1 p_2)
\]
\[
\delta_{m112} = \alpha_k (p_1 + 2p_2) - k_2 p_1 + b(p_1 - p_2 - m_1 p_1 p_2 + m_2 (1-p_1 p_2))
\]
\[
\delta_{m211} = \alpha_k (p_1 + 2p_2) - k_2 p_1 + b(p_1 - p_2 + m_1 (1-p_1 p_2) - m_2 p_1 p_2)
\]
\[
\delta_{m212} = \alpha_k (p_1 + 2p_2) - k_2 p_1 + b(p_1 - p_2 - m_1 p_1 p_2 + m_2 (1-p_1 p_2))
\]
\[
\delta_{m221} = \alpha_k (p_1 + 2p_2) + b(p_1 - p_2 + m_1 (1-p_1 p_2) - m_2 p_1 p_2)
\]
\[
\delta_{m222} = \alpha_k (p_1 + 2p_2) + b(p_1 - p_2 - m_1 p_1 p_2 + m_2 (1-p_1 p_2))
\]

Again defining the breeding value of a genotypic class as the sum of the additive effects of its genes [Lynch and Walsh, 1998], we may utilize the separate male and female additive effects to calculate male and female breeding values. Hence
\[
bv_{f11} = \alpha_+ + \alpha_-
\]
\[
= p_2 (2\alpha_f + \beta_f + \beta_m)
\]
\[
bv_{f21} = bv_{f12} = \alpha_+ + \alpha_-
\]
\[
= \frac{1}{2} (p_1 - p_2) (2\alpha_f + \beta_f + \beta_m)
\]
\[
bv_{f22} = \alpha_+ + \alpha_-
\]
\[
= p_1 (2\alpha_f + \beta_f + \beta_m)
\]
for females and
\[
bv_{m11} = \alpha_+ + \alpha_-
\]
\[
= 2p_2 \alpha_-
\]
\[
bv_{m12} = bv_{m12} = \alpha_+ + \alpha_-
\]
\[
= \alpha_-(p_1 - p_2)
\]
\[
bv_{m22} = \alpha_+ + \alpha_-
\]
\[
= 2p_1 \alpha_m
\]
for males. It is interesting to note that this approach recovers the male but not the female breeding values derived in Approach 1 (Table 4).

**Genetic variance components**

We may now calculate male and female variances associated with the population. The female offspring genotype additive genetic variation is the variance

6.17
associated with the average additive effects of alleles inherited maternally and can be shown to be

\[ \sigma^2_{A_{ij}f} = \sum_{i=1}^{2} 2p_i e_i^2 \]

\[ = \frac{1}{2} p_1 p_2 [2\alpha_j + \beta_f + \beta_m]^2. \]

Similarly the offspring female genotype dominance genetic variance is the genetic variance associated with the female dominance effects:

\[ \sigma^2_{D_{ij}f} = \sum_{i,j=1}^{2} p_i p_j \lambda^2_{ij} \]

\[ = p_1 p_2 [a^2 p_1 p_2 (k_1 + k_2)^2 + \frac{1}{2} (2a(k_1 - k_2) + \beta_f + \beta_m)^2] \]

and the combined female dominance genetic variance is the variance of the combined female dominance effects:

\[ \sigma^2_{D_{ijkl}f} = \sum_{ijkl} f_{ijkl} S_{ijkl} \]

\[ = \frac{1}{2} p_1 p_2 [4b^2 (m_1 - m_2)^2 + 2p_1 p_2 (m_1 + m_2)^2] \]

\[ + 2(\alpha_f + \beta_f + \beta_m)^2 + (\beta_f + \beta_m)^2]. \]

The variances in maternal genotype additive and dominance effects are those found in Approach 2a.

The female covariances are

\[ \sigma_{A_{ij}D_{kl}f} = -\frac{1}{2} p_1 p_2 [4a\alpha_f (k_1 - k_2) + (\beta_f + \beta_m)^2] \]

\[ + 2a\alpha_f (\beta_f + \beta_m) + 2a(k_1 - k_2)(\beta_f + \beta_m)] \]

\[ \sigma_{A_{ij}A_{kl}f} = \frac{1}{2} p_1 p_2 [2\alpha_f^2 + 2a\alpha_f (\beta_f + \beta_m) + (\beta_f + \beta_m)^2] = 2\sigma_{A_{ij}A_{kl}} \]

\[ \sigma_{A_{ij}D_{kl}f} = -\frac{1}{2} p_1 p_2 [2\alpha_f^2 + 3a\alpha_f (\beta_f + \beta_m) + (\beta_f + \beta_m)^2] \]

\[ = 2\sigma_{A_{ij}D_{kl}} \]

\[ \sigma_{D_{ijkl}A_{kl}f} = -\frac{1}{2} p_1 p_2 [2a\alpha_f (k_1 - k_2) + \alpha_f (\beta_f + \beta_m) + 4a\beta_m (k_1 - k_2) \]

\[ - b(m_1 - m_2)(\beta_f + \beta_m) + (\beta_f + \beta_m)^2] \]

\[ \sigma_{D_{ij}D_{kl}f} = abp_1^2 \beta_m^2 (k_1 + k_2)(m_1 + m_2) \]

\[ \sigma_{D_{ij}D_{kl}f} = \frac{1}{2} p_1 p_2 [-4abp_1 p_2 (k_1 + k_2)(m_1 + m_2) + 2a\alpha_f (k_1 - k_2) \]

\[ + 4a\beta_m (k_1 - k_2) + \alpha_f (\beta_f + \beta_m) \]

\[ - b(m_1 - m_2)(\beta_f + \beta_m) + (\beta_f + \beta_m)^2] \]

\[ \sigma_{A_{kl}D_{ij}f} = -\frac{1}{2} p_1 p_2 [b^2 (m_1 - m_2)^2 + (\alpha_f + \beta_f + \beta_m)^2] \]

\[ \sigma_{D_{ij}D_{kl}f} = -b^2 p_1^2 p_2^2 (m_1 + m_2)^2. \]

6.18
The two remaining covariances are zero. As expected, the total variance in the population (2) may be recovered from equation (25) for the corresponding female variances and covariances.

The male offspring genotype additive genetic variation is

$$\sigma^2_{A(e)m} = \sum_{i=1}^{2} 2p_i\epsilon_i^2$$

$$= 2p_1p_2\alpha_m^2.$$

Note that $$\sigma^2_{A(e)m} = \frac{1}{2}(\sigma^2_{f(e)} + \sigma^2_{m(e)}).$$

The male combined dominance variance is

$$\sigma^2_{D(e)m} = \sum_{ijkl} f_{ijkl}^2 \delta_{ijkl}$$

$$= p_1p_2[a^2((k_1-k_2)^2 + p_1p_2(k_1+k_2)^2)$$

$$+b^2(2m_1^2 + m_2^2 + 2(m_1+m_2)(p_1-p_2) - p_1p_2(m_1+m_2)^2)$$

$$+a(k_1-k_2)(\beta_f + \beta_m)].$$

Finally, the covariance between male additive and dominance effects is

$$\sigma_{A(e)D(e)m} = \sum_{ijkl} f_{ijkl}^2 (\epsilon_i + \epsilon_i) \delta_{ijkl}$$

$$= p_1p_2\alpha_m[a(k_1-k_2) + \frac{1}{2}(\beta_f + \beta_m)].$$

Here the total variance in the population (2) is

$$\text{var}(gd_{ijkl}) = \sigma^2_{A(e)m} + \sigma^2_{D(e)m} + 2\sigma_{A(e)D(e)m}$$

and is equivalent to that found in equation (2).

It is interesting to note that the male additive and dominance variances and additive by dominance covariance are identical to (6), (10) and (14), the variances and covariance found using a different method in Approach 1. In contrast, the female variances and covariances are not immediately comparable to those found in Approach 1. Further, these values cannot be recovered by ignoring maternal additive and dominance allelic effects so that we reduce the model to

$$G_{ijkl} = \mu + (\epsilon_i + \epsilon_i) + \delta_{ijkl}$$

and

$$\text{var}(gd_{ijkl}) = \sigma^2_{A(e)f} + \sigma^2_{D(e)f} + 2\sigma_{A(e)D(e)f}.$$

Resemblance between relatives

Using the separate male and female variance and covariance terms defined above and equations (19), (20), (22) and (23) from Spencer [2002], we may calculate
parent-offspring covariances and covariances between half sibs. We start with males and find that indeed

\[ \sigma_{OPm} = \frac{1}{2} (\sigma^2_{Ae}m + \sigma^2_{Ae}Dm}) \] and

\[ \sigma_{HSm} = \frac{1}{4} \sigma^2_{Ae}m. \]

In contrast, the female parent-offspring covariance (equations (17) and (19)) and covariance of half sibs sharing a mother (equation (22)) cannot be recovered from any linear combination of our values for female variances and covariances derived using our novel approach above.

**Discussion**

The importance of parental effects on the phenotype has long been realized. Nevertheless, the way in which various forms of parental effects alter the terms in quantitative genetic models has not always been clear. Here we show that two different kinds of parental effects – genomic imprinting and maternal genetic effects – alter the variance components in the simplest one-locus two-allele model in fundamental and revealing ways. Moreover, we find that different approaches to calculating these components, which work well for the standard model without such parental effects, cannot be relied upon when parental effects are present.

We used two approaches [Falconer and Mackay, 1996; Lynch and Walsh, 1998] to calculate additive, dominance and total genetic variance. Although both methods give identical total genetic variance terms, there are differences in the partitioning of the variance into additive, dominance and covariance terms. These methods differ in that the first approach uses progeny means to calculate breeding values, while the second method uses a least squares approach to define breeding values as the sum of the average allelic effects. Under a standard, one-locus diallelic model (that is, without any form of parental effects), the two approaches retrieve equivalent additive and dominance effects and no correlation between additive and dominance effects. However, maternal and imprinting effects introduce both sex-dependent and generation-dependent effects that result in differences in the way additive and dominance effects are defined for the two approaches. Specifically, Falconer and Mackay [1996] (Approach 1) use the variance of the breeding values to calculate additive genetic variances. Breeding values are calculated from the progeny means of each genotype, and this approach introduces a “generation” effect into the
additive dominance. In contrast, Lynch and Walsh [1998] (Approach 2) use additive effects of alleles to calculate additive variance. These additive allelic effects are found by averaging over the genotypic values of individuals expressing these alleles and so do not include the same generational effect as calculating breeding values does.

Approach 2 is a more straightforward method for calculating additive and dominance variances because it does not require consideration of mating tables. However we saw above that we were not able to recover the Approach 1 values for female additive and dominance variances and the additive by dominance covariance when we refined the least squares approach to include male and female effects (Approach 2a). It is interesting to note that Approach 2a was able to recover the male variances and covariance. Clearly calculation of male breeding values (Approach 1) and male allelic effects (Approach 2a) by averaging over female mates and mothers respectively has the same overall effect.

We may examine the covariances between relatives derived in Approach 1, and can see that imprinting and maternal effects both add extra terms. Ignoring imprinting and maternal effects may over- or under-estimate true covariances. For example, Tables 9 and 10 calculate parent-offspring, fullsib and halfsib covariances for six models: (i) a full model incorporating paternal inactivation and maternal effects, (ii) a model including paternal inactivation only, (iii) a full model incorporating maternal inactivation and maternal effects, (iv) a model including maternal inactivation only, (v) a model including maternal effects only, and (vi) a standard two-allele model without imprinting or maternal effects. Assuming both maternal effects and imprinting are influencing this trait, we have calculated the true expected population covariances both under paternal inactivation (model (i)) and maternal inactivation (model (iii)). Table 9 calculates these covariances for $a = 0.5$ and $b = 0.1$ (offspring genotype has largest influence on genotypic values) while Table 10 calculates these covariances for $a = 0.3$ and $b = 0.3$ (offspring and maternal genotypes have equal influence on genotypic values). Note that because we are assuming no imprinting in models (v) and (vi), covariances for these models need not be calculated separately for maternal and paternal inactivation as do models (i)-(iv).

A number of conclusions are apparent from examination of tables 9 and 10. For paternal inactivation and maternal effects in Table 9 (model (i)) we can see that $\sigma_{OPf} > \sigma_{FS} > \sigma_{HSf} > \sigma_{Opm} > \sigma_{HSm}$. Note also that models (ii), (v) and (vi)
underestimate the true values for $\sigma_{OPf}$, $\sigma_{FS}$ and $\sigma_{HSf}$ while overestimating values for $\sigma_{OPm}$ and $\sigma_{HSm}$. Model (ii) retains the relative ordering of covariances while model (v) incorrectly ranks $\sigma_{OPm}$ ahead of $\sigma_{HSf}$. Estimates for model (vi) do not compare well to the true values calculated in model (i).

For maternal inactivation with maternal effects in Table 9 (model (iii)) the relative ordering of covariances is $\sigma_{OPm} > \sigma_{FS} > \sigma_{HSm} > \sigma_{OPf} > \sigma_{HSf}$. Model (iv) overestimates while models (v) and (vi) underestimate $\sigma_{OPm}$, $\sigma_{FS}$ and $\sigma_{HSm}$. All three models (iv), (v) and (vi) underestimate $\sigma_{OPf}$ and $\sigma_{HSf}$. Model (iv) retains the relative ranking of covariances from the true model (iii), although estimates from and order ranking of models (v) and (vi) do not compare well to model (iii).

Quite different observations are apparent when examining Table 10, for covariances calculated assuming maternal effects and own genotype effects have equal impact on genotypic values of offspring. For paternal inactivation and maternal effects (model (i)), the relative ordering of covariances is now $\sigma_{FS} > \sigma_{HSf} > \sigma_{OPf} > \sigma_{OPm} > \sigma_{HSm}$. Once again models (ii), (v) and (vi) underestimate $\sigma_{OPf}$, $\sigma_{FS}$ and $\sigma_{HSf}$ while overestimating $\sigma_{OPm}$ and $\sigma_{HSm}$. In contrast to Table 9, however, model (v) now appears to best estimate relative sizes and ordering of covariances.

For maternal inactivation in Table 10, an even more surprising result is apparent. Because maternal alleles are almost completely inactivated, we would expect $\sigma_{OPm}$ and $\sigma_{HSm}$ to rank highly, as they did in Table 9. However our covariances between relatives now follow $\sigma_{FS} > \sigma_{OPf} > \sigma_{HSf} > \sigma_{OPm} > \sigma_{HSm}$. There is no consistent pattern of over- or under-estimation of covariances when comparing to the alternative models (iv), (v) and (vi). As was the case for paternal inactivation discussed above, model (v) (maternal effects alone) appears to best mimic the covariance structure. Despite maternal effects and offspring own genotype having equally-weighted contributions to offspring genotypic value ($a = b = 0.3$), it is apparent from this example that maternal genotype effects, and not imprinting effects, have greatest impact on the covariances between relatives. Further, simulation results (data not shown) suggest that maternal effects can outweigh imprinting effects even when $b \ll a$, especially when the difference between reciprocal heterozygotes is not large.
For example, if $a = 0.4$, $b = 0.2$, $k_1 = m_1 = -0.1$ and $k_2 = m_2 = 0.2$ (higher paternal than maternal expression of alleles, plus maternal effects), then

$$\sigma_{opf} = 0.0920 \text{ and } \sigma_{opm} = 0.0575.$$  

We are likely to have population estimates for covariances between relatives. It is pertinent to assess whether we can estimate values for $a, b, k_1, k_2, m_1$ and $m_2$ given these covariances. Let us take the parameters and calculated covariances from Model (i) in Table 9 (paternal inactivation with maternal effects). We assume $p_1 = p_2 = 0.5, a,b > 0$ and that heterozygotes are restrained to fall within the range of the homozygotes (that is, $k_1, k_2, m_1, m_2 \in [-1,1]$). We also set $k_1 = m_1$ and $k_2 = m_2$, so that mother and offspring genotypes act in the same way on overall offspring genotypic value. For example, an $A_2A_1$ offspring with an $A_2A_1$ mother will have a contribution to overall offspring genotypic value of $a(1+k_1)$ from its own genotype and a contribution of $b(1+ k_1)$ from its mother’s genotype.

We endeavor to retrieve known parameter values for $a, b, k_1 (=m_1)$ and $k_2 (=m_2)$ by setting the calculated values for covariances between relatives equal to their mathematical expressions, and solving simultaneously. We have five equations and four unknowns, but because all five covariances involve quadratic terms in the parameters we are trying to estimate ($a, b, k_1$ and $k_2$) they do not have unique solutions for the given calculated covariances. However, applying our range constraints gives two solutions,

$$a = 0.5, b = 0.1, k_1 = 0.9, k_2 = -0.8, m_1 = 0.9 \text{ and } m_2 = -0.8$$

(our original values) and

$$a = 0.5, b = 0.1, k_1 = -0.8, k_2 = 0.9, m_1 = -0.8 \text{ and } m_2 = 0.9$$

(Table 11, Full model, row 2). Values of $a$ and $b$ are the same for the two solutions, maintaining the relative contribution of maternal effects to the range of genotypic values. However it is interesting to note that the two solutions exchange values for $k_1$ and $k_2$ (and $m_1$ and $m_2$) as a consequence of our assumption of equal allele frequencies in the population. As seen in Table 9, if there are large differences between predicted values for reciprocal heterozygotes and between estimates for $a$ and $b$, a much larger population value for $\sigma_{opf}$ compared to $\sigma_{opm}$ is indicative of paternal inactivation. Therefore we are able to conclude that the first solution is the true solution for the population. However, as was clear from Table 10, without large differences between $a$
and $b$, and $k_1$ and $k_2$, it may not be possible to determine which set of values for $a$, $b$, $k_1$ and $k_2$ are true for the population. This highlights an important theoretical restriction: it may not be possible to differentiate maternal effects from imprinting using observed population covariances – even when assumptions are made about population allele frequencies and values and ranges for $k_1$, $k_2$, $m_1$ and $m_2$.

We may also assess how incorrectly specifying the model affects our estimates for $a$, $b$, $k_1$, $k_2$, $m_1$ and $m_2$. We again take the known values for covariances from Model (i) in Table 9, and use our expressions for covariances between relatives as derived in Approach 1 under the three reduced models: no imprinting (maternal effects only), no maternal effects (imprinting only) and no maternal effects or imprinting. By setting the reduced expressions for covariances equal to the true values and solving, we find that in many cases we are unable to recover consistent solutions for the reduced models (Table 11). We define consistent solutions as solutions satisfying our constraints on $a, b, k_1, k_2, m_1$ and $m_2$ (or $k$ and $m$). The lack of consistent solutions for the reduced models is an indication that the models are incomplete, and that additional genetic factors are acting that have not been specified.

Examining columns 1 and 3 in Table 11, we can see that the assumptions of the three reduced models affect the restraints that are placed on our parameters: for example, under a reduced model of maternal effects only, $k_1 = k_2 = k$ and $m_1 = m_2 = m$ for all covariances, and we now have a condition that $k, m \in [-1,1]$. Note that this also affects the number of parameters we are solving for in each of the reduced models, and hence to find a solution we must solve for subsets of covariances, rather than using all five true covariance values (column 2, Table 11). Interestingly, a consistent solution pair was found for all three reduced models using a subset of full sib and half sib covariances: for imprinting only:
$$\{a, k_1, k_2\} = \{0.6064, 0.8351, -0.9175\} \text{ or } \{0.6064, 0.9176, -0.8351\},$$
for maternal effects only:
$$\{a, b, k (= m)\} = \{0.0750, 0.5892, -0.3333\} \text{ or } \{0.0750, 0.5892, 0.3333\}$$
and for no maternal effects or imprinting:
$$\{a, k\} = \{0.8063, 0.0310\} \text{ or } \{0.8063, -0.0310\}.$$
in the no imprinting, no maternal effects model where the $A_1$ allele changed from recessive ($k = -0.0310$) to dominant ($k = 0.0310$) in two solutions to the same simultaneous equations. In addition, it is interesting to note that the maternal effects model estimated a much larger maternal effect ($b$) than the true value, while the other two models overestimated own genotype effect ($a$). This in general was also true of consistent estimates for $a$ and $b$ contained within inconsistent solution sets for these three reduced models. As would be expected, therefore, not including maternal effects in the model will overestimate the contribution from an offspring’s own genotype to genotypic values and covariances.

Many of the inconsistent solutions included imaginary numbers. Examining column 5 of Table 11, we see a large range in estimates for parameters contained within these inconsistent solutions. Perhaps not surprisingly, this result suggests that consistent parameter values contained within inconsistent solution sets should not be used to infer population parameters. It can be noted from this example that inconsistent solutions, solutions containing imaginary numbers and even the presence of more than one solution should highlight to the researcher that an incorrect model has been employed. In addition, in all of these full and restricted models, parameter estimation would be greatly aided by use of, for example, a maximum likelihood approach to utilise all of the available information.

From Tables 9, 10 and 11 we have seen that misspecification of the model can have huge implications on parameter and covariance estimation, and it is clearly important to allow for imprinting and maternal effects when estimating parameters and covariances. Nevertheless, researchers should be aware that even in using a complete model and known covariances between a range of relatives, they may not be able to differentiate between maternal and paternal expression if maternal genotype is having a significant effect and differences between reciprocal heterozygotes are small.
References


Table 1: Definition of parameters and notation used in text

<table>
<thead>
<tr>
<th>Parameter or term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_iA_j$</td>
<td>Individual with maternally inherited $A_i$ allele and paternally inherited $A_j$ allele</td>
</tr>
<tr>
<td>$A_{ijkl}$</td>
<td>$A_iA_j$ offspring with an $A_iA_j$ mother</td>
</tr>
<tr>
<td>$G_{ijkl}$</td>
<td>Genotypic value of $A_{ijkl}$</td>
</tr>
<tr>
<td>$f_{ijkl}$</td>
<td>Frequency of $A_{ijkl}$ in population</td>
</tr>
<tr>
<td>$gd_{ijkl}$</td>
<td>Genotypic deviation for $A_{ijkl}$, the difference between the genotypic value ($G_{ijkl}$) and the population mean</td>
</tr>
<tr>
<td>$bv_{fij}$; $bv_{mij}$;</td>
<td>Breeding value of female $AA_i$ genotype; breeding value of male $AA_j$ genotype</td>
</tr>
<tr>
<td>$dd_{fijkl}$; $dd_{mijkl}$</td>
<td>Dominance deviation for female $A_{ijkl}$; male $A_{ijkl}$</td>
</tr>
<tr>
<td>$\sigma^2_G$</td>
<td>Total genetic variance of population</td>
</tr>
<tr>
<td>$\sigma^2_{Af}$; $\sigma^2_{Am}$</td>
<td>Additive genetic variance for females; additive genetic variance for males</td>
</tr>
<tr>
<td>$\sigma^2_{Df}$; $\sigma^2_{Dm}$</td>
<td>Dominance genetic variance for females; dominance genetic variance for males</td>
</tr>
<tr>
<td>$\sigma_{ADF}$; $\sigma_{ADM}$</td>
<td>Covariance between breeding values (additive effects) and dominance deviations for females; males</td>
</tr>
<tr>
<td>$\sigma_{OPf}$; $\sigma_{OPm}$</td>
<td>Covariance between offspring and mother (female parent) genotypic values; covariance between offspring and father (male parent) genotypic values</td>
</tr>
<tr>
<td>$\sigma_{FS}$</td>
<td>Covariance between full sib genotypic values</td>
</tr>
<tr>
<td>$\sigma_{HSf}$; $\sigma_{HSm}$</td>
<td>Covariance between genotypic values of half sibs sharing a female parent; male parent</td>
</tr>
<tr>
<td>$\epsilon_{i\star}$; $\epsilon_{j\star}$</td>
<td>Additive effect of inheriting an $A_i$ allele from the mother; additive effect of inheriting an $A_j$ allele from the father</td>
</tr>
<tr>
<td>$\omega_{k\star}$; $\omega_{l\star}$</td>
<td>Additive effect of having a mother who received an $A_k$ allele from her mother; additive effect of having a mother who received an $A_l$ allele from her father</td>
</tr>
<tr>
<td>$G_{ij\star}$</td>
<td>Average genotypic value of $A_iA_j$ genotype</td>
</tr>
<tr>
<td>( G_{*ij} )</td>
<td>Average genetic value of individuals with an ( A_kA_l ) mother</td>
</tr>
<tr>
<td>( \lambda_{ij}; \theta_{ij}; \delta_{ijkl} )</td>
<td>Dominance effect of ( A_iA_j ) genotype; dominance effect for individual with ( A_kA_l ) mother; combined offspring-mother genotype dominance effect</td>
</tr>
<tr>
<td>( \sigma^2_{A(\epsilon)}; \sigma^2_{A(\omega)} )</td>
<td>Offspring genotype additive genetic variation; maternal genotype additive genetic variation</td>
</tr>
<tr>
<td>( \sigma^2_{D(\lambda)}; \sigma^2_{D(\theta)}; \sigma^2_{D(\delta)} )</td>
<td>Offspring genotype dominance genetic variance; maternal genotype dominance genetic variation; combined offspring-mother genotype dominance genetic variation</td>
</tr>
<tr>
<td>( \sigma_{AA}; \sigma_{AD} )</td>
<td>Covariance between additive and additive effects; covariance between additive and dominance effects</td>
</tr>
</tbody>
</table>
Table 2: Genotypic values for offspring dependent on the genotype of their mother

<table>
<thead>
<tr>
<th>Mother:</th>
<th>$A_1A_1$</th>
<th>$A_2A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1$</td>
<td>$G_{1111} = 0$</td>
<td>$G_{1121} = b(1+m_1)$</td>
<td>$G_{1112} = b(1+m_2)$</td>
<td>none</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>none</td>
<td>$G_{2121} = a(1+k_1)+b(1+m_1)$</td>
<td>$G_{2112} = a(1+k_1)+b(1+m_2)$</td>
<td>$G_{2122} = a(1+k_1)+2b$</td>
</tr>
<tr>
<td>$A_1A_2$</td>
<td>$G_{1211} = a(1+k_2)$</td>
<td>$G_{1221} = a(1+k_2)+b(1+m_1)$</td>
<td>$G_{1212} = a(1+k_2)+b(1+m_2)$</td>
<td>none</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>none</td>
<td>$G_{2221} = 2a+b(1+m_1)$</td>
<td>$G_{2212} = 2a+b(1+m_2)$</td>
<td>$G_{2222} = 2a+2b$</td>
</tr>
</tbody>
</table>
Table 3: Mating table of all possible offspring genotypes under imprinting and maternal effects

<table>
<thead>
<tr>
<th>Mother ($A_kA_l$)</th>
<th>Father</th>
<th>Offspring ($A_iA_j$)</th>
<th>Offspring genotypic value ($G_{ijkl}$)</th>
<th>Proportion of offspring</th>
<th>Frequency of mating</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1$</td>
<td>$A_1A_1$</td>
<td>$A_1A_1$</td>
<td>0</td>
<td>1</td>
<td>$p_1^4$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_2A_1$</td>
<td>$A_1A_1$</td>
<td>0</td>
<td>$\frac{1}{2}$</td>
<td>$p_1^3p_2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$A_1A_2$</td>
<td>$a(1+k_2)$</td>
<td>$\frac{1}{2}$</td>
<td>$p_1^3p_2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$A_2A_1$</td>
<td>$a(1+k_2)$</td>
<td>$\frac{1}{2}$</td>
<td>$p_1^3p_2$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_1A_2$</td>
<td>$A_1A_2$</td>
<td>$a(1+k_2)$</td>
<td>1</td>
<td>$p_1^2p_2^2$</td>
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<td>$A_1A_1$</td>
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<td>$p_1^3p_2$</td>
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<td>$a(1+k_1) + b(1+m_1)$</td>
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<td>$p_1^2p_2^2$</td>
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<td>$2a+b(1+m_1)$</td>
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<td>$p_1^2p_2^2$</td>
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<td>$A_2A_2$</td>
<td>$2a+b(1+m_1)$</td>
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<td>$A_2A_2$</td>
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<td>$p_1p_2^3$</td>
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<td>$A_1A_1$</td>
<td>$b(1+m_1)$</td>
<td>$\frac{1}{4}$</td>
<td>$p_1^3p_2$</td>
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<td>$A_2A_1$</td>
<td>$a(1+k_1) + b(1+m_2)$</td>
<td>$\frac{1}{4}$</td>
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<td>$A_2A_1$</td>
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<td>$\frac{1}{4}$</td>
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<td>$A_2A_1$</td>
<td>$a(1+k_1) + b(1+m_2)$</td>
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<td>$p_1^3p_2$</td>
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<td>$A_1A_2$</td>
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<td>$A_1A_1$</td>
<td>$b(1+m_1)$</td>
<td>$\frac{1}{4}$</td>
<td>$p_1^3p_2$</td>
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<td>$A_1A_2$</td>
<td>$A_1A_2$</td>
<td>$A_2A_2$</td>
<td>$a(1+k_2) + b(1+m_2)$</td>
<td>$\frac{1}{4}$</td>
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<tr>
<td>$A_1A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
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<td>$A_1A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1+k_1) + b(1+m_2)$</td>
<td>$\frac{1}{4}$</td>
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<tr>
<td>$A_1A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1+k_2) + b(1+m_2)$</td>
<td>$\frac{1}{4}$</td>
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<tr>
<td>$A_1A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$2a + b(1 + m_2)$</td>
<td>$\frac{1}{4}$</td>
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<td>$A_2A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1 + k_1) + 2b$</td>
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<tr>
<td>$A_2A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1 + k_1) + 2b$</td>
<td>$\frac{1}{2}$</td>
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</tr>
<tr>
<td>$A_2A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$2a + 2b$</td>
<td>$\frac{1}{2}$</td>
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<tr>
<td>$A_2A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$a(1 + k_1) + 2b$</td>
<td>$\frac{1}{2}$</td>
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<tr>
<td>$A_2A_2$</td>
<td>$A_2A_1$</td>
<td>$A_2A_2$</td>
<td>$2a + 2b$</td>
<td>$1$</td>
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6.32
Table 4: Genotypic values, frequencies, breeding values and dominance deviations for imprinting and additive maternal effects model

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_1$</th>
<th>$A_2A_2$</th>
</tr>
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<tbody>
<tr>
<td>Genotypic values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$G_{1111} = 0$;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$G_{1121} = b(1 + m_1)$;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$G_{1112} = b(1 + m_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$G_{2121} = a(1 + k_1) + b(1 + m_1)$;</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$G_{2112} = a(1 + k_1) + b(1 + m_2)$;</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$G_{2122} = a(1 + k_1) + 2b$</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Frequency of genotypic values</td>
<td></td>
<td></td>
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<tr>
<td>$f_{r111} = p_1^2$;</td>
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<tr>
<td>$f_{r121} = \frac{1}{2} p_1^2 p_2$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$f_{r112} = \frac{1}{2} p_1^2 p_2$</td>
<td></td>
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<td></td>
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<tr>
<td>$f_{r122} = p_1^2 p_2^2$</td>
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<td></td>
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<tr>
<td>$f_{r211} = \frac{1}{2} p_1^2 p_2$;</td>
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<tr>
<td>$f_{r212} = \frac{1}{2} p_1^2 p_2$;</td>
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<tr>
<td>$f_{r212} = \frac{1}{2} p_1^2 p_2$;</td>
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<td></td>
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<tr>
<td>$f_{r222} = p_2^2$</td>
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<td></td>
</tr>
<tr>
<td>Genotypic deviations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$gd_{111} = -p_2(a(2 + p_1(k_1 + k_2)) + b(2 + p_1(m_1 + m_2)));$</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$gd_{211} = a(p_1 - p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$+k_1(1 - p_1 p_2) - k_2 p_1 p_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$+b(p_1 - p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$+m_1(1 - p_2 p_1) - m_2 p_2 p_1);$</td>
<td></td>
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<tr>
<td>$gd_{121} = a(p_1 - p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-k_1 p_1 p_2 + k_2 (1 - p_1 p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-b p_2 (2 + p_1 (m_1 + m_2))$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$+m_1 (1 - p_2 p_1) - m_2 p_2 p_1);$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$gd_{221} = a(p_1 - p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-k_1 p_1 p_2 + k_2 (1 - p_1 p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$+b (p_1 - p_2)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$+m_1 (1 - p_2 p_1) - m_2 p_2 p_1);$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$gd_{222} = 2a + b(1 + m_1);$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$G_{2212} = 2a + b(1 + m_2);$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$G_{2222} = 2a + 2b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female progeny mean</td>
<td>Female breeding value</td>
<td>Male progeny mean</td>
<td>Male breeding value</td>
<td></td>
</tr>
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<td>---------------------</td>
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<td>------------------</td>
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<td></td>
</tr>
</tbody>
</table>
| \( gd_{111} = \)  
\(-ap_2(2 + p_1(k_1 + k_2))\)  
\(+b(p_1 - p_2)\)  
\(+m_1(1 - p_1p_2) - m_2p_1p_2)\) | \( bv_{f,11} = -2p_2(\alpha_f)\)  
\(+b(2 + p_1(m_1 + m_2))\) | \( gd_{11} = \)  
\(-ap_2(2 + p_1(k_1 + k_2))\)  
\(+b(p_1 - p_2)\)  
\(+m_1p_2p_1 + m_2(1 - p_1p_1)\) | \( bv_{f,12} = \)  
\(+2b(p_1 - p_2 + m_1)\)  
\(-p_1p_2(m_1 + m_2)\) |
| \( gd_{211} = \)  
\(a(p_1 - p_2)\)  
\(+k_1(1 - p_1p_2) - k_2p_1p_2)\)  
\(+b(p_1 - p_2)\)  
\(-m_1p_2p_1 + m_2(1 - p_1p_1)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_1 p_1 + k_2 p_2)\)  
\(+b(1 + m_1)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_2 p_1 + k_1 p_2)\)  
\(+b(2 + p_1(m_1 + m_2))\) | \( ap_2\)  
\(+ap_1(1 + k_1)\)  
\(+2b\) |
| \( gd_{212} = \)  
\(-k_1p_1p_2 + k_2(1 - p_1p_2)\)  
\(+b(p_1 - p_2)\)  
\(+m_1(1 - p_1p_1) - m_2p_1p_2)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_1 p_1 + k_2 p_2)\)  
\(+b(1 + m_2)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_2 p_1 + k_1 p_2)\)  
\(+b(2 + p_1(m_1 + m_2))\) | \( ap_2\)  
\(+ap_1(1 + k_2)\)  
\(+2b\) |
| \( gd_{221} = \)  
\(a(p_1 - p_2)\)  
\(+k_1(1 - p_1p_2) - k_2p_1p_2)\)  
\(+b(p_1 - p_2)\)  
\(-m_1p_2p_1 + m_2(1 - p_1p_1)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_1 p_1 + k_2 p_2)\)  
\(+b(1 + m_1)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_2 p_1 + k_1 p_2)\)  
\(+b(2 + p_1(m_1 + m_2))\) | \( ap_2\)  
\(+ap_1(1 + k_1)\)  
\(+2b\) |
| \( gd_{222} = \)  
\(-k_1p_1p_2 + k_2(1 - p_1p_2)\)  
\(+b(p_1 - p_2)\)  
\(+m_1(1 - p_1p_1) - m_2p_1p_2)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_1 p_1 + k_2 p_2)\)  
\(+b(1 + m_2)\) | \( ap_2\)  
\(+\frac{1}{2}a(1 + k_2 p_1 + k_1 p_2)\)  
\(+b(2 + p_1(m_1 + m_2))\) | \( ap_2\)  
\(+ap_1(1 + k_2)\)  
\(+2b\) |

Female progeny mean: \( a(1 + k_2) \) + \( b(1 + m_1) \) + 2\( b(1 + m_2) \)

Male progeny mean: \( a(1 + k_1) \) + \( b(2 + p_1(m_1 + m_2)) \)

Female breeding value: \( -2p_2(\alpha_f) \) + \( b(2 + p_1(m_1 + m_2)) \)

Male breeding value: \( +2b(p_1 - p_2 + m_1) \) - \( p_1p_2(m_1 + m_2) \)

6.34
<table>
<thead>
<tr>
<th>Male breeding value</th>
<th>( bv_{m21} = \alpha_m (p_1 - p_2) )</th>
<th>( bv_{m22} = 2 p_2 \alpha_m )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( dd_{f1111} = )</td>
<td>(- ap_2 (-k_1 p_1 + k_2 (1 + p_2)) + b p_2 (2 + p_1 (m_1 + m_2)));</td>
<td>( dd_{f2121} = )</td>
</tr>
<tr>
<td>( dd_{f1121} = )</td>
<td>(- ap_2 (-k_1 p_1 + k_2 (1 + p_2)) + b (p_1 + 3 p_2 + m_1 (1 + p_1 p_2) + m_2 p_1 p_2));</td>
<td>( dd_{f2112} = )</td>
</tr>
<tr>
<td>( dd_{f1112} = )</td>
<td>(- ap_2 (-k_1 p_1 + k_2 (1 + p_2)) + b (p_1 + 3 p_2 + m_1 p_1 p_2 + m_2 (1 + p_1 p_2)))</td>
<td>( dd_{f2122} = )</td>
</tr>
<tr>
<td>( dd_{f1211} = )</td>
<td>(- ap_2 (k_1 (-2 + p_2) + k_2) ) (- b (2 p_1 - m_1 p_1 p_2 + m_2 (2 - p_1 p_2)));</td>
<td>( dd_{f2211} = )</td>
</tr>
<tr>
<td>( dd_{f1212} = )</td>
<td>(- ap_2 (k_1 (-2 + p_2) + k_2) ) (+ b (-3 p_1 - p_2 + m_1 p_1 p_2 + m_2 (1 + p_1 p_2)));</td>
<td>( dd_{f2212} = )</td>
</tr>
<tr>
<td>( dd_{f1221} = )</td>
<td>(- ap_2 (k_1 (-2 + p_2) + k_2) ) (- b (-3 p_1 - p_2 + m_1 p_1 p_2 + m_2 (1 + p_1 p_2)));</td>
<td>( dd_{f2221} = )</td>
</tr>
<tr>
<td>( dd_{f2222} = )</td>
<td>( ap_1 (-k_1 p_1 + k_2 (1 + p_2)) ) (+ b (-3 p_1 - p_2 + m_1 p_1 p_2 + m_2 (1 + p_1 p_2)))</td>
<td>( dd_{f2222} = )</td>
</tr>
<tr>
<td>Male dominance deviation</td>
<td>( dd_{m1111} = )</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-ap_z(k_1(1 + p_2) - k_z p_1))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-bp_z(2 + p_1(m_1 + m_2));)</td>
<td></td>
</tr>
<tr>
<td>( dd_{m1121} = )</td>
<td>(-ap_z(k_1(1 + p_2) - k_z p_1))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(+b(p_1 - p_2 + m_1(1 - p_1 p_2))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-m_z p_1 p_2);)</td>
<td></td>
</tr>
<tr>
<td>( dd_{m1112} = )</td>
<td>(-ap_z(k_1(1 + p_2) - k_z p_1))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(+b(p_1 - p_2 - m_1 p_1 p_2)</td>
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</tr>
<tr>
<td></td>
<td>(+m_z(1 - p_1 p_2));)</td>
<td></td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{where } \alpha_f &= a(1 + k_1 p_1 - k_2 p_2) \quad \text{and} \quad \alpha_m = a(1 + k_2 p_1 - k_1 p_2) \\
\end{align*}
\]
Table 5: Mating table of all possible offspring genotypes under maternal effects only

<table>
<thead>
<tr>
<th>Mother (A_kA_l)</th>
<th>Father (A_iA_j)</th>
<th>Offspring (A_iA_j)</th>
<th>Offspring genotypic value ($G_{ijkl}$)</th>
<th>Proportion of offspring</th>
<th>Frequency of mating</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_1A_1</td>
<td>A_1A_1</td>
<td>A_1A_1</td>
<td>0</td>
<td>1</td>
<td>$p_1^4$</td>
</tr>
<tr>
<td>A_1A_1</td>
<td>A_1A_2</td>
<td>A_1A_1</td>
<td>0</td>
<td>$\frac{1}{2}$</td>
<td>$2p_1^3p_2$</td>
</tr>
<tr>
<td></td>
<td>A_1A_2</td>
<td>A_1A_2</td>
<td>$a(1+k)$</td>
<td>$\frac{1}{2}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A_1A_2</td>
<td>A_1A_2</td>
<td>$b(1+m)$</td>
<td>$\frac{1}{4}$</td>
<td>$4p_1^2p_2^2$</td>
</tr>
<tr>
<td></td>
<td>A_1A_2</td>
<td>A_1A_2</td>
<td>$a(1+k) + b(1+m)$</td>
<td>$\frac{1}{2}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A_1A_2</td>
<td>A_1A_2</td>
<td>$2a + b(1+m)$</td>
<td>$\frac{1}{4}$</td>
<td></td>
</tr>
<tr>
<td>A_1A_2</td>
<td>A_2A_2</td>
<td>A_1A_2</td>
<td>$a(1+k) + b(1+m)$</td>
<td>$\frac{1}{2}$</td>
<td>$2p_1p_2^3$</td>
</tr>
<tr>
<td></td>
<td>A_1A_2</td>
<td>A_1A_2</td>
<td>$2a + b(1+m)$</td>
<td>$\frac{1}{2}$</td>
<td></td>
</tr>
<tr>
<td>A_2A_2</td>
<td>A_1A_1</td>
<td>A_1A_2</td>
<td>$a(1+k) + 2b$</td>
<td>1</td>
<td>$p_1^2p_2^2$</td>
</tr>
<tr>
<td>A_2A_2</td>
<td>A_1A_1</td>
<td>A_1A_2</td>
<td>$a(1+k) + 2b$</td>
<td>$\frac{1}{2}$</td>
<td>$2p_1p_2^3$</td>
</tr>
<tr>
<td>A_1A_2</td>
<td>A_2A_2</td>
<td>A_2A_2</td>
<td>$2a + 2b$</td>
<td>1</td>
<td>$p_2^4$</td>
</tr>
</tbody>
</table>
Table 6: Genotypic values, frequencies, breeding values and dominance deviations for additive maternal effects and no imprinting model

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_1A_2$ ($=A_2A_1$)</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic values</td>
<td>0; $b(1+m)$</td>
<td>$a(1+k)$; $a(1+k)+b(1+m)$; $2a+b(1+m)$; $2a+2b$</td>
<td></td>
</tr>
<tr>
<td>Frequency of genotypic values</td>
<td>$p_1^3$; $p_1^2p_2$; $p_1p_2^2$; $p_2^3$</td>
<td>$p_1^3p_2$; $p_1p_2^2$; $p_2^3$</td>
<td></td>
</tr>
<tr>
<td>Genotypic deviations</td>
<td>$-2p_2(a(1+ kp_1)+b(1+ mp_1))$; $-2ap_2(1+k p_1)$; $-b(p_1 - p_2 + m(1-2p_1p_2))$</td>
<td>$a(p_1 - p_2 + k(1-2p_1p_2))$; $a(p_1 - p_2 + k(1-2p_1p_2))$; $2ap_1(1-kp_2)$; $2ap_1(1-kp_2)$; $+b(p_1 - p_2 + m(1-2p_1p_2))$; $+2bp_1(1-mp_2)$</td>
<td>$2ap_1(1-kp_2)$; $+b(p_1 - p_2 + m(1-2p_1p_2))$; $+2bp_1(1-mp_2)$</td>
</tr>
<tr>
<td>Female progeny mean</td>
<td>( ap_2(1+k) )</td>
<td>( ap_2 + \frac{1}{2}a(1+k) + b(1+m) )</td>
<td>( 2ap_2 + ap_1(1+k) + 2b )</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td>---------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Male progeny mean</td>
<td>( ap_2(1+k) )</td>
<td>( ap_2 + \frac{1}{2}a(1+k) + 2bp_2(1+m_p_1) )</td>
<td>( 2ap_2 + ap_1(1+k) + 2bp_2(1+m_p_1) )</td>
</tr>
<tr>
<td>Female breeding value</td>
<td>(-2p_2(\alpha + 2b(1+m_p_1)))</td>
<td>( \alpha(p_1 - p_2) + 2b(p_1 - p_2 + m(1-2p_1p_2)) )</td>
<td>( 2p_1(\alpha + 2b(1-m_p_2)) )</td>
</tr>
<tr>
<td>Male breeding value</td>
<td>(-2p_2\alpha)</td>
<td>( \alpha(p_1 - p_2) )</td>
<td>( 2p_1\alpha )</td>
</tr>
<tr>
<td>Female dominance deviations</td>
<td>(-2akp_2^2 + 2bp_2(1+m_p_1)); (-2akp_2^2 + b(1+2p_2 + m(1+2p_1p_2)))</td>
<td>( 2akp_1p_2, -2b(p_1 + m(1-p_1p_2)); )</td>
<td>(-2akp_1^2, -b(1+2p_1 - m(1+2p_1p_2)); -2akp_1^2 -2bp_1(1-m_p_2))</td>
</tr>
</tbody>
</table>
| Male dominance deviations | 2akp₁ᵖ₂ +2b(p₂ − m(1− p₁,p₂)) | -2akp₂²  
-2bp₂(1 + mp₁);  
  
2akp₁ᵖ₂  
-b(p₁ − p₂ + m(1− 2p₁,p₂));  
  
-2akp₂²  
+2bp₁(1 − mp₂) |
|------------------------|---------------------|------------------------|
| 2akp₁ᵖ₂  
-2bp₂(1 + mp₁);  
  
2akp₁ᵖ₂  
+b(p₁ − p₂ + m(1− 2p₁,p₂));  
  
2akp₁ᵖ₂  
+2bp₁(1 − mp₂) |
| 2akp₁ᵖ₂  
-2bp₂(1 + mp₁);  
  
2akp₁ᵖ₂  
+b(p₁ − p₂ + m(1− 2p₁,p₂));  
  
2akp₁ᵖ₂  
+2bp₁(1 − mp₂) |

where \( \alpha = a(1 + k(p₁ − p₂)) \) and \( \beta = b(1 + m(p₁ − p₂)) \)
Table 7: Genotypic values and progeny means for mother-offspring and father-offspring pairs under maternal effects and imprinting

<table>
<thead>
<tr>
<th>Parent genotype</th>
<th>Frequency</th>
<th>Genotypic value</th>
<th>Progeny mean of females</th>
<th>Progeny mean of males</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{1111}$</td>
<td>$f_{1111}$</td>
<td>0</td>
<td>$ap_2(1+k_2)$</td>
<td>$ap_2(1+k_1)$</td>
</tr>
<tr>
<td>$A_{1121}$</td>
<td>$f_{1121}$</td>
<td>$b(1+m_1)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{1112}$</td>
<td>$f_{1112}$</td>
<td>$b(1+m_2)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{2121}$</td>
<td>$f_{2121}$</td>
<td>$a(1+k_i) + b(1+m_1)$</td>
<td>$ap_2 + b(1+m_1)$</td>
<td>$ap_2 + \frac{1}{2}a(1+k_1p_1 + k_2p_2)$ + $bp_2(2 + p_1(m_1 + m_2))$</td>
</tr>
<tr>
<td>$A_{2112}$</td>
<td>$f_{2112}$</td>
<td>$a(1+k_i) + b(1+m_2)$</td>
<td>$ap_2 + b(1+m_2)$</td>
<td>$ap_2 + \frac{1}{2}a(1+k_1p_1 + k_2p_2)$ + $bp_2(2 + p_1(m_1 + m_2))$</td>
</tr>
<tr>
<td>$A_{2122}$</td>
<td>$f_{2122}$</td>
<td>$a(1+k_i) + 2b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{1211}$</td>
<td>$f_{1211}$</td>
<td>$a(1+k_2)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{1221}$</td>
<td>$f_{1221}$</td>
<td>$a(1+k_2) + b(1+m_1)$</td>
<td>$ap_2 + b(1+m_2)$</td>
<td>$ap_2 + \frac{1}{2}a(1+k_1p_1 + k_2p_2)$ + $bp_2(2 + p_1(m_1 + m_2))$</td>
</tr>
<tr>
<td>$A_{1212}$</td>
<td>$f_{1212}$</td>
<td>$a(1+k_2) + b(1+m_2)$</td>
<td>$ap_2 + b(1+m_2)$</td>
<td>$ap_2 + \frac{1}{2}a(1+k_1p_1 + k_2p_2)$ + $bp_2(2 + p_1(m_1 + m_2))$</td>
</tr>
<tr>
<td>$A_{2221}$</td>
<td>$f_{2221}$</td>
<td>$2a + b(1+m_1)$</td>
<td>$2ap_2 + 2b + ap_1(1+k_1)$</td>
<td></td>
</tr>
<tr>
<td>$A_{2212}$</td>
<td>$f_{2212}$</td>
<td>$2a + b(1+m_2)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{2222}$</td>
<td>$f_{2222}$</td>
<td>$2a + 2b$</td>
<td>$2ap_2 + ap_1(1+k_2)$</td>
<td></td>
</tr>
</tbody>
</table>

6.41
Table 8: Genotypic values for fullsib offspring pairs from mating combinations

<table>
<thead>
<tr>
<th>Mother Father</th>
<th>Offspring pair genotypic values [proportion of total offspring of mating class]</th>
<th>Frequency of mating class</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1A_1$</td>
<td>$A_1A_1$</td>
<td>$p_1^3$</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>$A_2A_2$</td>
<td>$2p_1^3p_2$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$A_2A_2$</td>
<td>$p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>$A_2A_1$</td>
<td>$p_1^3p_2$</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>$A_2A_1$</td>
<td>$2p_1^2p_2^2$</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>$A_2A_1$</td>
<td>$p_1p_2^3$</td>
</tr>
<tr>
<td>$A_1A_2$</td>
<td>$A_1A_2$</td>
<td>$p_1^3p_2$</td>
</tr>
<tr>
<td>$A_iA_j$</td>
<td>$A_iA_j$ and $A_jA_i$</td>
<td>\begin{align*} &amp; b(1+m_z), \ b(1+m_z) \left[ \frac{1}{16} \right] \ &amp; b(1+m_z), \ a(1+k_1)+b(1+m_z) \left[ \frac{1}{6} \right] \ &amp; b(1+m_z), \ a(1+k_1)+b(1+m_z) \left[ \frac{1}{4} \right] \ &amp; b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{6} \right] \ &amp; a(1+k_1)+b(1+m_z), \ a(1+k_1)+b(1+m_z) \left[ \frac{1}{6} \right] \ &amp; a(1+k_1)+b(1+m_z), \ a(1+k_1)+b(1+m_z) \left[ \frac{1}{4} \right] \ &amp; a(1+k_1)+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{4} \right] \ &amp; a(1+k_1)+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{6} \right] \ &amp; a(1+k_1)+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{6} \right] \ &amp; a(1+k_1)+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{4} \right] \ &amp; 2a+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{6} \right] \ \end{align*}</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>$A_iA_j$</td>
<td>$A_iA_j$</td>
<td>\begin{align*} &amp; a(1+k_2)+b(1+m_z), \ a(1+k_2)+b(1+m_z) \left[ \frac{1}{4} \right] \ &amp; a(1+k_2)+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{4} \right] \ &amp; 2a+b(1+m_z), \ 2a+b(1+m_z) \left[ \frac{1}{4} \right] \ \end{align*}</td>
</tr>
<tr>
<td>$A_iA_j$</td>
<td>$A_iA_j$</td>
<td>\begin{align*} &amp; a(1+k_1)+2b, \ a(1+k_1)+2b \left[ 1 \right] \ \end{align*}</td>
</tr>
<tr>
<td>$A_iA_j$ and $A_jA_i$</td>
<td>$A_iA_j$ and $A_jA_i$</td>
<td>\begin{align*} &amp; a(1+k_1)+2b, \ a(1+k_1)+2b \left[ \frac{1}{4} \right] \ &amp; a(1+k_1)+2b, \ 2a+2b \left[ \frac{1}{4} \right] \ &amp; 2a+2b, \ 2a+2b \left[ \frac{1}{4} \right] \ \end{align*}</td>
</tr>
<tr>
<td>$A_iA_j$</td>
<td>$A_iA_j$</td>
<td>\begin{align*} &amp; 2a+2b, \ 2a+2b \left[ 1 \right] \ \end{align*}</td>
</tr>
</tbody>
</table>

6.43
Table 9: Comparison of covariance predictions using incompletely specified models of imprinting only, maternal effects only and no imprinting or maternal effects, for $a = 0.5$ and $b = 0.1$

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Paternal inactivation</th>
<th>Maternal inactivation</th>
<th>Maternal inactivation</th>
<th>Maternal inactivation</th>
<th>Maternal inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Covariances for true full model with maternal effects (i)</td>
<td>Covariances for imprinting only (ii)</td>
<td>Covariances for true full model with maternal effects (iii)</td>
<td>Covariances for imprinting only (iv)</td>
<td>Covariances for standard model (vi)</td>
</tr>
<tr>
<td></td>
<td>$p_1 = p_2$, $a = 0.5$, $b = 0$, $k_1 = m_1 = 0.9$, $k_2 = m_2 = -0.8$</td>
<td>$p_1 = p_2$, $a = 0.6$, $b = 0$, $k_1 = 0.9$, $k_2 = -0.8$, $m_1 = m_2 = 0$</td>
<td>$p_1 = p_2$, $a = 0.5$, $b = 0$, $k_1 = m_1 = -0.8$, $k_2 = 0.9$, $m_1 = m_2 = 0$</td>
<td>$p_1 = p_2$, $a = 0.5$, $b = 0.1$, $k = \frac{1}{2} (k_1 + k_2)$, $m = \frac{1}{2} (m_1 + m_2)$ = 0.05, $m_1 = m_2 = 0$</td>
<td></td>
</tr>
<tr>
<td>$\sigma_{OPf}$</td>
<td>0.1749</td>
<td>0.1665</td>
<td>0.0538</td>
<td>0.0135</td>
<td>0.0963</td>
</tr>
<tr>
<td>$\sigma_{OPm}$</td>
<td>0.0103</td>
<td>0.0135</td>
<td>0.1272</td>
<td>0.1665</td>
<td>0.0688</td>
</tr>
<tr>
<td>$\sigma_{FS}$</td>
<td>0.1626</td>
<td>0.1551</td>
<td>0.1201</td>
<td>0.1551</td>
<td>0.0925</td>
</tr>
<tr>
<td>$\sigma_{HSf}$</td>
<td>0.1618</td>
<td>0.1540</td>
<td>0.0131</td>
<td>0.0010</td>
<td>0.0613</td>
</tr>
<tr>
<td>$\sigma_{HSm}$</td>
<td>0.0007</td>
<td>0.0010</td>
<td>0.1070</td>
<td>0.1540</td>
<td>0.0313</td>
</tr>
</tbody>
</table>
**Table 10:** Comparison of covariance predictions using incompletely specified models of imprinting only, maternal effects only and no imprinting or maternal effects, for $a = 0.3$ and $b = 0.3$

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Paternal inactivation</th>
<th>Maternal inactivation</th>
<th>Maternal inactivation</th>
<th>Covariances for maternal effects only (v)</th>
<th>Covariances for standard model (vi)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Covariances for true full model with maternal effects (i)</td>
<td>Covariances for imprinting only (ii)</td>
<td>Covariances for true full model with maternal effects (iii)</td>
<td>Covariances for imprinting only (iv)</td>
<td>Covariances for standard model (vi)</td>
</tr>
<tr>
<td>$p_1 = p_2$, $a = 0.3$, $b = 0$, $k_1 = m_1 = 0.9$, $k_2 = m_2 = -0.8$</td>
<td>$p_1 = p_2$, $a = 0.6$, $b = 0$, $k_1 = 0.9$, $k_2 = -0.8$, $m_1 = m_2 = 0$</td>
<td>$p_1 = p_2$, $a = 0.3$, $b = 0.3$, $k_1 = m_1 = -0.8$, $k_2 = 0.9$, $m_1 = m_2 = 0$</td>
<td>$p_1 = p_2$, $a = 0.6$, $b = 0$, $k = \frac{1}{2}(k_1 + k_2)$, $m = \frac{1}{2}(m_1 + m_2) = 0.05$, $m_1 = m_2 = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{OPf}$</td>
<td>0.1816</td>
<td>0.1665</td>
<td>0.0860</td>
<td>0.0135</td>
<td>0.1013</td>
</tr>
<tr>
<td>$\sigma_{OPm}$</td>
<td>0.0051</td>
<td>0.0135</td>
<td>0.0624</td>
<td>0.1665</td>
<td>0.0338</td>
</tr>
<tr>
<td>$\sigma_{FS}$</td>
<td>0.1996</td>
<td>0.1551</td>
<td>0.1231</td>
<td>0.1551</td>
<td>0.1126</td>
</tr>
<tr>
<td>$\sigma_{HSf}$</td>
<td>0.1993</td>
<td>0.1540</td>
<td>0.0846</td>
<td>0.0010</td>
<td>0.1013</td>
</tr>
<tr>
<td>$\sigma_{HSm}$</td>
<td>0.0003</td>
<td>0.0010</td>
<td>0.0385</td>
<td>0.1540</td>
<td>0.0113</td>
</tr>
</tbody>
</table>
Table 11: Parameter predictions when expressions for covariances are solved for true covariance values

<table>
<thead>
<tr>
<th>Model</th>
<th>Set of simultaneous equations solved</th>
<th>Constraints placed on parameters</th>
<th>Number of solutions to equations [number of consistent solutions to equations]</th>
<th>Solutions / consistent values for parameters contained in inconsistent solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full model</strong></td>
<td>( \sigma_{OFy} = 0.1749, \sigma_{OPm} = 0.0103, ) ( \sigma_{FS} = 0.1626, \sigma_{HSf} = 0.1618, ) ( \sigma_{HSm} = 0.0007 )</td>
<td>( p_1 = p_2 = 0.5, ) ( a, b &gt; 0 ) ( k_1, k_2, m_1, m_2 \in [-1,1]; ) ( k_1 = m_1, k_2 = m_2 )</td>
<td>4 [2]</td>
<td>( {a, b, k_1, k_2, m_1, m_2} = ) {0.5, 0.1, 0.9, -0.8, 0.9, -0.8}, {0.5, 0.1, -0.8, 0.9, -0.8, 0.9}</td>
</tr>
<tr>
<td><strong>Imprinting only</strong></td>
<td>(set ( b = 0 ) for all covariances)</td>
<td>( \sigma_{OFy} = 0.1749, \sigma_{OPm} = 0.0103, ) ( \sigma_{FS} = 0.1626, \sigma_{HSf} = 0.1618, ) ( \sigma_{HSm} = 0.0007 )</td>
<td>( p_1 = p_2 = 0.5, ) ( a &gt; 0, ) ( k_1, k_2 \in [-1,1] )</td>
<td>0 [0]</td>
</tr>
<tr>
<td></td>
<td>( \sigma_{OFy} = 0.1749, \sigma_{FS} = 0.1626, \sigma_{HSf} = 0.1618 )</td>
<td>( p_1 = p_2 = 0.5, ) ( a &gt; 0, ) ( k_1, k_2 \in [-1,1] )</td>
<td>4 [0]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \sigma_{OPm} = 0.0103, \sigma_{FS} = 0.1626, \sigma_{HSm} = 0.0007 )</td>
<td></td>
<td>4 [0]</td>
<td></td>
</tr>
</tbody>
</table>

6.46
<table>
<thead>
<tr>
<th>Model Description</th>
<th>Covariance Parameters</th>
<th>p₁, p₂, k, m</th>
<th>a, b, k, m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal effects only (set k₁ = k₂ = k and m₁ = m₂ = m for all covariances)</td>
<td>σₐₚᶠ = 0.1749, σₒᵖₘ = 0.0103, σₙˢ = 0.1626</td>
<td>p₁ = p₂ = 0.5, a, b &gt; 0, k, m ∈ [-1, 1]; k = m</td>
<td>a = 0.6086, b = 0.95</td>
</tr>
<tr>
<td></td>
<td>σₙˢ = 0.1626, σₙˢᶠ = 0.1618, σₙˢᵐ = 0.0007</td>
<td></td>
<td>{a, k₁, k₂} =</td>
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<td>{0.6064, 0.8351, -0.9175},</td>
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<td></td>
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<td>{0.6064, 0.9176, -0.8351}</td>
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<tr>
<td></td>
<td>σₒᵖₚ = 0.1749, σₒᵖₘ = 0.0103, σₙˢ = 0.1626</td>
<td></td>
<td>a = 0.075</td>
</tr>
<tr>
<td></td>
<td>σₙˢ = 0.1626, σₙˢᶠ = 0.1618, σₙˢᵐ = 0.0007</td>
<td></td>
<td>b = 1.3660, 0.7754</td>
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<td></td>
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<td>{a, b, k(= m)} =</td>
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<td></td>
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<td></td>
<td>{0.0750, 0.5892, -0.3333},</td>
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<td></td>
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<td></td>
<td>{0.0750, 0.5892, 0.3333}</td>
</tr>
<tr>
<td>No imprinting or maternal effects (set b = 0 and</td>
<td>σₒᵖᶠ = 0.1749, σₒᵖₘ = 0.0103, σₙˢ = 0.1626</td>
<td>p₁ = p₂ = 0.5, a, b &gt; 0, k, m ∈ [-1, 1]; k = m</td>
<td>a = 0.7388, 0.0869</td>
</tr>
<tr>
<td></td>
<td>σₙˢ = 0.1626, σₙˢᶠ = 0.1618, σₙˢᵐ = 0.0007</td>
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<td>b = 1.3660, 0.7754</td>
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<td>{a, b, k(= m)} =</td>
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<td>{0.0750, 0.5892, -0.3333},</td>
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<td>{0.0750, 0.5892, 0.3333}</td>
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</tbody>
</table>
\( k_1 = k_2 = k \) for all covariances; note now

\[
\sigma_{OP} = \sigma_{OPm} = \sigma_{OP}, \quad \sigma_{FS} = 0.1626, \quad \sigma_{HS} = (0.1618 + 0.0007)/2
\]

\( a > 0, \quad k \in [-1, 1] \)

\( a = 0.6086 \)

\{\( a, k \) = \\
(0.8063, 0.0310), \\
(0.8063, -0.0310)\}
7. Discussion

A number of exciting, and in some cases unexpected, findings have become apparent from our development of novel quantitative genetic models incorporating genomic imprinting. These findings have significant impact on the signatures we might expect to see when a quantitative trait is influenced by an imprinted gene, and in some cases our models demonstrate that it may not be theoretically possible to distinguish imprinting from other genetic and non-genetic influences.

The major results from our quantitative genetic modelling of imprinting, as discussed in previous chapters are:

- A number of different quantitative genetic approaches for calculating additive and dominance effects and variances are no longer equivalent when imprinting is acting, as imprinting introduces both sex- and generation-dependent effects to the inheritance of alleles (Chapter 3)
- Imprinting introduces a covariance that is zero under Mendelian expression (Chapter 3)
- For a single imprinted locus, one of the covariances between offspring and mother or offspring and father will exceed the covariance between full sibs: in the absence of imprinting the full sib covariance will always exceed that between offspring and parent (Chapter 3)
- Epistatic interactions between loci may mask the effect of imprinting on a quantitative trait, although imprinting will always cause differences in male and female additive genetic variances and parent-offspring covariances (Chapter 4)
- Genotype by environment interactions may significantly impact the phenotypic values of individuals in different environments. When comparing variances and covariances between two subpopulations in different environments, genotype by environment interactions may give conflicting indications of whether imprinting is acting (Chapter 5)
- Many of the signatures expected when imprinting is acting are also present under maternal effects (Chapter 6)
- Relative to the contribution towards offspring genotypic value, maternal effects have greatest impact on the covariances between relatives, and may
mask the influence of imprinting in population variances and covariances. Consequently, it may not be possible to identify which of maternal effects or imprinting, or both, are influencing a trait of interest (Chapter 6).

A number of these findings will have a significant role in identifying traits influenced by imprinted genes, and are discussed in more depth below.

Tables 1-4 review the genotypic and phenotypic values for the quantitative genetic models incorporating imprinting along with two loci, environmental and maternal genetic effects. Table 5 outlines important abbreviations and notation used in the following text. Note that we have used $G_{ijkl}$ to denote both the genotypic value of an $A_iA_jB_kB_l$ individual (in the two locus case) and an $A_iA_j$ individual with $A_kA_l$ mother (in the maternal effects case). We shall endeavour to make clear which of these definitions we are referring to in any subsequent discussion.

Chapter 3 demonstrates that for the simple one locus, biallelic case, a number of derivations of population genetic variances and covariances, and resemblances between relatives, are not equivalent when genomic imprinting is acting. Subsequent chapters 4 and 5, therefore, follow the treatment of Falconer and Mackay [1996] in defining progeny means, breeding values and dominance deviations in order to derive expressions for additive and dominance variances, a covariance between additive and dominance terms, and resemblances between relatives. Chapter 6, incorporating maternal genetic effects and genomic imprinting at a single locus, utilises both the Falconer and Mackay [1996] approach and a general least squares approach [Lynch and Walsh, 1998] revised to account for male and female effects (see Chapter 3). However, although this revision gives equivalent expressions for variances and covariances in the one locus imprinting case, when maternal genetic effects are added the equivalence is lost (Chapter 6). Thus, both for comparison and consistency, we utilise the expressions derived using the approach of Falconer and Mackay [1996] in the following discussion.

A number of general conclusions about the impact of imprinting may be made from the model in Chapter 3. Differential expression of maternal and paternal alleles leads to differences in the breeding values and dominance deviations for males and females. Male and female additive variances, equivalent under standard Mendelian expression, are no longer equal. In addition, imprinting creates a covariance between female breeding values and dominance deviations, and male breeding values and dominance deviations, that are generally zero when maternal and paternal alleles are
expressed equally [Spencer, 2002]. Further, as a consequence of an additional genotype (and hence additional genotypic value) in the presence of imprinting, the total genetic variation in a population increases. Finally, imprinting increases the dominance variance relative to a population without imprinting.

Resemblances between relatives are also affected by imprinting in a population. Whereas normally the covariance between offspring and parents is the same for male and female parents, this equivalence is lost under imprinting. Inactivation of alleles inherited from one parent decreases the resemblance between offspring and that parent, while increasing the covariance with the other parent. A sex difference in covariances is also true of half sibs sharing a parent [Spencer, 2002]. Finally, in the absence of imprinting the covariance between full sibs exceeds the covariance between offspring and parent. This property is lost when imprinting is acting; one of the covariances between offspring and mother or offspring and father will exceed the covariance between full sibs.

We may examine some of the situations under which these “signatures of imprinting” are present when additions are made to our standard one locus model of imprinting (Chapters 4, 5 and 6):

**Total and dominance genetic variation**

Genomic imprinting always increases the total and dominance variation relative to a population with no imprinting acting. For a standard biallelic locus under Mendelian (M) expression, the total genetic variance is

\[ \sigma^2_{G(M)} = 2p_1p_2(2a^2k^2p_1p_2 + \alpha^2); \]

\[ \alpha = a(1+k(p_1-p_2)) \]

while for an imprinted (I) locus the total genetic variance is

\[ \sigma^2_{G(I)} = p_1p_2(\alpha_f^2 + \alpha_m^2 + a^2 p_1p_2(k_1+k_2)^2); \]

\[ \alpha_f = a(1+k_1p_1-k_2p_2), \]

\[ \alpha_m = a(1+k_2p_1-k_1p_2). \]

Letting \( k = \frac{1}{2}(k_1+k_2) \) we have

\[ \sigma^2_{G(M)} = 2p_1p_2(2a^2p_1p_2(\frac{1}{4}(k_1+k_2))^2 + a^2(1+\frac{1}{4}(k_1+k_2)(p_1-p_2))^2)) \]
and
\[
\sigma^2_{G(i)} - \sigma^2_{G(M)} = p_1p_2(a^2_1 + \alpha^2_m - 2(a^2(1 + 1/2(k_1 + k_2)(p_1 - p_2))^2)) = \frac{1}{2}a^2_1p_1p_2(k_1 - k_2)^2 > 0
\]
so the total variance in a population under imprinting will always exceed the variance in a population with Mendelian expression.

Similarly, for the variance in dominance deviations,
\[
\sigma^2_{D(i)} = (2ak_1p_2)^2
\]
\[
\sigma^2_{D(M)} = a^2p_1p_2((k_1 - k_2)^2 + p_1p_2(k_1 + k_2)^2)
\]
Again letting \( k = \frac{1}{2}(k_1 + k_2) \) in the Mendelian case, we have
\[
\sigma^2_{D(M)} = (a(k_1 + k_2)p_1p_2)^2
\]
and
\[
\sigma^2_{D(i)} - \sigma^2_{D(M)} = a^2p_1p_2(k_1 - k_2)^2 > 0
\]
and consequently dominance variation in a population with imprinting will exceed that in a non-imprinted population.

**Additions to model**

We wish to assess whether this increase in dominance and total variation is unique to the addition of imprinting to a quantitative genetic model, or whether other factors in the absence of imprinting also increase dominance and total variation.
Consider first the extension to two loci and the difference in variances when we compare one locus with no imprinting to two loci with no imprinting. Let genotypic values for both models range from 0 to 1, so that for the one locus model \( a = \frac{1}{2} \) and
\[
\sigma^2_{G(M)} = p_1p_2(k^2p_1p_2 + \frac{1}{4}(1 + k(p_1 - p_2))^2)
\]
while for the two locus model \( a_A = a_B = \frac{1}{4} \) (so \( 2a_A + 2a_B = 1 \)) and
\[
\sigma^2_{G(M, 2 locus)} = p_{1A}p_{2A} \left( \frac{1}{4}k_A^2p_{1A}p_{2A} + \frac{1}{8}(1 + k_A(p_{1A} - p_{2A}))^2 \right) + p_{1B}p_{2B} \left( \frac{1}{4}k_B^2p_{1B}p_{2B} + \frac{1}{8}(1 + k_B(p_{1B} - p_{2B}))^2 \right) + \epsilon_{ijkl} \text{ terms}.
\]
To compare the one locus with the two locus case, we set \( k \) equal to the mean of \( k_A \) and \( k_B \), and \( p_2 \) equal to the mean of \( p_{2A} \) and \( p_{2B} \) for one locus under Mendelian expression, so now
\[
\sigma_{G(M)}^2 = \frac{1}{2}(1 - \frac{1}{2}(p_{2A} + p_{2B}))(p_{2A} + p_{2B})(\frac{1}{8}(k_A + k_B)^2(1 - \frac{1}{2}(p_{2A} + p_{2B}))(p_{2A} + p_{2B}) + \frac{1}{2}(1 + \frac{1}{2}(k_A + k_B)(1 - p_{2A} - p_{2B}))^2).
\]

For the special case where \( k = k_A = k_B, \ p_2 = p_{2A} = p_{2B} \) and \( \epsilon_{ijkl} = 0 \) we find
\[\sigma_{G(M)}^2 - \sigma_{G(M, 2 \text{ locus})}^2 > 0.\] However this is not true in general, with the difference between genetic variances for the one and two locus model taking both positive and negative values across the range of parameter values. Selecting \( k_A, k_B \) and epistatic interactions randomly from the interval \([-1,1]\) and \( p_{2A} \) and \( p_{2B} \) randomly from the interval \((0,1)\), in 10,000 evaluations around half of one locus total genetic variances exceed the corresponding two locus variance. If epistatic interactions are instead selected randomly from the interval \([\pm \frac{1}{2}, \pm \frac{1}{2}]\), then \( \sigma_{G(M)}^2 - \sigma_{G(M, 2 \text{ locus})}^2 > 0 \) in the majority (\( \approx \frac{4}{5} \)) of cases. If we set epistatic interactions to zero, the proportion of negative values for \( \sigma_{G(M)}^2 - \sigma_{G(M, 2 \text{ locus})}^2 \) decreases to less than 0.2%. Thus in the absence of significant epistatic interactions, an expansion to two loci describing genetic values for a quantitative trait will not in general increase the total genetic variance relative to one locus.

Consider now the difference between dominance variances for two loci and one locus, assuming again that for the one locus case \( k \) equals the mean of \( k_A \) and \( k_B \), and \( p_2 \) equals the mean of \( p_{2A} \) and \( p_{2B} \). Note that in the absence of imprinting, dominance variances for males and females are equivalent. From simulations we find that in the absence of epistatic interactions, in general if \( k_A \) and \( k_B \) take the same sign, then \( \sigma_{D(M)}^2 - \sigma_{D(M, 2 \text{ locus})}^2 > 0 \), and if \( k_A \) and \( k_B \) are of different sign then \( \sigma_{D(M)}^2 - \sigma_{D(M, 2 \text{ locus})}^2 < 0 \). As a consequence, around half of the dominance variances for two loci exceed the corresponding one locus dominance variation. As the magnitude of epistatic interactions increase, the proportion of negative values for \( \sigma_{D(M)}^2 - \sigma_{D(M, 2 \text{ locus})}^2 \) increases for parameter space where \( k_A \) and \( k_B \) are the same sign.

For significant epistatic interactions (that is, the absolute value of epistatic interactions ranging from 0 to 1, corresponding to the total range in underlying genetic values) the variance in dominance deviations is in general higher for two loci compared to one across all values of \( k_A \) and \( k_B \). Thus even with small epistatic interactions between loci, dominance variances will in general increase for two loci.
relative to one locus, and consequently imprinting is not unique in increasing dominance variation in a population.

For environmental effects, the population total and dominance variances in the absence of imprinting are dependent on the value of \( k \), allele frequencies and genotype by environment interaction terms \( I_{ij} \) for each subpopulation. Not surprisingly, therefore, total and dominance variance may increase or decrease relative to a one locus case without environmental effects impacting. Consider for example the one locus case where allele frequencies are equal, genotypic values range from 0 to 1 and the heterozygote genotypic value is \( \frac{1}{2} \) \((k = 0)\). The expression for population total genetic variance is

\[
\sigma_{G(M)}^2 = 2p_1p_2(2a^2k^2p_1p_2 + a^2(1+k(p_1-p_2))^2)
\]

which equals 0.125 for this example. If we assume \( I_{11} = 0 \) and \( I_{12} = I_{21} = 0 \) but let \( I_{22} = \frac{1}{2} \) we can see that genotypic values for \( \{A_iA_i, A_iA_j, A_jA_j\} \) are now \( \{0, \frac{1}{2}, \frac{3}{2}\} \) and \( \{0, \frac{1}{2}, \frac{1}{2}\} \) for environments \( Y \) and \( Z \) respectively, and corresponding subpopulation variances become 0.2969 and 0.0469. Similarly, dominance variances in each subpopulation may increase or decrease relative to a one locus case without imprinting or environmental effects acting.

Finally, let us consider the impact of maternal genetic effects on total and dominance variances. Again let genotypic values for both models range from 0 to 1, so that for the one locus model with Mendelian expression \( a = \frac{1}{2} \) and

\[
\sigma_{G(M)}^2 = p_1p_2(k^2p_1p_2 + \frac{1}{2}(1+k(p_1-p_2))^2)
\]

while for the maternal effects model \( b = (\frac{1}{2}-a) \) (so \( 2a+2b = 1 \)) and

\[
\sigma_{G(M, \text{ maternal})}^2 = p_1p_2[4p_1p_2(a^2k^2 + (\frac{1}{2}-a)^2m^2) + 2a^2(1+k(p_1-p_2))^2 \\
+2a(\frac{1}{2}-a)(1+k(p_1-p_2))(1+m(p_1-p_2)) \\
+2(\frac{1}{2}-a)^2(1+m(p_1-p_2))^2].
\]

As with the environmental effects model, the difference in total variance between one locus with Mendelian expression and one locus with maternal effects acting is parameter-dependent and may take both positive and negative values. Across the range of values for \( k \) and \( m \) \([-1,1]\), for around half of cases \( \sigma_{G(M, \text{ maternal})}^2 > \sigma_{G(M)}^2 \).

Interestingly, male and female dominance variances differ, and for both we find that for the majority of parameter values \( \approx \frac{9}{10} \) for females and \( \approx \frac{12}{20} \) for males in 10,000
runs) the dominance variance for one locus with Mendelian expression is less than the dominance variance for one locus with maternal effects

\[ \sigma_{Df(M \text{, maternal})}^2 \sigma_{Dm(M \text{, maternal})}^2 > \sigma_{D(M \text{, maternal})}^2. \]

Further, if \( a < \frac{1}{4} \) both the male and female dominance variances under maternal effects will almost always exceed that under Mendelian expression (0 for females and \( \approx \frac{1}{1000} \) for males in 10,000 runs). If maternal genotype contributes more than the offspring’s own genotype to the genotypic value of the offspring, then the male and female dominance variances for this model will be generally be greater than the dominance variance for a model with offspring genotype alone impacting genotypic values.

The results above suggest that, unfortunately, an increase in total and dominance genetic variance for a quantitative trait, relative to a population with Mendelian expression of a single biallelic locus, is not unique to genomic imprinting. Increases in total and dominance variances may be seen where two loci, environmental effects or maternal genetic effects are contributing to a quantitative trait. The strongest conclusion that can be made is that if the observed variation in a population is less than what would be expected from a single locus with Mendelian expression, the quantitative trait of interest is not impacted by a single genomically imprinted locus.

One other feature of the variance in dominance deviations in the models above is worth mentioning. For the one locus imprinting model, and for the one locus imprinting model incorporating environmental effects, the dominance variances are the same for males and females. Considering two imprinted loci, male and female dominance deviations are the same in the absence of epistatic interactions. As mentioned previously, when epistatic interactions are nonzero, male and female dominance variances differ, but are equivalent when imprinting is absent. For the maternal effects model, however, male and female dominance variances differ even when imprinting is absent. If a trait is clearly influenced by one locus, a difference in the variation of male and female dominance deviations is a characteristic signature of maternal effects.
Male and female breeding values and additive genetic variances

One of the most striking features of genomic imprinting is the large differences in breeding values for males and females, and consequently the difference between male and female additive genetic variances (the variances of the respective male and female breeding values). Recall that, for a given parental genotype, breeding values are defined as twice the difference between the mean value of offspring and the overall population mean [Falconer and Mackay, 1996]. For the simple one locus biallelic case under genomic imprinting, progeny means are different for males and females because of the difference in genotypic values in reciprocal heterozygotes. For example, an $A_2A_2$ mother may have progeny with genotype $A_2A_1$ or $A_2A_2$, and her offspring mean will be

$$p_2(a(1+k_i)) + p_2(2a) = a(p_1(1+k_i) + 2p_2)$$

while an $A_2A_2$ father may have $A_1A_2$ or $A_2A_2$ offspring, with a progeny mean of

$$p_1(a(1+k_i)) + p_2(2a) = a(p_1(1+k_i) + 2p_2).$$

Consider, for example, complete maternal inactivation, with genotypic values of $\{0,0,1,1\}$ for genotypes $\{A_1A_1, A_2A_1, A_1A_2, A_2A_2\}$ and equal allele frequencies $a = 1/4, p_1 = p_2 = 1/2, k_1 = -1, k_2 = 1$. The progeny means for $A_2A_2$ individuals are $1/4$ for females and $1$ for males – a difference of half of the range of genotypic values in the population.

Additions to model

We have noted in previous chapters that our derivations for breeding values differ for males and females for two loci (Chapter 4), environmental effects (Chapter 5) and for maternal effects (Chapter 6). In the absence of imprinting, the models for two loci and for one locus with environmental effects give identical expressions for male and female breeding values and additive genetic variances (as does a single locus under Mendelian expression). This equality is not, however, true for maternal effects in the absence of imprinting. For example, the breeding value of an $A_1A_1$ female ($bv_{j11}$) is

$$bv_{j11} = -2p_2(\alpha_j + b(2 + p_1(m_1 + m_2)))$$
while the breeding value for an \( A_1A_1 \) male (\( bv_{m1} \)) is

\[ bv_{m1} = -2p_2\alpha_m. \]

In the absence of imprinting, \( \alpha_f = \alpha_m = \alpha \) and \( m_i = m_z = m \) and these expressions become

\[ bv_{f1} = -2p_2(\alpha + 2b(1+mp_1)) \]

and

\[ bv_{m1} = -2p_2\alpha. \]

Similarly, the expressions for additive genetic variances are

\[ \sigma^2_{Af} = 2p_1p_2(b^2((m_1 - m_2)^2 + 2mp_2(m_1 + m_2)^2) + (\alpha_f + \beta_f + \beta_m)^2) \]

for females and

\[ \sigma^2_{Am} = 2p_1p_2\alpha_m^2 \]

for males (where \( \beta_f = b(1+mp_1-m_2p_2) \) and \( \beta_m = b(1+m_2p_1-m_1p_2) \)); these become

\[ \sigma^2_{Af} = 2p_1p_2[8b^2m^2p_1p_2 + \alpha^2 + 4\alpha\beta + 4\beta^2] \]

and

\[ \sigma^2_{Am} = 2p_1p_2\alpha^2 \]

in the absence of imprinting (where \( \beta = b(1+m(p_1-p_2)) \); refer Chapter 6).

Interestingly, the difference between male and female additive variances under maternal effects alone is never positive nor zero for \( p_1, p_2 \in (0,1) \) and \( k, m \in [-1,1] \) - that is, if \( b \neq 0 \) (maternal effects are acting), the female additive variance will exceed the male additive variance. In contrast, for \( p_1, p_2 \in (0,1) \), \( k_1, k_2 \in [-1,1] \) and \( k_1 \neq k_2 \) the difference between male and female additive variances under imprinting alone may be positive or negative but is never zero. More specifically, if \( k_1 > k_2 \) (paternal inactivation) then \( \sigma^2_{Af} > \sigma^2_{Am} \), if \( k_1 < k_2 \) (maternal inactivation) then \( \sigma^2_{Af} < \sigma^2_{Am} \), and only if imprinting is absent \( (k_1 = k_2 = k) \) will \( \sigma^2_{Af} = \sigma^2_{Am} \). As a consequence, if male and female additive variances differ, maternal effects or imprinting may be acting, but if the male additive variance exceeds the female additive variance then imprinting must be influencing the quantitative trait of interest.
Male and female covariances between breeding values and dominance deviations

For a single locus with Mendelian expression of alleles there is no correlation between breeding values and dominance deviations. Inactivation of alleles creates a covariance between both male breeding values and dominance deviations and female breeding values and dominance deviations. The female covariance between breeding values and dominance deviations is negative under paternal inactivation and positive under maternal inactivation, while the male covariance is positive under paternal inactivation and negative under maternal inactivation. Recall from above that the difference between male and female additive variances is also dependent on the direction of inactivation.

Additions to model

Referring to chapters 4, 5 and 6, a covariance between breeding values and dominance deviations is also present when imprinting is included in models for two loci, environmental effects and maternal effects. When imprinting is absent from a population, covariances between breeding values and dominance deviations remain present for two loci with epistatic interactions between loci, and for maternal effects. For the two locus case (in the absence of imprinting) the covariance between breeding values and dominance deviations is the same for males and females and is always positive if the epistatic interactions 
\[ \epsilon_{1212} = \epsilon_{2112} = \epsilon_{1221} = \epsilon_{2121} = \epsilon_{2212} = \epsilon_{2221} = \epsilon_{2222} \]
lie in the interval \([-1,1]\) (and zero if all epistatic interactions are zero as the model simplifies to two Mendelian loci expressed independently of each other).

For the maternal effects case, in the absence of imprinting the covariance between dominance deviations and breeding values remains different for males and females. Setting \(k_1 = k_2 = k\) and \(m_1 = m_2 = m\), the expressions are
\[
\sigma_{\text{Adj}} = p_1 p_2 (8abkmp_1 p_2 - 16b^3 m^2 p_1 p_2 - 3\beta(\alpha + 2\beta))
\]
for females and
\[
\sigma_{\text{Adm}} = p_1 p_2 \alpha \beta
\]
Interestingly, the covariance between breeding values and dominance deviations for males is strictly positive for \(\{a,b\} > 0, \{k,m\} \in [-1,1]\) and \(\{p_1, p_2\} \in (0,1)\). The sign of the female covariance is
dependent upon values for $a$, $b$, $k$, $m$ and the allele frequencies. However, if $a \leq b$ the female covariance between breeding values and dominance deviations is always negative, and for $a > b$ only if values of $k$ and $m$ are both close to 0 or both close to 1 will the female covariance become positive. For example, in 10,000 runs where $k$ and $m$ are selected randomly from the interval $[-1, 1]$, we set $a = \frac{4}{10}$ and $b = \frac{1}{10}$, and $p_1 (=1-p_2)$ is selected randomly from $(0,1)$, the female covariance was positive only 4 times ($<0.1\%$). In general, therefore, maternal effects influencing a trait of interest will generate a negative covariance between female breeding values and dominance deviations and a corresponding positive male covariance.

Covariance between offspring and parent

Consider the one locus imprinting case (Chapter 3). If alleles are (partially or fully) inactivated when inherited from one parent, it is expected that offspring will resemble more closely the parent whose alleles are not inactivated. Recall that the expressions for the covariance between offspring and parents under imprinting are

$$\sigma_{OPf} = \frac{1}{2} (\sigma_{Af}^2 + \sigma_{ADf}^2)$$

for offspring and female parents and

$$\sigma_{OPm} = \frac{1}{2} (\sigma_{Am}^2 + \sigma_{ADm}^2)$$

for offspring and male parents. As we have seen above, under paternal inactivation $\sigma_{Af}^2 > \sigma_{Am}^2$ and the covariance between breeding values and dominance deviations is negative for females and positive for males, while under maternal inactivation $\sigma_{Af}^2 < \sigma_{Am}^2$ and the covariance between breeding values and dominance deviations is positive for females and negative for males. Therefore it is unclear whether the covariances between offspring and parent would indeed differ for males and females, as we would expect. Consider however the difference between the covariances for this one locus case:

$$\sigma_{OPf} - \sigma_{OPm} = \frac{1}{2} (\sigma_{Af}^2 + \sigma_{ADf}^2 - \sigma_{Am}^2 - \sigma_{ADm}^2)
= \frac{1}{2} a^2 p_1 p_2 (k_1 - k_2) (2 + (k_1 + k_2)(p_1 - p_2)).$$

Given that $\{a, p_1, p_2\} > 0$ and $(2 + (k_1 + k_2)(p_1 - p_2)) > 0$ we can see that if $k_1 > k_2$ (paternal inactivation), then $\sigma_{OPf} > \sigma_{OPm}$, while if $k_1 < k_2$ (maternal inactivation), then $\sigma_{OPf} < \sigma_{OPm}$. As one would expect, therefore, the covariance between offspring and
parent differs for males and females under imprinting and is dependent on the direction of inactivation.

**Additions to model**

This difference in the relationships between male and female parents and their offspring is also present for genomic imprinting at two loci, for genomic imprinting and environmental effects, and for imprinting and maternal effects. When imprinting is absent, however, only a model including maternal effects retains the difference in parent-offspring covariances. Further, the difference between the covariance between offspring and mothers and offspring and fathers is

\[
bp_1 p_2 \left( (1 + m (p_1 - p_2))^2 + 2a(1 + m(p_1 - p_2) + k(p_1 - p_2 + m(1-2p_1p_2))) \right)
\]

This difference is strictly positive for \(a, b > 0\), \(\{k, m\} \in [-1,1]\) and \(\{p_1, p_2\} \in (0,1)\). This, again, is as expected – with maternal effects acting, mothers will have more of an effect on offspring genotypic values than will fathers. As with our conclusion regarding female and male additive variances, therefore, if male and female parent-offspring covariances differ then maternal effects or imprinting may be acting, but maternal effects will not be influencing the trait of interest if \(\sigma_{opy} < \sigma_{opm}\).

**Comparison of covariance between offspring and parent and full sibs**

A final relationship of interest is that between the expectations for parent-offspring covariances and the covariance between full sibs. For a locus under Mendelian expression, the covariance between offspring and (both male and female) parent is

\[
\sigma_{OP} = \frac{1}{2} \sigma_A^2
\]

while the resemblance between full sibs is

\[
\sigma_{FS} = \frac{1}{2} \sigma_A^2 + \frac{1}{4} \sigma_D^2,
\]
thus the covariance between full sibs will always exceed that between offspring and parent by an amount proportional to the dominance variation. Under genomic imprinting these expressions become

\[ \sigma_{OPf} = \frac{1}{2}(\sigma^2_{Af} + \sigma^2_{Adf}) \]
\[ \sigma_{OPm} = \frac{1}{2}(\sigma^2_{Am} + \sigma^2_{Adm}) \]

and

\[ \sigma_{FS} = \frac{1}{4}(\sigma^2_{Af} + \sigma^2_{Am} + \sigma^2_{D} + \sigma^2_{Adf} + \sigma^2_{Adm}). \]

The differences between the covariance between full sibs and that between offspring and parent are

\[ \sigma_{FS} - \sigma_{OPf} = \frac{1}{4}(-\sigma^2_{Af} + \sigma^2_{Am} + \sigma^2_{D} - \sigma^2_{Adf} + \sigma^2_{Adm}) \]

and

\[ \sigma_{FS} - \sigma_{OPm} = \frac{1}{4}(-\sigma^2_{Am} + \sigma^2_{Af} + \sigma^2_{D} - \sigma^2_{Adm} + \sigma^2_{Adf}) \]

For maternal inactivation \((k_1 < k_2)\) the difference \(\sigma_{FS} - \sigma_{OPf}\) is always positive, while \(\sigma_{FS} - \sigma_{OPm}\) is always positive under paternal inactivation \((k_1 > k_2)\). However, these two differences may be negative (such that the full sib covariance does not exceed one of the parent offspring covariances) under paternal and maternal inactivation respectively. Consider \(\sigma_{FS} - \sigma_{OPf}\) under paternal inactivation. If \(k_1 > 0\) and \(k_2 < 0\) then \(\sigma_{OPf} > \sigma_{FS}\). For \(k_1, k_2 > 0\), \(\sigma_{OPf} > \sigma_{FS}\) if \(k_1 > 3k_2\). Finally, for \(k_1, k_2 < 0\), the covariance between offspring and female parents exceeds the covariance between full sibs provided \(k_1 > \frac{1}{3}k_2\) (see Figure 1, following page). In the two remaining regions of parameter space bounded by \((k_1, k_2) = (0, 0), (1, 1), (1, \frac{1}{3}), (0, 0)\) and \((0, 0), (\frac{1}{3}, -1), (-1, -1), (0, 0)\) the sign of \(\sigma_{FS} - \sigma_{OPf}\) is dependent on allele frequencies.

Figure 2 (following page) similarly shows the sign \(\sigma_{FS} - \sigma_{OPm}\) takes under maternal and paternal inactivation. The sign of \(\sigma_{FS} - \sigma_{OPm}\) in regions bound by \((k_1, k_2) = (0, 0), (1, 1), (\frac{1}{3}, 1), (0, 0)\) and \((0, 0), (-1, \frac{1}{3}), (-1, -1), (0, 0)\) is again determined by the allele frequencies in the population. Note also that whenever \(\sigma_{OPf} > \sigma_{FS}\), \(\sigma_{OPm} < \sigma_{FS}\) and whenever \(\sigma_{OPm} > \sigma_{FS}\), \(\sigma_{OPf} < \sigma_{FS}\).
Figure 1: Sign of the difference in the covariance between offspring and female parents and full sibs across values of $k_1$ and $k_2$; unshaded region either covariance may be largest

Figure 2: Sign of the difference in the covariance between offspring and male parents and full sibs across values of $k_1$ and $k_2$; unshaded region either covariance may be largest
Of most importance here is that for our “classical” definition of imprinting – that is, complete (or almost complete) inactivation of alleles from one parent (with \( k_1 \) and \( k_2 \) taking values of opposing sign), we would expect the covariance between offspring and one parent to always exceed the covariance between full sibs.

**Additions to model**

Consider now the values parent offspring and full sib covariances take for models incorporating two loci, environmental effects and maternal effects. As we saw above, in the absence of imprinting the covariance between offspring and parent is the same for male and female parents for both two loci and environmental effects. Regardless of the values for epistatic interactions or genotype by environment interactions, the difference between the full sib and offspring parent covariances is always positive for these two models. For maternal effects, however, the covariance between offspring and female parents differs from that between offspring and male parents even when imprinting is not acting. For all values of \( a, b, k \) and \( m \) and across the range of allele frequencies the covariance between offspring and male parents is always less than that between full sibs. The difference between mother-offspring and full sib covariances \( (\sigma_{opf} - \sigma_{fs}) \) is always negative if \( a \leq b \) (that is, the maternal contribution to offspring genotypic value equals or exceeds the contribution from the offspring’s own genotype) but may take positive or negative values when \( a > b \), depending on other parameter values. For example, when parameter values were chosen randomly from \([-1,1]\) for \( k \) and \( m \), \( p_1 \) and \( p_2 \) were chosen randomly from \((0,1)\) and we set \( a = \frac{4}{10} \) and \( b = \frac{1}{10} \), in 10,000 runs the mother offspring covariance always exceeded the full sib covariance between the lines \( m = \frac{4}{10}k + 1 \) and \( m = \frac{1}{10}k - 1 \) while taking both positive and negative values outside these lines. If heterozygotes fall around the midpoint of the two homozygotes, and the impact of a heterozygous mother lies at the middle of the impact of the two homozygous mothers, then we would expect the full sib covariance to lie between the covariance between father and offspring and the covariance between mother and offspring.

**Overall summary**

From the discussion above we have see that a number of signatures of imprinting, apparent when we compare to a locus under Mendelian expression alone,
are not necessarily unique to genomic imprinting. Imprinting, environmental effects and maternal effects may all increase the total and dominance variances relative to a population with Mendelian expression of alleles. Both maternal effects and imprinting result in a difference between male and female breeding values and hence additive genetic variances. A covariance between breeding values is present for a trait influenced by genomic imprinting, two loci or by maternal effects, although differences in male and female covariances are only present for imprinting or maternal effects. Similarly, maternal effects and imprinting both cause differences in the covariance between offspring and mothers and offspring and fathers. One of these parent-offspring covariances may also exceed the covariance between full sibs for traits influenced by either of genomic imprinting or maternal effects.

These results suggest that, while it should be straightforward to determine that parent-of-origin or maternal genetic effects are not influencing a trait of interest (for example, if there is no difference in the covariance between offspring and male or female parents), differentiating between maternal effects and imprinting may be more challenging. A higher male than female additive genetic variance, higher male than female parent offspring resemblance or a negative male covariance between breeding values and dominance deviations all indicate that a trait is influenced by a locus with (partial or complete) maternal inactivation of alleles. Unfortunately, however, these evidence do not exclude maternal effects impacting the trait of interest.

Perhaps the most promising finding from development of the above quantitative genetic models is that maternal genetic effects are unique in creating a difference in the male and female dominance variances. This difference is not seen in the other quantitative genetic models and consequently its absence may exclude maternal effects from impacting a trait of interest. Therefore if female exceed male additive variances, offspring more closely resemble a female parent, the covariance between breeding values is negative in females and positive in males, and there is no evidence of a sex difference in the dominance variance, we may be confident that a paternally inactivated locus is influencing our quantitative trait of interest.

A wide range of methods for detection of imprinting in quantitative and complex traits was discussed in Chapter 2. Although there are extensions to include imprinting in numerous methods for dissecting the architecture of quantitative and complex traits where both marker information and phenotype are available, there has been relatively little exploration of imprinting for traits where only the phenotype of
individuals is known. This research adds therefore to the analysis of such phenotypes and suggests a way forward to testing for imprinting in quantitative traits. If sibships and parentage in a natural population are easily identified, examining trait covariances between full and half sibs and parents and their offspring may easily indicate the presence of imprinting.

Further, the development of expressions for heritability and response to selection as discussed in Chapter 3 will allow partitioning of the total variance in the population into genetic and environmental components. Given covariances between relatives and an estimate for the total genetic variance, we could develop a forward or backward stepwise procedure to test the significance of genomic imprinting, maternal genetic effects and multiple loci as components of the overall genetic variance in a population.

Another approach to testing the significance of imprinting is to formulate a maximum likelihood approach to modelling the quantitative trait of interest. Likelihood approaches have been utilised to test for genomic imprinting or parent-of-origin effects both in the presence and absence of marker information (see Chapter 2). In particular, for General Mixed Models without marker information de Vries et al [1994] and Engellandt and Tier [2002] utilised likelihood ratio tests to assess the support for the addition of separate maternal and paternal expression into the genetic model. Therefore for the quantitative genetic models described in previous chapters, a maximum likelihood approach could be used both to assign parameter values and to assess support for different genetic models incorporating, for example, maternal effects and/or imprinting, given the observed quantitative trait data.

**Future research**

There are a number of exciting possibilities for extending the quantitative genetic models described in the previous chapters, with the ultimate aim of enhancing understanding of the impact of genomic imprinting on quantitative traits. One interesting extension is the inclusion of sex-specific expression, along with genomic imprinting, to a one locus quantitative genetic model. There is growing evidence for significant differences in the expression profiles of genes, depending on the sex of the individual. One such example is genes on the X chromosome in females. Because males carry only one copy of the X chromosome, one of the two X chromosomes in
female mammals is generally inactivated, a process termed dosage compensation [Lyon, 1961]. However, only around 65 percent of genes on one X chromosome are fully inactivated in females, with the remainder either partially or full expressed from both X chromosomes (where they are only expressed from the single X chromosome in males). Inactivation is also variable between individuals and within different cells in an individual [Carrel and Willard, 2005].

The expression profile of autosomal genes may also be different between males and females - one clear example is the sexual dimorphism in anatomical traits such as muscle mass distribution. Further, complex or quantitative traits such as diabetes, asthma and autism exhibit sex specific differences in disease severity and age of onset [reviewed in Weiss et al., 2006]. Because males and females vary considerably in their chemical environments as a result of differences in sex and growth hormones, the sex of an individual can be considered to exert an environmental effect on the expression of genes it contains [Rinn and Snyder, 2005].

The possibility that quantitative traits are being influenced both by sex differences in gene expression and by genomic imprinting is not unlikely; diabetes, asthma and autism all show parent-of-origin effects [reviewed in Chapter 2]. The inclusion of both sex-specific and imprinted gene expression to a quantitative genetic model has great potential in the elucidation of traits that manifest differently or have different incidence patterns in males and females.

A further area for future research is the extension of the two locus quantitative genetic model incorporating imprinting to linked loci. In humans, recombination rates are generally higher in females than males [Broman et al., 1998; Kong et al., 2002]. However, imprinted domains appear to exhibit an even stronger bias towards female recombination events and as a result, the sex-averaged recombination rate is higher for imprinted regions than in the rest of the genome [Lercher and Hurst, 2003]. Large differences in the predicted male and female recombination frequencies between marker loci may be a consequence of imprinting [Smalley, 1993], but it is also possible that for chromosomal regions where male and female recombination rates do differ, stronger evidence for linkage to the trait of interest may be seen in transmitting families for which the parental sex has a lower recombination rate [Nothen et al., 1999]. The inclusion of sex-specific recombination rates to a quantitative genetic model incorporating two linked loci will aid understanding of the importance of sex differences in recombination rates for traits influenced by imprinted loci.
Finally, as discussed above and in Chapter 3, it is intended that the more general identity-by-descent procedure presented by Dai and Weeks [2006] be used to determine an expression for the heritability of a trait influenced by an imprinted locus. Also of interest is derivation of the expected response to selection when an imprinted gene is affecting a trait of interest. It is estimated that phenotypic selection may be up to 50% less efficient when a trait is influenced by imprinting, and as a result imprinting may contribute to lower than expected selection responses in genetic improvement schemes [de Vries et al., 1994]. Given the significance of imprinting to agriculturally important traits (for example the impact of $IGF2$ on muscle mass in pigs; [Nezer et al., 1999]) full derivation of the response to selection across generations will be an exciting development.
References


Table 1: Genotypic values and frequencies for one
locus diallelic imprinting model
(Chapter 3)

<table>
<thead>
<tr>
<th>Genotype $A_iA_j$</th>
<th>$A_iA_i$</th>
<th>$A_iA_i$</th>
<th>$A_iA_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>$p_1p_1$</td>
<td>$p_1p_2$</td>
<td>$p_1p_2$</td>
<td>$p_2p_2$</td>
</tr>
<tr>
<td>Genotypic Value</td>
<td>$G_{11} = 0$</td>
<td>$G_{21} = a(1 + k_1)$</td>
<td>$G_{12} = a(1 + k_2)$</td>
<td>$G_{22} = 2a$</td>
</tr>
<tr>
<td>Parameter ranges</td>
<td>$k_1, k_2 \in [-1, 1], \ a &gt; 0$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Genotypic values for two locus imprinting model incorporating epistasis
(Chapter 4)

<table>
<thead>
<tr>
<th>A locus genotype</th>
<th>B locus genotype</th>
<th>( B_1B_1 )</th>
<th>( B_2B_1 )</th>
<th>( B_1B_2 )</th>
<th>( B_2B_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_1A_1 )</td>
<td>( G_{1111} ) ( = 0 )</td>
<td>( G_{1121} ) ( = a_B(1+k_{1B}) )</td>
<td>( G_{1112} ) ( = a_B(1+k_{2B}) )</td>
<td>( G_{1122} ) ( = 2a_B )</td>
<td></td>
</tr>
<tr>
<td>( A_2A_1 )</td>
<td>( G_{2111} ) ( = a_A(1+k_{1A}) )</td>
<td>( G_{2112} ) ( = a_A(1+k_{1A}) )</td>
<td>( G_{2122} ) ( = a_A(1+k_{1A}) )</td>
<td>( G_{2121} ) ( = 2a_A )</td>
<td></td>
</tr>
<tr>
<td>( A_1A_2 )</td>
<td>( G_{1211} ) ( = a_A(1+k_{2A}) )</td>
<td>( G_{1221} ) ( = a_A(1+k_{2A}) )</td>
<td>( G_{1212} ) ( = a_A(1+k_{2A}) )</td>
<td>( G_{1222} ) ( = 2a_A )</td>
<td></td>
</tr>
<tr>
<td>( A_2A_2 )</td>
<td>( G_{2211} ) ( = 2a_A )</td>
<td>( G_{2221} ) ( = 2a_A )</td>
<td>( G_{2212} ) ( = 2a_A )</td>
<td>( G_{2222} ) ( = 2a_A )</td>
<td></td>
</tr>
</tbody>
</table>

Parameter ranges: \( k_{1A}, k_{2A}, k_{1B}, k_{2B} \in [-1,1], \ a_A, a_B > 0 \)
### Table 3: Phenotypic values and frequencies for imprinting model incorporating environmental effects

*(Chapter 5)*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$A_1A_1$</th>
<th>$A_2A_1$</th>
<th>$A_1A_2$</th>
<th>$A_2A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>$p_i^2$</td>
<td>$p_ip_2$</td>
<td>$p_ip_2$</td>
<td>$p_2^2$</td>
</tr>
<tr>
<td>Phenotypic value: environment $Y (z_Y)$</td>
<td>$z_{Y11} = I_{11} + E$</td>
<td>$z_{Y21} = a(1 + k_1) + I_{21} + E$</td>
<td>$z_{Y12} = a(1 + k_2) + I_{12} + E$</td>
<td>$z_{Y22} = 2a + I_{22} + E$</td>
</tr>
<tr>
<td>Phenotypic value: environment $Z (z_Z)$</td>
<td>$z_{Z11} = -I_{11} - E$</td>
<td>$z_{Z21} = a(1 + k_1) - I_{21} - E$</td>
<td>$z_{Z12} = a(1 + k_2) - I_{12} - E$</td>
<td>$z_{Z22} = 2a - I_{22} - E$</td>
</tr>
<tr>
<td>Mean across $Y$ and $Z$</td>
<td>$0$</td>
<td>$a(1 + k_1)$</td>
<td>$a(1 + k_2)$</td>
<td>$2a$</td>
</tr>
<tr>
<td>Parameter ranges</td>
<td>$k_1 , k_2 \in [-1,1]$, $a &gt; 0$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Genotypic values for imprinting model incorporating maternal genetic effects
(Chapter 6)

<table>
<thead>
<tr>
<th>Offspring genotype:</th>
<th>Maternal genotype:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$A_1A_1$</td>
<td>$A_2A_1$</td>
<td>$A_1A_2$</td>
<td>$A_2A_2$</td>
</tr>
<tr>
<td>$A_1A_1$</td>
<td>$G_{1111} = 0$</td>
<td>$G_{1121} = b(1+m_1)$</td>
<td>$G_{1112} = b(1+m_2)$</td>
<td>none</td>
</tr>
<tr>
<td>$A_2A_1$</td>
<td>none</td>
<td>$G_{2121} = a(1+k_1)+b(1+m_1)$</td>
<td>$G_{2112} = a(1+k_1)+b(1+m_2)$</td>
<td>$G_{2122} = a(1+k_1)+2b$</td>
</tr>
<tr>
<td>$A_1A_2$</td>
<td>$G_{1211} = a(1+k_2)$</td>
<td>$G_{1221} = a(1+k_2)+b(1+m_1)$</td>
<td>$G_{1212} = a(1+k_2)+b(1+m_2)$</td>
<td>none</td>
</tr>
<tr>
<td>$A_2A_2$</td>
<td>none</td>
<td>$G_{2221} = 2a+b(1+m_1)$</td>
<td>$G_{2212} = 2a+b(1+m_2)$</td>
<td>$G_{2222} = 2a+2b$</td>
</tr>
</tbody>
</table>

Parameter ranges:

$k_1, k_2, m_1, m_2 \in [-1, 1], \ a, b > 0$
### Table 5: Definition of parameters and notation used in discussion

<table>
<thead>
<tr>
<th>Parameter or term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_iA_j$</td>
<td>Individual with maternally inherited $A_i$ allele and paternally inherited $A_j$ allele</td>
</tr>
<tr>
<td>$A_iA_jA_kA_l$</td>
<td>$A_iA_j$ offspring with $A_kA_l$ mother</td>
</tr>
<tr>
<td>$G_{ij}$</td>
<td>Average genotypic and phenotypic value of $A_iA_j$ individuals in a population</td>
</tr>
<tr>
<td>$G_{ijkl}$ (two locus)</td>
<td>Average genotypic and phenotypic value of $A_iA_jA_kA_l$ individuals in a population</td>
</tr>
<tr>
<td>$z_{hij}$</td>
<td>Phenotype of an $A_iA_j$ individual in environment $h$</td>
</tr>
<tr>
<td>$G_{ijkl}$ (maternal effects)</td>
<td>Average genotypic and phenotypic value of $A_iA_jA_kA_l$ individuals in a population</td>
</tr>
<tr>
<td>$\sigma^2_G$</td>
<td>Total genetic variance in the population</td>
</tr>
<tr>
<td>$\sigma^2_{A_f}$; $\sigma^2_{A_m}$</td>
<td>Additive genetic variance for females; additive genetic variance for males</td>
</tr>
<tr>
<td>$\sigma^2_{D_f}$; $\sigma^2_{D_m}$</td>
<td>Dominance genetic variance for females; dominance genetic variance for males</td>
</tr>
<tr>
<td>$\sigma_{AD_f}$; $\sigma_{AD_m}$</td>
<td>Covariance between breeding values (additive effects) and dominance deviations for females; males</td>
</tr>
<tr>
<td>$\sigma_{OP_f}$; $\sigma_{OP_m}$</td>
<td>Covariance between offspring and mother (female parent) genotypic values; covariation between offspring and father (male parent) genotypic values</td>
</tr>
<tr>
<td>$\sigma_{FS}$</td>
<td>Covariance between full sib genotypic values</td>
</tr>
<tr>
<td>$\sigma_{HS_f}$; $\sigma_{HS_m}$</td>
<td>Covariance between genotypic values of half sibs sharing a female parent; male parent</td>
</tr>
</tbody>
</table>