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The effect of linkage on the additive by additive covariance between relatives¹

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Abstract – The additive \times additive relationship coefficient needs to be calculated in order to compute genetic covariance between relatives. For linked loci, the computation of this coefficient is not as simple as for unlinked loci. Recursive formulae are given to compute the additive \times additive relationship coefficient for an arbitrary pedigree. Based on the recursive formulae, numerical values of the desired coefficient for selfed or outbred individuals are examined. The method presented provides the means to compute the additive \times additive relationship coefficient for any situation assuming linkage. The effect of linkage on the covariance was examined for several pairs of relatives. In the absence of inbreeding, linkage has no effect on the parent–offspring covariance. All of the other relationships examined were affected by linkage. As recombination rate increased from 0.1 to 0.5, in descending order of percentage change in the covariance, the relationships ranked as follows: first cousins, double first cousins, grandparent–grandoffspring, half sibs, aunt–nephew, full sibs, parent–offspring. With inbreeding, the parent–offspring covariance is also affected by linkage.
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additive \times additive relationship coefficient / covariance between relatives / identity by descent

Résumé – Effet du linkage sur les covariances entre apparentés pour les interactions de type additif \times additif. En cas d'épistasie, le calcul de la covariance génétique entre apparentés nécessite le calcul du coefficient de parenté pour les termes d'interaction additif \times additif. Quand les loci sont liés, le calcul de ce coefficient n'est pas aussi simple que dans le cas de loci indépendants. Des formules récursives sont données pour calculer le coefficient de parenté additif \times additif

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dans le cas d'un pedigree quelconque. À partir des formules récursives, des valeurs numériques correspondant au cas d'individus issus d'autofécondation et de parents sexués sont examinées. La méthode présentée fournit le moyen de calculer le coefficient de parenté additif \times additif pour toute situation impliquant le linkage. L'effet du linkage sur la covariance a été examiné pour plusieurs paires d'apparentés. En l'absence de consanguinité, le linkage n'a pas d'effet sur la covariance parent-descendant. Toutes les autres parentés examinées ont été affectées par le linkage. Quand le taux de recombinaison augmente de 0,1 à 0,5, les parentés présentées suivant l'ordre décroissant de sensibilité des covariances sont les suivantes : cousins germains, cousins issus de germains, grands-parents petits-fils, demi-frères, oncle-neveux, pleins-frères, parent-descendants. En cas de consanguinité, la covariance parent-descendant est aussi affectée par le linkage. © Inra/Elsevier, Paris

coefficient de parenté additif \times additif / covariance entre apparentés / identité par descendance mendélienne

1. INTRODUCTION

Genetic covariance between relatives can be expressed as a linear combination of genetic variance components. In order to compute the covariance between relatives, coefficients associated with the variance components need to be calculated from pedigree relationships. Additive and dominance relationship coefficients can be computed through several methods for arbitrary pedigrees [4–6, 8, 10]. The additive \times additive relationship coefficient between unlinked loci can be obtained as the square of the additive relationship coefficient [7].

When loci are linked, the additive \times additive relationship coefficient cannot be computed simply as the square of the additive relationship coefficient. Now this coefficient may depend on the recombination rate and it has been derived for several common relationships [2, 3, 12]. A general approach for computing the additive \times additive relationship coefficient for collateral relatives has been developed by Schnell [9]. For general pedigrees, this approach becomes very complicated. More recently, Thompson [11] has described a recursive approach for computing two-locus identity probabilities that can be applied to any pedigree.

In this paper we present independently derived recursive formulae that are different from those of Thompson for computing the additive \times additive relationship coefficient for an arbitrary pedigree. These formulae can be used to examine the effect of linkage on the additive \times additive relationship coefficient for any pair of relatives. Based on the results obtained in this paper, the situations when the effect of linkage on the additive \times additive covariance between relatives can be ignored are examined. Some examples are given here and a C++ implementation of the recursive method with some numerical examples is available on the Web at <http://www.public.iastate.edu/~rohan> by following the link Software.

2. THEORY

Additive \times additive coefficients are generated by epistatic effects in the covariance. Consider a two-locus model with an arbitrary number of alleles

at each locus. The additive \times additive genotypic value of an individual I with alleles k and k' at the first locus and alleles l and l' at the second locus can be written as

$$I_{kk' ll'} = \delta_{kl} + \delta_{kl'} + \delta_{k'l} + \delta_{k'l'} \quad (1)$$

where δ is the additive \times additive effect. Similarly, the additive \times additive genotypic value for an individual J with alleles n, n', p and p' is

$$J_{nn' pp'} = \delta_{np} + \delta_{np'} + \delta_{n'p} + \delta_{n'p'} \quad (2)$$

The additive \times additive contribution to the covariance between I and J can be written as a sum of 16 covariances.

$$\begin{aligned} \text{Cov}[(AA)_I, (AA)_J] &= \text{Cov}[\delta_{kl} + \delta_{kl'} + \delta_{k'l} + \delta_{k'l'}, \delta_{np} + \delta_{np'} + \delta_{n'p} + \delta_{n'p'}] \\ &= \text{Cov}(\delta_{kl}, \delta_{np}) + \dots + \text{Cov}(\delta_{k'l'}, \delta_{n'p'}) \end{aligned} \quad (3)$$

Each of the 16 covariances can be written as the product between one-fourth of the additive \times additive variance component (V_{AA}) and a probability that pairs of alleles are identical by descent (IBD). For example $\text{Cov}(\delta_{kl}, \delta_{np})$ in equation (3) is

$$\text{Cov}(\delta_{kl}, \delta_{np}) = \frac{1}{4} V_{AA} \text{Pr}(k \equiv n, l \equiv p) \quad (4)$$

where $\text{Pr}(k \equiv n, l \equiv p)$ is the probability that the allele k of individual I is IBD with allele n of individual J and allele l of I is IBD with allele p of J . The additive \times additive relationship coefficient ($\phi_{I,J}$) is one-fourth of the sum of the 16 IBD probabilities corresponding to the 16 covariances in equation (3). Each of these probabilities can be obtained recursively as explained below.

3. RECURSIVE COMPUTATION OF IBD PROBABILITIES

The principle underlying the recursive method for computing IBD probabilities is first described for a single locus. Then we show how to compute recursively IBD probabilities for two loci.

3.1. Single-locus computations

The basic principle underlying the recursive method is that the maternal (paternal) allele at a given locus in an individual is a copy of either the maternal or paternal allele at the same locus of its mother (father). To illustrate, consider an individual I with parents S and D . The maternal and paternal alleles of I , for example, at locus A are denoted by A_I^m and A_I^f . Based on the principle mentioned above, the probability that the maternal allele of I is IBD to the paternal allele of relative J can be written as

$$\begin{aligned} \text{Pr}(A_I^m \equiv A_J^f) &= \text{Pr}(A_I^m \leftarrow A_D^m) \text{Pr}(A_D^m \equiv A_J^f | A_I^m \leftarrow A_D^m) \\ &\quad + \text{Pr}(A_I^m \leftarrow A_D^f) \text{Pr}(A_D^f \equiv A_J^f | A_I^m \leftarrow A_D^f) \end{aligned} \quad (5)$$

where, for example, $A_I^m \leftarrow A_D^m$ is the condition that A_I^m is a copy of A_D^m . If J is not a descendent of I , equation (5) can be simplified to

$$Pr(A_I^m \equiv A_J^f) = \frac{1}{2}[Pr(A_D^m \equiv A_J^f) + Pr(A_D^f \equiv A_J^f)] \quad (6)$$

However, equation (6) is not true when J is a descendent of I , because now the IBD relationships between A_J^f and A_D^m and between A_J^f and A_D^f depend on whether A_I^m is a copy of A_D^m or of A_D^f . In order to take advantage of equation (6), it is necessary to determine whether I or J is younger, and always recurse on the younger allele. Using this procedure the recursion can be performed until both alleles in an IBD relationship are from founders. In founders, the IBD probability between two different alleles is defined to be null and is unity for an allele with itself. Several authors have used recursion to compute IBD probabilities between alleles at a single locus [6, 8, 10].

3.2. Two-locus computations

The principle used here is, as for the single-locus case, that the maternal (paternal) allele of an individual can be traced back to its mother's (father's) maternal or paternal allele. Consider computing the additive \times additive relationship coefficient ($\phi_{I,J}$) between I and J , where I is younger than J . The parents of I are denoted by S and D . Using the same notation as in the single-locus case for alleles at locus B, the probability in equation (4) can be written as

$$Pr(k \equiv n, l \equiv p) = Pr[A_I^m \equiv A_J^m, B_I^m \equiv B_J^m] \quad (7)$$

where we have assumed that k and l are the maternal alleles of I , and n and p are maternal alleles of J . For notational simplicity the probability in equation (7) will be denoted by $Pr[(A_I^m, B_I^m) \equiv (A_J^m, B_J^m)]$. Now, $\phi_{I,J}$ can be written as

$$\begin{aligned} \phi_{I,J} = & \frac{1}{4} \{ Pr[(A_I^m, B_I^m) \equiv (A_J^m, B_J^m)] + Pr[(A_I^m, B_I^m) \equiv (A_J^m, B_J^f)] \\ & + Pr[(A_I^m, B_I^m) \equiv (A_J^f, B_J^m)] + Pr[(A_I^m, B_I^m) \equiv (A_J^f, B_J^f)] \\ & + Pr[(A_I^f, B_I^f) \equiv (A_J^m, B_J^m)] + Pr[(A_I^f, B_I^f) \equiv (A_J^m, B_J^f)] \\ & + Pr[(A_I^f, B_I^f) \equiv (A_J^f, B_J^m)] + Pr[(A_I^f, B_I^f) \equiv (A_J^f, B_J^f)] \\ & + Pr[(A_I^m, B_I^f) \equiv (A_J^m, B_J^m)] + Pr[(A_I^m, B_I^f) \equiv (A_J^m, B_J^f)] \\ & + Pr[(A_I^m, B_I^f) \equiv (A_J^f, B_J^m)] + Pr[(A_I^m, B_I^f) \equiv (A_J^f, B_J^f)] \\ & + Pr[(A_I^f, B_I^m) \equiv (A_J^m, B_J^m)] + Pr[(A_I^f, B_I^m) \equiv (A_J^m, B_J^f)] \\ & + Pr[(A_I^f, B_I^m) \equiv (A_J^f, B_J^m)] + Pr[(A_I^f, B_I^m) \equiv (A_J^f, B_J^f)] \} \end{aligned}$$

Note that the pairs of alleles from I can be classified into two types: those that can be thought of as being either a recombinant gamete from I or those that can be thought of as being a non-recombinant. For example, in the first

probability the pair of alleles from I is of the non-recombinant type. This pair is a copy of either one of the two non-recombinant or one of the two recombinant gametes of D . Thus, using recursion, this probability can be written as

$$\begin{aligned}
 Pr[(A_I^m, B_I^m) \equiv (A_J^m, B_J^m)] &= \frac{(1-r)}{2} Pr[(A_D^m, B_D^m) \equiv (A_J^m, B_J^m)] \\
 &+ \frac{r}{2} Pr[(A_D^m, B_D^f) \equiv (A_J^m, B_J^m)] \\
 &+ \frac{r}{2} Pr[(A_D^f, B_D^m) \equiv (A_J^m, B_J^m)] \\
 &+ \frac{(1-r)}{2} Pr[(A_D^f, B_D^f) \equiv (A_J^m, B_J^m)] \quad (8)
 \end{aligned}$$

where r is the recombination rate between A and B . The pairs of alleles from I in the first eight probabilities are of the non-recombinant type, and can be computed as shown in equation (8). The pairs of alleles from I in the last eight probabilities are of the recombinant type. For example, in the ninth probability the pair of alleles from I is (A_I^f, B_I^f) . In this pair (A_I^f) is either the maternal or the paternal allele of D , and (B_I^f) is either the maternal or the paternal allele of S . Thus, using recursion, the ninth probability can be written as

$$\begin{aligned}
 Pr[(A_I^f, B_I^f) \equiv (A_J^m, B_J^m)] &= \frac{1}{4} Pr[(A_D^m, B_S^m) \equiv (A_J^m, B_J^m)] \\
 &+ \frac{1}{4} Pr[(A_D^m, B_S^f) \equiv (A_J^m, B_J^m)] \\
 &+ \frac{1}{4} Pr[(A_D^f, B_S^m) \equiv (A_J^m, B_J^m)] \\
 &+ \frac{1}{4} Pr[(A_D^f, B_S^f) \equiv (A_J^m, B_J^m)] \quad (9)
 \end{aligned}$$

This probability is not a function of the recombination rate between A and B because (A_I^f) and (B_I^f) are inherited independently from D and S .

In the two IBD probabilities computed above, the pair of alleles that were traced back were from the same individual. However, when recursion is continued it will be necessary to trace back alleles that belong to two different individuals. For example, if S and D are younger than J , computing the first probability in equation (9) will require tracing back alleles from S and D to alleles of their parent. General rules to compute IBD probabilities that accommodate all cases encountered in recursion are described below.

Consider computing $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)]$, where alleles in the first pair are from individuals X and Y , alleles in the second pair are from individuals W and Z , and superscripts $x, y, w, z = m$ or f . Without loss of generality, we assume that X is younger than W and Y is younger than Z . All cases encountered in recursion can be classified into two types: where (A_X^x, B_Y^y) is of the non-recombinant type (type-1); or where (A_X^x, B_Y^y) is of the recombinant type or where A_X^x and B_Y^y are from different individuals (type-2). Rules for recursion will be described separately for type-1 and type-2 cases.

3.2.1. Recursion for type-1 cases

Type-1 cases are encountered when $X = Y$ and $x = y$. Now, if the condition

$$c : X = W, x = w, Y = Z, y = z$$

is true, then $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)] = 1$; if the condition c is not true, but all four alleles are from founders then, $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)] = 0$, because different alleles in founders are assumed to be not IBD.

Suppose condition c is not true, none of the four alleles is from a founder, and alleles at one of the two loci are the same. For example, if $X = W, Y \neq Z$, $x = w = m$ and $z = f$, then $Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)]$ can be recursively computed as

$$\begin{aligned} Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)] &= \frac{(1-r)}{2} Pr[(A_P^m, B_P^m) \equiv (A_P^m, B_Z^f)] \\ &+ \frac{r}{2} Pr[(A_P^m, B_P^f) \equiv (A_P^m, B_Z^f)] \\ &+ \frac{r}{2} Pr[(A_P^f, B_P^m) \equiv (A_P^f, B_Z^f)] \\ &+ \frac{(1-r)}{2} Pr[(A_P^f, B_P^f) \equiv (A_P^f, B_Z^f)] \quad (10) \end{aligned}$$

where P is the mother of X . Here, A_X^x and A_W^w are the same allele, and, therefore, in the desired probability we have only three different alleles. As a result, only B_Z^f is not traced back to its parental alleles. Note that here and in all type-1 cases both alleles A_X^x and B_Y^y are traced back to the same parent; as a result, recombination rate enters into the formula for recursion.

Suppose condition c is not true, none of the four alleles is from a founder, and alleles at neither of the two loci are the same. For example, if $X \neq W$, $Y \neq Z$, $x = m$, $w = m$ and $z = f$, then $Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)]$ can be recursively computed as

$$\begin{aligned} Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)] &= \frac{(1-r)}{2} Pr[(A_P^m, B_P^m) \equiv (A_W^m, B_Z^f)] \\ &+ \frac{r}{2} Pr[(A_P^m, B_P^f) \equiv (A_W^m, B_Z^f)] \\ &+ \frac{r}{2} Pr[(A_P^f, B_P^m) \equiv (A_W^m, B_Z^f)] \\ &+ \frac{(1-r)}{2} Pr[(A_P^f, B_P^f) \equiv (A_W^m, B_Z^f)] \quad (11) \end{aligned}$$

where P is the mother of X . This is the same situation given by equation (8).

3.2.2. Recursion for type-2 cases

Type-2 cases are encountered when $X = Y$ and $x \neq y$ or when $X \neq Y$. Even here, if the condition

$$c : X = W, x = w, Y = Z, y = z$$

is true, $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)] = 1$. If condition c is not true and all four alleles are from founders then, $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)] = 0$. Suppose now that $X = Y = Z = W$ but $x \neq y$ and $w \neq z$. For example, if $x = m$, $y = f$, $w = f$ and $z = m$, then

$$\begin{aligned} Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)] &= Pr[(A_X^m, B_X^f) \equiv (A_X^f, B_X^m)] \\ &= Pr[(A_X^m, B_X^m) \equiv (A_X^f, B_X^f)] \end{aligned} \quad (12)$$

where (A_X^m, B_X^m) is of the non-recombinant type. Recursion can then be done as described for type-1 cases.

Suppose that condition c is not true and alleles at only one of the two loci are from founders. Then, if the alleles from the founders are not the same, $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)] = 0$; on the other hand, if the alleles from the founders are the same, recursion will be applied to the other locus. For example, if A_X^x and A_W^w are the same founder allele, $Y \neq Z$, $x = w = m$, $y = m$ and $z = f$, then $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)]$ can be recursively computed as

$$\begin{aligned} Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)] &= \frac{1}{2} Pr[(A_X^m, B_R^m) \equiv (A_X^m, B_Z^f)] \\ &+ \frac{1}{2} Pr[(A_X^m, B_R^f) \equiv (A_X^m, B_Z^f)] \end{aligned} \quad (13)$$

where R is the mother of Y . Here, A_X^x and A_W^w are the same allele, and it is not traced back to parental alleles because $X = W$ is a founder. As a result, only B_Y^m is traced back to its parental alleles. Note that here and in all type-2 cases the alleles A_X^x and B_Y^y are traced back to different parents; as a result, recombination rate does not enter into the formula for recursion.

Now suppose condition c is not true, none of the four alleles is from founders, but alleles at one of the two loci are the same. For example if, $X = W$, $Y \neq Z$, $x = w = m$, $y = m$ and $z = f$, then alleles at locus A are the same and $Pr[(A_X^x, B_Y^y) \equiv (A_W^w, B_Z^z)]$ can be written recursively as

$$\begin{aligned} Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)] &= \frac{1}{4} Pr[(A_P^m, B_R^m) \equiv (A_P^m, B_Z^f)] \\ &+ \frac{1}{4} Pr[(A_P^m, B_R^f) \equiv (A_P^m, B_Z^f)] \\ &+ \frac{1}{4} Pr[(A_P^f, B_R^m) \equiv (A_P^f, B_Z^f)] \\ &+ \frac{1}{4} Pr[(A_P^f, B_R^f) \equiv (A_P^f, B_Z^f)] \end{aligned} \quad (14)$$

where P is the mother of X and R is the mother of Y . Again, A_X^x and A_W^w are the same allele, and as a result in the desired probability we have only three different alleles. Thus, the only allele that is not traced back is B_Z^f .

Finally, suppose condition c is not true, none of the four alleles is from a founder, and alleles at neither of the two loci are the same. For example,

$X \neq W$, $Y \neq Z$, $x = m$, $y = m$, $w = m$ and $z = f$, then $Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)]$ can be recursively computed as

$$\begin{aligned} Pr[(A_X^m, B_Y^m) \equiv (A_W^m, B_Z^f)] &= \frac{1}{4} Pr[(A_P^m, B_R^m) \equiv (A_W^m, B_Z^f)] \\ &+ \frac{1}{4} Pr[(A_P^m, B_R^f) \equiv (A_W^m, B_Z^f)] \\ &+ \frac{1}{4} Pr[(A_P^f, B_R^m) \equiv (A_W^m, B_Z^f)] \\ &+ \frac{1}{4} Pr[(A_P^f, B_R^f) \equiv (A_W^m, B_Z^f)] \end{aligned} \quad (15)$$

where P is the mother of X and R is the mother of Y . Now, in the desired probability we have four different alleles, and only A_X^m and B_Y^m are traced back.

4. NUMERICAL EXAMPLES

The recursive formulae are used here to examine the effect of linkage on the additive \times additive relationship coefficient. Cockerham [2] stated that the covariance between two relatives, where one is an ancestor of the other, is not affected by linkage. Schnell [9] as well as Chang [1] showed that the previous statement is not always true. It can be shown that the covariance between a parent and its non-inbred offspring is not affected by linkage. However, the covariance between a parent and its inbred offspring, as well as between grandparent and grandoffspring, will be affected by linkage.

Consider first the covariance between parent (W) and a non-inbred offspring (X). The additive \times additive relationship coefficient ($\phi_{X,W}$) can be computed using two-locus computations. However, of the 16 probabilities, only four are non-zero because the parents of X are assumed to be unrelated. For example, if W is the mother of X , two-locus computation reduces to

$$\begin{aligned} \phi_{X,W} &= \frac{1}{4} \{ Pr[(A_X^m, B_X^m) \equiv (A_W^m, B_W^m)] \\ &+ Pr[(A_X^m, B_X^m) \equiv (A_W^m, B_W^f)] \\ &+ Pr[(A_X^m, B_X^m) \equiv (A_W^f, B_W^m)] \\ &+ Pr[(A_X^m, B_X^m) \equiv (A_W^f, B_W^f)] \} \end{aligned} \quad (16)$$

where A and B are the two loci. Note that the four probabilities in equation (16) are of type 1 and as a result we can write

$$\begin{aligned} \phi_{X,W} &= \frac{1}{4} \left[\frac{(1-r)}{2} + \frac{(r)}{2} + \frac{(1-r)}{2} + \frac{(r)}{2} \right] \\ &= \frac{1}{4} \end{aligned} \quad (17)$$

because the recombination rate cancels out in equation (17). As a result the recombination rate plays no role in the covariance between parent and offspring.

Assume now that X is inbred, its parents being full sibs. Assume also that the parents of W are unrelated. In this case all 16 probabilities in section 3.2 will have non-zero values, and $\phi_{X,W}$ is given by

$$\phi_{X,W} = \frac{1}{4} \left\{ 2 + 4 \left[\frac{(1-r)^3}{8} + \frac{(1-r)(r)^2}{2 \cdot 4} \right] + \frac{(r)}{4} \right\} \quad (18)$$

Note that in this case the recombination rate will affect the covariance between parent and offspring.

Consider now computing the additive \times additive relationship coefficient $\phi_{G,W}$ between grandparent (W) and grandoffspring (G). Let W be the maternal grandparent of G , X the daughter of W and the mother of G , and Y the father of G . Again, $\phi_{G,W}$ can be written using two-locus computation. As in the parent-offspring case, there are only four probabilities that are non-zero

$$\begin{aligned} \phi_{G,W} = \frac{1}{4} \{ & Pr[(A_G^m, B_G^m) \equiv (A_W^m, B_W^m)] \\ & + Pr[(A_G^m, B_G^m) \equiv (A_W^m, B_W^f)] \\ & + Pr[(A_G^m, B_G^m) \equiv (A_W^f, B_W^m)] \\ & + Pr[(A_G^m, B_G^m) \equiv (A_W^f, B_W^f)] \} \end{aligned} \quad (19)$$

because Y is considered to be unrelated to W . Applying equation (11) to the four probabilities in equation (19) gives

$$\begin{aligned} Pr[(A_G^m, B_G^m) \equiv (A_W^m, B_W^m)] &= \frac{(1-r)}{2} Pr[(A_X^m, B_X^m) \equiv (A_W^m, B_W^m)] \\ &+ \frac{r}{2} Pr[(A_X^m, B_X^f) \equiv (A_W^m, B_W^m)] \\ &+ \frac{r}{2} Pr[(A_X^f, B_X^m) \equiv (A_W^m, B_W^m)] \\ &+ \frac{(1-r)}{2} Pr[(A_X^f, B_X^f) \equiv (A_W^m, B_W^m)] \\ &= \frac{(1-r)}{2} * \frac{(1-r)}{2} \\ &= \frac{(1-2r+r^2)}{4} \end{aligned} \quad (20)$$

$$Pr[(A_G^m, B_G^m) \equiv (A_W^m, B_W^f)] = \frac{(r-r^2)}{4} \quad (21)$$

$$Pr[(A_G^m, B_G^m) \equiv (A_W^f, B_W^m)] = \frac{(r-r^2)}{4} \quad (22)$$

and

$$Pr[(A_G^m, B_G^m) \equiv (A_W^f, B_W^f)] = \frac{(1-2r+r^2)}{4} \quad (23)$$

As a result $\phi_{G,W}$ can be written as

$$\phi_{G,W} = \frac{1}{4} \frac{(1-r)}{2} \quad (24)$$

which is a function of the recombination rate r .

The recursive method was used to compute numerical values of the additive \times additive relationship coefficient for different relatives and different recombination rates (*table I*). As expected, when linkage is absent ($r = 0.5$) the additive \times additive coefficient is equal to the square of the additive coefficient. In the absence of linkage, the genetic covariance will be identical for certain pairs of relatives. For example, the covariance between grandparent–grandoffspring, half sibs and aunt–nephew, is equal to $0.25 V_A + 0.0625 V_{AA}$. However, if loci are linked, the genetic covariance for these pairs of relatives will not be the same (*table I*). The numerical values of the additive \times additive relationship coefficient increase as the linkage becomes tighter (r becomes smaller). As a result, when we assume that linkage is absent, the additive \times additive variance component will be overestimated.

Table I. Effect of linkage on the additive \times additive relationship coefficient between outbred relatives.

Relationship	Recombination rate (r)				
	0.1	0.2	0.3	0.4	0.5
Parent–offspring	0.25	0.25	0.25	0.25	0.25
Grandpar.–grandoff.	0.1125	0.1	0.0875	0.075	0.0625
Full sibs	0.33	0.295	0.27	0.255	0.25
Half sibs	0.1025	0.085	0.0725	0.065	0.0625
Aunt–nephew	0.0985	0.0805	0.0695	0.064	0.0625
First cousins	0.0418	0.02845	0.02057	0.0167	0.015625
Double first cousins	0.1148	0.08815	0.0724	0.06465	0.0625

Numerical values for the additive \times additive relationship coefficient for full sib and for parent–offspring relationships, after several generations of selfing, are given in *tables II* and *III*. In this design, individuals in generations i are the offspring of selfed individuals from generation $i - 1$. The numerical values in *table II* are for the relationship between the offspring of a single selfed individual from generation n . The numerical values in *table III* are for the relationship between a parent in generation n and its offspring in generation $n + 1$. Note that after t generations, if linkage is absent, the additive \times additive relationship coefficient for full sibs has the same value as the additive \times additive relationship coefficient for parent–offspring. When linkage is present the two values are different. The additive \times additive relationship coefficient of a founder with any individual obtained through selfing will be always one. The numerical value of additive \times additive relationship coefficient will converge to four, because each of the 16 probabilities converges to one, after several generations of selfing. As the number of generations of selfing increases, the effect of linkage decreases.

Table II. Effect of linkage on the additive \times additive relationship coefficient between selfed full sibs.

Generations of selfing	Recombination rate (r)				
	0.1	0.2	0.3	0.4	0.5
1	1.16	1.09	1.04	1.01	1
2	2.4756	2.3706	2.3016	2.2626	2.25
3	3.195	3.126	3.08746	3.06828	3.0625
4	3.57995	3.54284	3.52536	3.51775	3.51562
5	3.78278	3.76457	3.75736	3.75462	3.75391
6	3.88844	3.87995	3.87713	3.8762	3.87598

Table III. Effect of linkage on the additive \times additive relationship coefficient between parent and offspring obtained through selfing.

Generations of selfing	Recombination rate (r)				
	0.1	0.2	0.3	0.4	0.5
1	1	1	1	1	1
2	2.41	2.34	2.29	2.26	2.25
3	3.1681	3.1156	3.0841	3.0676	3.0625
4	3.56892	3.5393	3.52439	3.51758	3.51562
5	3.77826	3.76336	3.75707	3.75457	3.75391
6	3.88659	3.87954	3.87705	3.87619	3.87598

5. DISCUSSION

This paper describes a recursive method to compute the additive \times additive relationship coefficient for arbitrary pedigrees in the presence of linkage. The additive \times additive relationship coefficient can be described as one-fourth the sum of 16 two-locus IBD probabilities that can be recursively traced back to known values. We have given five recursive equations to compute these IBD probabilities, where the origin of the younger pair of alleles is traced back to the previous generation.

Thompson [11] gave six recursive equations to address the same problem. However her approach differs from ours. Some of these differences are briefly described below using our notation. Thompson's approach is based on recursive equations for two-locus IBD probabilities involving only the alleles of parent P in its offspring X or X' , where P is not Y , W or Z nor an ancestor of any of them. Further her recursive equations are linear combinations of one- and two-locus IBD probabilities while our equations are linear combination of only two-locus IBD probabilities and do not involve one-locus IBD probabilities.

While all the recursive equations given in the present paper are based on tracing alleles back to the previous generation, not all of Thompson's [11] equations are based on this principle. For example, consider equation (8) in

Thompson [11], which in our notation becomes

$$Pr[(A_X^x, B_Y^y) \equiv (A_{X'}^{x'}, B_Z^z)] = \frac{1}{2}Pr(B_Y^y \equiv B_Z^z) + \frac{1}{2}Pr[(A_P^m, B_Y^y) \equiv (A_P^f, B_Z^z)] \tag{25}$$

where alleles A_X^x and $A_{X'}^{x'}$ are from parent P . This equation is obtained by observing that alleles A_X^x and $A_{X'}^{x'}$ will be the same with probability one half; if the two alleles are the same, then the two-locus IBD probability on the left hand side of equation (25) becomes the one-locus probability $Pr(B_Y^y \equiv B_Z^z)$; if the two alleles are not the same, the two-locus IBD probability is $Pr[(A_P^m, B_Y^y) \equiv (A_P^f, B_Z^z)]$.

In contrast, we trace back the alleles A_X^x and B_Y^y to the previous generation. Suppose $x = x' = m$ and $y = m$, then the two-locus IBD probability on the left hand side of equation (25) becomes

$$\begin{aligned} Pr[(A_X^x, B_Y^y) \equiv (A_{X'}^{x'}, B_Z^z)] &= \frac{1}{4}Pr[(A_P^m, B_R^m) \equiv (A_{X'}^m, B_Z^z)] \\ &+ \frac{1}{4}Pr[(A_P^m, B_R^f) \equiv (A_{X'}^m, B_Z^z)] \\ &+ \frac{1}{4}Pr[(A_P^f, B_R^m) \equiv (A_{X'}^m, B_Z^z)] \\ &+ \frac{1}{4}Pr[(A_P^f, B_R^f) \equiv (A_{X'}^m, B_Z^z)] \end{aligned} \tag{26}$$

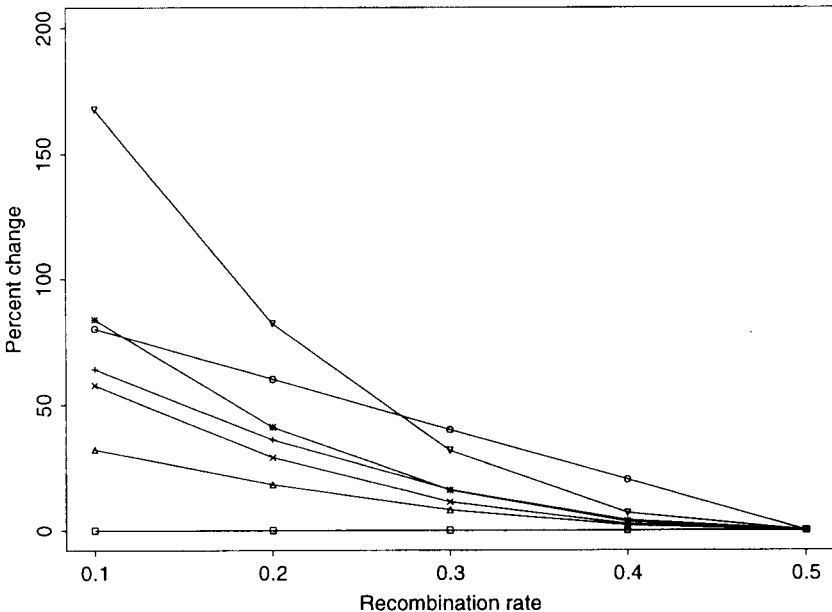


Figure 1. Percentage change of the additive by additive covariance as a function of the recombination rate for different outbred relatives. □ parent-offspring; △ full sibs; × aunt-nephew; + half sibs; ○ grandparent-grandoffspring; * double first cousins; ▽ first cousins.

where P is the mother of X and X' , and R is the mother of Y . This is clearly different from equation (25). Although these two approaches use different recursive equations the final results for the IBD probabilities are identical. This demonstrates that there is more than one approach to compute IBD probabilities by recursion.

Based on the recursive method described in this paper, numerical values of the desired coefficient for selfed or outbred individuals are given. Using the computer program available at <http://www.public.iastate.edu/~rohan>, the effect of linkage on the additive by additive covariance can be examined for any type of relationship. This would be useful to examine the potential bias in covariance estimates when linkage is ignored. *Figure 1* gives the rate of change in the additive by additive covariance for several relationships. Relationships with flatter curves are less biased by linkage.

Other applications are in linkage analysis and the identification of pairwise relationships based on data at linked loci [11].

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