MENDELIAN CORRELATIONS BETWEEN RELATIVES — EQUATIONS DEFINING BI-UNIKINS UNIKINS AND BIKINS AND THEIR APPLICATIONS

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SYNOPSIS

The established order of 'unilineal' relatives has 2 relationships that do not satisfy the criteria of its own classification when there is consanguinity in the pedigree. They are the child to parent relationship and the nephew or neice to uncle or aunt relationship. We have named them "bi-unikins" to distinguish from the rest of the relationships in the unilineal order, which are now designated as "unikins". Both the bi-unikins and the unikins have been resolved by one set of equations appropriately called the bi-unikin equations, which will define the Mendelian probabilities of 2 genes, one gene and zero gene in common between the kins with and without consanguinity considerations.

Members of the 'bilineal' order of relatives have long been separately defined by their individual bilineal constants, and even so consanguinity considerations have not been integrated into them. Here we have one set of equations for all, the "bikin" equations.

The bi-unikin and bikin equations will allow systematic algorithms for computer programmes to be written for a variety of application examples in genetic counselling.

INTRODUCTION

Genotypic and phenotypic correlations between kins or genetic relatives are (I) fundamental to the clerking of relevant family history for (a) the ascertainment of familial tendencies, (b) the estimation of risks of genetic traits from ancestral, descendant and collateral members of the pedigree, (c) the quantitative placement of clinical test data in perspective; and (II) essential to an understanding of specific allelic polymorphisms eg. the statistics of tissue graft matchings and questions of graft compatibility between relatives with and without inbreeding in the family. It is therefore unfortunate that a subject of such magnitude had been largely concealed from the medical fraternity, willy-nilly by the web of algebraic manipulations (1) and tables of seemingly abstract and incomprehensible p's and q's (2), since as far back as 1918. In 1934 Sewall Wright had brilliantly reduced much of the calculations to simple counts of the numbers of sticks or 'paths' between squares and circles in pedigree diagrams (3) to give the proportion of genes in common, r, but left aside considerations of gene mutations and frequency distributions in the population. Then in combination with a masterly division of genetic relationships into 'unilineal' and 'bilineal' orders by Cotterman in 1941 (4) and the I.T.O. matrices of Li and Sacks (5) we have a reversed parallel of Fisher's marriage of Mendelian principles with quantitative Galtonian genetics, conditional probabilities which relate the probabilities of a relative being of a particular genotype or phenotype with the other relative's state of nature, the frequency distribution in the population and the mutation rate. This clever window in the darkness however have the following faults: (a) the existing equations that define the coefficients of each kinship for the Mendelian probabilities of whether they have in common both genes of a particular locus, one gene of that locus or no gene at all, when it is a unilineal kinship and when a bilineal kinship, do not include any means for dealing with consanguinity in the relevant parents; (b) the parent/child kinship and the nephew or neice to aunt or uncle kinship which have been traditionally defined as unilineal are in fact bilineal given the possibility of genetically related parents; and (c) while it is possible to derive from first principles the relevant coefficients needed to deal with inbred family trees, much is left to the individual ingenuity of the genetic counsellor. In short, there is no systematic approach. Computer programs that are supposed to compute the genotypic and phenotypic correlations between kins (6) omit pedigrees with inbreeding, because the equations required for a systematic algorithm have not been derived, and as such are of limited application in both medicine and animal husbandry.

I present here the equations that will address these problems and subdivide the 'unilineal' order into (a) bi-unikins, and (b) unikins, but unify the 'bilineal' order as bikins, which are justified by their respective Mendelian coefficients: CI, CT and CO. My kinship classification thus follows the criteria of the lineal classification, but points out the discrepancies of the order.

RESULTS AND DISCUSSION

BI-UNIKINS

Table 1 gives the usual textbook classification of the 'unilineal' relatives with $CI = 0$, $CT = 2r$ and $CO = 1 - 2r$; where CI is the coefficient for the I matrix of the I.T.O. (5) or the probability of two genes in common, CT is the coefficient for the T matrix or the probability of one gene in common, and CO is the coefficient for the O matrix or the probability of no gene in common. The genotypic correlation coefficient, r, is the proportion of genes in common between kins and perhaps more easily derived from the formula $(\frac{1}{2})^{\text{degree of kinship}}$, than from Wright paths. These unilineal coefficients are correct only when there is no possibility of the parents having genes in common, and therefore conceptually limits all vectors to the same conditions when multiplied with these coefficients. I present the following 'bi-unikin' equations that do not have such limitations:

$$CI = r^2gb$$

$$CT = \tfrac{1}{2}r(4+g) - 2r^2gb$$

$$CO = 1 - \tfrac{1}{2}r(4+g) + r^2gb$$

where, g = genes in common in parents of the consultand relative

b = 1 for bi-unikins, viz. parent/child and nephew or neice/uncle or aunt

b = 0 for unikins viz. truly unilineal kins who can at most have one gene in common irrespective of whether the relevant parents are inbred or not.

TABLE 1
CLASSICAL DEFINITION OF UNILINEAL RELATIVES

Degree of Relationship	Coefficient of Relationship (proportion of genes in common)	Name of relatives	Coefficient for 2 genes, 1 gene or zero gene in common (probability of 2 genes, 1 gene or no gene in common)		
			CI	CT	CO
first	$(\frac{1}{2})^1$	parent/child	0	1	0
second	$(\frac{1}{2})^2$	uncle or aunt/nephew or neice. nephew or neice/uncle or aunt grandparent/grandchild, half sibs	0	½	½
third	$(\frac{1}{2})^3$	first cousins, great grandparent/great grandchild uncle/nephew once removed	0	¼	¾
fourth	$(\frac{1}{2})^4$	first cousins once removed	0	1/8	7/8
fifth	$(\frac{1}{2})^5$	second cousins	0	1/16	15/16

(see (7) & (8) for reference)

Since g can have a value of 2, 1 or zero, there are three sets of CI, CT and CO values. The bi-unikin equations will therefore give correlations between bi-unikins conditional upon the parents of the consultand kin having identical genotype at the particular locus, one of two genes of the locus being the same, and none of their genes at the locus being the same, respectively. Thus, (see figs. 1 & 2) show that the assertion of "uncle/nephew transition matrix is also the nephew/uncle matrix" (5) is incorrect with inbreeding considerations. Here I distinguish the nephew/uncle relationship as bi-unikinship, from the uncle/nephew relationship which is strictly a unilineal or unikin relationship. Thus by the unikin equations, we have fig. 3.

parent and child correlation coefficients:

Fig. 1			CI	CT	CO
$BU_{child/parent}$ =	when parents of child have in common:	2 genes	2/4	2/4	0
		1 gene	1/4	3/4	0
		0 gene	0	4/4	0

(see Appendix A for proof of the BU matrix that relates a child with parent). See also Table 2.

Similarly, the nephew or neice as the consultand kin, correlating with uncle or aunt, may be very quickly defined with the bi-unikin equations: (see Fig. 2)

nephew and uncle correlation coefficients:

Fig. 2			CI	CT	CO
$BU_{nephew/uncle}$ =	when parents of nephew have in common:	2 genes	2/16	8/16	6/16
		1 gene	1/16	8/16	7/16
		0 gene	0	8/16	8/16

(see Appendix B for proof of the BU matrix that relates a nephew or neice as the consultand kin with uncle or aunt)

Fig. 3			CI	CT	CO
$BU_{uncle/nephew}$ =	parents of have in common:	2 genes	0	6/8	2/8
		1 gene	0	5/8	3/8

(see Appendix C for proof of the BU matrix that relates the uncle as the consultand kin, to a nephew)

Bi-unikinis are therefore those classically defined 'unilineal' relatives who become 'bilineal', (ie. could have a chance of identical genotype at a locus, which is sharing 2 genes in common), given that the parents of the consultand kin could have genes in common to whatever extent, (ie. genetically related).

UNIKINS

I shall now define the 'unikins' as those kins who at most would share only one gene in commn irrespective of whether the parents of the consultand kin are consanguineous or not, and whose Mendelian coefficients for 2 genes, one gene and zero gene in common are given by the bi-unikin equations with the 'b' factor = 0. Thus the 'unikin' equations are simply a reduced version of the 'bi-unikin' equations, when b = 0:

$$CI = 0$$

$$CT = \tfrac{1}{2}r(4 + g)$$

$$CO = 1 - \tfrac{1}{2}r(4 + g)$$

It is obvious then that unikins will never have 2 genes in common even if the parents of the consultand kin were identical twins, in contradistinction to the aforementioned bi-unikin relationships. We shall now Compare this $BU_{uncle/nephew}$ with the previous $BU_{nephew/uncle}$ and note that they are fundamentally different, (fig 3 cf. fig. 2)

BIKINS

Siblings are the most important example of bilineal kinships since apart from identical twins, they represent the closest kinship correlation, which are also significantly affected by consanguineous parents. The Mendelian coefficients for siblings, classically given as $CI = \tfrac{1}{4}$, $CT = 2(r - \tfrac{1}{4})$ and $CO = 1 - 2r + \tfrac{1}{4}$, will not show the influence of inbred parents, and in fact correct only when the parents are assumed to have zero genes in common. My 'bikin' equations are applicable with or without consanguinity in the parents of the siblings:

$$CI = (r^2 + r^2g)(\tfrac{1}{2})^{g/g}$$

$$CT = 2r - (2r^2 + 2r^3)(\tfrac{1}{2})^{g/g}$$

$$CO = 1 - 2r + r^2.r^{g/g}$$

Thus knowing that siblings are first degree relatives, the coefficient of relationship, $r = (\tfrac{1}{2})^1$, we could very quickly write:

$B_{siblings}$ = Parents of have in common:

	CI	CT	CO
2 genes	3/8	4/8	1/8
1 gene	2/8	5/8	1/8
0 gene	2/8	4/8	2/8

(see appendix D for proof of the B matrix that relates two siblings). Here g/g is defined as zero if g = zero,

TABLE 2
DEFINITION OF BI-UNIKINS, UNIKINS AND BIKINS

Kinship	Consultand kin	The other kin	Common genes parents of consultand kin	Coefficient for 2 genes, 1 gene or zero gene in common*		
				CI	CT	CO
Bi-unikin first degree	child	parent	g = 2	½	½	0
			g = 1	¼	¾	0
			g = 0	0	1	0
Bi-unikin second degree	nephew or neice	uncle or aunt	g = 2	1/8	1/2	3/8
			g = 1	1/16	1/2	7/16
			g = 0	0	1/2	1/2
Unikin second second	uncle or aunt, half sib, grandchild	nephew or neice, half sib, grandparent	g = 2	0	3/4	1/4
			g = 1	0	5/8	3/8
			g = 0	0	1/2	1/2
Unikin third degree	first cousin, great grandchild second degree unikin once removed	first cousin, great grandparent, second degree unikin once removed	g = 2	0	3/8	5/8
			g = 1	0	5/16	11/16
			g = 1	0	1/4	3/4
Unikin fourth degree	first cousin once removed, third degree unikin once removed	first cousin once removed, third degree unikin once removed	g = 2	0	3/16	13/16
			g = 1	0	5/32	27/32
			g = 0	0	1/8	7/8
Unikin fifth degree	second cousin, fourth degree unikin once removed	second cousin, fourth degree unikin once removed	g = 2	0	3/32	29/3
			g = 1	0	5/64	59/64
			g = 0	0	1/16	15/16
Unikin sixth degree	second cousin once removed, fifth degree unikin once removed	second cousin once removed, fifth degree unikin once removed	g = 2	0	3/64	61/64
			g = 1	0	5/128	123/128
			g = 0	0	1/32	31/32
Unikin seventh degree	third cousin, sixth degree unikin once removed	third cousin, sixth degree unikin once removed	g = 2	0	3/128	125/126
			g = 1	0	5/256	251/256
			g = 0	0	1/64	63/64
Bikin zero degree	monozygotic twin	monozygotic twin	g = 2	1	0	0
			g = 1	1	0	0
			g = 0	1	0	0
Bikin first degree	sibling	sibling	g = 2	3/8	1/2	1/8
			g = 1	1/4	5/8	1/8
			g = 0	1/4	1/2	1/4
Bikin second degree	double first cousin	double first cousin	g = 0 imperative	1/16	6/16	9/16

(*defined by bi-unikin, unikin and bikin equations)

Identical twins have a coefficient of relationship, $r = (\frac{1}{2})^0 = 1$ and thus will always have 2 genes in common for a locus irrespective of whether the parents are genetically related or not. The other, occassionally mentioned, bilineal relative is the double first cousin which by definition cannot have genetically related parents, as such. Nevertheless, given that $g = 0$, and the coefficient of relation of double first cousins is $(\frac{1}{2})^2 = \frac{1}{4}$, since they are second degree relatives, the bikin equations given here will also define CI, CT and CO for double first cousins, which however are usually defined as $CI = 1/16$, $CT = 2(r - 1/16)$ and $CO = 1 - 2r + 1/16$. Although the results given by the bikin equations are numerically identical to the usual calculations for double first cousins, they are conceptually important in unifying the bikins as a group, apart from being the only way to obtain the full set of Mendelian coefficients for siblings without memorizing table 2 or reproofing from first principles.

APPLICATION EXAMPLES

Now if we ask about the compatibility of tissue grafts between siblings in terms of the Major Histocompatibility Complex in chromosome 6p21, then (a) the answere must be in the third row of the B matrix for siblings if the parents are assumed to be genetically unrelated, ie. with $g = 0$, the probability of both haplotypes in common = CI which is 1/4, and the probability of one haplotype in common = CT which is 1/2, while the probability of no haplotype in common or incompatible with respect to the MHC = CO which is 1/4; however, (b) if the parents are first cousins, then the answer is obtained by a premultiplication of the B matrix for siblings with the likelihood of first cousins sharing 2 genes, 1 gene or zero gene in common, viz.

$$\begin{array}{lllll} & & ci & ct & co \\ L_{\text{first cousins}} & = & [0 & 2\times(\frac{1}{2})^3 & 1 - 2x(\frac{1}{2})^3] \\ & = & [0 & 1 & 3] \end{array}$$

and therefore, L.B becomes

$$[0 \quad 1 \quad 3] \begin{bmatrix} 3 & 4 & 1 \\ 2 & 5 & 1 \\ 2 & 4 & 2 \end{bmatrix} = \begin{array}{ccc} CI & CT & CO \\ [8 & 17 & 7] \end{array} = \text{coefficients with consanguinity weightage}$$

ie. $CI = 8/32$, $CT = 17/32$ and $CO = 7/32$ on normalisation. That means the probability of two haplotypes in commoin remains at 1/4, but the probability of one haplotype in common is now 17/32 and the probability of no haplotype in commoin is 7/32.

A more involved usage of CTI, CT and CO values could be in qualifying the I.T.O. matrices to give the conditional probabilities of the 3 states of nature, viz. AA, Aa and aa, separately or in combination, as specified by Li and Sacks (5). By first deriving the coefficients with consanguinity weightage, the resultant conditional probabilities too will have the same weightage. In this way we have an enhancement of the Li and Sacks method. This enhancement is practicable only because the bi-unikin and bikin equations have been derived. The calculation of the weighted Mendelian coefficients from first principles in pedigrees with several parts inbred and several generations, is simply too inhibitive for most. However, used in Bayesian risk estimatioIns (9) the enhanced Li and Sacks technique will provide specific prior probability with consanguinity consideratioins by formula, whereupon the algorithm for consanguinity weighted prior probability risks could be written for computer programmes (6).

Clinical tests unless absolute should not define an individual in isolation but perhaps on quantitative integration by vector multiplication with prior probability, and if available with posterior probability, could be better evaluated.

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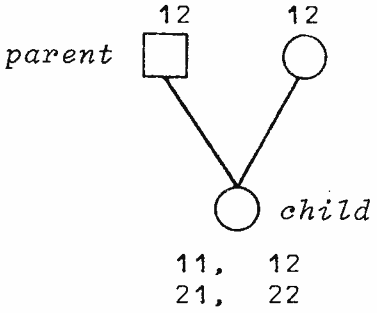
Appendix A :

(I) Consultand kin = child, and her parents have two genes in common



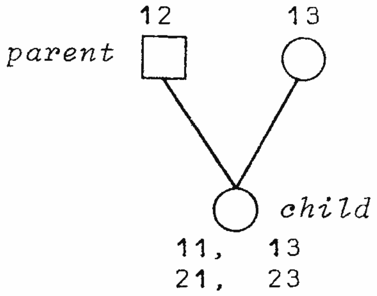
parents have two
genes in common
viz. "1" and "2"

	CI	CT	CO
Thus given parent = 12,	2/4	2/4	0

This gives the first row of the BU matrix relating the child to her parent.

Appendix A

(II) Consultand kin = child, and her parents have one gene in common



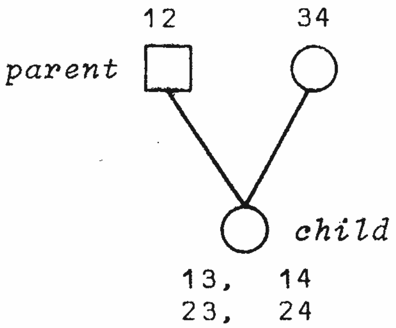
parents have one
gene in common
viz. "1" only

	CI	CT	CO
Thus given parent = 12,	$\frac{1}{4}$	$\frac{3}{4}$	0
parent = 13,	$\frac{1}{4}$	$\frac{3}{4}$	0
NORMALISED:	$\frac{1}{4}$	$\frac{3}{4}$	0

This gives the second row of the BU matrix relating the child to her parent.

Appendix A

(III) Consultand kin = child, and her parents have no gene in common



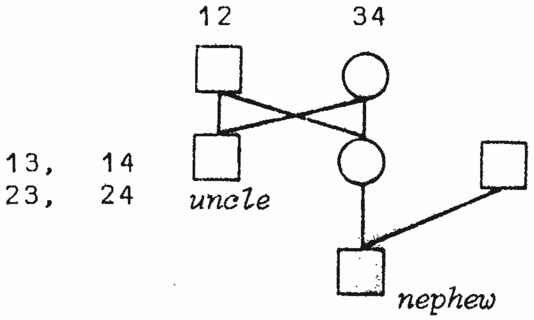
parents have zero gene in common

	CI	CT	CO
Thus given parent = 12,	0	4/4	0
parent = 34,	0	4/4	0
NORMALISED:	0	1	0

This gives the third row of the BU matrix relating the child to her parent.

Appendix B

(I) Consultand kin = nephew, and his parents have two genes in common



parents of nephew have two genes in common

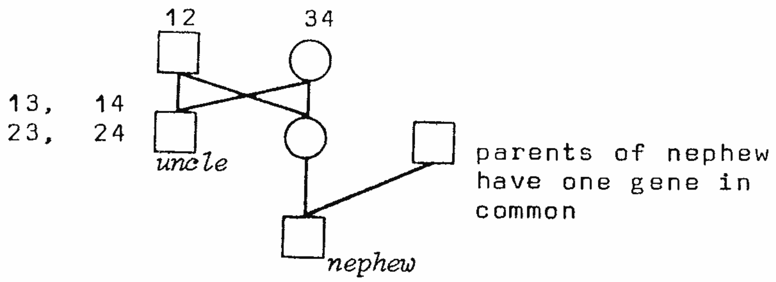
parental mating:	13 x 13	14 x 14	23 x 23	24 x 24
Nephew's genotypes:	11, 13 31, 33	11, 14 41, 44	22, 23 32, 33	22, 24 42, 44

	CI	CT	CO
Thus given uncle = 13,	2/16	8/16	6/16
uncle = 14,	"	"	"
uncle = 23,	"	"	"
uncle = 24,	"	"	"
NORMALISED:	2/16	8/16	6/16

This gives the first row of the BU matrix relating the nephew to the uncle.

Appendix B

(II) Consultand kin = nephew, and his parents have one gene in common



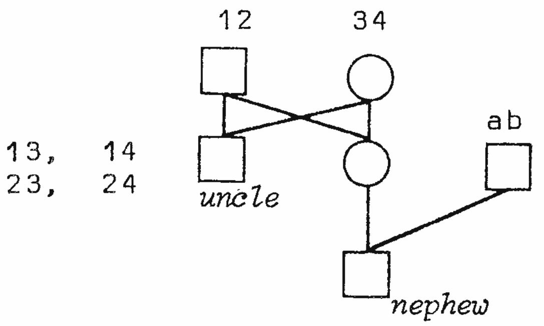
Parental mating:	13x1a	13x3a	14x1a	14x4a	23x2a	23x3a	24x2a	24x4a
Nephew's genotypes:	11,1a 31,3a	13,1a 33,3a	11,1a 41,4a	14,1a 44,4a	22,2a 32,3a	23,2a 33,3a	22,2a 42,4a	24,2a 44,4a

Thus given uncle = 13,	2/32	16/32	14/32
uncle = 14,	"	"	"
uncle = 23,	"	"	"
uncle = 24,	"	"	"
NORMALISED:	2/32	16/32	14/32

This gives the second row of the BU matrix relating the nephew to the uncle.

Appendix B

(III) Consultand kin = nephew, and his parents have no gene in common



parents of nephew
have zero gene in
common

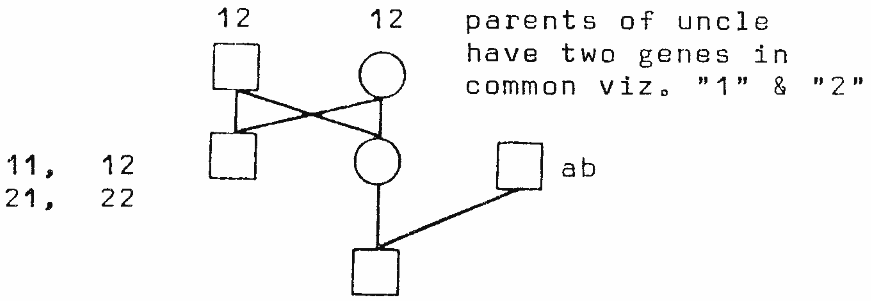
Parental mating:	13 x ab		14 x ab		23 x ab		23 x ab	
Nephew's Genotypes:	1a, 3a,	1b 3b	1a, 4a,	1b 4b	2a, 3a,	2b 3b	2a, 3a,	2b 3b

	CI	CT	CO
Thus given uncle = 13,	0	10/16	6/16
uncle = 14	0	6/16	10/16
uncle = 23	0	10/16	6/16
uncle = 24	0	6/16	10/16
NORMALISED:	0	1/2	1/2

This gives the first row of the BU matrix relating the nephew to the uncle.

Appendix C

(I) Consultand kin = uncle, and his parents have two genes in common



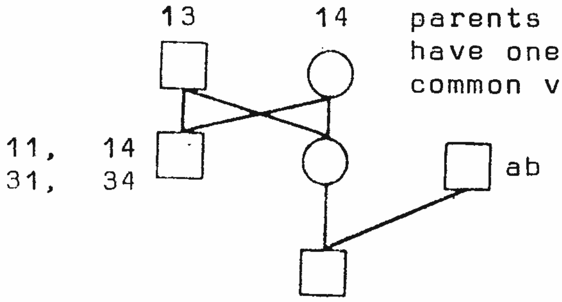
mating types of parents of nephew:	11 x ab	12 x ab	21 x ab	22 x ab
Nephew's genotypes	1a, 1b 1a, 1b	1a, 1b 2a, 2b	2a, 2b 1a, 1b	2a, 2b 2a, 2b

	CI	CT	CO
Thus given uncle = 11,	0	8/16	8/16
uncle = 12,	0	16/16	0
uncle = 21,	0	16/16	0
uncle = 22,	0	8/16	8/16
NORMALISED:	0	3/4	1/4

This gives the first row of the BU matrix relating the uncle to the nephew

Appendix C

(II) Consultand kin = uncle, and his parents have one gene in common



parents of uncle
have one gene in
common viz. "1"

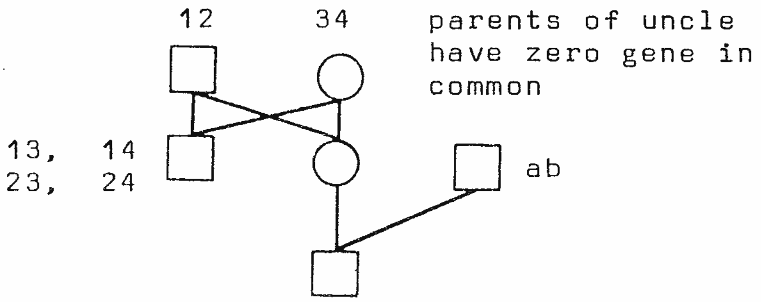
mating types of parents of nephew:	11 x ab	14 x ab	31 x ab	34 x ab
Nephew's genotypes	1a, 1b 1a, 1b	1a, 1b 4a, 4b	3a, 3b 1a, 1b	3a, 3b 4a, 4b

	CI	CT	CO
Thus given uncle = 11,	0	8/16	8/16
uncle = 14,	0	12/16	4/16
uncle = 31,	0	12/16	4/16
uncle = 34,	0	8/16	8/16
NORMALISED:	0	5/8	3/8

This gives the second row of the BU matrix relating the uncle to the nephew.

Appendix C

(III) Consultand kin = uncle, and his parents have no gene in common



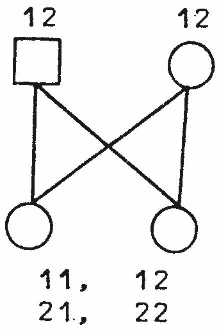
mating types of parents of nephew:	13 x ab	14 x ab	23 x ab	24 x ab
Nephew's genotypes	1a, 1b 3a, 3b	1a, 1b 4a, 4b	2a, 2b 3a, 3b	2a, 2b 4a, 4b

Thus given uncle = 13,	0	8/16	8/16
uncle = 14,	0	8/16	8/16
uncle = 23,	0	8/16	8/16
uncle = 24,	0	8/16	8/16
NORMALISED:	0	1/2	1/2

This gives the third row of the BU matrix relating the uncle to the nephew

Appendix D

(I) Consultand kin = one sibling, and her parents have two genes in common



parents of siblings have two genes in common viz. "1" & "2"

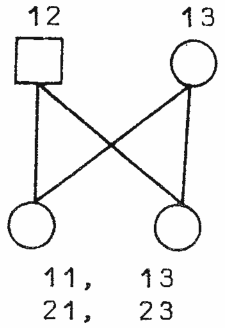
genotypes of siblings

	CI	CT	CO
Thus given one sibling = 11,	1/4	2/4	1/4
one sibling = 12,	2/4	2/4	0
one sibling = 21,	2/4	2/4	0
one sibling = 22,	1/4	2/4	1/4
NORMALISED:	3/8	1/2	1/8

This gives the first row of the B matrix relating one sibling to another.

Appendix D

(II) Consultand kin = one sibling, and her parents have one gene in common



parents of siblings
have one gene
in common viz. "1"

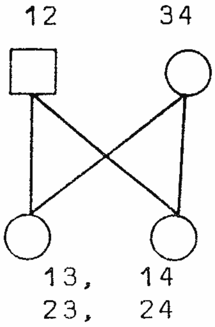
genotypes of
siblings

Thus given one sibling = 11,	1/4	2/4	1/4
one sibling = 13,	1/4	3/4	0
one sibling = 21,	1/4	3/4	0
one sibling = 22,	1/4	2/4	1/4
NORMALISED:	1/4	5/8	1/8

This gives the second row of the B matrix relating one sibling to another.

Appendix D

(III) Consultand kin = one sibling, and her parents have no gene in common



parents of siblings
have zero gene
in common

genotypes of
siblings

	CI	CT	CO
Thus given one sibling = 13,	1/4	2/4	1/4
one sibling = 14,	1/4	2/4	1/4
one sibling = 23,	1/4	2/4	1/4
one sibling = 24,	1/4	2/4	1/4
NORMALISED:	1/4	1/2	1/4

This gives the third row of the B matrix relating one sibling to another.