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Calculation of Likelihood Ratio Y/X in Diagnosis of Paternity Using Computer Methods

Minoru Asano, Kayoko Minakata, and Hideki Hattori

Department of Legal Medicine, Hamamatsu University, School of Medicine, 3600 Handa-Cho, Hamamatsu 431–31, Japan

Summary. A new computational method using a Monte Carlo technique is described for the calculation of plausibility of paternity in blood group systems.

In this study gene frequencies of a blood group system are simulated by the range of the seven digit random numbers. By using a Monte Carlo method, four random numbers are generated and converted into paternal and maternal genotypes. Then the genotype of the child is determined according to the law of inheritance, and finally genotypes of the father, mother and child are converted into phenotypes.

Repeating this process more than one hundred thousand times, the phenotypic frequencies of child-mother-father combinations (trio) and the likelihood ratio of paternity in any blood group system are calculated for all phenotypic combinations of the trios.

This method is much easier than methods reported previously, and is sufficiently accurate.

Key words: Paternity likelihood ratio – Rh blood groups, computer program

Zusammenfassung. Aus siebenstelligen Zufallszahlen im Bereich der Genfrequenzabstände des Rh-Systems werden die Genfrequenzen simuliert und daraus mit Hilfe eines Monte-Carlo-Verfahrens sukzessive über Schätzungen der Geno- und Phänotypen die zur Bildung des Likelihood-Quotienten nach Essen-Möller erforderlichen Größen Y und X und der Quotient Y/X selbst ermittelt. Der Vergleich mit den aus den tatsächlich beobachteten Frequenzen berechneten Größen (Y und X) zeigt, daß die Differenzen so gering sind, daß man die so geschätzten Größen ohne Bedenken für die biostatistische Vaterschafts-Begutachtung verwenden kann.

Das Verfahren ist auf andere Systeme anwendbar und viel schneller als die herkömmlichen Berechnungsmethoden.

Schlüsselwörter: Vaterschaft, Wahrscheinlichkeitsberechnung – Rh-Gruppen, Computer Programm

Offprint requests to: Prof. Dr. M. Asano (address see above)

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Table 1. Indices of haplotypes and the haplotype frequencies in Rh system

Index of haplotype	Haplotype	Haplotype frequency	Partition of random number
1	cde	0.40894	$0 < r \leqq 0.40894$
2	CDe	0.40703	$0.40894 < r \leqq 0.81597$
3	cDE	0.13638	$0.81597 < r \leqq 0.95235$
4	cDe	0.01750	$0.95235 < r \leqq 0.96985$
5	$C^{W}De$	0.01251	$0.96985 < r \leqq 0.98236$
6	Cde	0.01164	$0.98236 < r \leqq 0.99400$
7	cdE	0.00450	$0.99400 < r \leqq 0.99850$
8	CDE	0.00097	$0.99850 < r \leqq 0.99947$
9	$C^{W}de$	0.00036	$0.99947 < r \leqq 0.99983$
10	CdE	0.00014	$0.99983 < r \leqq 0.99997$
11	$C^{W}DE$	0.00003	$0.99997 < r \leqq 1.00000$

The haplotype $C^{W}dE$ is neglected because its haplotype frequency is less than 10^{-5}

A number of studies have been made of the probability of paternity concerning blood groups [1, 2, 3, 4]. The essential value for the calculation of paternity is Y/X, where Y stands for the frequency of corresponding phenotype of a man among normal male population, i. e. non-father, and X for the frequency of corresponding phenotype of the true father for a given child-mother combination [3]. This quantity Y/X is called "critical value" or "likelihood ratio". These quantities X and Y/X are usually expressed as algebraic formulas of corresponding gene frequencies. In cases of blood groups such as ABO, MN and P the number of genetically distinct characters is small, so that the derivations of these formulas are rather easy for all combinations of trios. However, in systems having many genetically distinct characters such as Rh and HL-A, a great number of formulas must be derived for all combinations of trios [5, 6]. In order to avoid these tedious derivations we wrote a computer program which gives the values of X and Y/X for all combinations of trios. The only necessary input data are gene frequencies and a translation matrix for the conversion of genotype into phenotype. The program is based on a Monte Carlo method in which random numbers are generated and converted into genotypes of father and mother. The genotypes of the parents and their children are converted into the phenotypes. Finally, the probabilities of various phenotypes (phenotypic frequencies of child-mother-father combinations, those of child-mother combinations, and those of father) are derived. Using these phenotypic frequencies the probability of paternity is calculated for all the combinations of trios.

Description of the Computer Program

Index Coding

The structure of a blood group system with one locus is expressed by the number of its genes (NG) and the number of its phenotypes (NP). We will characterize genes by indices i and j ($1 \leqq i, J \leqq NG$) and code a genotype by the matrix (i, j) and phenotype by indices K, M, V ($1 \leqq K, M, V \leqq NP$) (See Tab. 1 and 2). In the present calculation haplotypes and haplotypic frequencies for the system with several linked loci are treated in the same way as genes and gene frequencies for a system with one locus. The frequency of a gene or a haplotype is represented by the range of random numbers.

Table 2. Indices of phenotype and genotypes in Rh system

Index of phenotype	Phenotype	Genotype	Index of genotype
1	ccddee	(cde/cde)	(1,1)
2	ccddEe	(cde/cdE)	(1,7), (7,1)
3	ccddEE	(cdE/cdE)	(7,7)
4	ccDee	(cde/cDe)	(1,4), (4,1)
		(cDe/cDe)	(4,4)
5	ccDEe	(cde/cDE)	(1,3), (3,1)
		(cDE/cDe	(3,4), (4,3)
		(cDe/cdE)	(4,7), (7,4)
.	.	.	.
.	.	.	.
.	.	.	.
29	C^WDEe	(C^WDE/C^WDe)	(5,11), (11,5)
.	.	.	.
.	.	.	.
.	.	.	.

Method of Calculation

Actual calculation is carried out as follows (see flowchart of the program).

1. Generation of four genes: By use of a Monte Carlo method, four seven-digit uniformly distributed random numbers are generated. These four numbers are converted into indices of haplotypes or genes (i, j, k, l) (Table 1).

2. The above mentioned four genes determine the genotypes of father (i, j) and mother (k, l). Then the expression of genotypes of the children are determined as the following four types, (i, k), (j, k), (i, l), (j, l).

3. Generation of phenotypes: These genotypes are converted into corresponding phenotypes by using a translation matrix. The concept of dominant and recessive genes is implied in this classification of the genotype. The phenotype of child, mother and father are designated by K, M and V, respectively ($1 \leqq K, M, V \leqq NP$).

4. Repetition of the steps from 1 to 3: By repeating the basic steps from 1 to 3 more than 10^5 times depending on the desired accuracy, and by normalizing the phenotypic frequencies (once out of 10^5 times is counted as 0.00001), the following phenotypic frequencies can be obtained.

a) phenotypic frequency of father P1 (V),
b) phenotypic frequency of mother-father combination P2 (M, V),
c) phenotypic frequency of child-mother-father combination, trio P3 (K, M, V).

In calculating phenotypic frequencies of trios, the quantity P3 is multiplied by 1/4, since each parent produces four distinct children with equal prababilities.

5. Calculation of phenotypic frequency of child-mother combination: Summing up phenotype frequencies of trios P3 (K, M, V) for all phenotypes of father, V, the phenotypic frequency of child-mother combination P4 (K, M) is obtained.

6. Calculation of Y/X: Y, X and Y/X can be evaluated according to the following formulas for all phenotype combinations of trios.

$Y(V) = P1(V)$

$X(K, M, V) = P3(K, M, V) / P4(K, M)$ for $P4(K, M) \neq 0$

$Y/X(K, M, V) = P1(V) \times P4(K, M) / P3(K, M, V)$ for $P3(K, M, V) \neq 0$

7. Tabulation: P1 (V), P2 (M, V) P3 (K, M, V), P4 (K, M) and Y/X (K, M, V) are printed out for any desired combinations of the phenotypes.

Table 3. Phenotype frequencies in Rh system (%)

Phenotype-number	(1)	(2)
1	16.69	16.72
2	0.35	0.39
3	< 0.01	< 0.01
4	1.51	1.46
5	11.65	11.65
6	2.02	1.98
7	0.96	0.95
8	0.03	0.02
10	34.70	34.76
11	11.89	11.87
12	0.02	0.03
13	0.01	0.01
16	17.55	17.51
17	0.05	0.09
19	0.05	0.03
22	1.04	1.07
23	0.35	0.36
24	< 0.01	< 0.01
25	< 0.01	< 0.01
28	1.13	1.09
29	0.01	0.01

(1) those of the present calculation using a Monte Carlo simulation
(2) those calculated theoretically

Table 4. Likelihood ratio Y/X in Rh system

Phenotype combination				
C	M	F	(1)	(2)
1	1	1	0.4083	0.4089
1	1	4	0.8090	0.8354
1	1	5	0.8513	0.8541
1	1	10	0.8570	0.8539
1	4	10	0.8615	0.8539
1	5	5	0.8536	0.8541
1	5	10	0.8538	0.8539
1	10	10	0.8547	0.8539
4	1	4	0.0342	0.0343
4	1	10	0.8381	0.8303
4	4	10	0.8575	0.8519
4	10	10	0.8403	0.8418
5	1	5	0.2722	0.2731
5	1	6	0.1450	0.1407
5	1	11	0.2835	0.2835
5	5	5	0.5642	0.5633
5	5	6	0.5722	0.5797
5	5	10	1.1304	1.1127
5	5	11	1.1470	1.1159
5	6	10	0.8531	0.8529
5	10	11	0.2832	0.2835
6	5	5	0.2848	0.2817

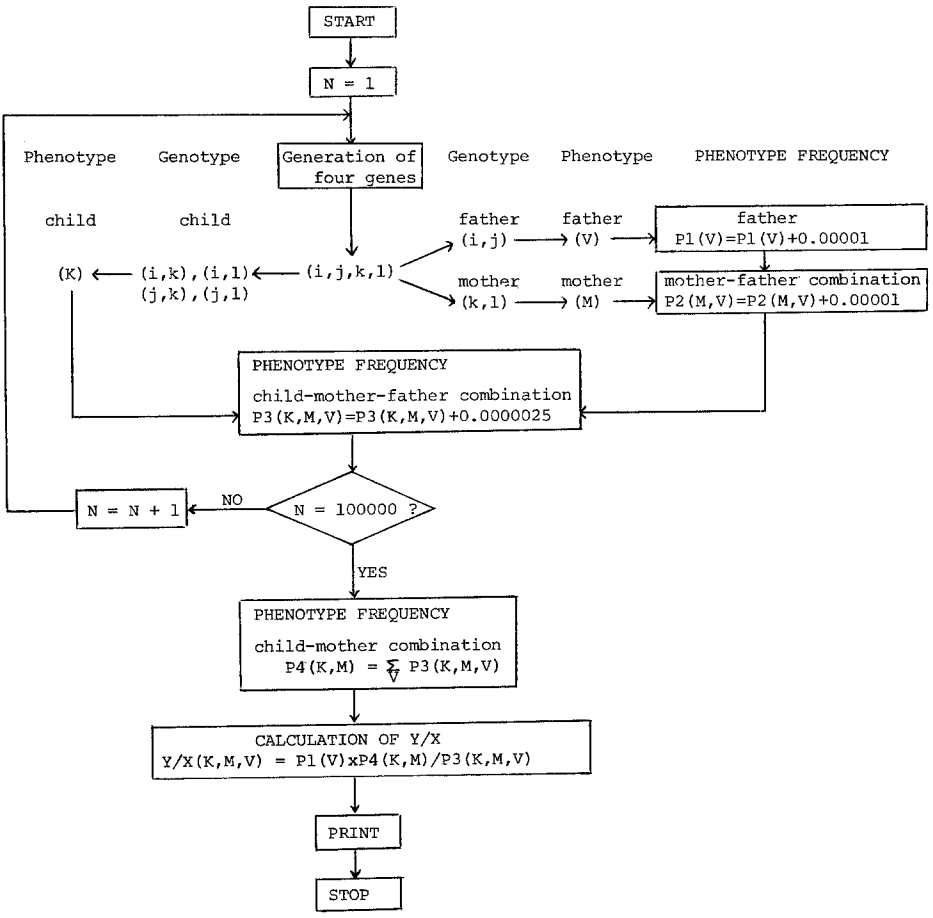
Table 4. (continued)

6	5	6	0.1386	0.1409
6	5	11	0.2844	0.2837
6	6	11	0.2857	0.2837
6	11	11	0.2866	0.2837
10	1	10	0.8149	0.8151
10	1	11	0.8450	0.8426
10	1	16	0.4187	0.4183
10	4	10	0.8193	0.8265
10	4	16	0.4200	0.4185
10	5	10	0.8165	0.8160
10	5	11	0.8347	0.8426
10	5	16	0.4194	0.4184
10	10	10	0.8349	0.8345
10	10	11	1.7089	1.7108
10	10	16	0.8577	0.8557
11	5	10	0.8399	0.8392
11	5	11	0.8283	0.8393
11	5	16	0.4208	0.4197
11	6	10	0.8498	0.8366
11	6	11	0.8389	0.8431
11	6	16	0.4122	0.4187
11	10	11	0.2830	0.2837
11	11	11	0.5725	0.5665
11	11	16	0.5617	0.5627
16	10	10	0.8358	0.8374
16	10	11	0.8457	0.8433
16	10	16	0.4196	0.4187
16	11	11	0.8493	0.8431
16	11	16	0.4165	0.4187
16	16	16	0.4166	0.4187
16	16	28	0.8238	0.8502
28	10	28	0.0254	0.0254
28	16	28	0.0257	0.0254

(1) Y/X of the present calculation using Monte Carlo simulation
(2) that calculated theoretically using algebraic formula of gene frequencies (that converted from the value of log (Y/X) reported by Hummel [3]

Example

Let us consider the Rh blood group system in German population. Indices of haplotypes with haplotype frequencies are written in Table 1. The required input data are 11 gene frequencies and a translation matrix with the rank of 11^2 (i.e. $1 \leqq i, j \leqq 11$). The distinct number of phenotypes is 29. The values of X and Y/X are obtained as matrix elements with the rank of 29^3. Table 2 represents the coding of phenotypes and haplotypes of the Rh system where haplotypes are coded by cde (1), cde (2) and so on. In this Monte Carlo simulation random numbers are generated 2.5×10^6 times. The results of the computer calculation of phenotype frequency are listed in Table 3 together with those calculated theoretically [3]. Likelihood ratios (Y/X) calculated by this Monte Carlo method are also listed in Table 4 with those by Hummel [3] for the trios where the values of P3 (child-mother-father combination) are greater than 0.001.



Scheme 1. Flowchart of program

Program Specification

This program was written in Fortran and run on a Facom 230-75 (Nagoya University Computation Center). The required space depends mainly on the size of the matrices X (NP, NP, NP) and Y/X (NP, NP, NP), where NP is the number of phenotypes. The maximum allowable number of phenotypes is 45 in this machine, larger than the number of phenotypes in the Rh system.

The execution time for Rh system in Germany is 226 seconds. The values of X and Y/X for all the phenotype combinations of a blood group system are calculated by a single run. This program is applicable to any blood group system by replacing gene frequencies an the translation matrix of a blood group system by those of the other blood group system.

Discussion

The method proposed here has no theoretical ambiguities because the genotypes of parents and their children are used instead of their phenotypes. The present results give the frequency of phenotype with sufficiently high accuracy. The observed maximum difference between the phenotype frequencies calculated by the present method and those calculated theoretically is 6×10^{-4}, as shown in Table 3. Table 4 lists the values of Y/X for 55 trios where the values of P3 (child-mother-father combination) are greater than 0.001. The above 55 trios cover most of the possible child-mother-father combinations; that is, the sum of the probability for 55 combinations is 0.9, and the observed maximum difference between the values of Y/X calculated by the present method and those calculated using algebraic formulas is 0.03. The mean difference of Y/X for 55 trios is 0.002. These differences of Y/X correspond to the differences of 8×10^{-3} and 5×10^{-4}, respectively in Essen-Möller values, and are small enough for the calculation of paternity.

This program lists the values of X and Y/X for all the phenotype combinations of trios. The tabulation of these values is necessary when the distribution of Y/X and the mean value of Y/X for a given child-mother combination are considered [3, 7].

The above-mentioned method based on a Monte Carlo simulation can be modified easily for the cases where many children, relatives and aliens are related [8, 9, 10].

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