Letters to the Editor

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Reply to Weeks and Sinsheimer

To the Editor:
In their letter, Weeks and Sinsheimer (1998 [in this issue]) point out some mistakes in the mathematical derivations in our article published in an earlier issue of the *Journal* (Génin and Clerget-Darpoux 1996). Although the main results of our earlier article are not invalidated, there were undoubtedly some errors in the formulas that it presented in Appendixes A and B.

First, contrary to what is believed by Weeks and Sinsheimer, it is possible to derive the IBW-state probabilities (or condensed identity coefficients) for two individuals in a population as a function of the mean inbreeding coefficient α of this population. The argument of Weeks and Sinsheimer is indeed based on an example that did not follow our basic assumption of a mean inbreeding coefficient α constant over time and equal to the mean kinship coefficient. Hence, Weeks and Sinsheimer give the example of a population in which $\frac{1}{4}$ of the individuals, C, are offspring from the same first-cousin marriage and in which the remaining $\frac{3}{4}$ of the individuals, U, are noninbred unrelated individuals. We agree that the mean inbreeding coefficient of the population is thus $\frac{1}{64}$, but, in this case, the mean kinship coefficient is different from the mean inbreeding coefficient.

However, we agree that the IBW-state probabilities of Appendix A of our earlier article were incorrect, and we have corrected them in Appendix A below. It should be noted that, with these corrected IBW-state probabilities, Δ_i (i = 1–9), the two consistency checks noted by Weeks and Sinsheimer are satisfied:

1. The kinship coefficient between the siblings, ϕ_{34}, is

$$\phi_{34} = \Delta_1 + \frac{1}{2}(\Delta_3 + \Delta_5 + \Delta_7) + \frac{1}{4}\Delta_8 = \frac{1}{4}(1 + 3\alpha) \ ;$$

that is consistent with the result obtained, by means of classical recursion methods, by Weeks and Sinsheimer.

2. The second check is the use of matrix **K** of Karigl (1981) to derive the vector $\mathbf{V}_{ij}$ of kinship coefficients from the vector $\mathbf{I}_{ij}$ of IBW-state probabilities between two individuals i and j. If we apply matrix **K** to $\mathbf{I}_{34}$, the vector of IBW-state probabilities of the two siblings, we obtain the correct vector $\mathbf{V}_{34}$ (see Appendix A below).

With these IBW-state probabilities, it is possible to derive the probability that the sib pair shares zero, one, or two alleles identical by descent (the IB-state probabilities). The correct IB-state probabilities are also reported below in Appendix A. Using these formulas, we have redone the study of the robustness of the three tests (the t_1 test, the t_2 test, and the IB test) considered in our earlier article (Génin and Clerget-Darpoux 1996). For small values of the mean inbreeding coefficient α, the type 1 error of the three tests is not changed; for greater values of α, the type 1 error increases slightly, as shown in table 1, in a manner dependent on the type of test.

In Appendix B of our earlier article, we did not, as is noted by Weeks and Sinsheimer, consider that kinship sampling is done with replacement. This leads to small differences in the IBW-state probabilities, Δ_i, which have been corrected in Appendix B below. For $\alpha = 0$, there is no difference, and, for $\alpha < .05$, the difference is negligible. The power results are thus almost not changed, and the figures given in our earlier article are still valid.

Although there were some regrettable errors in our earlier article (Génin and Clerget-Darpoux 1996), which Weeks and Sinsheimer detected and which have been independently noted by Cannings (1998 [in this issue]), we have shown that it is possible to correct them and that they do not invalidate the robustness and power results.

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Table 1

Corrected (and Original [Génin and Clerget-Darpoux 1996]) Type 1 Errors for Three Tests of Linkage, for Samples of 100 Affected Sib Pairs in a Population with Mean Inbreeding Coefficient α

	Corrected (Original) Type 1 Error		
α	t_1	t_2	IB
.000	.050 (.050)	.050 (.050)	.050 (.050)
.001	.051 (.051)	.052 (.052)	.050 (.050)
.005	.057 (.057)	.061 (.060)	.051 (.051)
.010	.064 (.064)	.075 (.070)	.054 (.053)
.020	.082 (.082)	.108 (.097)	.066 (.060)
.030	.103 (.103)	.150 (.129)	.086 (.073)
.040	.128 (.127)	.202 (.169)	.115 (.090)
.050	.156 (.155)	.263 (.215)	.152 (.114)
.060	.189 (.187)	.332 (.268)	.198 (.143)
.070	.226 (.223)	.407 (.326)	.252 (.179)
.080	.266 (.262)	.486 (.390)	.312 (.220)
.090	.311 (.305)	.565 (.456)	.377 (.267)
.010	.358 (.350)	.641 (.523)	.446 (.318)

Table A1

K Matrix and I and V Vectors

K									$\mathbf{I}_{12}$	$\mathbf{V}_{12}$
1	1	1	1	1	1	1	1	1	Δ_1	1
2	2	2	2	1	1	1	1	1	Δ_2	$2\phi_{11}$
2	2	1	1	2	2	1	1	1	Δ_3	$2\phi_{22}$
4	0	2	0	2	0	2	1	0	Δ_4	$4\phi_{12}$
8	0	4	0	2	0	2	1	0	Δ_5	$8\phi_{112}$
8	0	2	0	4	0	2	1	0	Δ_6	$8\phi_{122}$
16	0	4	0	4	0	2	1	0	Δ_7	$16\phi_{1122}$
4	4	2	2	2	2	1	1	1	Δ_8	$4\phi_{11,22}$
16	0	4	0	4	0	4	1	0	Δ_9	$16\phi\Delta_{12,12}$

Table A2

IBW States of Parents and Sibs

IBW State of Sib	IBW State of Parents								
	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9
S_1	1	0	$\frac{1}{4}$	0	$\frac{1}{4}$	0	$\frac{1}{8}$	$\frac{1}{16}$	0
S_2	0	0	0	0	0	0	$\frac{1}{8}$	0	0
S_3	0	0	$\frac{1}{4}$	0	$\frac{1}{4}$	0	$\frac{1}{4}$	$\frac{1}{8}$	0
S_4	0	0	0	0	0	0	0	$\frac{1}{16}$	0
S_5	0	0	$\frac{1}{4}$	0	$\frac{1}{4}$	0	$\frac{1}{4}$	$\frac{1}{8}$	0
S_6	0	0	0	0	0	0	0	$\frac{1}{16}$	0
S_7	0	1	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{3}{16}$	$\frac{1}{4}$
S_8	0	0	0	$\frac{1}{2}$	0	$\frac{1}{2}$	0	$\frac{3}{8}$	$\frac{1}{2}$
S_9	0	0	0	0	0	0	0	0	$\frac{1}{4}$

Appendix A

IBW-State Probabilities for Two Sibs in a Consanguineous Population

Let us consider that the population from which sib pairs are sampled has a mean inbreeding coefficient α equal to the mean kinship coefficient in a same generation. Let individuals "1" and "2" be the parents of the sib pair, "3" and "4." Let Δ_k denote the probability for IBW state S_k ($k = 1$–9). Let $\mathbf{I}_{ij}$ be the vector of Δ_k ($k = 1$–9) for the two individuals i and j. It is possible to compute $\mathbf{I}_{12}$ as a function of α, by use of Karigl's (1981) extended-kinship coefficient. Eight extended-kinship coefficients should be computed:

$$\phi_{11} = \phi_{22} = \frac{1}{2}(1 + \alpha) \ ;$$

$$\phi_{12} = \alpha \ ;$$

$$\phi_{112} = \phi_{122} = \frac{1}{2}\alpha(1 + \alpha) \ ;$$

$$\phi_{1122} = \frac{1}{4}\alpha(1 + \alpha)^2 \ ;$$

$$\phi_{11,22} = \frac{1}{4}(1 + \alpha)^2 \ ;$$

$$\phi_{12,12} = \frac{1}{4}\alpha(1 + 3\alpha) \ .$$

Karigl (1981) showed that the matrix $\mathbf{K}$ multiplied by $\mathbf{I}_{12}$ equals $\mathbf{V}_{12}$, where the matrix $\mathbf{K}$ and the vectors $\mathbf{I}_{12}$ and $\mathbf{V}_{12}$ are as reported in table A1; by use of that relation, it is thus possible to derive the vector $\mathbf{I}_{12}$ of IBW-state probabilities:

$$S_1 \ (1111) = \alpha^3 \ ;$$

$$S_2 \ (1122) = \alpha^2(1 - \alpha) \ ;$$

$$S_3 \ (1112) = 2\alpha^2(1 - \alpha) \ ;$$

$$S_4 \ (1123) = \alpha(1 - \alpha)(1 - 2\alpha) \ ;$$

$$S_5 \ (1222) = 2\alpha^2(1 - \alpha) \ ;$$

$$S_6 \ (1233) = \alpha(1 - \alpha)(1 - 2\alpha) \ ;$$

$$S_7 \ (1212) = 2\alpha^2(1 - \alpha) \ ;$$

$$S_8 \ (1213) = 4\alpha(1 - \alpha)(1 - 2\alpha) \ ;$$

$$S_9 \ (1234) = (1 - \alpha)(1 - 2\alpha)(1 - 3\alpha) \ .$$

Once the IBW-state probabilities of parents are known, the IBW-state probabilities for the sib pair can be obtained by use of matrix $\mathbf{M}_{ps}$, shown in table A2. The IBW-state probabilities for the sib pair, individuals 3 and 4, are thus the product $\mathbf{M}_{ps}\mathbf{I}_{12}$:

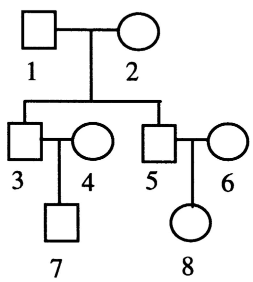

Figure B1 Pedigree in which individuals 7 and 8 are first cousins

$$\Delta_1 = \frac{1}{4}\alpha^3 + \frac{1}{2}\alpha^2 + \frac{1}{4}\alpha\ ;$$

$$\Delta_2 = -\frac{1}{4}\alpha^3 + \frac{1}{4}\alpha^2\ ;$$

$$\Delta_3 = -\frac{1}{2}\alpha^3 + \frac{1}{2}\alpha\ ;$$

$$\Delta_4 = \frac{1}{2}\alpha^3 - \frac{3}{4}\alpha^2 + \frac{1}{4}\alpha\ ;$$

$$\Delta_5 = -\frac{1}{2}\alpha^3 + \frac{1}{2}\alpha\ ;$$

$$\Delta_6 = \frac{1}{2}\alpha^3 - \frac{3}{4}\alpha^2 + \frac{1}{4}\alpha\ ;$$

$$\Delta_7 = -\frac{1}{2}\alpha^3 + \frac{1}{4}\alpha + \frac{1}{4}\ ;$$

$$\Delta_8 = 2\alpha^3 - 2\alpha^2 - \frac{1}{2}\alpha + \frac{1}{2}\ ;$$

$$\Delta_9 = -\frac{3}{2}\alpha^3 + \frac{11}{4}\alpha^2 - \frac{3}{2}\alpha + \frac{1}{4}\ .$$

These IBW-state probabilities verify the two consistency checks discussed by Weeks and Sinsheimer:

1. The kinship coefficient between the siblings, ϕ_{34}, is

$$\phi_{34} = \Delta_1 + \frac{1}{2}(\Delta_3 + \Delta_5 + \Delta_7) + \frac{1}{4}\Delta_8$$
$$= \frac{1}{4}(1 + 3\alpha)\ .$$

2. By multiplying this vector, $\mathbf{I}_{34}$, by the matrix $\mathbf{K}$, we obtained

$$\mathrm{V}_{34} = \begin{pmatrix} 1 \\ 1+\alpha \\ 1+\alpha \\ 1+3\alpha \\ 1+5\alpha+2\alpha^2 \\ 1+5\alpha+2\alpha^2 \\ 1+8\alpha+6\alpha^2+\alpha^3 \\ 1+\frac{9}{4}\alpha+\frac{3}{4}\alpha^2 \\ \frac{3}{2}+\frac{17}{2}\alpha+6\alpha^2 \end{pmatrix},$$

which is the correct vector of kinship coefficient for two sibs in a population with mean inbreeding coefficient α. The IB-state probabilities for the sib pair are then

$$P(\mathrm{IB}=0) = \Delta_2 + \Delta_4 + \Delta_6 + \Delta_9$$
$$= \frac{1}{4} - \alpha + \frac{3}{2}\alpha^2 - \frac{3}{4}\alpha^3\ ;$$

$$P(\mathrm{IB}=1) = \Delta_3 + \Delta_5 + \Delta_8 = \frac{1}{2} + \frac{1}{2}\alpha - 2\alpha^2 + \alpha^3\ ;$$

$$P(\mathrm{IB}=2) = \Delta_1 + \Delta_7 = \frac{1}{4} + \frac{1}{2}\alpha + \frac{1}{2}\alpha^2 - \frac{1}{4}\alpha^3\ .$$

Appendix B

Corrections of Appendix B in Our Earlier Article (Génin and Clerget-Darpoux 1996)

In Appendix B of our earlier article, we showed how to account for the remote consanguinity in the computation of IBW-state probabilities for two sibs from first-cousin matings, using the algorithm of Karigl (1981). The pedigree in which extended-kinship coefficients have been computed is shown in figure B1.

As is pointed out by Weeks and Sinsheimer, there was an error in the computation of the extended-kinship coefficients, because we did not consider that kinship sampling is done with replacement. This leads to some differences in the kinship coefficients ϕ_{778}, ϕ_{7788}, and $\phi_{78,78}$:

$$\phi_{778} = \phi_{887} = \frac{1}{32} + \frac{17}{32}\alpha + \frac{7}{16}\alpha^2 \ ;$$

$$\phi_{7788} = \frac{1}{64} + \frac{19}{64}\alpha + \frac{1}{2}\alpha^2 + \frac{3}{16}\alpha^3 \ ;$$

$$\phi_{78,78} = \frac{1}{64} + \frac{21}{64}\alpha + \frac{21}{32}\alpha^2 \ .$$

The kinship coefficients ϕ_{77}, ϕ_{78}, and $\phi_{77,88}$ are not changed:

$$\phi_{77} = \phi_{88} = \frac{1}{2}(1+\alpha) \ ;$$

$$\phi_{78} = \frac{1}{16}(1+15\alpha) \ ;$$

$$\phi_{77,88} = \frac{1}{4}(1+\alpha)^2 \ .$$

The IBW-state probabilities for individuals 7 and 8, obtained by use of the inverse of matrix **K**, as explained in Appendix A above, are thus

$$P(S_1) = \frac{1}{4}\alpha^2(1+3\alpha) \ ;$$

$$P(S_2) = \frac{3}{4}\alpha^2(1-\alpha) \ ;$$

$$P(S_3) = \frac{1}{4}\alpha(1+5\alpha-6\alpha^2) \ ;$$

$$P(S_4) = \frac{3}{4}\alpha(1-3\alpha+6\alpha^2) \ ;$$

$$P(S_5) = \frac{1}{4}\alpha(1+5\alpha-6\alpha^2) \ ;$$

$$P(S_6) = \frac{3}{4}\alpha(1-3\alpha+6\alpha^2) \ ;$$

$$P(S_7) = \frac{1}{4}\alpha(1+5\alpha-6\alpha^2) \ ;$$

$$P(S_8) = \frac{1}{4}(1+9\alpha-34\alpha^2+24\alpha^3) \ ;$$

$$P(S_9) = \frac{1}{4}(3-18\alpha+33\alpha^2-18\alpha^3) \ .$$

The use of matrix $\mathbf{M}_{ps}$, defined in Appendix A above, allows derivation of the IBW-state probabilities for sib pairs from first-cousin marriages in this population:

$$P(S_1) = \frac{3}{16}\alpha^3 + \frac{1}{2}\alpha^2 + \frac{19}{64}\alpha + \frac{1}{64} \ ;$$

$$P(S_2) = -\frac{3}{16}\alpha^3 + \frac{5}{32}\alpha^2 + \frac{1}{32}\alpha \ ;$$

$$P(S_3) = -\frac{3}{8}\alpha^3 - \frac{1}{8}\alpha^2 + \frac{15}{32}\alpha + \frac{1}{32} \ ;$$

$$P(S_4) = \frac{3}{8}\alpha^3 - \frac{17}{32}\alpha^2 + \frac{9}{64}\alpha + \frac{1}{64} \ ;$$

$$P(S_5) = -\frac{3}{8}\alpha^3 - \frac{1}{8}\alpha^2 + \frac{15}{32}\alpha + \frac{1}{32} \ ;$$

$$P(S_6) = \frac{3}{8}\alpha^3 - \frac{17}{32}\alpha^2 + \frac{9}{64}\alpha + \frac{1}{64} \ ;$$

$$P(S_7) = -\frac{3}{8}\alpha^3 - \frac{3}{32}\alpha^2 + \frac{15}{64}\alpha + \frac{15}{64} \ ;$$

$$P(S_8) = \frac{3}{2}\alpha^3 - \frac{21}{16}\alpha^2 - \frac{21}{32}\alpha + \frac{15}{32} \ ;$$

$$P(S_9) = -\frac{9}{8}\alpha^3 + \frac{33}{16}\alpha^2 - \frac{9}{8}\alpha + \frac{3}{16} \ .$$

These IBW-state probabilities verify the two consistency checks discussed by Weeks and Sinsheimer:

1. The kinship coefficient of the two sibs is, as expected, $\frac{9}{32} + \frac{23}{32}\alpha$. If $\alpha = 0$, then we obtain $\frac{9}{32}$; that is the correct kinship coefficient for two siblings whose parents are first cousins.

2. Using matrix **K** of Karigl (1981), we obtained the correct vector **I** of extended-kinship coefficients:

$$\mathbf{I} = \begin{pmatrix} 1 \\ \frac{17}{16} + \frac{15}{16}\alpha \\ \frac{17}{16} + \frac{15}{16}\alpha \\ \frac{9}{8} + \frac{23}{8}\alpha \\ \frac{5}{4} + 5\alpha + \frac{7}{4}\alpha^2 \\ \frac{5}{4} + 5\alpha + \frac{7}{4}\alpha^2 \\ \frac{23}{16} + \frac{133}{16}\alpha + \frac{11}{2}\alpha^2 + \frac{3}{4}\alpha^3 \\ \frac{73}{64} + \frac{141}{64}\alpha + \frac{21}{32}\alpha^2 \\ \frac{61}{32} + \frac{281}{32}\alpha + \frac{85}{16}\alpha^2 \end{pmatrix} .$$

We can verify our formulas, since, for $\alpha = 0$, the extended-kinship coefficients for the two sibs, individuals 9 and 10, are

$$\phi_{99} = \phi_{1010} = \frac{1}{2}\left(1 + \frac{1}{16}\right) = \frac{17}{32} \text{(and the second entry and the third entry } [2\phi_{99}] \text{ of } \mathbf{I} \text{ are correct)} ;$$

$$\phi_{910} = \frac{9}{32} \text{(and the fourth entry } [4\phi_{910}] \text{ of } \mathbf{I} \text{ is correct)} ;$$

$$\phi_{9910} = \phi_{10109} = \frac{1}{2}(\phi_{910} + \phi_{7810}) = \frac{1}{2}\left\{\frac{9}{32} + \left[\frac{1}{16}\left(\frac{1}{2}\right)\right]\right\} = \frac{5}{32}$$

(and the fifth entry and the sixth entry $[8\phi_{9910}]$ of **I** are correct) ;

$$\phi_{991010} = \frac{1}{2}(\phi_{91010} + \phi_{781010}) = \frac{5}{64} + \frac{1}{256} + \left[\frac{1}{4}\left(\frac{1}{32}\right)\right] = \frac{23}{256} \text{ (and the seventh entry } [16\phi_{91010}] \text{ is correct)} ;$$

$$\phi_{99,1010} = \frac{1}{2}(\phi_{1010} + \phi_{78,1010}) = \frac{73}{256} \text{ (and the eighth entry } [4\phi_{991010}] \text{ is correct)} ;$$

$$\phi_{910,910} = \frac{1}{2}(\phi_{91010} + \phi_{710,810}) = \frac{5}{64} + \frac{1}{8}(2\phi_{7810} + \phi_{77,88} + \phi_{78,78}) = \frac{61}{512}$$

(and the last entry $[16\phi_{910910}]$ is correct) .

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