

A Mathematical Model of Interference for Use in Constructing Linkage Maps From Tetrad Data

Jeff S. King* and Robert K. Mortimer†

*Graduate Group in Biophysics, University of California, Berkeley, California 94720, †Department of Molecular and Cell Biology, Division of Genetics, University of California, Berkeley, California 94720, and Division of Cellular and Molecular Biology, Lawrence Berkeley Laboratory, Berkeley, California 94720

Manuscript received February 4, 1991
Accepted for publication June 21, 1991

ABSTRACT

In determining genetic map distances it is necessary to infer crossover frequencies from the ratios of recombinant and parental progeny. To do this accurately, in intervals where multiple crossovers may occur, a mathematical model of chiasma interference must be assumed when mapping in organisms displaying such interference. In *Saccharomyces cerevisiae* the model most frequently used is that of R. W. Barratt. An alternative to this model is presented. This new model is implemented using a microcomputer and standard numerical methods. It is demonstrated to fit ranked tetrad data from *Saccharomyces* more closely than the Barratt model and thus generates more accurate estimates of map distances when used with two-point data. A computer program implementing the model has been developed for use in calculating map distances from tetrad data in *Saccharomyces*.

GENETIC interference, as observed in *Drosophila* by MULLER in 1916, is a reduction in the probability of occurrence of a crossover in one region associated with a crossover in an adjacent region. When calculating map distances in organisms displaying interference the reduction in probability of multiple crossovers must be taken into account if the number of crossovers in an interval is to be inferred from the ratios of recombinant and parental progeny. Models of interference can be tested directly in organisms in which the absolute number of crossovers in any one meiosis can be determined. In the ascomycetes all four products of an individual meiosis can be analyzed, and in those ascomycetes with suitable genetic markers, regions can be multiply marked at small enough distances that the probability of more than two crossovers occurring between any two markers is very low. The tetrad rank is the number of crossovers between the outermost markers, which is determined by summing the crossovers in the smaller intervals between the outer markers. Models that fit the ranked tetrad data can be used to calculate map distances in other crosses in the same organism in which the number of crossovers must be inferred.

In *Saccharomyces* ranked tetrad data can be used to test models of interference. However, most data are from two-point crosses in which the two markers defining the interval are separated by a distance of sufficient length that multiple crossovers occur, and the number of crossovers in the recombinant progeny can not be determined directly. Genetic map distances are calculated in tetrad organisms as follows:

Genetic map distances are measured in centimorgans (cM) and are defined as 100 times the frequency

of crossovers per chromatid. The map distance, x , is

$$x = \frac{100}{2} \sum_{r=0}^{\infty} r \rho(r) \text{ cM.} \quad (1)$$

where r is the number of crossovers and $\rho(r)$ is the probability of r . If exchanges occurred independently, the number of crossovers in an interval would follow a Poisson distribution.

$$\rho(r) = \frac{(2x)^r e^{-2x}}{r!} \text{ for } r = 0 \text{ to } \infty. \quad (2)$$

If only zero, one or two crossovers occur in an interval the map distance can be calculated using PERKINS' (1949) equation.

$$x = \frac{100}{2} \left[\frac{T + 6N}{P + N + T} \right] \text{ cM.} \quad (3)$$

P , N and T are the numbers of parental ditype, non-parental ditype, and tetratype tetrads, respectively. PERKINS' equation is derived by assuming that the probability of double crossovers, $\rho(2)$, is four times the frequency of nonparental ditype tetrads and the probability of single crossovers, $\rho(1)$, is the frequency of tetratype tetrads minus twice the frequency of nonparental ditype tetrads. The relationship between the number of crossovers and the ratios of tetrad types is derived by excluding sister-chromatid exchanges from the crossover total and by assuming that the distribution of crossovers between the four chromatids is random and independent of previous crossovers (*i.e.*, no chromatid interference). Table 3 is a list of the ratios of P , N and T tetrads resulting from zero through four crossovers. PERKINS' equation can

be used to determine map distances accurately if there are no more than two crossovers in an interval. When this is not the case, PERKINS' equation underestimates map distance (for discussion of this, see SNOW 1979a; MORTIMER and SCHILD 1981; MA and MORTIMER 1983).

In *Saccharomyces*, fewer tetrads of rank greater than one are observed than would be expected if the number of crossovers were random. Because the crossovers are not independent, it is necessary to assume a mathematical model of interference that reduces the expected numbers of multiple crossovers. One model of interference is the BARRATT model (BARRATT *et al.* 1954) which has been implemented by SNOW (1979a). The BARRATT model reduces the Poisson terms used to predict tetrad rank by k^{r-1} for r greater than one.

$$\begin{aligned} \rho(0) &= e^{-2x_0} \\ \rho(r) &= \frac{k^{r-1}(2x_0)^r e^{-2x_0} S}{r!} \quad r = 1 \text{ to } \infty. \end{aligned} \quad (4)$$

S is a normalization factor:

$$S = \frac{k(e^{-2x_0} - 1)}{(e^{-2kx_0} - 1)}. \quad (5)$$

It is assumed here that the rank zero term is unaffected and it is thus excluded from the renormalization. Interference is expressed in the term k , which varies from zero (absolute interference) to greater than one (negative interference) and equals one if the data do not display interference. The term x_0 is the map distance that would be expected if there were no interference. The actual map distance, x , is determined from x_0 and k using Equation 1, which simplifies to (SNOW 1979b):

$$x = \frac{100kx_0(1 - e^{-2x_0})}{(1 - e^{-2kx_0})} \text{ cM}. \quad (6)$$

SNOW (1979a) used the maximum likelihood method and numerical methods described by MATHER (1957) to determine map distance and k values from ranked tetrad data and from two-point data in the fungi *Saccharomyces* and *Neurospora*. The algorithms he produced are those currently used for mapping in *Saccharomyces*. However, as SNOW pointed out, the BARRATT model does not generate a good fit to ranked tetrad data from *Saccharomyces*. For the ranked tetrad data analyzed in this paper (see Table 1), the BARRATT model typically predicts a greater frequency of rank one and rank four tetrads and a lower frequency of rank two tetrads than observed. Because of this, the BARRATT model does not provide a good overall fit to the data from *Saccharomyces*. In this paper we propose a mathematical model of interference that provides a good fit to the ranked tetrad data from *Saccharomyces*.

The model was implemented on an Apple Macin-

tosh IIcx computer using the C language compiler, THINK C, from Symantec Corporation. This work has been incorporated into the user-friendly tetrad analysis program from MORTIMER *et al.* 1989 that incorporates the work of SNOW (1979a). This program will run on Macintosh computers and is available on a 3½-inch diskette on request.

MODEL AND DISCUSSION

The model proposed here, like BARRATT's, is a mathematical model to be used in constructing linkage maps. In this model the number of crossovers in a genetic interval in a single meiosis is calculated in a manner analogous to a binomial distribution. Since tetrads with a high number of crossovers in an interval are rare, the model mathematically limits the maximum number of crossovers that can occur in an interval. For example, even in an interval spanning most of the length of the right arm of chromosome III (approximately 90 cM), we do not observe significant numbers of tetrads with more than four crossovers (KING and MORTIMER 1990). Based on this observation the model limits the number of crossovers that can occur in an interval to four.

To formulate the model, an event is defined as a potential crossover and the event is a success if it results in a crossover. Each successful event reduces by a factor k the probability of other events being successful. If the probability of an event being successful if no other events are successful is p , and we "pull events out of a hat" the probability of no successful events in four tries is $(1 - p)^4$. If any one of the four events is successful, the probability of the other events being successful is set to kp . Thus, the probability of one success and three failures is $p(1 - kp)^3$. When the probabilities are derived in this manner they must then be multiplied by the number of combinations that can generate the specified result. The probabilities and number of combinations of each possible outcome are shown in Table 2. The equations shown in Table 2 are then normalized by multiplying each term by S , where:

$$\begin{aligned} \frac{1}{S} &= (1 - p)^4 + 4p(1 - kp)^3 + 6p^2(kp)(1 - k^2p)^2 \\ &\quad + 4p(kp)(k^2p)(1 - k^3p) + p(kp)(k^2p)(k^3p). \end{aligned} \quad (7)$$

The predicted frequencies of rank zero (m_0), rank one (m_1), rank two (m_2), rank three (m_3), and rank four (m_4) tetrads are:

$$m_0 = S[(1 - p)^4] \quad (8)$$

$$m_1 = S[4p(1 - kp)^3] \quad (9)$$

$$m_2 = S[6p^2(kp)(1 - k^2p)^2] \quad (10)$$

$$m_3 = S[4p(kp)(k^2p)(1 - k^3p)] \quad (11)$$

$$m_4 = S[p(kp)(k^2p)(k^3p)]. \quad (12)$$

TABLE 1
Comparison of interference models

r	Hybrid and chromosome														
	4579 III			X2961 VIII			5571 VIII			43XX VI			M522 & M537 II		
	Observed	King	Barratt	Observed	King	Barratt	Observed	King	Barratt	Observed	King	Barratt	Observed	King	Barratt
0	53	60	53	333	336	333	128	128	128	449	449	449	158	158	158
1	254	235	291	1406	1393	1438	753	754	772	598	600	601	600	599	637
2	291	305	245	367	379	304	188	187	152	54	53	48	272	271	206
3	156	157	137	14	15	43	5	5	20	0	1	3	21	25	44
4	30	27	58	3	0	5	0	0	2	0	0	0	2	0	8
$\chi^2 =$		3.34	29.5		3.61	34.1		0.01	22.2		1.03	3.76		2.77	63.4
$p =$	0.47 ± 0.01			0.33 ± 0.01			0.36 ± 0.01			0.18 ± 0.01			0.34 ± 0.01		
$k =$	0.96 ± 0.02			0.40 ± 0.02			0.34 ± 0.02			0.29 ± 0.03			0.29 ± 0.02		
$x(cM) =$	90.8 ± 2.0			51.7 ± 0.7			53.2 ± 1.0			32.1 ± 0.9			57.7 ± 1.3		

Comparison of interference models. The genetic intervals for the crosses are: 4579, leu2-MAT-thr4-MAL2 (S. FOGEL, personal communication); X2961, cen8-pet1-arg4-thr1-CUP1 (MORTIMER and FOGEL 1974); 5571, cen8-pet1-arg4-thr1-CUP1 (S. FOGEL, personal communication); 43XX, cen6-his2-SUP6-met10, 43XX denotes data compiled from hybrids 4339, 4351, 4350, 4334, 4338 and 4352 (S. FOGEL, personal communication); M522, lys2-tyr1-pet11-dur1-met8; M537, lys2-tyr1-pet11-dur2 (COOPER, LAM, and TUROSCY 1980). The p , k and x values listed are from the model presented in this paper. From the χ^2 analysis it is evident that the model presented in this paper provides a better fit to ranked tetrad data from *Saccharomyces* than the BARRATT model.

For ranked tetrad data the above equations can be directly fitted to the data. For two-point data the probabilities determined by equations eight through twelve must be multiplied by the fraction of tetrads of a specific rank that contribute to a particular class (listed in Table 3). Using Table 3 the predicted frequencies of parental (m_P), nonparental ditype (m_N) and tetratype (m_T) tetrads are:

$$m_P = S[(1 - p)^4 + 3p(kp)(1 - k^2p)^2/2 + 4p(kp)(k^2p)(1 - k^3p)/8 + 3p(kp)(k^2p)(k^3p)/16] \tag{13}$$

$$m_N = S[3p(kp)(1 - k^2p)^2/2 + 4p(kp)(k^2p)(1 - k^3p)/8 + 3p(kp)(k^2p)(k^3p)/16] \tag{14}$$

$$m_T = S[4p(1 - kp)^3 + 3p(kp)(1 - k^2p)^2 + 3p(kp)(k^2p)(1 - k^3p) + 5p(kp)(k^2p)(k^3p)/8]. \tag{15}$$

Equations 13 through 15 are then fitted to the two-point data.

For ranked tetrad data, solutions were found by maximizing the log likelihood expression:

$$L = a_0 \ln(m_0) + a_1 \ln(m_1) + a_2 \ln(m_2) + a_3 \ln(m_3) + a_4 \ln(m_4), \tag{16}$$

where a_0, a_1, a_2, a_3, a_4 are the number of observed tetrads of rank zero through four and m_0 through m_4 are the predicted frequencies of tetrads of the corresponding rank. The values of p and k that maximized this function are then found using POWELL's method as outlined in and using the code from PRESS *et al.*

TABLE 2

Derivation of the tetrad rank probability distribution

No. of crossovers	Probability	No. of combinations
0	$(1 - p)^4$	1
1	$p(1 - kp)^3$	4
2	$p(kp)(1 - k^2p)^2$	6
3	$p(kp)(k^2p)(1 - k^3p)$	4
4	$p(kp)(k^2p)(k^3p)$	1

The tetrad rank probability distribution is derived by multiplying the probability of a particular outcome (0, 1, 2, 3 or 4 crossovers) by the number of combinations that can result in the outcome. The probability of a potential crossover resulting in an actual crossover is p , and k is an interference term used to reduce the probability of multiple crossovers.

TABLE 3

Expected fractions from tetrad types

Tetrad	r				
	0	1	2	3	4
P	1	0	1/4	1/8	3/16
N	0	0	1/4	1/8	3/16
T	0	1	1/2	3/4	5/8

The expected fraction of tetrads of P , N and T resulting from r crossovers (calculated according to HALDANE 1931). As an example 1/4 of all the rank two tetrads (tetrads with a double crossover) will be parental ditype (P), 1/4 nonparental ditype (N) and 1/2 will be tetratype (T).

1989. The log likelihood method used is described in MATHER (1957) and in SNOW (1979a). The log likelihood expression is used because it is at its maximum value when the frequencies of predicted tetrad types are equal to the frequencies observed. Map distance is calculated directly, using equation one.

For two-point data the log likelihood expression to be maximized is:

$$L = a_p \ln(m_p) + a_N \ln(m_N) + a_T \ln(m_T), \quad (17)$$

where a_p is the observed number of parentals, a_N is the number of nonparental ditypes and a_T is the observed number of tetratypes. m_p , m_N and m_T are the frequencies predicted by equations thirteen through fifteen. Solutions are found using the same methods and code as that used for the ranked tetrad data. Map distance is calculated according to equation one. This is done by using the p and k values from the maximization to determine the m_r values from equations eight through twelve and setting $\rho(r)$ equal to m_r .

The standard error in map distance is determined by propagation of errors, using the standard errors in p and k . The standard errors in p and k , σ_p and σ_k , are determined by assuming the log likelihood expressions are Gaussian around the solution. Setting M to be the total number of tetrads, the standard errors are given by:

$$\frac{1}{(\sigma_p)^2} = \frac{\partial^2 L}{\partial p^2} = \sum_{i=0}^j \frac{a_i}{m_i^2} \left(\frac{\partial m_i}{\partial p} \right)^2 \cong M \sum_{i=0}^j \frac{1}{m_i} \left(\frac{\partial m_i}{\partial p} \right)^2 \quad (18)$$

$$\frac{1}{(\sigma_k)^2} = \frac{\partial^2 L}{\partial k^2} = \sum_{i=0}^j \frac{a_i}{m_i^2} \left(\frac{\partial m_i}{\partial k} \right)^2 \cong M \sum_{i=0}^j \frac{1}{m_i} \left(\frac{\partial m_i}{\partial k} \right)^2. \quad (19)$$

The approximation, $a_i \cong M m_i$, is valid when a solution has been found that predicts tetrad types matching those observed. For ranked tetrad data $j = 4$. For two-point data $j = 2$ and $j = 0, 1, \text{ and } 2$ refer to P, N and T . Equations eighteen and nineteen are the formulas for variance determined by MATHER (1957). Graphical analysis was carried out on the ranked tetrad data to verify that the maximized functions are approximately Gaussian near the numerically determined solutions.

Table 1 is a comparison of the BARRATT model of interference to the model presented in this paper for several sets of ranked tetrad data. It is apparent from Table 1 that this model provides a better fit to the data than the BARRATT model and, based on χ^2 analysis, differs insignificantly from observation. For distances greater than the length of the studied interval on chromosome III (approximately 90 cM) the maximum number of events allowed may need to be increased to five or more, however two-point crosses rarely extend over such long intervals. The data in Table 1 were analyzed allowing up to five crossovers along an interval. This did not result in significant changes. We also compared the map distances calculated according to our model to the map distances calculated according to SNOW (1979a). Figure 1 is a graph of all the two-point data from the 1980 version of the genetic map of *Saccharomyces* (MORTIMER and SCHILD 1980) with two or more nonparental ditype tetrads and more than one hundred total tetrads. From this graph it is evident that our model predicts

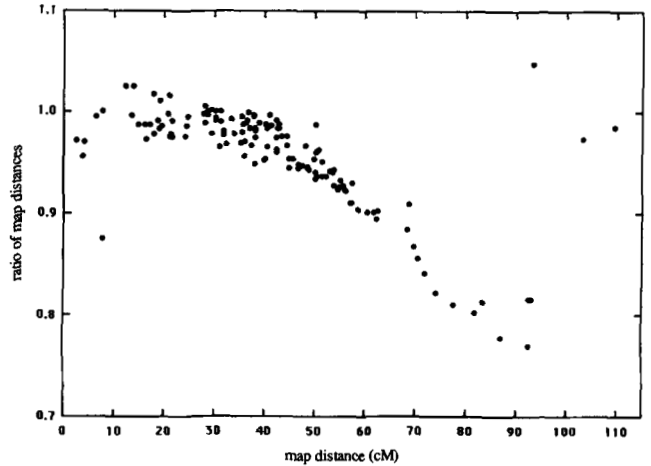


FIGURE 1.—Comparison of the map distance calculated using the BARRATT model of interference to the map distance calculated using the model presented in this paper. The graph is derived from all the two-point data from the 1980 version of the genetic map of *Saccharomyces* (MORTIMER and SCHILD 1980) with two or more nonparental ditype tetrads and more than one hundred total tetrads. The ratio of map distances is the map distance calculated according to our model divided by the map distance calculated according to SNOW (1979a). The horizontal axis is the map distance according to our model. For distances greater than approximately 30 cM, our model predicts shorter map distances, and since our model produces a better fit to the ranked tetrad data it results in more accurate estimates of map distance. The three points in the upper right hand corner of the graph came from two-point data with negative interference and had uncertainties of 0.4, 0.6 and 0.7 (typical uncertainties for the remainder of the data are 0.05 to 0.2).

shorter map lengths, particularly above 60 cM, than the BARRATT model.

To further test the model, the data in Table 1 were translated into two-point data (P, N and T type tetrads) to give two-point data with known map distances. Table 4 displays the results of calculating the map distance from this data using PERKINS' equation, the BARRATT model, and the model we present here. It is evident that at 30 cM or less, all three methods accurately calculate distance, but at longer distances PERKINS' equation underestimates distance and the BARRATT model overestimates distance. Our model provides the most accurate estimate of distance of the methods tested.

In *Drosophila* (CHARLES 1938) and *Saccharomyces* (MORTIMER and FOGEL 1974) interference is typically strong over short intervals and decreases with increasing distance. However, SNOW (1979a) did not detect a correlation between map distance and interference in the data he analyzed. The analysis of the data used for Figure 1 resulted in significant positive correlation coefficients for both the BARRATT model and the model presented here (correlation coefficients of 0.260 and 0.267, respectively, sample size = 137). In the BARRATT model of interference and the model we present, interference is stronger over short distances than it is over longer distances.

Typically the computer program written calculates

TABLE 4
Comparison of methods used in calculating map distances from two-point data

Method	Hybrid				
	4579	X2961	5571	43XX	M522 & M537
	<i>P:N:T</i> 151:98:535	<i>P:N:T</i> 427:94:1602	<i>P:N:T</i> 176:48:851	<i>P:N:T</i> 463:14:625	<i>P:N:T</i> 229:71:753
Map distance determined from ranked tetrad data: $x =$	90.8 ± 2.0	51.7 ± 0.7	53.2 ± 1.0	32.1 ± 0.9	57.7 ± 1.3
PERKINS' equation: $x =$	71.6	51.0	52.9	32.1	56.0
BARRATT estimate: $x =$	108.1 ± 15.5	53.4 ± 1.8	55.3 ± 2.4	32.4 ± 1.3	62.6 ± 3.9
KING estimate: $x =$	83.8 ± 7.6	51.5 ± 1.1	53.4 ± 1.6	32.2 ± 1.0	57.7 ± 2.3

The actual map distances were determined from the ranked tetrad data in Table 1. The number of *P*, *N* and *T* tetrads predicted by the ranked tetrad data were determined using the ratios of tetrad types from Table 3.

map distances and interference values. However, in two-point crosses in which all the parameters of the model cannot be determined, the program determines the maximum probable values of the parameters. The first such case is when there are only parental ditype tetrads. In this case the program calculates the map distance at which the probability of observing only parental ditype tetrads would be five percent. The calculation is based on the binomial distribution in which the number of successful trials is zero, the number of trials is *P* (the number of parental type tetrads) and the probability of a trial being successful is $2x/100$, where x is the map distance. The probability of the outcome (only parentals) is b , which is set to 0.05. x is then given by:

$$x_{\max} = \frac{100}{2} [1 - e^{\ln(b)/P}] = \frac{100}{2} [1 - b^{1/P}] \text{ cM.} \quad (20)$$

The other special case considered is when there are both parental and tetratype tetrads but no nonparental type tetrads. The map distance is given by PERKINS' equation (Equation 3), which simplifies to:

$$x = \frac{100}{2} \left[\frac{T}{P + T} \right] \text{ cM.} \quad (21)$$

After calculating the map distance the program calculates the maximum value of interference. Again the binomial distribution is used in which the number of trials is the number of tetratypes, and the probability of success is $2kx/400$ (the probability of a second crossover given an initial crossover being $2kx/100$, where x is the map distance, and only one fourth of the double crossovers producing a nonparental ditype tetrad).

$$k_{\max} = \frac{200}{x} [1 - e^{\ln(b)/T}] = \frac{200}{x} [1 - b^{1/T}]. \quad (22)$$

Two issues that researchers involved in the use of mapping functions must be aware of are the ordering of genes and the combining of heterogeneous data.

This model can improve calculations of map distance but it is not a substitute for multipoint crosses. A gene of unknown location must still be mapped against two linked genes of known position and orientation. When combining or comparing map distances from multiple crosses it is important to be aware of the significant variation that can arise due to differences in genetic backgrounds of the strains involved. In *Saccharomyces* the recombination rate between two identical markers in different genetic backgrounds can vary up to 50% (MORTIMER and SCHILD 1980).

CONCLUSION

To accurately calculate map distances between genetic markers, separated by distances such that multiple crossovers occur, it is necessary to have a mathematical model that can fit the known crossover frequencies in the organism being studied. The model of interference presented in this paper fits ranked tetrad data from *Saccharomyces* better than the BARRATT model of interference. Because this model fits the ranked tetrad data it is a more appropriate model to use in constructing linkage maps from two-point data in *Saccharomyces*. This model may also prove useful in other tetrad organisms displaying chiasma interference.

We would like to thank SEYMOUR FOGEL for unpublished data, JONATHAN KANS for incorporating this work into the tetrad analysis program, and JOHN GAME, DAVID SCHILD and GEORGE BASILE for critical readings of the manuscript. This work was supported by a grant from the office of Health and Environmental Research of the U.S. Department of Energy under contract DE-AC03-76SF00098 and by U.S. Public Health Service grants GM30990, 5 P40 RR04231-02 and ES07075.

LITERATURE CITED

- BARRATT, R. W., D. NEUMEYER, D. D. PERKINS and L. GARNJOBST, 1954 Map construction in *Neurospora crassa*. *Adv. Genet.* **6**: 1-93.
 CHARLES, D. R., 1938 The spatial distribution of cross-overs in

- X-chromosome tetrads of *Drosophila melanogaster*. *J. Genetics* **36**: 103–126.
- COOPER, T. G., C. LAM and V. TUROSCY, 1980 Structural analysis of the *dur* loci in *Saccharomyces cerevisiae*: two domains of a single multifunctional gene. *Genetics* **94**: 555–580.
- HALDANE, J. B. S., 1931 The cytological basis of genetical interference. *Cytologia* **3**: 54–65.
- KING, J. S., and R. K. MORTIMER, 1990 A polymerization model of chiasma interference and corresponding computer simulation. *Genetics* **126**: 1127–1138.
- MA, C., and R. K. MORTIMER, 1983 Empirical equation that can be used to determine genetic map distances from tetrad data. *Mol. Cell Biol.* **3**: 1886–1887.
- MATHER, K., 1957 *The Measurement of Linkage in Heredity*, Ed. 2. Methuen & Co., London.
- MORTIMER, R. K., and S. FOGEL, 1974 Genetical interference and gene conversion, pp. 263–275 in *Mechanisms in Recombination*, edited by R. F. GRELL. Plenum, New York.
- MORTIMER, R. K., and D. SCHILD, 1980 Genetic map of *Saccharomyces cerevisiae*. *Microbiol. Rev.* **44**: 519–571.
- MORTIMER, R. K., and D. SCHILD, 1981 Genetic mapping in *Saccharomyces cerevisiae*, pp. 11–26 in *The Molecular Biology of the Yeast Saccharomyces cerevisiae Life Cycle and Inheritance*, edited by J. N. STRATHERN, E. W. JONES and J. R. BROACH. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.
- MORTIMER, R. K., D. SCHILD, C. R. CONTOPOULOU and J. A. KANS, 1989 Genetic map of *Saccharomyces cerevisiae*, edition 10. *Yeast* **5**: 321–403.
- MULLER, H. J., 1916 The mechanism of cross-over. *Am. Nat.* **50**: 193–221.
- PERKINS, D. D., 1949 Biochemical mutants in the smut fungus *Ustilago maydis*. *Genetics* **34**: 607–626.
- PRESS, W. H., B. P. FLANNERY, S. A. TEUKOLSKY and W. T. VETTERLING, 1989 *Numerical Recipes in C*. Cambridge University Press, New York.
- SNOW, R., 1979a Maximum likelihood estimation of linkage and interference from tetrad data. *Genetics* **92**: 231–245.
- SNOW, R., 1979b Comment concerning maximum likelihood estimation of linkage and interference from tetrad data. *Genetics* **93**: 285.

Communicating editor: E. W. JONES