Models for Chromatid Interference With Applications to Recombination Data

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ABSTRACT

Genetic interference means that the occurrence of one crossover affects the occurrence and/or location of other crossovers in its neighborhood. Of the three components of genetic interference, two are well modeled: the distribution of the number and the locations of chiasmata. For the third component, chromatid interference, there exists only one model. Its application to real data has not yet been published. A further, new model for chromatid interference is presented here. In contrast to the existing model, it is assumed that chromatid interference acts only in the neighborhood of a chiasma. The appropriateness of this model is demonstrated by its application to three sets of recombination data. Both models for chromatid interference increased fit significantly compared to assuming no chromatid interference, at least for parts of the chromosomes. Interference does not necessarily act homogeneously. After extending both models to allow for heterogeneity of chromatid interference, a further improvement in fit was achieved.

DURING meiotic prophase 1 in diploid individuals, each chromosome is paired with its homologue. Each homologue is duplicated, producing two identical chromatids, the sister strands. A crossover represents an event where two nonsister chromatids form chiasmata, break, and reunite, enforced by the tight contact and the twisting between the chromatids and the subsequent repair mechanism. After meiosis, one of the four resulting gametes is randomly chosen for further inheritance. For clarity we use the term chiasma at the four-strand stage, while the term crossover is used with single strands or gametes. Hence, from one nonsister strand chiasma, two crossovers result. An example of a meiosis at the four-strand stage is given in Figure 1. It has often been proven that chiasma or crossover events are not independent. The notion of genetic interference describes the effect on crossovers of neighboring crossovers. The components of interference are as follows:

i. Non(complete)randomness in the number of crossovers: The no-interference model applies if the crossover numbers are Poisson distributed. All other count distributions yield deviations from no interference.
ii. Non(complete)randomness in crossover locations: The suppression of nearby crossovers has been modeled by nonuniformly distributed locations and by nonexponentially distributed intercrossover distances with renewal point processes.
iii. Chromatid interference (CI): The strands actually involved in a crossover depend in some way on those strands involved in neighboring crossovers.

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Substantial progress has been made in investigating and modeling the first two components. For these cases we use the term suppression interference (SI). For SI models, no chromatid interference (NCI) is assumed. For recent reviews see Karlin and Liberman (1994) and McPeek and Speed (1995). The χ^2-model of recombination (Foss *et al.* 1993; Zhao *et al.* 1995a) is accepted as a satisfying model for positive SI. Negative SI, *i.e.*, one chiasma enforcing the occurrence of another one, can be described, for example, by a negative binomial count distribution for the number of chiasmata.

The investigation of CI has not reached the same level yet. It started in the 1930s when recombination fractions >0.5 had been observed. This phenomenon was termed pseudolinkage. Models have been developed for data exhibiting pseudolinkage (Winge 1935; Mather 1938). Particularly, Mather found that this phenomenon could result only from CI. However, little evidence was found for it in diploid organisms. For a review and a test procedure, see Zhao *et al.* (1995b). Recently, Zhao and Speed (1998, 1999) developed a model for CI. To our knowledge, an application has not been published so far. Summarizing the literature, the general view is that CI is not evident. This is reflected by widely distributed mapping software (*e.g.*, CRIMAP) that reduce recombination fractions >0.5 to 0.5. Yet, recombination fractions $\theta > 0.5$ are accepted in tetraploids. Recombination fractions of up to 0.8 have been found in tetraploid fish (Wright *et al.* 1983). Since $\theta \leq 0.5$ is valid even for tetraploid species under NCI [see formula (6) with $Q = 0.25$], there is evidence for an action of CI.

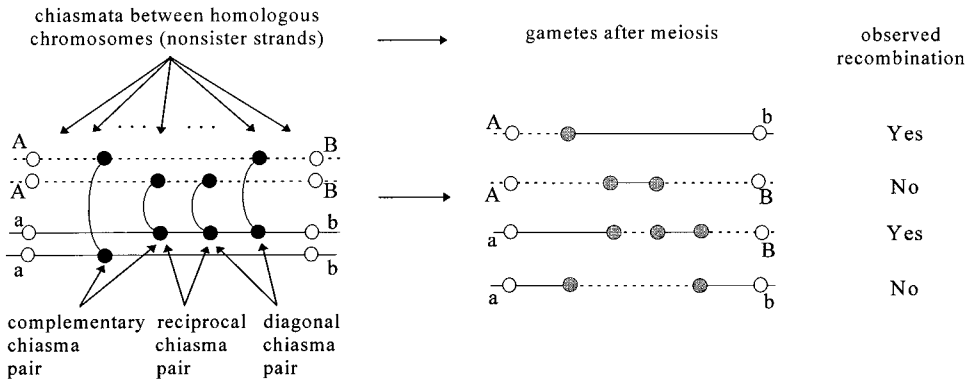

FIGURE 1.—Example of a four-strand-stage meiosis with four chiasmata and resulting gametes. A pair of vertically linked, solid circles indicates a chiasma: two nonsister strands break and recombine. Shaded circles denote resulting crossovers on the gametes. Open circles define loci with observable genotypes. Two-neighbored chiasmata are called complementary if they have no strand in common, reciprocal if they have two strands, and diagonal if they have one strand in common.

Hence, CI cannot be excluded, either from a theoretical point of view, or from empirical evidence. It therefore appears to be helpful to derive alternative models to the existing model of ZHAO and SPEED (1998), either to increase the evidence for CI in diploids or to strengthen the conviction that there is none. The objective of the present study was to develop a model allowing parallel nonsister strand chiasmata, which could not arise under high SI if one assumes suppression on all four strands, and sister strand chiasmata, which also have not been modeled so far but could play a role at high SI. In analyzing a number of recombination data sets we found evidence for SI and CI. Until now heterogeneity of interference has not been investigated. We incorporated CI heterogeneity into both CI models and obtained further improvement in fit.

METHODS

The CI(η) model of ZHAO and SPEED (1998): ZHAO and SPEED (1998) treated WEINSTEIN's (1936) and MATHER's (1938) approach of modeling CI by introducing a parameter η that defines the probability that a strand involved in a chiasma is also involved in the following chiasma. From this, the probabilities for complementary, diagonal, and reciprocal chiasma pairs (*cf.* Figure 1) are $(1-\eta)^2$, $2\eta(1-\eta)$, and η^2, respectively. Under NCI these are ¼, ½, and ¼. Thus $\eta > 0.5$ indicates an increased and $\eta < 0.5$ a reduced amount of reciprocal chiasma pairs compared to complementary pairs. The force of CI is assumed to be independent of the distance between the neighbored chiasmata. For the underlying SI process the χ^2-model of recombination was chosen; *i.e.*, suppression of nearby chiasmata is working on all four strands. This model here is called CI(η).

The CI(*Q*) model allowing sister strand and parallel nonsister strand chiasmata: JARRELL *et al.* (1995) found an increased occurrence of four-strand double crossovers at the centromere of bovine chromosome 23. For all models of SI derived for the four-strand bundle, such a finding can occur only if suppression is absent, since otherwise SI would act on all four strands.

To develop a CI model that takes this into account and gives additional information compared to the CI(η) model, we assume here that CI acts only in the neighborhood of a chiasma. Then a complementary chiasma pair is modeled by a parallel nonsister strand pair; *i.e.*, two complementary chiasmata occur close to one site. As mentioned above, this would lead to the phenomenon of double crossovers. On the other hand, nearby reciprocal chiasmata would look like sister strand chiasmata since they would seldom lead to observable recombinations. Thus we also allow sister strand chiasmata.

Let us again consider the question whether suppression of nearby chiasmata acts on all four strands or only on those involved in the chiasma. So far an answer to this question is not known. If we assume the highest amount of suppression in the first case, then the maximum average suppression distance is 0.5 M since within this distance the next chiasma must appear. In the latter case, the maximum average suppression distance is 1 M, since a chiasma on the complementary strands could restore the needed expected number of chiasmata. In this way, complementary pairs are enforced, which can be considered to be parallel from a model point of view. Additionally, sister strand chiasmata have been observed repeatedly. Although they are invisible to the observer of recombinations, they influence the location of neighbored nonsister strand chiasmata if suppression is a property of nonsister as well as sister strand chiasmata. Therefore, they must be taken into account.

Assume the four-strand stage of meiosis of diploids. We define a chiasma site to be a location on a chromosome, where strands break and reunite. Let P be the probability that exactly two nonsister strand chiasmata occur at a chiasma site and S that one or two sister strand chiasmata occur. Consequently, $1-P-S$ is the probability that exactly one nonsister chiasma appears at the chiasma site. The chance of a chiasma site producing a crossover on a gamete is then $Q = (1+P-S)/2$. We assumed that there are no dependencies between different chiasma sites; *i.e.*, for this, NCI is assumed.

Consider two loci on a random gamete with map distance x; *i.e.*, the expected number of crossovers is

x and an appropriate recombination fraction θ. The relationship between x and θ is given by the map function $\theta(x)$. Let $c_i'(x)$ be the probability that i crossovers appear between the loci on the gamete. Then for the expected number of crossovers

$$x = \sum_{i=1}^{\infty} i c_i'(x) \tag{1}$$

must be valid. A crossover results from a chiasmata site with probability Q. Under the given assumptions, with $c_i(x)$ being the probability that the interval carries i chiasma sites, we determine

$$\begin{aligned} c_i'(x) &= \sum_{j=i}^{\infty} P(i \text{ crossovers} \mid j \text{ chiasma sites})\, c_j(x) \\ &= Q^i \sum_{j=i}^{\infty} \binom{j}{i} (1 - Q)^{j-i} c_j(x). \end{aligned} \tag{2}$$

From the expectation condition (1) at the gamete level we obtain the requirement

$$x = \sum_{j=0}^{\infty} \sum_{i=0}^{j} \binom{j}{i} i Q^i (1 - Q)^{j-i} c_j(x) = Q \sum_{j=1}^{\infty} j c_j(x) \tag{3}$$

at the four-strand stage. An obvious consequence is the limitation of the distance given as

$$x \le nQ \tag{4}$$

if n is the maximum number of chiasmata. From the fact that a recombination results from an odd number of crossovers,

$$\begin{aligned} \theta(x) &= \frac{1}{2}\left\{1 - \sum_{i=0}^{\infty} (1 - 2Q)^i c_i(x)\right\} \\ &= \frac{1}{2}\left\{\sum_{i=0}^{\infty} (1 - (1 - 2Q)^i)\, c_i(x)\right\} \end{aligned} \tag{5}$$

can be evaluated for the recombination fraction. Its upper bounds are

$$\theta(x) \le 0.5 \quad \text{for } Q \le 0.5, \tag{6}$$

and

$$\theta(x) \le Q \quad \text{for } Q > 0.5. \tag{7}$$

Remember that $Q < 0.5$ indicates the preference of reciprocal pairs and $Q > 0.5$ the preference of complementary chiasma pairs. By this we have a CI model that is in concordance with the finding of Mather (1938) that a recombination fraction exceeding a half may only be the result of an enlarged number of complementary chiasmata.

Before we can apply the model we have to define the chiasma site distribution $\{c_i(x)\}$. As done by Zhao and Speed (1998), we use the χ^2-model of recombination. The combined model is denoted with CI(Q).

Note that (5) can be viewed as a general formula for an arbitrary strand stage of meiosis under NCI. A chiasma is involved in two of, say, a strands. A crossover will result from a chiasma on a random gamete with probability $Q = 2/a$. Therefore, for $Q = 1$, (5) coincides with the map function of the two-strand stage,

$$\theta(x) = \sum_{i=0}^{\infty} c_{2i+1}'(x) = \frac{1}{2}\left\{1 - \sum_{i=0}^{\infty} (-1)^i c_i(x)\right\}; \tag{8}$$

cf. Bailey (1961). For $Q = 0.5$, with the four-strand stage of diploids,

$$\theta(x) = \{1 - c_0(x)\}/2 \tag{9}$$

found by Mather (1938), and for $Q = 0.25$ with the eight-strand stage of tetraploids.

The map function for CI(Q): Recall the χ^2-model of recombination. The chiasma formation process is described by a stationary renewal process, where the intercrossover distances follow a χ^2-distribution with $2(m + 1)$ d.f. For the theory derived by Zhao *et al.* (1995a) the model of Foss *et al.* (1993) of the same process is helpful. In this model the locations C of so-called gene conversions are assumed to be uniformly and independently distributed on a scale y. Their values follow a Poisson distribution. By this, not every gene conversion C leads to a nonsister strand chiasma Cx. One realized Cx is followed by m gene conversions Co, from which no crossovers result. Afterward the next Cx is produced. Parameter m is the interference parameter, $m = 0$ indicates no interference. The probability of no crossovers was determined to be

$$c_0(x) = \sum_{i=0}^{m} \left(1 - \frac{i}{m + 1}\right) h_i(y), \tag{10}$$

with $h_i(y) = e^{-y} y^i / i!$. The relationship between the scale y with the genetic scale x is $y = 2(m + 1)x$ under NCI.

The application of the CI(Q) model is based on the assumption that an event Cx represents a chiasma site now, which leads to a crossover on a gamete with probability Q. The relation between the model scale y and the genetic scale x then changes to $y = (m + 1)x/Q$. The probability of the crossover number $i = 0$ is given by (10) and those for $i = 1, 2, \ldots$ are found to be

$$c_i(x) = h_{i(m+1)}(y) + \sum_{j=1}^{m} \frac{j}{m + 1} \{h_{(i-1)(m+1)+j}(y) + h_{(i+1)(m+1)-j}(y)\} \tag{11}$$

for $m \ge 1$ and $c_i(x) = h_i(y)$ for $m = 0$. The map function can be evaluated via (5) now. As for the map function of the CI(η) model of Zhao and Speed (1998), recombination fractions >0.5, monotone decreasing parts, and even wave shapes may arise. For $m \to \infty$ and $Q = 1$, the map function converges to the periodic map function of complete interference investigated by Teuscher (1997).

Note that for $m = 0$ (Haldane's model) the CI parameter Q does not influence the map function if $0 < Q \le 1$ holds. This can be proved by solving (3) and (5) with $\{c_i(x)\}$ following the Poisson distribution.

The distribution of recombination patterns for CI(Q): To find the theoretical distribution $\{\gamma(i)\}$ of the multilocus recombination pattern $i = (i_1, i_2, \cdots, i_r)$ for the gametes, where $i_k = 1$ indicates a recombination and $i_k = 0$ indicates absence of recombination between markers k and $k + 1$ on a randomly chosen gamete, we can follow the Appendix of Zhao *et al.* (1995a). Besides $y = (m + 1)x/Q$, a difference is the chance of s chiasmata in an interval to produce a recombination, which is $(1 - (1 - 2Q)^s)/2$ now, derived from (5). Thus we obtain

$$\gamma(i) = \frac{1}{m+1} 1' M_1 M_2 \cdots M_r 1 \qquad (12)$$

with $M_j = \Sigma_{k=0}^{\infty}(1 + (-1)^{ij}(1 - 2Q)^k)D_k(y_j)/2$ and $y_j = (m + 1)x_j/Q$. $D_k(y)$ is the $(m + 1) \times (m + 1)$ matrix whose i, jth entry is $e^{-y}\, y^{(m+1)k+j-i}/((m + 1)k + j - i)!$.

Definition of models CI(Q_i) and CI(η_i) for the investigation of heterogeneity of interference: Assume the frequent case that a model of a crossover formation process does not fit recombination data. Two reasons might explain this. The data set may be too small or unreliable, or the model might not be appropriate. For the latter case we have to check the assumptions. In all models created so far the real process is assumed to be homogeneous over the whole chromosome. This is not necessarily true. We therefore investigate heterogeneous processes. Our hypothesis is that when finding the same degree of interference for two adjacent or overlapping regions of a chromosome, the model is applicable if it fits both parts together. On the other hand, we cannot expect a model to fit data for a certain region if it already failed for a part of it, or if different parts of it show different characteristics of interference.

From a preliminary analysis we concluded that interference is likely to act heterogeneously. A generalization of the CI models to regard heterogeneous SI appears to be difficult. We propose the incorporation of CI heterogeneity. We therefore introduce CI parameters into the models that may vary between different parts of the chromosome. For the CI(Q) model, like the CI(η) model of Zhao and Speed (1998), we assign CI parameters Q_i and η_i to intervals i, which does not change the theory in any significant way. These models are denoted by CI(Q_i) and CI(η_i), respectively. However, the two-locus recombination fractions then are not only a function of the distance between the loci but of their locations. To ensure $0 \le Q_i, \eta_i \le 1$ during numerical calculations, we fit auxiliary variables z_i and put $Q_i, \eta_i = \sin^2(z_i)$.

Given a recombination data set we apply the following procedure. First we fit Haldane's no-interference model, then a NCI model like the χ^2-model of recombination for positive SI or alternatively the negative binomial map function for negative SI. To test CI *vs.* no interference, we use the model CI(η) with $m = 0$. Then the homogeneous CI models are applied. If they do not fit the data, the models for heterogeneous CI are used. If these models are significantly better than the homogeneous CI models, one source of the heterogeneity is proved. If the data still do not fit satisfactorily, heterogeneous SI appears to act and is subject to further investigations: We divide the chromosome and start with the analysis of all pairs of adjacent intervals. For each pair there are four possible recombination patterns, (0, 0), (1, 0), (0, 1), and (1, 1), to which we have to fit the observations. Since the sample size is known, three equations have to be solved. Practice shows that this can be realized by the two genetic distances to be estimated and by the introduction of one parameter to estimate SI. Following this, we analyze all triples of adjacent intervals, then the quadruples, etc.

The test criterion for the fit of the models to real data: Commonly, the multilocus concept of Weeks *et al.* (1993) is used to analyze recombination data. For a directly observable multilocus recombination pattern, the criterion of fit is the log-likelihood

$$\ln L = \max\left(\sum_i n(i)\ln(\gamma(i))\right), \qquad (13)$$

where $n(i)$ is the observed number and $\gamma(i)$ is the theoretical probability of recombination pattern i. The $r + 1$ markers are assumed to be ordered, with genetic distances between each consecutive pair of markers $x_1, x_2, \cdots, x_r$. The maximum has to be determined by varying the genetic distances and the parameters of the model.

Haldane's no-interference model is nested in the χ^2-model of recombination, representing the NCI model. The NCI model is nested in both models for homogeneous CI; *i.e.*, a likelihood-ratio test can be applied to test whether CI is acting or not. Also, the CI(Q) and CI(η) models are nested in the CI(Q_i) and CI(η_i) models, respectively, and we can test whether CI heterogeneity is significant. To compare two nested models, a likelihood-ratio test is applied. Following the asymptotic theory, twice the difference of the two log-likelihoods of the models is χ^2-distributed with the difference of the number of parameters being the degrees of freedom.

In the application of the models for heterogeneous CI, the interval-wise CI parameters $\hat{Q}_i$ and $\hat{\eta}_i$, $i = 1, \cdots, r$, have to be estimated. To obtain a statement for interval i, whether deviations from NCI are significant, we compare the complete models for each i with the model restricted by $Q_i = 0.5$ or $\eta_i = 0.5$, respectively.

We evaluate the quality of a fitted model by comparing its log-likelihood value with the ideal log-likelihood value theoretically achievable by an unknown model that fits the observed gamete distribution exactly; *i.e.*, for this model, $\gamma(i) = n(i)/N$ with $N = \Sigma_i\, n(i)$ is valid. If twice the difference of the two log-likelihoods is smaller than the $1 - \alpha$-quantile of the χ^2-distribution with 1 d.f., which is 3.841 for $\alpha = 0.05$, a model of a significantly better fit than that of the model analyzed does not exist.

For this case we use the phrase that the model fits the data.

RESULTS

Application to the data of Morgan *et al.* (1935): The nine-locus Drosophila data of Morgan *et al.* (1935) have often been used to compare crossover formation models (see McPeek and Speed 1995). The data have not been fitted well by any model. Compared with the ideal log-likelihood of −36,899.5, we obtained ln $L = -37{,}956.6$ for Haldane's no-interference model, ln $L = -36{,}987.1$ for the NCI model (χ^2-model of recombination with $\hat{m} = 4$; similar to the gamma model of McPeek and Speed 1995), and ln $L = -37{,}122.1$ for the CI(η) model under absence of SI ($m = 0, \hat{\eta} = 0$). We find significance for the effects of both SI and CI. Models CI(Q) and CI(η) are not significantly better than the NCI model, thus proving that homogeneous CI is not evident in addition to SI. Models CI(Q_j) and CI(η_i) with ln $L = -36{,}943.0$ and ln $L = -36{,}950.0$, respectively, however, yield a highly significant gain in fit when considering heterogeneous CI. To investigate the heterogeneity of SI, we analyzed first pairs of adjacent intervals by the NCI model. We obtained $\hat{m} = 4$ for the first pair and $\hat{m} = 5, 4, 3, 4, 4$, and 2 for the subsequent interval pairs. All models fitted the data. The analysis of three neighboring intervals with the NCI, CI(Q), and CI(η) models gave the results summarized in the appendix, Table A1. Only the triple of intervals (5, 6, 7) could be fitted well. This was supported by the same interference strength $m = 4$ in intervals (5, 6) and intervals (6, 7). Different SI strengths at neighbored interval pairs led to triples not fitting. At the first and second triples we found significant improvement of the NCI model by the CI models. Both models suggest an increased occurrence of complementary chiasmata.

Then we analyzed the quadruples of intervals. The results are shown in the appendix, Table A2. For the first quadruple, termed the "five-locus data of Morgan *et al.* (1935)" in the literature, and the second and fourth quadruple a highly significant improvement over the NCI model is evident. Deviating from the former conclusions, both CI models indicate a significant effect of dominating reciprocal chiasmata at quadruple (4, 5, 6, 7). However, from quadruples onward, no model fits the data. The analysis of the quintuples (Table A3) underlines the tendency of the telomeric part to carry an increased number of reciprocal chiasma pairs. The dominance of complementary chiasma pairs at the centromere region is still visible. The analysis of six neighboring intervals with the CI(Q) model indicates the same result. There, model CI(η) showed significance only at the telomeric part. With seven or eight intervals, no improvements over the NCI model are found.

We applied the CI(Q_j) and CI(η_i) models to the four-interval case. The results compared with the eight-interval analysis are displayed in the appendix, Tables A4 and A5. A significant improvement over the models assuming homogeneous CI is observed.

Application to the data of Weinstein (1936): The seven-locus Drosophila data of Weinstein (1936) have also often been analyzed (*e.g.*, Zhao *et al.* 1995a). All models applied here yield a significant gain in fit when compared to nested models. The log-likelihood for Haldane's model is −56,394.3 and that of the CI(η) model under absence of interference ($m = 0$, $\hat{\eta} = 0$) is −55,096.2. The results for the other models are shown in Table 1. Again we see that the effect of SI is larger than that of CI. However, both effects and even the effect of heterogeneous CI are significant. To investigate the heterogeneity of SI we analyzed adjacent intervals by the NCI model. We obtained $\hat{m} = 4$ for the first two intervals and $\hat{m} = 5, 4, 3$, and 3 for the subsequent interval pairs. All models fitted the data. Analysis of three neighboring intervals with the NCI, CI(Q), and CI(η) models led to the results summarized in the appendix, Table A6. Only the triple of intervals (4, 5, 6) almost fitted. This was supported by the same interference strength of $m = 3$ in intervals (4, 5) and (5, 6). Different interference strengths in neighboring intervals led to triples not fitting. At the first, second, and third triples we found significant improvement of the NCI models by the CI models. Both models suggest an increased occurrence of complementary chiasmata.

Then we analyzed the quadruples of adjacent intervals. The results are shown in the appendix, Table A7. For the first and second quadruples we again found a highly significant improvement over the NCI model.

We applied the CI(Q_j) and CI(η_i) models to the four-interval case and compared the results with the six-interval analysis (Table A8). Some significant improvements over the models of homogeneous CI were found.

Application to the data of Blank *et al.* (1988): The recombination data of Blank *et al.* (1988) on chromosome 12 of mice have been used repeatedly for investigations on the phenomenon of interference (Weeks *et al.* 1994; Lin and Speed 1996). The analysis of the whole data set led to results shown in Table 2. Furthermore, we obtained ln $L = -564.67$ for fitting Haldane's model and ln $L = -547.63$ for fitting CI(η) under absence of SI ($m = 0$, $\hat{\eta} = 0$); *i.e.*, the effects of SI (ln $L = -547.12$ under NCI) and CI nearly agree. Both effects are significant compared to assuming no interference. The CI(Q) and CI(η) models are significantly better than the NCI model, which was so far viewed to fit best (Lin and Speed 1996). For the CI(Q_j) model we obtained the best fit for $\hat{m} = 6$, $\hat{Q}_1 = 0.19$, $\hat{Q}_2 = \cdots = \hat{Q}_5 = 1$, $\hat{Q}_6 = 0.87$, and $\hat{Q}_7 = 0.72$. This model is significantly better than the NCI model but not significantly better than the model for homogeneous CI. Only $\hat{Q}_1$ differs significantly from 0.5. For the CI(η_i) model we obtained the best fit for $\hat{m} = 1$, $\hat{\eta}_1 = \hat{\eta}_2 = 1$, and $\hat{\eta}_3 = \cdots = \hat{\eta}_7 = 0$. This model fits significantly better than the

TABLE 1

Observed gamete counts of the data of WEINSTEIN (1936) and counts expected for the χ^2-model under NCI and under different models for chromatid interference

		Expected				
Gamete	Observed	NCI: $\hat{m} = 4$, $Q = \eta = 0.5$	CI(Q): $\hat{m} = 3$, $\hat{Q} = 0.60$	CI(η): $\hat{m} = 4$, $\hat{\eta} = 0.46$	CI(Q_j): $\hat{m} = 3$, $\hat{Q}_j$ (see Table 9)	CI(η_i): $\hat{m} = 3$, $\hat{\eta}_i$ (see Table 9)
(0, 0, 0, 0, 0, 0)	12,776	13,054.0	12,771.5	12,759.5	12,777.5	12,774.3
(1, 0, 0, 0, 0, 0)	1,407	1,267.7	1,310.9	1,313.7	1,393.0	1,402.8
(0, 1, 0, 0, 0, 0)	2,018	1,893.7	1,964.7	1,959.7	2,072.9	2,049.6
(0, 0, 1, 0, 0, 0)	1,976	1,793.0	1,856.1	1,850.9	1,910.3	1,912.9
(0, 0, 0, 1, 0, 0)	3,378	3,324.0	3,428.3	3,426.0	3,394.1	3,416.9
(0, 0, 0, 0, 1, 0)	2,356	2,404.5	2,474.4	2,484.0	2,366.2	2,360.2
(0, 0, 0, 0, 0, 1)	2,067	2,101.8	2,179.5	2,178.1	2,053.0	2,063.5
(1, 1, 0, 0, 0, 0)	9	9.0	11.8	8.6	7.6	11.5
(1, 0, 1, 0, 0, 0)	16	44.6	45.1	42.5	29.1	21.1
(1, 0, 0, 1, 0, 0)	142	211.1	189.4	199.3	150.3	144.6
(1, 0, 0, 0, 1, 0)	198	226.2	206.0	211.7	196.6	196.9
(1, 0, 0, 0, 0, 1)	206	214.0	211.2	202.1	213.0	209.2
(0, 1, 1, 0, 0, 0)	11	13.8	18.0	13.4	9.7	9.4
(0, 1, 0, 1, 0, 0)	136	170.7	163.0	163.6	126.5	135.0
(0, 1, 0, 0, 1, 0)	261	274.7	243.7	259.0	241.4	249.2
(0, 1, 0, 0, 0, 1)	318	305.7	285.9	286.5	295.8	294.2
(0, 0, 1, 1, 0, 0)	42	47.9	54.1	46.8	47.6	48.7
(0, 0, 1, 0, 1, 0)	148	163.6	148.9	156.4	165.6	166.6
(0, 0, 1, 0, 0, 1)	212	247.6	221.9	232.6	242.2	245.0
(0, 0, 0, 1, 1, 0)	123	88.2	93.3	85.5	130.5	110.7
(0, 0, 0, 1, 0, 1)	315	270.2	247.1	256.4	298.6	291.9
(0, 0, 0, 0, 1, 1)	59	43.1	47.9	41.2	56.1	61.2
(1, 1, 0, 1, 0, 0)	3	0.7	0.8	0.6	0.4	0.7
(1, 1, 0, 0, 1, 0)	1	1.2	1.4	1.1	0.9	1.3
(1, 1, 0, 0, 0, 1)	2	1.4	1.7	1.2	1.1	1.6
(1, 0, 1, 0, 1, 0)	3	3.8	3.5	3.4	2.4	1.8
(1, 0, 1, 0, 0, 1)	3	6.0	5.3	5.2	3.6	2.7
(1, 0, 0, 1, 1, 0)	10	4.8	4.6	4.3	5.1	4.3
(1, 0, 0, 1, 0, 1)	15	16.1	12.9	14.0	12.5	11.9
(1, 0, 0, 0, 1, 1)	1	3.9	3.9	3.4	4.3	5.0
(0, 1, 1, 1, 0, 0)	1	0.3	0.4	0.3	0.2	0.2
(0, 1, 0, 1, 1, 0)	2	3.3	3.5	3.0	4.0	3.6
(0, 1, 0, 1, 0, 1)	10	12.2	10.6	10.8	10.2	10.7
(0, 1, 0, 0, 1, 1)	1	4.6	4.4	4.0	5.0	6.2
(0, 0, 1, 1, 0, 1)	5	3.0	3.2	2.7	3.6	3.6
(0, 0, 1, 0, 1, 1)	5	2.5	2.6	2.2	3.1	3.9
(0, 0, 0, 1, 1, 1)	1	1.1	1.4	1.0	1.9	2.3
(1, 1, 1, 1, 0, 0)	1	0.001	0.002	0.0005	0.0004	0.001
(1, 1, 1, 0, 0, 1)	1	0.004	0.008	0.004	0.003	0.004
ln L	−54,850.1[a]	−54,950.2	−54,931.8	−54,935.8	−54,890.0	−54,887.8

[a] Ideal case: theoretical and observed distributions agree.

homogeneous model CI(η). Estimates $\hat{\eta}_3$, $\hat{\eta}_6$, and $\hat{\eta}_7$ differ significantly from 0.5. From the estimates of the heterogeneity parameters we hypothesize that the problem is to fit the first three intervals and the last six. Analysis of the first three intervals gave ln $L = -277.62$ for the NCI model ($m = 1$), ln $L = -276.72$ for the CI(η) model ($\hat{\eta} = 0.23$, $\hat{m} = 1$), ln $L = -276.95$ for the CI(Q) model ($\hat{Q} = 1$, $\hat{m} = 1$), and ln $L = -272.28$ for the CI(η_i) model ($\hat{\eta}_1 = \hat{\eta}_2 = 1$, $\hat{\eta}_3 = 0$, and $\hat{m} = 1$). Compared to the ideal log-likelihood of ln $L = -270.96$, only the CI(η_i) model fitted the data, indicating substantial heterogeneity in the first three intervals. The results of analyzing the first adjacent pairs with NCI models are shown in the APPENDIX, Table A9. For the first two intervals, the result $\hat{m} = 0$ suggests that Haldane's model fitted best. The model fitted the data. We also applied the negative binomial map function and fitted the data exactly. This is a hint of the action of negative rather

TABLE 2

Observed gamete counts of the data of Blank *et al.* (1988) and counts expected for the χ^2-model under NCI and under different models for chromatid interference

		Expected				
Gamete	Observed	NCI: $\hat{m} = 6$, $Q = \eta = 0.5$	CI(Q): $\hat{m} = 2$, $\hat{Q} = 1$	CI(η): $\hat{m} = 2$, $\hat{\eta} = 0.15$	CI(Q_j): $\hat{m} = 6$, $\hat{Q}_j$ (see text)	CI(η_i): $\hat{m} = 1$; $\hat{\eta}_i$ (see text)
(0, 0, 0, 0, 0, 0, 0)	148	159.3	148.0	148.4	149.4	146.4
(1, 0, 0, 0, 0, 0, 0)	27	30.8	32.9	31.9	26.1	31.7
(0, 1, 0, 0, 0, 0, 0)	5	6.0	6.6	6.5	6.1	5.8
(0, 0, 1, 0, 0, 0, 0)	45	36.6	41.5	41.7	43.1	43.7
(0, 0, 0, 1, 0, 0, 0)	4	3.2	3.6	3.6	3.7	3.8
(0, 0, 0, 0, 1, 0, 0)	6	4.8	5.4	5.4	5.6	5.7
(0, 0, 0, 0, 0, 1, 0)	24	20.3	22.9	23.3	24.1	24.1
(0, 0, 0, 0, 0, 0, 1)	47	39.3	44.8	46.1	46.9	46.5
(1, 1, 0, 0, 0, 0, 0)	2	0.01	0.02	0.04	0.2	0.7
(1, 0, 0, 0, 0, 1, 0)	2	2.1	1.3	1.0	1.9	0.9
(1, 0, 0, 0, 0, 0, 1)	5	7.2	4.5	3.3	5.6	3.5
(0, 0, 1, 0, 0, 0, 1)	2	3.6	2.6	2.3	1.2	2.3
ln L	−531.92[a]	−547.12	−543.28	−542.93	−538.60	−536.21

[a] Ideal case: theoretical and observed distributions agree.

than positive interference. For the second pair we found ln $L = -165.52$ for $\hat{m} = 15$. Although not significant compared to Haldane's model, a strong positive interference seems to act.

For intervals 2–7 the NCI model already fits the data ($\hat{m} = 29$). We evaluated ln $L = -430.03$, which was highly significantly better than Haldane's model (ln $L = -452.48$). For comparison, the ideal log-likelihood was −428.96.

DISCUSSION

A long-known reason for the occurrence of chiasmata is to help organize meioses by fixing strands. On the other hand, it turned out that molecular strategies of inheritance play an important role in the biological process of evolution. It is not clear if or how chiasmata are involved in this process. Only trivial statements can be made, such as negative or absence of genetic interference increases genetic variability on the gametes more than high positive interference. The investigation of meiotic processes with particular sets of recombination data is only one but an important step in contributing knowledge in this area.

The NCI models routinely used in mapping today reflect only SI. We have proved that, as well as SI, CI and even interference heterogeneity may play an important role in meiosis. We found evidence for heterogeneous SI and CI. The SI heterogeneity differed among the three data sets considered. While we found positive, slightly varying intermediate SI for the data of Morgan *et al.* (1935) and Weinstein (1936), we found slightly negative or absent SI at the centromere region and high SI at the telomeric part of the chromosome for the data of Blank *et al.* (1988).

The results on CI also differ between data sets. We therefore conclude that no general rules for interference heterogeneity exist. Using the data of Morgan *et al.* (1935) and Weinstein (1936) we found an increased amount of complementary chiasmata at the centromere region. For the data of Morgan *et al.* (1935) we additionally found an increased amount of reciprocal chiasma pairs at the telomeric part of the chromosome. This is particularly evident from the results for the CI(Q) model and could result from sister strand chiasmata. Using the data of Blank *et al.* (1988) we proved an intensification of complementary chiasma pairs that are concentrated mainly in the telomeric part. The findings for the centromere weakly indicate either an increased amount of reciprocal chiasmata or simply negative SI.

One should note that Morgan *et al.* (1935) and Weinstein (1936) examined the same chromosome of the same species. It is of particular interest that the first five loci and the seventh locus were identical. Comparing Tables A1 and A6, A2 and A7, A4 and A8, and A5 and A8, we indeed observe a congruence of parameter estimates and interference behavior. Both models for CI behaved similarly. Therefore it is not clear whether CI works better at small or large distances. We note that numerically the CI(Q) model is about five times faster than the CI(η) model.

We have shown that chromatid and suppression interference are not completely separable. Especially, positive SI may partially be compensated by a greater

amount of complementary chiasma pairs and negative SI by an enlarged amount of reciprocal chiasma pairs. For the data of MORGAN *et al.* (1935) and WEINSTEIN (1936), SI dominates CI, while for the data of BLANK *et al.* (1988) both kinds of interference have the same strength. However, separation would be easier if we were dealing with data exhibiting obvious deviations from NCI, such as recombination fractions >0.5 or decreasing recombination fractions for increasing distances. Let us consider the data of BLANK *et al.* (1988). The data do not cover the whole chromosome. The maximum recombination fraction is 0.498. The CI models fitted suggest that the recombination fractions would exceed 0.5 if the whole chromosome had been investigated. If this is not true, the gain in fit explained with CI is an artifact. Then we would have proved that the χ^2-model of recombination is not appropriate to the data, but that another chiasma formation process is adequate, and may be a nonstationary renewal one. However, our experience with mouse markers (BROCKMANN *et al.* 1998) shows that recombination fractions can exceed 0.5.

From our results and from the indications found for CI acting in tetraploids, we conclude that chromatid interference is likely to act. We encourage geneticists to be aware of recombination fractions exceeding one-half and that the phenomenon of interference heterogeneity should not be ruled out.

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APPENDIX

TABLE A1

Log-likelihoods and estimated parameters for different models of interference fitted to three adjacent intervals of the data of MORGAN *et al.* (1935)

	Analyzed intervals					
Model	1, 2, 3	2, 3, 4	3, 4, 5	4, 5, 6	5, 6, 7	6, 7, 8
Data[a]	−12,745.2	−15,650.7	−15,049.3	−17,531.2	−15,511.3	−13,918.1
NCI	−12,753.6 $\hat{m} = 5$	−15,659.7 $\hat{m} = 5$	−15,051.4 $\hat{m} = 3$	−17,534.5 $\hat{m} = 3$	−15,512.4[b] $\hat{m} = 4$	−13,921.9 $\hat{m} = 4$
CI(Q)	−12,750.7 $\hat{m} = 3$ $\hat{Q} = 0.87$*	−15,655.1 $\hat{m} = 3$ $\hat{Q} = 0.73$**	−15,051.4 $\hat{m} = 3$ $\hat{Q} = 0.50$	−17,534.5 $\hat{m} = 3$ $\hat{Q} = 0.50$	−15,512.4[b] $\hat{m} = 4$ $\hat{Q} = 0.50$	−13,920.9 $\hat{m} = 3$ $\hat{Q} = 0.60$
CI(η)	−12,749.5 $\hat{m} = 2$ $\hat{\eta} = 0.09$**	−15,654.2 $\hat{m} = 2$ $\hat{\eta} = 0.25$**	−15,051.4 $\hat{m} = 3$ $\hat{\eta} = 0.51$	−17,534.4 $\hat{m} = 3$ $\hat{\eta} = 0.50$	−15,512.4[b] $\hat{m} = 4$ $\hat{\eta} = 0.50$	−13,920.8 $\hat{m} = 3$ $\hat{\eta} = 0.36$

Significantly better than NCI model. *$P < 0.05$; **$P < 0.01$.
[a] Ideal case: theoretical and observed distributions agree.
[b] Model is not significantly improved.

TABLE A2

Log-likelihoods and estimated parameters for different models of interference fitted to four adjacent intervals of the data of MORGAN *et al.* (1935)

	Analyzed intervals				
	1, 2, 3, 4	2, 3, 4, 5	3, 4, 5, 6	4, 5, 6, 7	5, 6, 7, 8
Data[a]	−18,751.3	−20,099.7	−21,820.1	−21,655.2	−18,343.3
NCI	−18,776.2 $\hat{m} = 5$	−20,125.1 $\hat{m} = 4$	−21,827.3 $\hat{m} = 3$	−21,670.9 $\hat{m} = 4$	−18,348.3 $\hat{m} = 4$
CI(Q)	−18,762.0 $\hat{m} = 2$ $\hat{Q} = 1.0$***	−20,120.6 $\hat{m} = 3$ $\hat{Q} = 0.61$**	−21,827.2 $\hat{m} = 4$ $\hat{Q} = 0.44$	−21,667.7 $\hat{m} = 4$ $\hat{Q} = 0.45$*	−18,347.1 $\hat{m} = 3$ $\hat{Q} = 0.57$
CI(η)	−18,761.0 $\hat{m} = 3$ $\hat{\eta} = 0.24$***	−20,120.5 $\hat{m} = 3$ $\hat{\eta} = 0.37$**	−21,827.3 $\hat{m} = 3$ $\hat{\eta} = 0.50$	−21,667.3 $\hat{m} = 3$ $\hat{\eta} = 0.58$**	−18,347.8 $\hat{m} = 3$ $\hat{\eta} = 0.41$

Significantly better than NCI model. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a] Ideal case: theoretical and observed distributions agree.

TABLE A3

Log-likelihoods and estimated parameters for different models of interference fitted to five adjacent intervals of the data of MORGAN *et al.* (1935)

	Analyzed intervals			
	1, 2, 3, 4, 5	2, 3, 4, 5, 6	3, 4, 5, 6, 7	4, 5, 6, 7, 8
Data[a]	−23,196.6	−26,868.9	−25,943.6	−24,486.8
NCI	−23,243.9 $\hat{m} = 4$	−26,901.4 $\hat{m} = 4$	−25,963.7 $\hat{m} = 3$	−24,506.5 $\hat{m} = 3$
CI(Q)	−23,230.9 $\hat{m} = 3$ $\hat{Q} = 0.64$***	−26,900.9 $\hat{m} = 3$ $\hat{Q} = 0.56$	−25,959.2 $\hat{m} = 4$ $\hat{Q} = 0.46$**	−24,503.4 $\hat{m} = 4$ $\hat{Q} = 0.46$*
CI(η)	−23,231.4 $\hat{m} = 3$ $\hat{\eta} = 0.35$***	−26,901.4 $\hat{m} = 4$ $\hat{\eta} = 0.50$	−25,961.2 $\hat{m} = 4$ $\hat{\eta} = 0.55$*	−24,503.6 $\hat{m} = 4$ $\hat{\eta} = 0.56$*

Significantly better than NCI model. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[a] Ideal case: theoretical and observed distributions agree.

TABLE A4

Estimated chromatid interference parameters $\hat{Q}_i$ and obtained log-likelihoods for the five- and nine-locus analyses of the data of Morgan *et al.* (1935) with model CI(Q_i)

Analyzed intervals	ln L (m with best fit)	$\hat{Q}_i$ for interval i							
		$i = 1$	$i = 2$	$i = 3$	$i = 4$	$i = 5$	$i = 6$	$i = 7$	$i = 8$
1, 2, 3, 4	−18,757.3* (3)	0.51	1[a]	1[a]	0.52				
2, 3, 4, 5	−20,102.2** (3)		1[a]	1[a]	0.51	0.37			
3, 4, 5, 6	−21,824.2 (3)			0.90[a]	0.46	0.40	0.70[a]		
4, 5, 6, 7	−21,662.0* (4)				0.34	0.51	0.46	0.82	
5, 6, 7, 8	−18,344.5 (3)					0.36	0.73	0.54	0.30
1, 2, 3, 4, 5, 6, 7, 8	−36,943.0** (3)	0.52	1[a]	1[a]	0.51	0.34[a]	0.73[a]	0.49	0.34
1, 2, 3, 4, 5, 6, 7, 8	−36,944.4** (4)	0.35	0.88[a]	0.99[a]	0.42	0.38	0.55	0.53	0.23

Significantly better than model for homogeneous interference. *$P < 0.01$; **$P < 0.001$.
[a] Estimate differs significantly from 0.5 ($P < 0.05$).

TABLE A5

Estimated chromatid interference parameters $\hat{\eta}_i$ and obtained log-likelihoods for the five- and nine-locus analyses of the data of Morgan *et al.* (1935) with model CI(η_i)

Analyzed intervals	ln L (m with best fit)	$\hat{\eta}_i$ for interval i							
		$i = 1$	$i = 2$	$i = 3$	$i = 4$	$i = 5$	$i = 6$	$i = 7$	$i = 8$
1, 2, 3, 4	−18,756.2* (2)	0	0.14[a]	0.08[a]	0.20[a]				
2, 3, 4, 5	−20,102.3** (2)		0	0.07[a]	0.19[a]	0.40[a]			
3, 4, 5, 6	−21,825.9 (3)			0	0.39	0.55	0.50		
4, 5, 6, 7	−21,661.2* (4)				1	0.98[a]	0.58[a]	0.54	
5, 6, 7, 8	−18,346.9 (3)					1	0.40	0.37[a]	0.45
1, 2, 3, 4, 5, 6, 7, 8	−36,953.0** (3)	0	0.29	0.13[a]	0.26[a]	0.46	0.50	0.52	0.50

Significantly better than model for homogeneous interference. *$P < 0.01$; **$P < 0.001$.
[a] Estimate differs significantly from 0.5 ($P < 0.05$).

TABLE A6

Log-likelihoods and estimated parameters for different models of interference fitted to three adjacent intervals of the data of Weinstein (1936)

Model	Analyzed intervals			
	1, 2, 3	2, 3, 4	3, 4, 5	4, 5, 6
Data[a]	−24,108.8	−28,569.3	−29,527.1	−31,329.6
NCI	−24,128.5 $\hat{m} = 5$	−28,575.2 $\hat{m} = 5$	−29,537.4 $\hat{m} = 4$	−31,331.9 $\hat{m} = 3$
CI(Q)	−24,120.1 $\hat{m} = 3$ $\hat{Q} = 0.80$**	−28,572.5 $\hat{m} = 3$ $\hat{Q} = 0.69$*	−29,534.9 $\hat{m} = 3$ $\hat{Q} = 0.57$*	−31,331.9 $\hat{m} = 3$ $\hat{Q} = 0.50$
CI(η)	−24,115.6 $\hat{m} = 2$ $\hat{\eta} = 0.12$**	−28,572.5 $\hat{m} = 4$ $\hat{\eta} = 0.38$*	−29,534.7 $\hat{m} = 3$ $\hat{\eta} = 0.41$*	−31,331.9 $\hat{m} = 3$ $\hat{\eta} = 0.50$

Significantly better than NCI model. *$P < 0.05$; **$P < 0.001$.
[a] Ideal case: theoretical and observed distributions agree.

TABLE A7

Log-likelihoods and estimated parameters for different models of interference fitted to four adjacent intervals of the data of WEINSTEIN (1936)

	Analyzed intervals		
	1, 2, 3, 4	2, 3, 4, 5	3, 4, 5, 6
Data[a]	−35,471.3	−38,214.4	−39,280.8
NCI	−35,513.0	−38,239.2	−39,304.1
	$\hat{m} = 5$	$\hat{m} = 4$	$\hat{m} = 4$
CI(Q)	−35,491.8	−38,234.1	−39,297.5
	$\hat{m} = 3$	$\hat{m} = 3$	$\hat{m} = 3$
	$\hat{Q} = 0.71$**	$\hat{Q} = 0.60$*	$\hat{Q} = 0.55$**
CI(η)	−35,494.0	−38,235.2	−39,297.1
	$\hat{m} = 3$	$\hat{m} = 4$	$\hat{m} = 3$
	$\hat{\eta} = 0.29$**	$\hat{\eta} = 0.46$*	$\hat{\eta} = 0.45$**

Significantly better than NCI model. *$P < 0.01$; **$P < 0.001$.
[a] Ideal case: theoretical and observed distributions agree.

TABLE A8

Estimated chromatid interference parameters $\hat{Q}_i$ and $\hat{\eta}_i$ and obtained log-likelihoods for the five- and seven-locus analyses of the data of WEINSTEIN (1936) with models CI(Q_i) and CI(η_i)

	CI(Q_i)							CI(η_i)						
		$\hat{Q}_i$ for interval i							$\hat{\eta}_i$ for interval i					
Analyzed intervals	ln L ($\hat{m}$)	1	2	3	4	5	6	ln L ($\hat{m}$)	1	2	3	4	5	6
1, 2, 3, 4	−35,488.6 (3)	0.56	0.92[a]	0.78[a]	0.58			−35,483.9**(3)	0	0.33	0.15[a]	0.31[a]		
2, 3, 4, 5	−38,220.6**(3)		0.58	1	0.56[a]	0.45[a]		−38,221.9* (3)		0	0.20[a]	0.31[a]	0.45[a]	
3, 4, 5, 6	−39,286.6**(3)			1	0.60[a]	0.41	0.77[a]	−39,289.9* (3)			0	0.28[a]	0.44[a]	0.47
1, 2, 3, 4, 5, 6	−54,890.0**(3)	0.57	0.97[a]	0.69[a]	0.62[a]	0.38[a]	0.96[a]	−54,887.8**(3)	0	0.30	0.16[a]	0.31[a]	0.45[a]	0.49

Significantly better than model for homogeneous interference. *$P < 0.01$; **$P < 0.001$.
[a] Estimate differs significantly from 0.5 ($P < 0.05$).

TABLE A9

Observations of the first two interval pairs of the data of Blank *et al.* (1988) with expected numbers obtained by fitting different models

	Analyzed intervals						
	1, 2				2, 3		
		Expected				Expected	
Gamete	Observed	Haldane	Negative binomial: $\hat{\alpha} = 0.41$	CI(η): $\hat{\eta} = 1$, $\hat{m} = 0$	Observed	Haldane	χ^2-model: $\hat{m} = 15$
(0, 0)	276	274.8	276.0	275.5	263	264.0	263.0
(1, 0)	34	35.2	34.0	34.5	7	6.0	7.0
(0, 1)	5	6.2	5.0	5.4	47	46.0	47.0
(1, 1)	2	0.8	2.0	1.6	0	1.0	0.0
ln L	−145.01[a]	−145.80	−145.01	−145.08	−165.52[a]	−166.65	−165.52

[a] Ideal case: theoretical and observed distributions agree.