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Parameters in gene conversion

An algebraic analysis of the hybrid DNA model at the *gray* locus of *Sordaria fimicola*.*

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SUMMARY

We have extended previous algebraic analyses of aberrant segregation at the *gray* locus of *Sordaria fimicola* (Whitehouse, 1965; Emerson, 1966; Fincham, Hill & Reeve, 1980) to the more complex situation where aberrant segregations are detected in three factor crosses involving two flanking markers. This algebra has been applied to seven *gray* alleles which have been extensively characterized for their pattern of gene conversion and postmeiotic segregation by Kitani & Olive (1967). It is based on seven major types of aberrant segregation which can be distinguished in the presence of flanking markers spanning the converting site, and allows us to use up to six parameters to describe hDNA formation and mismatch repair. We present solutions which predict a spectrum of aberrant segregation fitting the experimental data at the $P > 0{\cdot}05$ level for six of the seven alleles tested. They are consistent with the following properties of hDNA at the *gray* locus: (1) the single stranded DNA transferred during hDNA formation has always the same chemical polarity. (2) hDNA is mostly, if not entirely, symmetric, and its probability of formation is constant over the whole gene. (3) Disparity in aberrant segregation is mostly, if not entirely due to disparity in mismatch repair.

1. INTRODUCTION

The hybrid DNA (hDNA) model proposed by Holliday and by Whitehouse provides a general explanation of the properties of genetic recombination. In particular, it explains the various classes of aberrant segregation associated with recombination in Ascomycetes (see Catcheside, 1977). The model is amenable to an algebraic formulation where the probability of each class of aberrant segregation is a function of a few parameters defining the properties of hDNA formation and of heteroduplex repair (Whitehouse, 1965; Emerson, 1966). Given n classes of

* A la mémoire d'Ilan Deak.

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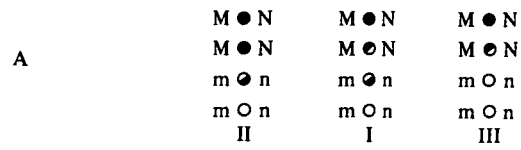
aberrant segregation, the n corresponding independent equations may contain up to $n-1$ parameters if all these parameters have to be solved whilst keeping at least one degree of freedom (D.F.) for testing the goodness of fit of the model considered. In addition, the solutions must fall between 0 and 1 since they correspond to probabilities of certain molecular events.



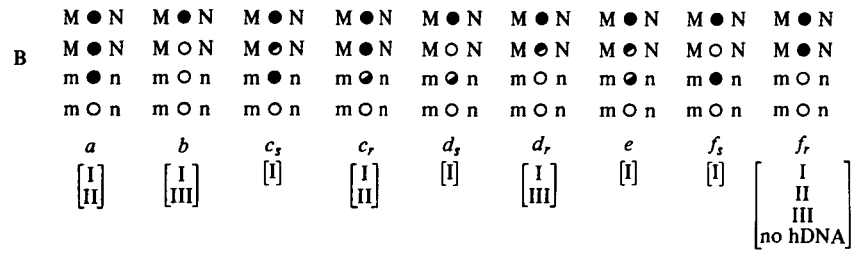


Fig. 1. Origin and segregation pattern of aberrant asci. The cross performed was $(M●N) \times (m○n)$. (A) Hybrid DNA formation: (I) hDNA formed on two chromatids (symmetric); (II) hDNA formed on the $m○n$ chromatid (asymmetric); (III) hDNA formed on the $M●N$ chromatid (asymmetric). (B) Segregation pattern after correction or not of the mismatches formed in A. In brackets hDNA distribution which can lead to the segregation considered.

So far, the algebra of the hDNA model was restricted to the relatively simple situation of a monofactorial cross where only five types of aberrant segregation can be detected. One algebraic treatment assumes a fully symmetric hDNA and its relevance to data on gene conversion at the *gray* locus of *Sordaria fimicola* has been explored by Fincham *et al.* (1980). Another approach allows for asymmetric hDNA and accounts for about two thirds of the segregation spectra observed at the *b1* and *b2* loci of *Ascobolus immersus* (Paquette & Rossignol, 1978; Arnaise, 1980). As shown here, it also roughly explains the data in *S. fimicola*.

We have considered a three factor cross situation, where the allele analysed is combined with flanking markers. In this case, seven major classes of aberrant segregation can be recognized (Fig. 1), allowing the use of up to six parameters to describe hDNA formation and heteroduplex repair whilst retaining one degree of freedom. At present, the only experimental system which can be analysed in this way is the *gray* locus of *S. fimicola* thanks to the very extensive data of Kitani and co-workers. Their work, which paved the way to the hDNA model (see the paper of Kitani, Olive & El-Ani, 1962) has been summarized by Kitani & Whitehouse (1974). Our analysis gives solutions which fit at $P > 0{\cdot}05$ for six of the seven alleles studied by Kitani *et al.*

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2. SYSTEMS OF EQUATIONS

(A) *Parameters in hDNA formation and base pair mismatch repair*

Four parameters define hDNA formation (γ, α, β and δ), and four define the repair of base pair mismatches (p, q, r and s). γ is the probability of forming hDNA at the site considered (Emerson, 1966). α is the probability that the hDNA will

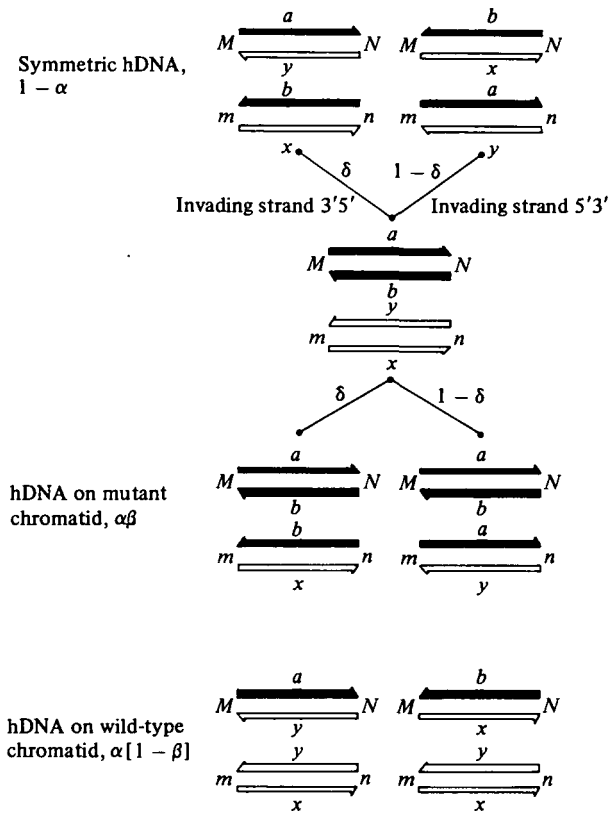

Fig. 2. hDNA distribution as a function of the parameters α, β and δ. Dark lines represent DNA strands of the wild-type chromatid (base pair ab); light lines represent DNA strands of the mutant chromatid (base pair xy).

be asymmetric, i.e. will be restricted to one of the two recombining chromatids (Paquette & Rossignol, 1978). β is the probability that the recipient chromatid will carry the mutant allele (Paquette, 1979). Finally, δ is the probability that the invading DNA strand which generates the hDNA has a given 3′5′ polarity. Fig. 2 illustrates the frequencies of the configuration taken by the hDNA in terms of these parameters. On this figure, ab and xy are the two base pairs corresponding respectively to the wild type and to the mutant allele, with a and x being carried by the 5′3′ strand. Parameter p is the probability of repairing the ay base pair mismatch, and r is the probability of this repair being toward ab. q and s are the

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corresponding parameters for the *xb* mismatch (see Emerson, 1966). Note that Fincham *et al.* (1980) used the same symbols to designate repair parameters which are defined in a different way. The correspondence between the 2 sets of symbols is given in Table 1.

Table 1. *Correspondence between Fincham* et al. *(1980) and Emerson (1966) terminology*

Fincham *et al.*	Emerson
p	pr
q	$p(1-r)$
r	qs
s	$q(1-s)$

(B) *Assumptions about hDNA formation and base pair mismatch repair*

Equations (1)–(7) which describe the hDNA model, are based on the following assumptions about hDNA formation and mismatch repair.

(i) *Formation of symmetrical hDNA requires the exchange of copolar DNA strands (Holliday, 1964)*

An alternative model (Whitehouse, 1963) proposes the exchange of antipolar strands (see Gutz, 1971 for its algebra). Both models are equally acceptable as an explanation of aberrant segregation patterns associated with recombination. However, Holliday's model allows the hDNA to move along the chromatids by a process called branch migration for which there is fairly convincing evidence based on *in vitro* studies (Potter & Dressler, 1976; Thompson, Camien & Warner, 1976).

(ii) *Aberrant segregations are entirely due to hDNA formation*

This implies that spurious aberrant segregations due for example to non-disjunction, spindle overlap or genetic suppression have either been recognized as such or can be neglected. More fundamentally, it discounts models of gene conversion such as the one proposed by Stahl (1969) which do not rely on hDNA formation.

(iii) *The formation of a base pair mismatch is entirely determined by the four parameters* γ, α, β *and* δ. *Its repair is entirely determined by* p, q, r *and* s.

This neglects for example the possibility raised by Holliday (1974) that back-migration of the hDNA along the chromatids may restore a homoduplex base pair (when the mismatch has not yet been repaired) or instead may generate a mismatch if repair has previously occurred on the opposite chromatid. It also assumes that there is no influence of strand isomerization on the efficiency and/or direction of mismatch repair.

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(iv) *The parameters are independent of each other*

We shall for example assume that the choice of the recipient chromatid is independent of the chemical polarity of the invading strand, and that mismatch repair is independent of the symmetry of the hDNA. There is already evidence that mismatch repair is independent of the chromatid harbouring the mismatch (Hastings, Kalogeropoulos & Rossignol, 1980).

(v) *On symmetric hDNA, the repair of one mismatch does not affect the repair of the other*

There is so far no evidence against this assumption. Its plausibility is discussed by Fincham *et al.* (1980).

(vi) *The relation between hDNA formation and crossing over of the flanking markers is independent of the symmetry of hDNA formation, and of mismatch repair*

The c_s and d_s segregation (Fig. 1) can only be scored in the absence of crossovers between the flanking markers. The present assumption allows us to claim that the c_s/c_r (and d_s/d_r) ratio is the same in crossover and non-crossover asci and therefore to estimate c_s, c_r, d_s and d_r even in crossover asci. According to Kitani *et al.* (1962) and Whitehouse (1974), this assumption does not strictly hold since segregation class *e* has slightly but significantly more crossovers between the flanking markers than the other classes. This suggests that crossover may somehow interact with mismatch repair or with the asymmetric versus symmetric configuration of hDNA (see also Sang & Whitehouse, 1979).

(vii) *There is no clustering of crossovers around the hDNA region*

In asci with a parental segregation of flanking markers, we have distinguished between the c_s (or d_s) segregation, which can only be generated by symmetric hDNA, and the c_r (or d_r) segregation which can be generated by both symmetric and asymmetric hDNA. It is crucial here that asci with this parental segregation of flanking markers really result from the absence of a crossover rather than from a two chromatid double crossover which would have the same final result. This amounts to saying that there is no clustering of crossovers around the converting allele.

Two lines of evidence suggest that two chromatid double crossovers are rare. The first is that c_r and d_r segregations combined with a two chromatid double crossover should mimic c_s and d_s segregations, whereas the latter are conspicuously rare at several loci (Stadler & Towe, 1971; Di Caprio & Hastings, 1976; Fogel *et al.* 1979; Sang & Whitehouse, 1979), a feature which is explained by the predominance of asymmetric hDNA at the locus considered. A second argument is based on the observation that reciprocal intragenic recombinants at the *his*1 locus of yeast (Fogel & Hurst, 1967) and the *hyaline* locus of *S. brevicollis* (Fields & Olive, 1967) are almost invariably associated with a reciprocal recombination of flanking markers, whereas parental segregations should be observed if multiple crossovers

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were frequent. Therefore, we have considered that two chromatid double crossovers leading to spurious c_s or d_s asci would only result from rare coincidental exchanges unrelated to the presence of hDNA at the *gray* locus in the ascus considered. The flanking markers used by Kitani *et al.* are close enough (0·4 and 3·4 centimorgans) to permit us to ignore this contribution. A correction factor can be introduced (see Sang & Whitehouse, 1979) but would hardly alter the data.

Mismatch *ay* / *bx* Mismatch		Correction (q) (s)	Correction (q) ($1-s$)	No correction ($1-q$)
Correction (p)	(r)	a	f_r	c_r
	($1-r$)	f_s	b	d_s
No correction	($1-p$)	c_s	d_r	e

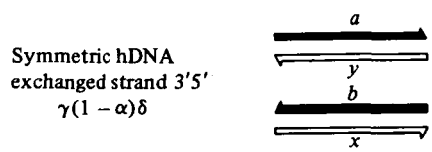

Fig. 3. Segregation classes obtained after mismatch formation depending on the pattern of base pair mismatch repair. In this example two mismatches are formed (ay and bx) on symmetric hDNA with exchange of the 3′5′ strand (probability of the event: $\gamma(1-\alpha)\delta$). p, q, r, s are the repair parameters defined by Emerson (1966).

(C) *General equations*

Equations (1)–(7) were constructed by the method used by Emerson (1966) and Paquette & Rossignol (1978) in the simple case where only five classes of aberrant segregations were considered. We shall illustrate this (Fig. 3) by the example of equation (1), which gives the frequency of the a class (6+ : 2m gene conversion). The first term of the equation corresponds to the symmetric formation of hDNA (with exchanged strands 3′5′ or 5′3′), which is given by the probability $\gamma(1-\alpha)$. Since both mismatches must be repaired to wild type to generate a 6+ : 2m the probability of the symmetric term of the a class is given by $\gamma(1-\alpha)\,pqrs$. The second term corresponds to the asymmetric formation of hDNA whose probability is $\gamma\alpha$. A 6+ : 2m segregation requires the hDNA to be on the mutant chromatid (probability β) and mismatch repair to be toward wild type. Depending on the polarity of the invading strand, either one or the other mismatch is formed. As a result, the probability of a 6+ : 2m gene conversion arising from asymmetric hDNA is given by the sum $\delta qs+(1-\delta)\,pr$, and $\gamma\alpha\beta\{\delta qs+(1-\delta)\,pr\}$ is the second

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term of the equation (1). Equations (2)–(7) are constructed on the same principle, giving the following set of equations:

$$a/N = \gamma(1-\alpha)\,pqrs + \gamma\alpha\beta\{\delta qs + (1-\delta)pr\}, \tag{1}$$

$$b/N = \gamma(1-\alpha)\,pq(1-r)\,(1-s) + \gamma\alpha(1-\beta)\{\delta p(1-r) + (1-\delta)\,q(1-s)\}, \tag{2}$$

$$c_s/N = \gamma(1-\alpha)\{\delta(1-p)\,qs + (1-\delta)\,p(1-q)\,r\}, \tag{3}$$

$$c_r/N = \gamma(1-\alpha)\{\delta p(1-q)\,r + (1-\delta)\,(1-p)\,qs\} + \gamma\alpha\beta\{\delta(1-q) + (1-\delta)\,(1-p)\}, \tag{4}$$

$$d_s/N = \gamma(1-\alpha)\{\delta p(1-q)\,(1-r) + (1-\delta)\,(1-p)\,q(1-s)\}, \tag{5}$$

$$d_r/N = \gamma(1-\alpha)\{\delta(1-p)\,q(1-s) + (1-\delta)p(1-q)\,(1-r)\} + \gamma\alpha(1-\beta)\{\delta(1-p) + (1-\delta)\,(1-q)\}, \tag{6}$$

$$e/N = \gamma(1-\alpha)\,(1-p)\,(1-q). \tag{7}$$

Equations (1)–(7) describe the aberrant segregations which are detected in a three factor cross (see Fig. 1). In a monofactorial cross, there is no distinction between the c_s and c_r (or d_s and d_r) asci. The corresponding pooled classes c and d are given by

$$c/N = \gamma(1-\alpha)\{p(1-q)\,r + (1-p)\,qs\} + \gamma\alpha\beta\{\delta(1-q) + (1-\delta)\,(1-p)\}, \tag{8}$$

$$d/N = \gamma(1-\alpha)\{p(1-q)\,(1-r) + (1-p)\,q(1-s)\} + \gamma\alpha(1-\beta)\{\delta(1-p) + (1-\delta)\,(1-q)\}. \tag{9}$$

(D) *Restricted models*

The two general systems of equations (1)–(7) (three factor crosses) or (1), (2), (8), (9) and (7) (monofactorial crosses) have been further simplified so as to eliminate some parameters in order to gain 1 or 2 D.F.

(*a*) *Monofactorial crosses*

By introducing the additional assumption that both base pair mismatches have the same repair properties ($p = q$, $r = s$) equations (1), (2), (8), (9) and (7) simplify to a new set of five equations:

$$a/N = \gamma(1-\alpha)\,p^2r^2 + \gamma\alpha\beta pr, \tag{10}$$

$$b/N = \gamma(1-\alpha)\,p^2(1-r)^2 + \gamma\alpha(1-\beta)\,p(1-r), \tag{11}$$

$$c/N = 2\gamma(1-\alpha)\,pr(1-p) + \gamma\alpha\beta(1-p), \tag{12}$$

$$d/N = 2\gamma(1-\alpha)\,p(1-r)\,(1-p) + \gamma\alpha(1-\beta)\,(1-p), \tag{13}$$

$$e/N = \gamma(1-\alpha)\,(1-p)^2, \tag{14}$$

which can be further simplified by considering the following restricted models.

Model A. $\beta = 0{\cdot}5$ (*equal probability of hDNA formation on either chromatid*). This

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is the model considered by Paquette & Rossignol (1978) in their analysis of the *b2* locus of *A. immersus*.

Model B. $\alpha = 0$ (*fully symmetric hDNA*). This is equivalent to model 1 of Fincham *et al.* (1980), except that the repair parameters were defined in a different way.

Model C. $r = 0{\cdot}5$ (*equal probability of repair toward the wild type or mutant allele*). This is the model considered by Arnaise (1980) in her analysis of the *b1* and *b2* loci of *A. immersus*.

(*b*) *Three factor crosses*

Model I. $p = q$, $r = s$ (*the two mismatches have the same repair properties*). The seven corresponding equations are easily derived from equations (1)–(7). δ disappears from the equations, which means that the segregation pattern does not depend on the chemical polarity of the invading strand.

Model II. $r = s = 0{\cdot}5$ (*correction occurs with the same probability toward the wild type and mutant allele*). This corresponds to model *C* in monofactorial crosses. On this model, disparity in gene conversion is entirely due to the pattern of hDNA formation i.e. to the values taken by β and δ.

Model III. $\beta = 0{\cdot}5$ (*The two chromatids have the same probability of harbouring asymmetrical hDNA*). This corresponds to model A in monofactorial crosses. On this model, disparity is entirely determined by the properties of mismatch repair, i.e. the values taken by p, q, r and s. We have considered two submodels where δ takes the constant value 0·5 (III a) or 0 (III b). Note that to any solution found for $\delta = 0$ corresponds a solution for $\delta = 1$ obtained by interchanging the values of p and q, and of r and s. $\delta = 0$ would correspond to a situation where strand displacement is generated by a 5′3′ polymerase (see Meselson & Radding, 1975).

Model IV. $\alpha = 0$ (*the hDNA is fully symmetric*). This corresponds to our model B and to model 1 of Fincham *et al.* (1980) in monofactorial crosses. We have considered three submodels. Model IV a makes no prediction on the value taken by δ. Model IV b states that $\delta = 0$ (or 1), and model IV c states that $\delta = 0{\cdot}5$.

3. RESULTS

(A) *Organization of the experimental data available at the gray locus*

Table 2 gives the segregation patterns of the 7 *gray* mutants analysed by Kitani and co-workers (see Kitani & Whitehouse, 1974, table 5 for a compilation of these data). Up to fourteen classes of aberrant segregation can be identified in three factor crosses, but they can be pooled into the seven classes depicted in Fig. 1. Classes *a*, *b* and *e* correspond respectively to aberrant segregations of the 6+ : 2m, 2+ : 6m and aberrant 4+ : 4m types, no matter whether recombination between the flanking markers *mat* and *cor* was present (Rp asci of Kitani & Whitehouse, 1974) or absent (Ra asci). When 5+ : 3m and 3+ : 5m segregations are considered, there are four subclasses (Ra1, Ra2, Rp1, Rp2) that can be scored. Our basic assumptions imply that Ra2 asci can only be generated by symmetric hDNA. They

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Table 2. *Segregation patterns of the* gray *locus alleles of* Sordaria fimicola

Allele		a	b	c_s		c_r	d_s		d_r	e	f†	N	Total aberrant
gl	Ra	237	15	73		99	4		23	14	—	—	465
	Rp	163	13		150			23		9	—	—	358
	Total	400	28	137*		185*	7*		43*	23	404595	405418	823
g6	Ra	33	3	17		31	4		9	9	—	—	106
	Rp	27	2		40			18		8	—	—	95
	Total	60	5	32*		56*	10*		21*	17	89133	89334	201
g7	Ra	46	6	15		42	7		7	26	—	—	149
	Rp	25	3		53			24		17	—	—	122
	Total	71	9	29*		81*	19*		19*	43	124617	124888	271
h2	Ra	22	13	29		68	23		63	147	—	—	365
	Rp	18	7		87			61		138	—	—	311
	Total	40	20	55*		129*	39		108*	285	322769	323445	676
h3	Ra	1	6	6		9	3		36	20	—	—	81
	Rp	0	4		6			20		28	—	—	58
	Total	1	10	8*		13*	5*		54*	48	60296	60445	139
h4	Ra	3	11	5		17	12		37	26	—	—	111
	Rp	2	5		11			39		23	—	—	80
	Total	5	16	7*		26*	22*		66*	49	91416	91607	191
h5	Ra	22	7	17		31	7		16	30	—	—	130
	Rp	9	2		32			7		29	—	—	79
	Total	31	9	28*		52*	9*		21*	59	98376	98585	209
Pooled	Ra	364	61	162		297	60		191	272	—	—	1404
	Rp	244	36		379			192		252	—	—	1106
	Total										1191212	1193722	2510
Rp/(Ra+Rp)		0·40	0·37		0·45			0·43		0·48	—	—	0·44

Ra (recombination absent): parental segregation for the flanking markers; Rp (recombination present): recombinant segregation for flanking markers.

* Events corresponding to the $c_s(d_s)$ and $c_r(d_r)$ segregations are assumed to be in the same proportion among Ra and Rp asci.

Source: Kitani & Whitehouse, 1974.

† f is the number of regular 4+:4m segregations.

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correspond to the c_s and d_s classes of Table 2, and are called tetratypes by Whitehouse (1974). The Ra1 asci, which can be generated by symmetric or asymmetric hDNA, correspond to the c_r and d_r classes of Table 2 and to the tritypes

Table 3. *Solutions obtained using one factor crosses (no flanking markers)*

Model A ($p = q$; $r = s$; $\beta = 0{\cdot}5$)

Allele	γ ($\times 10^{-3}$)	$N\gamma$	α	p	r	χ^2	D.F.
g1	2·6	1034	0·00	0·79	0·81	23·98	1
g6	2·8	247	0·51	0·58	0·89	*2·44*	1
g7	2·6	321	0·04	0·63	0·75	*0·04*	1
h2	2·3	728	0·00	0·38	0·57	*1·79*	1
h3†	2·5	149	0·33	0·29	0·11	*1·41*	1
h4	2·3	215	0·32	0·39	0·22	5·90	1
h5	2·4	238	0·00	0·52	0·69	*2·92*	1

Model B ($p = q$, $r = s$, $\alpha = 0$)

Allele	γ ($\times 10^{-3}$)	$N\gamma$	p	r	χ^2	D.F.
g1	2·6	1034	0·79	0·81	23·98	2
g6	2·8	245	0·68	0·75	*4·95*	2
g7	2·6	322	0·64	0·74	*0·07*	2
h2	2·3	728	0·38	0·57	*1·79*	2
h3	2·5	150	0·41	0·27	*2·39*	1*
h4	2·4	216	0·49	0·31	6·43	2
h5	2·4	238	0·52	0·69	*2·92*	2

Model C ($p = q$, $r = s = 0{\cdot}5$)

Allele	γ ($\times 10^{-3}$)	$N\gamma$	α	β	p	χ^2	D.F.
g1	3·1	1248	0·80	1·00	0·72	*1·55*	1
g6	3·0	271	0·59	1·00	0·60	*3·38*	1
g7	2·8	347	0·52	1·00	0·54	6·15	1
h2	2·3	730	0·10	1·00	0·35	*2·62*	1
h3†	2·5	151	0·38	0·02	0·28	*1·00*	1
h4	2·3	212	0·54	0·16	0·29	*0·02*	1
h5	2·5	245	0·35	1·00	0·43	5·23	1

Model A. Equation system as described by Paquette & Rossignol (1978).

Model B. Equation system derived from the former by assuming that $\alpha = 0$.

Model C. Equation system as described by Arnaise (1980). This system is derived from the one of Paquette and Rossignol but in this case $r = 0{\cdot}5$ and β is free to vary.

* Classes *a* and *b* pooled for the χ^2 test.

† χ^2 calculated with Yates correction. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$.

of Whitehouse. The Rp1 and Rp2 asci give no information on the symmetry of hDNA, but allow allocation of the crossovers to the *mat-gray* or *gray-cor* interval, respectively. We have assumed that the c_s/c_r ratio of the Rp asci was the same as in the Ra asci, i.e. was given by the Ra2/Ra1 ratio. A similar treatment was applied to the 3+ : 5m asci to calculate the d_s and d_r classes of Table 2.

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(B) *Estimates of the best fitting solutions by the minimum χ^2 method*

We have used an iterative computing procedure where all the parameters were allowed to vary between 0 and 1 (see below for the special case of γ). The predicted pattern of segregation was computed for each set of values taken by the parameters and compared with the experimental data of Table 2 by a χ^2 test.

Table 4. *Solutions obtained using three factor crosses (with flanking markers); restricted model* I ($p = q$, $r = s$)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	α	β	p	r	χ^2	D.F.
g1	2·6	1052	0·32	0·52	0·76	0·88	30·30	2
g6	2·8	245	0·37	0·69	0·61	0·77	*3·65*	2
g7	2·6	326	0·36	1·00	0·56	0·63	*0·83*	2
h2	2·2	726	0·27	0·52	0·28	0·60	*5·00*	2
h3	2·5	151	0·47	0·09	0·24	0·58	*0·50*	1*
h4	2·3	211	0·44	0·30	0·33	0·31	*3·04*	2
h5	2·4	238	0·27	0·68	0·44	0·69	*4·04*	2

* Classes *a* and *b* pooled for the χ^2 test. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$.

Table 5. *Solutions obtained using three factor crosses (with flanking markers); restricted model* II ($r = s = 0{\cdot}5$)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	α	β	δ	p	q	χ^2 (D.F. = 1)
g1	3·2	1284	0·72	1·00	0·09	0·88	0·32	53·96
g6	3·0	266	0·58	1·00	0·21	0·81	0·24	*2·48*
g7	2·8	350	0·50	1·00	0·00	0·59	0·47	5·86
h2	2·3	730	0·28	0·70	0·00	0·32	0·23	5·05
h3*	2·5	150	0·47	0·10	0·38	0·25	0·22	*1·93*
h4	2·4	216	0·47	0·12	0·19	0·18	0·45	*2·82*
h5	2·5	246	0·35	1·00	0·00	0·51	0·32	4·55

* χ^2 calculated with Yates correction. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$. There is formally a second solution obtained by interchanging the values of p and q and of r and s, and by replacing δ by $1-\delta$.

In a first approach, we used a grid where each parameter was allowed to vary between 0 and 1 by steps of 0·1. $N\gamma$, which is the number of asci where hDNA formation did occur in the sample of N asci considered, was allowed to vary between the total number of aberrant asci in that sample and twice that number. The steps were of four asci, except for allele g1 where steps of ten asci were used. All the domains with solutions giving χ^2 values lower than 20 were further explored using, this time, steps of one ascus for N_γ and of 0·01 for the other parameters. The solutions with the smallest χ^2 are given in Table 3 for the restricted models

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Table 6. *Solutions obtained using three factor crosses (with flanking markers); restricted model* III a ($\beta = \delta = 0{\cdot}5$)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	α	p	q	r	s	χ^2 (D.F. = 1)
g1	3·0	1200	0·30	0·66	0·93	0·55	1·00	*1·42*
g6	2·7	240	0·32	0·42	0·82	0·92	0·78	*1·42*
g7	2·7	336	0·23	0·56	0·62	0·87	0·68	17·75
h2	2·2	726	0·27	0·28	0·28	0·61	0·61	5·05
h3*	2·7	161	0·40	0·10	0·41	0·61	0·29	23·84
h4	2·4	218	0·40	0·19	0·54	0·67	0·08	5·20
h5	2·4	239	0·25	0·45	0·45	0·73	0·74	5·17

* χ^2 calculated with Yates correction. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$. There is formally a second solution obtained by interchanging the values of p and q, and of r and s.

Table 7. *Solution obtained using three factor crosses (with flanking markers); restricted model* III b ($\beta = 0{\cdot}5$; $\delta = 0$)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	α	p	q	r	s	χ^2 (D.F. = 1)
g1	2·6	1054	0·25	0·76	0·77	0·84	0·88	29·28
g6	2·8	247	0·34	0·59	0·65	0·85	0·81	*3·66*
g7	2·6	325	0·12	0·53	0·70	0·71	0·80	*0·83*
h2	2·2	702	0·38	0·20	0·21	0·93	0·42	5·01
h3*	2·5	153	0·20	0·52	0·20	0·14	0·41	*1·93*
h4*	2·4	220	0·29	0·48	0·35	0·17	0·36	*2·92*
h5	2·4	241	0·17	0·45	0·51	0·67	0·76	4·04

* χ^2 calculated with Yates correction. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$. There is formally a second solution with $\delta = 1$, obtained by interchanging the values of p and q, and of r and s.

Table 8. *Solutions obtained using three factor crosses (with flanking markers); restricted model* IV a ($\alpha = 0$, δ *free to vary*)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	δ	p	q	r	s	χ^2 (D.F. = 1)
g1	3·3	1340	0·37	0·76	0·92	0·45	0·95	17·78
g6	3·6	320	0·29	0·71	0·81	0·34	0·96	*0·06*
g7	2·6	326	0·00	0·56	0·72	0·63	0·82	*0·84*
h2	2·3	745	0·00	0·39	0·40	0·36	0·77	5·05
h3*	2·6	156	0·01	0·58	0·29	0·11	0·64	*2·17*
h4	2·6	240	0·15	0·63	0·45	0·08	0·73	*1·33*
h5	2·5	242	0·00	0·50	0·55	0·55	0·80	4·05

* χ^2 calculated with Yates correction. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$. There is formally a second solution obtained by interchanging the values of p and q, and r and s, and by replacing δ by $1-\delta$.

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A, B and C (monofactorial crosses) and in Tables 4–10 for the restricted models I–IV (three factor crosses), respectively. In some cases, doublets of best fitting solutions were found for some parameters (δ, p, q, r and s). There is no way to calculate the variance of these best fitting estimates.

Table 9. *Solutions obtained using three factor crosses (with flanking markers); restricted model* IV b ($\alpha = 0$; $\delta = 0$)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	p	q	r	s	χ^2	D.F.
g1	2·6	1068	0·79	0·80	0·69	0·90	29·31	2
g6	2·9	255	0·67	0·72	0·60	0·86	*3·66*	2
g7	2·6	326	0·56	0·72	0·63	0·82	*0·84*	2
h2	2·3	745	0·39	0·40	0·36	0·77	*5·05*	2
h3	2·6	155	0·57	0·29	0·12	0·63	*0·82*	1*
h4	2·5	226	0·57	0·46	0·12	0·60	*2·48*	1*
h5	2·5	242	0·50	0·55	0·55	0·80	*4·05*	2

* Classes *a* and *b* pooled for the χ^2 test. This explains the difference in the χ^2 value for h3 between Table 8 and 9. Italic figures indicate values of χ^2 correspond to P values $> 0{\cdot}05$. There is formally a second solution with $\delta = 1$, obtained by interchanging the values of p and q, and of r and s.

Table 10. *Solutions obtained using three factor crosses (with flanking markers); restricted model* IV c ($\alpha = 0$, $\delta = 0{\cdot}5$)

Allele	$\gamma(\times 10^{-3})$	$N\gamma$	p	q	r	s	χ^2	D.F.
g1	2·7	1074	0·66	0·94	0·70	0·86	30·41	2
g6	2·8	247	0·86	0·50	0·75	0·74	10·89	2
g7	2·7	341	0·57	0·71	0·61	0·84	23·38	2
h2	2·4	763	0·43	0·35	0·48	0·67	59·89	2
h3	3·0	181	0·34	0·60	0·72	0·04	36·62	1*
h4	2·5	227	0·26	0·71	0·49	0·25	30·94	2
h5	2·5	244	0·53	0·51	0·70	0·67	13·68	2

* Classes *a* and *b* pooled for the χ^2 test.

4. DISCUSSION

Algebraic formulations of the hDNA model allow the analysis of the model at a quantitative level by testing whether it can explain not only the existence of the various classes of aberrant segregation but also their actual frequencies at a given locus. If the model fits the data, quantitative conclusions on the properties of hDNA formation and mismatch repair can be drawn from the known frequencies of aberrant segregations at the locus considered.

The number of parameters considered is not *a priori* limited. For example, we could have considered a parameter describing the possibility for the half-chromatid chiasma to migrate back and forth on the chromatid (Holliday, 1974), or a

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parameter related to strand isomerization. A crucial point here is whether the number of parameters leaves a D.F. (degree of freedom) or not. If no D.F. is available (see for example Emerson, 1966), one may consider a certain model which appears to be chemically plausible and explore its quantitative implications by asking whether algebraic solutions falling between 0 and 1 can be found. If so, one can say that the model is biologically realistic, even though there is no statistical way of testing it. On the other hand, if the number of parameters is limited so as to keep at least 1 D.F., the models considered can be tested for their goodness of fit. If they do not fit the data, they will have to be rejected as a general explanation of the segregation pattern at the *gray* locus of *Sordaria fimicola*, even if they are *a priori* plausible in the sense that algebraic solutions comprised between 0 and 1 can be found.

(A) *Analysis of monofactorial crosses (Table 3)*

The algebraic analysis of monofactorial crosses at the *gray* locus was initiated by Whitehouse (1965) and Emerson (1966), and carried out more systematically by Fincham *et al.* (1980). The latter authors analysed a model based on fully symmetric hDNA. In one of the models considered, they assumed the frequencies of base pair mismatch correction to be the same on both chromatids. This model describes hDNA formation and mismatch repair with three parameters only, thus leaving 2 D.F. Fitting solutions were found for four alleles out of five, and were extended to five alleles out of seven in the present work (Table 3).

These results suggest that fully symmetric hDNA may well be compatible with the data available at the *gray* locus. The lack of fitting solutions for the alleles g1 and h4 may be due to the fact that the simplification $p = q$, $r = s$ does not hold for these alleles, rather than to $\alpha = 0$ being wrong. One way of testing this would be to consider models allowing α to vary, thus introducing α as a fourth parameter, leaving 1 D.F. Such models have been investigated for two loci of *A. immersus* and strongly support the conclusion that hDNA formation is partly asymmetric (Paquette & Rossignol, 1978; Arnaise, 1980). When applied to the *gray* locus of *S. fimicola*, this analysis (models A and C of Table 3) accounts for five alleles out of seven, with best fitting solutions which are close to 0 for parameter α in the case of three alleles. The hypothesis of a fully symmetric hDNA can therefore not be rejected on this basis.

(B) *Analysis of three factor crosses*

(1) *Fitness of the models tested*

There are two models which basically fit the experimental data although neither fit allele g1. One of them (model IV b) is based on fully symmetric hDNA and allows the two mismatches to have different repair properties ($p \neq q$, $r \neq s$). As can be seen from Table 9 this model fits six alleles out of seven, under the assumption that the DNA strand transferred during hDNA formation has always the same chemical polarity ($\delta = 0$ or 1) (compare with Tables 8 and 10).

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An alternative hypothesis allowing for asymmetric hDNA but requiring the two mismatches to have the same repair properties (model I) fits the same six alleles. The best fitting solutions give low values for α, so that both models support the idea that hDNA formation at *gray* is mainly symmetric. A curious feature of model I is shown by two alleles for which the best fitting solutions found for β imply a strong bias toward the mutant (g7) or the wild type chromatid (h3) in the formation of asymmetric hDNA. Such a bias is not easy to explain on current models of hDNA formation, and we are inclined to believe that it is due to the constraint $p = q$, $r = s$ being unrealistic in the case of these two alleles. To test this possibility, we have examined submodels (III a and III b) which impose $\beta = 0{\cdot}5$. On model I, δ can take any value since it does not appear in the corresponding equations, and we may therefore arbitrarily define the value taken by δ. Table 6 shows that model III a (where $\delta = 0{\cdot}5$) fits only two alleles out of seven and is not consistent with alleles g7 and h3, even though the two mismatches are allowed to have different repair properties. Fitting solutions are however found for both alleles under the hypothesis that $\delta = 0$ or 1 (model III b). On the whole, model III b accounts for four of the six alleles fitted by model I. The experimental data may therefore well be consistent with the asymmetric hDNA having about the same probability to reside on either chromatid, *provided that δ is close to 0 or to 1.*

Allele g1 cannot be fitted by the models considered with the exception of model III a ($\beta = 0{\cdot}5$, $\delta = 0{\cdot}5$) which must be rejected since it accounts for only two alleles out of seven. This underlines the limits of our algebraic approach. If we ignore this allele, however, the solutions obtained on the two types of models considered (fully symmetric versus partly asymmetric hDNA) suggest some properties of hDNA formation and mismatch repair which will be discussed below.

(2) *Properties of hDNA formation and mismatch repair at the gray locus*

(*a*) *Lack of polarity in hDNA formation.* The value taken by γ (probability of hDNA formation) are practically the same for all the alleles, as expected from the constancy of the basic frequencies of conversion (Kitani & Olive, 1967). A similar lack of polarity in hDNA formation is suggested by the basic frequencies of conversion measured at the *buff* locus of *Sordaria brevicollis* (Sang & Whitehouse, 1979) and in the *sup3* gene of *Schizosaccharomyces pombe* (Thuriaux *et al.* 1980). Yet, the frequency of aberrant segregation is polarized at the *b2* locus of *A. immersus* (Paquette & Rossignol, 1978) and in the *arg4* gene of *S. cerevisiae* (Fogel *et al.* 1979). At *b2*, polarity in the frequency of aberrant segregation is correlated with an increase in the probability of symmetric hDNA toward the region showing a low frequency of hDNA formation. This supports the Aviemore model of hDNA formation which predicts an asymmetric initiation of hDNA followed by a symmetrization away from the initiation region (Meselson & Radding, 1975). Such a gradient maybe smooth enough to escape detection over certain regions of the genome, or in some organisms. In that case, the *gray* locus may be similar to the right part of *b2*, and would then be expected to lie relatively far from the initiation

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region. Alternatively, initiation may occur at a number of possible sites at or near the *gray* locus.

(*b*) *Symmetry in hDNA formation.* The experimental data are consistent with hDNA formation being mostly or even fully symmetric, *on the assumption that* $\delta = 0$ *or 1*. This strengthens the conclusion suggested by the analysis of monofactorial crosses (Fincham *et al.* 1980 and Table 3 of the present work) where five alleles out of seven tested are fitted by a symmetric model, albeit under the probably unrealistic assumption that both mismatches have the same repair properties. It is generally assumed that the lack of 'tetratypes' among 5:3 asci corresponds to a lack of symmetric hDNA (Stadler & Towe, 1971; Whitehouse, 1974). Our data (Table 9) suggest that this argument should be taken with some caution and that the frequency of tetratypes among 5:3 asci is a rather crude estimate of the contribution of symmetric hDNA.

(*c*) *Chemical polarity of the invading strand.* As already discussed, both the symmetric and asymmetric hDNA model suggest that δ is close to 0 (or to 1), i.e. that the strand transferred during hDNA formation is always of the same chemical polarity. Models IIIa and IVc which are based on the hypothesis that $\delta = 0{\cdot}5$, fail to fit the data. This would be consistent with a mechanism of hDNA initiation where strand invasion leading to hDNA formation is driven or facilitated by a 5′3′ polymerase activity, in which case δ would be equal to 0 (see Meselson & Radding, 1975).

(*d*) *Disparity in aberrant segregations.* Aberrant segregations are often characterized by a marked disparity such that $a \neq b$ and $c \neq d$ (see Table 2). Frameshift mutants of *A. immersus* show a strong disparity which has been explained by a preferential repair toward the wild type or mutant chromatid, depending on the nature of the frameshift considered (Leblon, 1972; 1979). The *gray* mutants analysed here are probably base pair substitution mutants (Yu Sun, Wickramaratne & Whitehouse, 1977). On a model allowing for asymmetric hDNA, disparity can result from a disparity in mismatch repair, and from a preferential formation of the hDNA on one of the two chromatids. Disparity in repair certainly contributes to disparity in aberrant segregations, otherwise it would be hard to see why model II (Table 5), which imposes parity in repair ($r = s = 0{\cdot}5$) but leaves all the other parameters free to vary, fits only two alleles out of seven. We cannot decide whether asymmetric hDNA – if it occurs at all – is preferentially formed on one chromatid (see above discussion of the fitness of model I), but the results obtained with model IIIb (Table 7) suggest that this need not be the case.

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