WebmedCentral Zoology 2011, 2(3):WMC002464

Concordance of the predictions of a simulation model for the evolutionary advantage of sex with observational evidence

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Abstract

Evolutionary advantage of sex is a widely discussed topic with multiple and clashing theories. A simulation model is proposed, based on the "classic" hypothesis that sex is advantageous because it allows faster attainment of favourable genetic combinations.
The model shows the substitution of 2 (or 3) genes with advantageous alleles and calculates in which conditions a further gene allowing recombination is advantaged or disadvantaged in comparison with an allele not allowing recombination. With no epistasis, in infinite population sex results neutral, while in finite populations, in particular if the population is divided in demes, sex results advantageous.
Considering the disadvantages caused by mating necessities, "classic" theory predicts the trends of ecological conditions in which sexual/asexual species of the same taxonomic group (or sexual/asexual stages of the same species) will prevail. Predictions of the "classic" theory with the above-mentioned specifications are compared with predictions of other hypotheses and data from natural observation: only the "classic" theory is confirmed by empirical evidence.

Keywords: sex, evolution, epistasis, red queen, finite populations

Introduction

The evolutionary justification of gene recombination between two individuals, defined with the technical term "mixis" but usually referred to using the popular word "sex", is a widely discussed topic (Ghiselin, 1974; Williams, 1975; Maynard Smith, 1978; Bell, 1982; Ridley, 1993).
The "classic" hypothesis (alias Fisher-Muller hypothesis) that sexual reproduction is evolutionarily advantageous because it allows a continuous rearrangement of genes (Fig. 1), which Bell called "The Vicar of Bray" (Bell, 1982), was first expressed by Weismann (Weismann, 1889) and later by Guenther (Guenther, 1906). Afterwards, it was been formulated in terms of population genetics by Fisher (Fisher, 1930) and Muller (Muller, 1932) and later, with greater mathematical formalism, by Muller (Muller, 1958, 1964) and Crow and Kimura (Crow and Kimura 1965).

Maynard Smith (Maynard Smith, 1968) criticised the "classic" hypothesis with the following, simple but effective, argument.
If, in an infinite population of a haploid species, there are two genes (a, b), with alleles (A, B) having an advantage (s_A, s_B) over a and b, respectively, combinations frequencies in the next generation will be:

$$\begin{aligned} P_{n+1,ab} &= P_{n,ab} / T \\ P_{n+1,Ab} &= P_{n,Ab} (1 + s_A) / T \\ P_{n+1,aB} &= P_{n,aB} (1 + s_B) / T \\ P_{n+1,AB} &= P_{n,AB} (1 + s_{AB}) / T \end{aligned} \quad (1)$$

where:
$P_{n,xy}$ = frequency of combination xy at generation n;
$P_{n+1,xy}$ = frequency of combination xy at generation n+1;

k = interaction (epistasis) between the fitnesses;
T = the sum of numerators;

$$s_{AB} = [(1 + s_A)(1 + s_B) - 1]\ k \qquad (2)$$

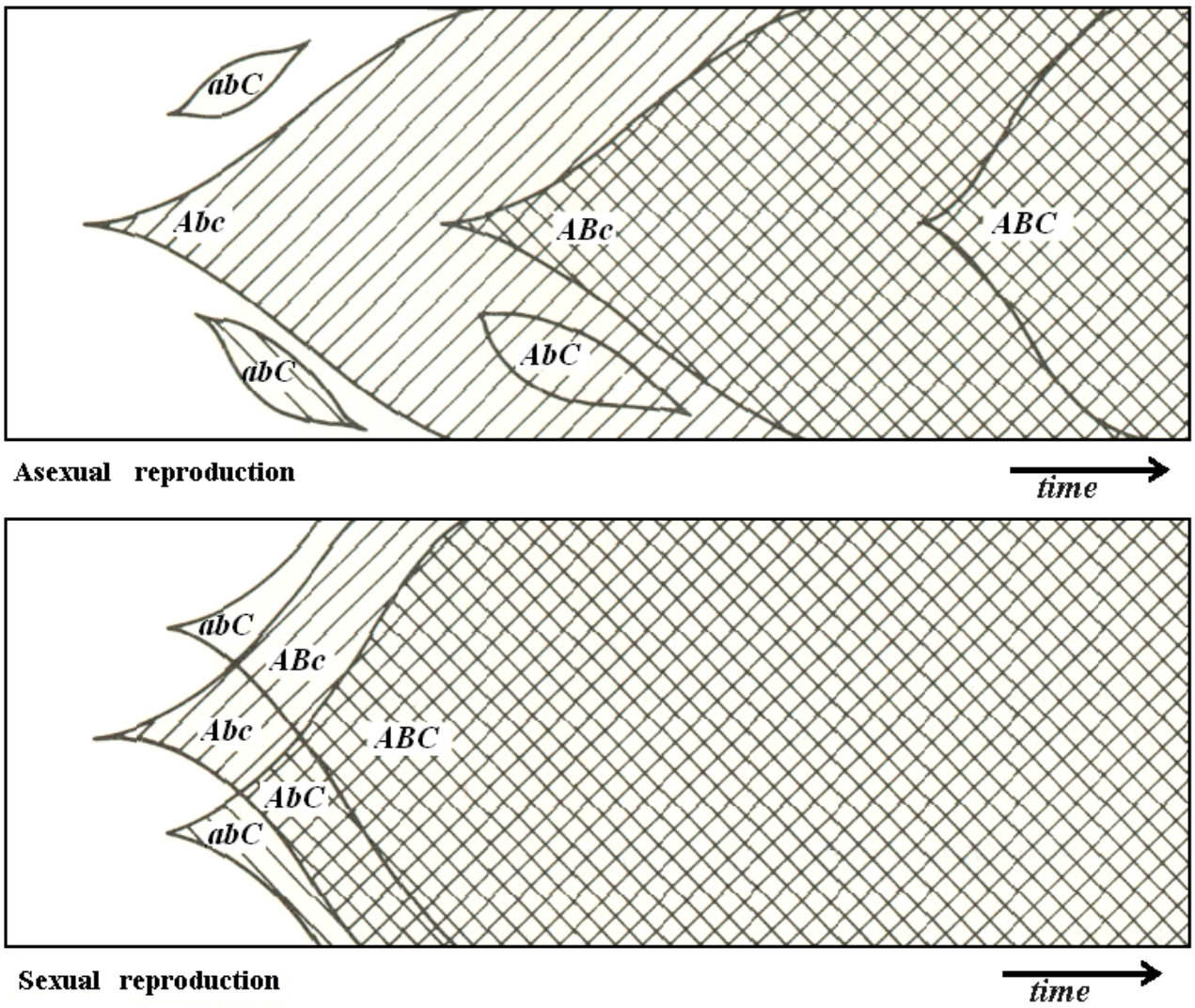


Fig. 1. For the "classic" hypothesis, sex is evolutionarily advantageous because it allows a continuous rearrangement of genes and therefore the attainment of the best combinations earlier than with asexual reproduction (from Crow & Kimura, 1965; partially redrawn).

If, at generation n, there is no linkage disequilibrium (D), that is, if:

$$D = P_{n,ab}\ P_{n,AB} - P_{n,Ab}\ P_{n,aB} = 0 \qquad (3)$$

with no epistasis ($k = 1$), Eq. (1) determine that in the next generation it will be always:

$$D = P_{n+1,ab}\ P_{n+1,AB} - P_{n+1,Ab}\ P_{n+1,aB} = 0 \qquad (4)$$

with or without recombination, which can only halve linkage disequilibrium at each generation (Maynard Smith, 1978). Therefore, with these conditions sex is not advantageous.
With negative linkage disequilibrium ($D < 0$) sex would be advantageous, while with positive linkage disequilibrium sex would be disadvantageous.

If there is positive epistasis ($k > 1$) between the fitnesses, sex is disadvantageous because it breaks the more advantageous combination AB. The contrary happens if there is negative epistasis ($k < 1$).
Maynard Smith tried to overcome his argument (Maynard Smith, 1978), observing, in particular, that it was valid only for infinite populations but that "linkage disequilibrium is bound to arise by chance in a finite population" (p. 15) and in conditions of negative linkage disequilibrium sex would be advantageous, as previously observed by Felsenstein (Felsenstein, 1974).
Many scholars did not accept the counter-arguments of Maynard Smith (Crow and Kimura, 1969; Williams, 1975), and it must be asked why conditions of negative linkage equilibrium, favourable for sex, should prevail over positive occurrences?

The doubts about the validity of Fisher-Muller "classic" explanation of sex caused the flourishing of alternative hypotheses such as, to use the eponyms of Bell (Bell, 1982):
- Muller's ratchet (Muller, 1964; Felsenstein, 1974; Butcher, 1995; Gordo and Charlesworth, 2000; Keightley and Otto, 2006; Gordo and Campos, 2008) ("sex ... facilitates the elimination of unfavourable mutations." (Bell, 1982); "In the absence of recombination, ... mutations will continually accumulate in the population, leading to the decline of its mean fitness." (Gordo and Charlesworth, 2000));
- Best-Man (Williams, 1966; Emlen, 1973; Treisman, 1976) (Recombination produces "a few individuals of extraordinarily high fitness. If only these individuals have any appreciable chance of surviving, then sexual parents will contribute a disproportionately large number of progeny to the next generation ..." (Bell, 1982));
- Hitch-hiker (Hill and Robertson, 1966; Felsenstein, 1974) (Stochastically generated linkage disequilibria increase the variance of fitness of any single-locus genotype and so retard the fixation of a favourable allele. An allele increasing the rate of recombination reduces linkage disequilibria and accelerates the fixation of favourable alleles and thus, for selection, it is hitch-hiked by these favourable alleles);
- Tangled Bank (Ghiselin, 1974; Burt and Bell, 1987; Ridley, 1993) (Sex diversifies progeny and its advantage is greater in conditions of environmental spatial heterogeneity, that is various "ecological niches in the same small geographical area – in an environment which does not change in time" (Bell, 1982));
- Red Queen (Van Valen, 1973; Hamilton, 1975; Levin, 1975; Charlesworth, 1976; Glesener and Tilman, 1978; Glesener, 1979; Bell, 1982; Bell and Maynard Smith, 1987; Ridley, 1993; Peters and Lively, 1999, 2007; Otto and Nuismer, 2004; Kouyos et al., 2007; Salathé et al., 2008) ("The Red Queen hypothesis posits that sex has evolved in response to the shifting adaptive landscape generated by the evolution of interacting species." (Otto and Nuismer, 2004); "The Red Queen Hypothesis ... suggests that the coevolutionary dynamics of host-parasite systems can generate selection for increased host recombination. ... A prerequisite for this mechanism is that host-parasite interactions generate persistent oscillations of linkage disequilibria ..." (Kouyos et al., 2007));
- Historical hypothesis (Williams, 1975) (sex has no general evolutionary cause and sexual / asexual condition is mainly determined by ancestor sexuality / asexuality).
and, moreover, the hypotheses that:
- sex is advantageous because it slows down evolution and excessive specialization (William, 1975; Stanley, 1978);
- recombination eliminates the negative linkage disequilibrium generated by synergistic epistasis (Kondrashov, 1984; Charlesworth, 1990; Barton, 1995; Otto and Feldman, 1997);
- a plurality of theories is necessary to explain the existence of sex (West et al., 1999);
and others theories, on the whole classified by Kondrashov (Kondrashov 1993).

This paper originates both from the facts that many of these hypotheses are weakened by old serious criticisms (Bell, 1982) and that various subsequent attempts to explain sex advantage in finite populations appear too complex (Kondrashov and Yampolsky, 1996; Bürger, 1999; Pálsson, 2002;

Iles et al., 2003; Barton and Otto, 2005; Martin et al., 2006; Tannenbaum, 2008), as well as from the conviction that sex evolutionary advantage must be investigated without hypothesizing artful and / or unduly limiting mechanisms.
I want to formulate a model that shows for sex - in terms of individual selection, as indicated by Felsenstein (Felsenstein, 1974) - both advantage in finite populations and no advantage in infinite populations. Moreover, the model must consider the important suggestion that natural populations are subject to genetic drift and are spatially structured (Otto and Lenormand, 2002).

In the first section, based on the classic Fisher-Muller hypothesis, stated in terms of individual selection and, for the sake of brevity, referred to as the "classic" hypothesis, I will illustrate a model for an infinite population that confirms Maynard Smith's predictions (Maynard Smith, 1968, 1978).
In the subsequent section, I will insert in the model the condition of a finite population that demonstrates in this case an advantage for sexual reproduction, in accordance with a key observation on Fisher-Muller's hypothesis expressed by Felsenstein (Felsenstein, 1974): " ... those authors who have allowed finite-population effects into their models have been the ones who found an advantage to having recombination, while those whose models were completely deterministic found no consistent advantage." (p. 738)
The method utilized is the precise definition of a theoretical model and the following computer-aided verification, as discussed by Bell (Bell, 1982, pp. 79-84).
Finally, predictions of the "classic" hypothesis are compared with predictions of other theories and with data from natural observation.

The simulation model for infinite populations

Let us consider a species:
a) that is haploid;
b) with an infinite population;
c) with half of the individuals at generation zero having - in a specific locus - a gene R+ allowing conjugation and free recombination only with other individuals having R+, while the others have an allele R- allowing conjugation and recombination only in a fraction z of individuals.
If $z > 0$ the pool of recombining individuals is constituted by all R+ individuals and a fraction z of R- individuals. If $z = 0$, as in most of the following simulations, there is "no sharp distinction between individual selection and group selection", as underlined by Felsenstein and Yokoyama (Felsenstein and Yokoyama ,1976), but the selection will actually be considered only in strict terms of individual selection.
d) with mutation rates of R+ in R-, namely turning a sexual individual into an asexual individual, or vice versa, of zero frequency;
e) with R+ and R- individuals having the same ecological niche and being by no means distinguishable except for the condition expressed in d;
f) with the disadvantage for sexual individuals of finding a mate and of coupling and with any other possible disadvantage of sex, the so-called "cost of sex" included, considered negligible;
g) with new alleles (A, B, C, ...) more advantageous than those prevailing in the species (a, b, c, ...), supposed at generation zero with frequency = 1;
h) with independent gene transmission of any allele", i.e. the recombination fraction is assumed 0.5;
i) with the mutation rate, at each generation, of an allele x in X equal to u_x and the back-mutation rate of X in x equal to w_x.

The question is, whether there is an advantage of sexual on asexual individuals, or vice versa, that is, whether there is a spreading or a decay of R+.

The model is restricted to the cases of:
I) two genes (a, b) and their respective new alleles (A, B) ("two genes case"), with four possible

combinations (ab, Ab, aB, AB);
II) three genes (a, b ,c) and the respective new alleles (A, B, C) ("three genes case"), with eight possible combinations (abc, Abc, aBc, abC, ABc, aBC, AbC, ABC).
These restrictions are not a limitation, because if sex will be proved advantageous with only 2 or 3 genes, its greater fitness will be self-evident with more genes.
For the sake of simplicity, the following is hypothesized:

$$u = u_a = u_b = u_c \quad (5)$$

$$w = w_a = w_b = w_c \quad (6)$$

$$s = s_A = s_B = s_C \quad (7)$$

With two and three genes, the possible cases of mutations from one combination into another are 10 (Fig. 2 and Table 1) and 38 (Fig. 3 and Table 2), respectively. The probabilities of transformations are indicated in the tables.

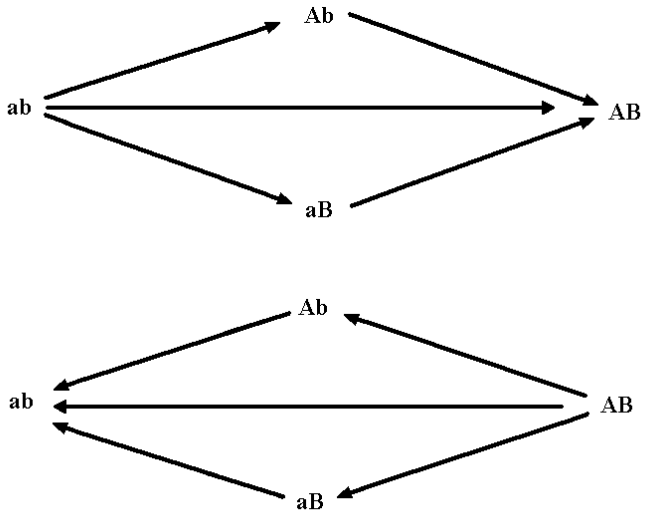


Fig. 2. Two genes case. Possible transformations of one combination into another.

Table 1. Two genes case. Possible transformations of one combination into another and their probabilities

	From	To	Probabilities
1	aB	AB	u
2	Ab	AB	u
3	ab	aB	$u - u^2$
4	ab	Ab	$u - u^2$
5	ab	AB	u^2
6	aB	ab	w
7	Ab	ab	w
8	AB	aB	$w - w^2$
9	AB	Ab	$w - w^2$
10	AB	ab	w^2

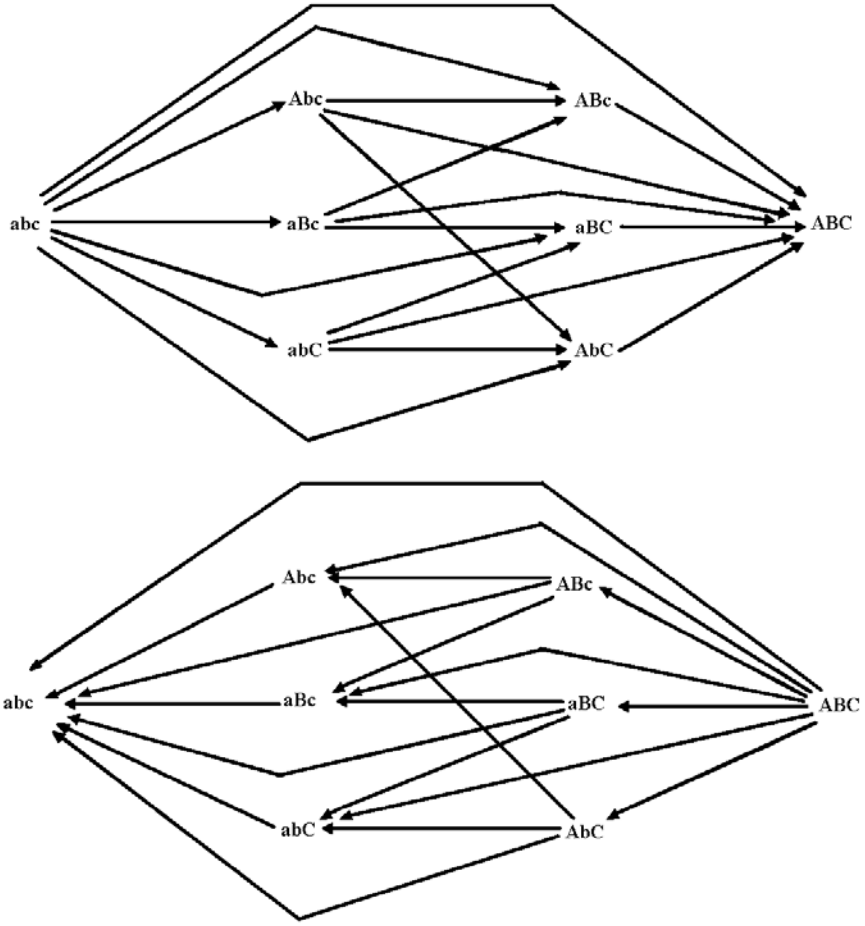


Fig 3. Three genes case. Possible transformations of one combination into another.

Table 2. Three genes case. Possible transformations of one combination into another and their probabilities

	From	To	Probabilities			From	To	Probabilities
1	ABc	ABC	u		20	Abc	abc	w
2	aBC	ABC	u		21	aBc	abc	w
3	AbC	ABC	u		22	abC	abc	w
4	Abc	ABc	$u - u^2$		23	ABc	Abc	$w - w^2$
5	Abc	AbC	$u - u^2$		24	ABc	aBc	$w - w^2$
6	aBc	ABc	$u - u^2$		25	aBC	aBc	$w - w^2$
7	aBc	aBC	$u - u^2$		26	aBC	abC	$w - w^2$
8	abC	aBC	$u - u^2$		27	AbC	Abc	$w - w^2$
9	abC	AbC	$u - u^2$		28	AbC	abC	$w - w^2$
10	Abc	ABC	u^2		29	ABc	abc	w^2
11	aBc	ABC	u^2		30	aBC	abc	w^2
12	abC	ABC	u^2		31	AbC	abc	w^2
13	abc	Abc	$u - 2\,u^2$		32	ABC	ABc	$w - 2\,w^2$
14	abc	aBc	$u - 2\,u^2$		33	ABC	aBC	$w - 2\,w^2$
15	abc	abC	$u - 2\,u^2$		34	ABC	AbC	$w - 2\,w^2$
16	abc	ABc	$u^2 - u^3$		35	ABC	Abc	$w^2 - w^3$
17	abc	aBC	$u^2 - u^3$		36	ABC	aBc	$w^2 - \mathrm{w}^3$
18	abc	AbC	$u^2 - u^3$		37	ABC	abC	$w^2 - w^3$
19	abc	ABC	u^3		38	ABC	abc	w^3

The fitness for individuals with two advantageous alleles (F_{XY}; XY means AB, for the two genes case; AB or BC or AC, for the three genes case) is:

$$F_{XY} = 1 + k\,[(1 + s)^2 - 1] \qquad (8)$$

(where $k = 1$ when there is no interaction - or epistasis - between the genes).

In the case of three advantageous alleles:

$$F_{ABC} = 1 + k^2\,[(1 + s)^3 - 1] \qquad (9)$$

If we indicate the frequency of combination xy in R+ individuals at the n-th generation with $P_{xy,n}$ and that in R- individuals with $P_{xy',n}$, recombination for R+ individuals is simulated, in the two genes case, by calculating the frequencies of a, A, b, B, over the total of individuals with R+ (P_{R+}):

$$P_{a,n} = P_{ab,n} + P_{aB,n};\ \ldots \qquad (10)$$

and, afterwards, by using the equations:

$$P_{ab,n+1} = \tfrac{1}{2}\,P_{ab,n} + \tfrac{1}{2}\,\frac{P_{a,n}}{P_{R+,n}}\,\frac{P_{b,n}}{P_{R+,n}}\,P_{R+,n};\ \ldots \qquad (11)$$

The first part of the solution of each equation means that, in the recombination between individual I and another individual, in half of the cases the allele present in I does not change. The second part means that, in the remaining 50%, the allele present in I is substituted by other alleles from other individuals: the frequencies of the substituting alleles are given by the multiplication of the relative frequencies of each allele ($P_{x,n} / P_{R+,n}$), with the result multiplied for the frequency of R+ ($P_{R+,n}$).
On the contrary, for R- individuals and with $z = 0$ (see condition [c]), there is no calculation:

$$P_{ab',n+1} = P_{ab',n}\ ;\ \ldots \qquad (12)$$

In the three genes case, recombination for R+ individuals is simulated by calculating the frequencies of a, A, b, B, c, C over the total of individuals with R+:

$$P_{a,n} = P_{abc,n} + P_{aBc,n} + P_{abC,n} + P_{aBC,n};\ \ldots \qquad (13)$$

and, afterwards, by using the equations:

$$P_{abc,n+1} = \tfrac{1}{2}\,P_{abc,n} + \tfrac{1}{2}\,\frac{P_{a,n}}{P_{R+,n}}\,\frac{P_{b,n}}{P_{R+,n}}\,\frac{P_{c,n}}{P_{R+,n}}\,P_{R+,n}\ ;\ \ldots \qquad (14)$$

while for R- individuals:

$$P_{abc',n+1} = P_{abc',n}\ ;\ \ldots \qquad (15)$$

The simulation model for finite populations

All these equations are correct in the abstract case of an infinite population, but real populations are made up of N individuals, with N a finite and not fractional number, and are subject to random fluctuations for the number of individuals of the whole population and for each gene combination

present therein.
By mutation, at each generation, an allele x may be transformed into another allele X with a probability equal to the frequency of mutation u_x. Therefore, depending on the value u_x, the frequencies of x and X at generation n ($P_{x,n}$ and $P_{X,n}$) are expected to pass to the frequencies $P_{x,n+1}$ and $P_{X,n+1}$ in the next generation with a difference $\Delta_x = -u_x P_{x,n}$ and $\Delta_x = +u_x P_{X,n}$ respectively.
More generally, because of mutations, advantage, recombination, genetic drift or other causes, the frequency of a combination xy is expected to pass from $P_{xy,n}$ to $P_{xy,n+1}$ in the next generation with a difference Δ_{xy} in absolute value between $P_{xy,n}$ to $P_{xy,n+1}$.
For real populations, Δ_{xy} values, multiplied by N, must always be integer numbers.
In the program, each of these integer numbers is obtained emulating the function "rbinom" of the package R of *The R Foundation for Statistical Computing*© (http://www.r-project.org/), which generates integer random deviates.

This function is used in the program to simulate the variations of frequencies due to:
- mutations (e.g., a → A);
- back-mutations (e.g., A → a);
- advantage;
- recombination;
- genetic drift;
- diffusion of combinations among demes, when the population is not composed of a single deme (d = 1), but of several demes (d > 1) each composed of N individuals and with a mean interdemic diffusion of genes at each generation equal to f.

At each generation, the function is used several times (up to 13,000 times in 3 genes case and 100 demes).

Results for an infinite population

With no epistasis (k = 1) and no linkage disequilibrium (D = 0), sex is neutral with any value of u, w or s (Fig. 4).
In the figures, the value of R+ after 250 generations ($P_{R+,250}$) is 0.499997620408316 in the two genes case and 0.499998194700698 in the three genes case. The slight differences between these values and 0.5, the frequency of R+ at generation 0, are due to the little positive linkage disequilibria caused by mutations. The frequencies of R+ and R- at generation 0 ($P_{R+,0}$; $P_{R-,0}$) have been set equal to 0.5 to give to sex and asex individuals the same starting conditions. With any other value as well, (e.g., $P_{R+,0}$ = 0.6; $P_{R-,0} = 1 - P_{R+,0}$ = 0.4), the model shows in infinite populations no significant variation from the initial frequencies of R+ and R-, as predicted by Maynard Smith (Maynard Smith, 1978). The simulations, in this and in the following figures, have been extended up to 250 generations, quite sufficient to stabilise combination and R+ values (except for fig. 14, simulation series with s = 0.01).
With any time-dependent variation of the values of s, sex is neutral too (Fig. 5). This result needs to be remarked upon.
Red Queen theory rightly underlines that biotic are quantitatively more important than physical factors as selective forces. From this splendid idea (“Red Queen concept”), which is undoubtedly true considering the infinite interactions between predator-prey, parasite-host, herbivore-grass, competitors for the same resource of different species, intraspecific competitors, etc., and considering the fact that in many cases these interactions cause oscillating values of selective pressures, the theory deduces the evolutionary justification of sex (Bell, 1982; Otto and Nuismer, 2004; Kouyos et al., 2007).

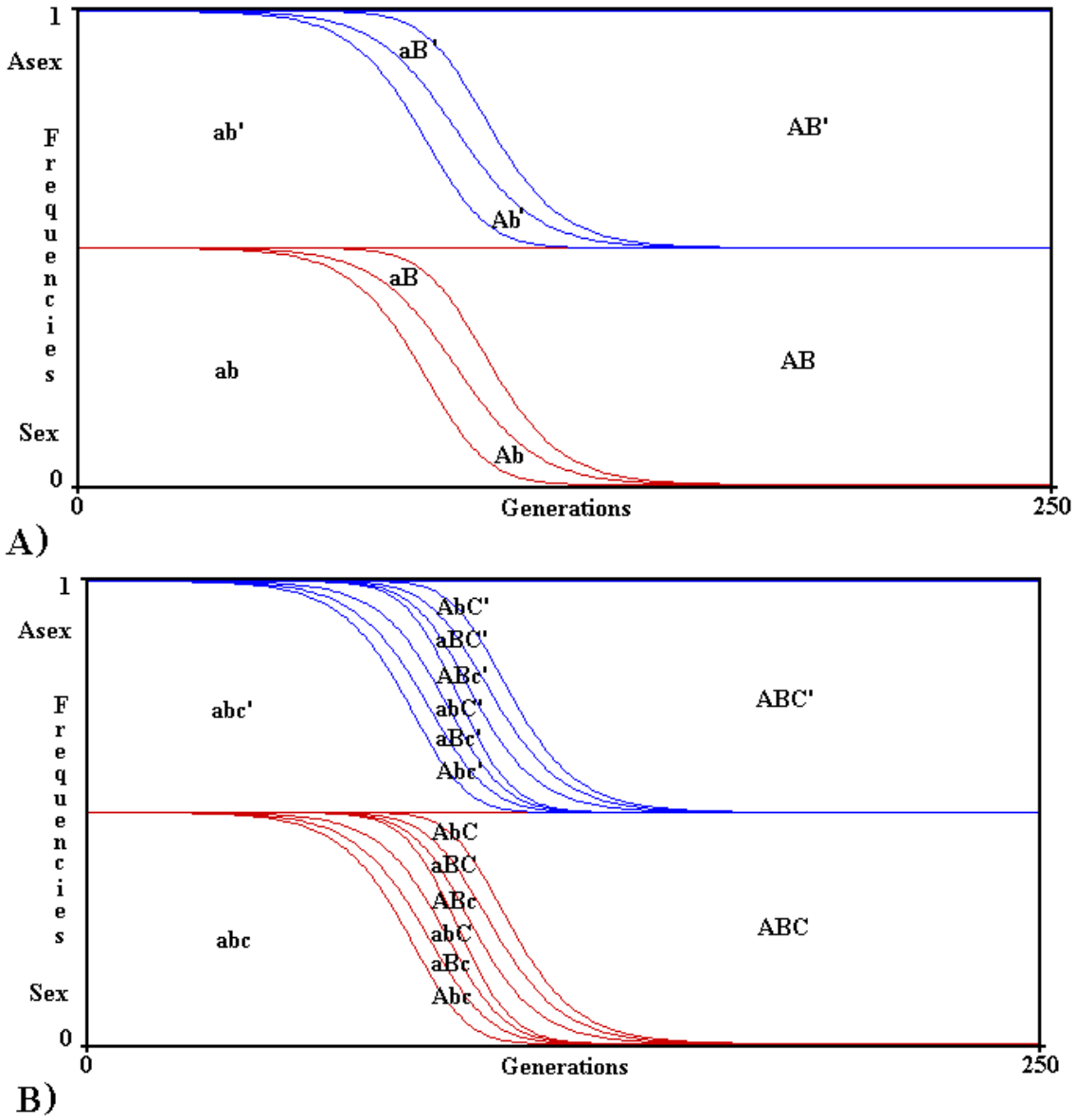


Fig. 4. A) Two genes case; B) Three genes case. In both examples and in the following figures, if not specified otherwise: $u = w = 0.00001$; $s = 0.1$; $k = 1$; $D = 0$. The value of R+ after 250 generations ($P_{R+,250}$) is 0.499997620408316 in the first case and 0.499998194700698 in the second case. The slight differences between these values and 0.5, the frequency of R+ at generation 0, are due to the little positive linkage disequilibria caused by mutations. The frequencies of R+ and R- at generation 0 ($P_{R+,0}$; $P_{R-,0}$) have been set equal to 0.5 to give to sex and asex individuals the same starting conditions. With any other value as well, (e.g., $P_{R+,0} = 0.6$; $P_{R-,0} = 1 - P_{R+,0} = 0.4$), the model shows in infinite populations no significant variation from the initial frequencies of R+ and R-, as predicted by Maynard Smith [Maynard Smith, 1978]. The simulations, in this and in the following figures, have been extended up to 250 generations, quite sufficient to stabilise combination and R+ values (except for fig. 14, simulation series with $s = 0.01$).

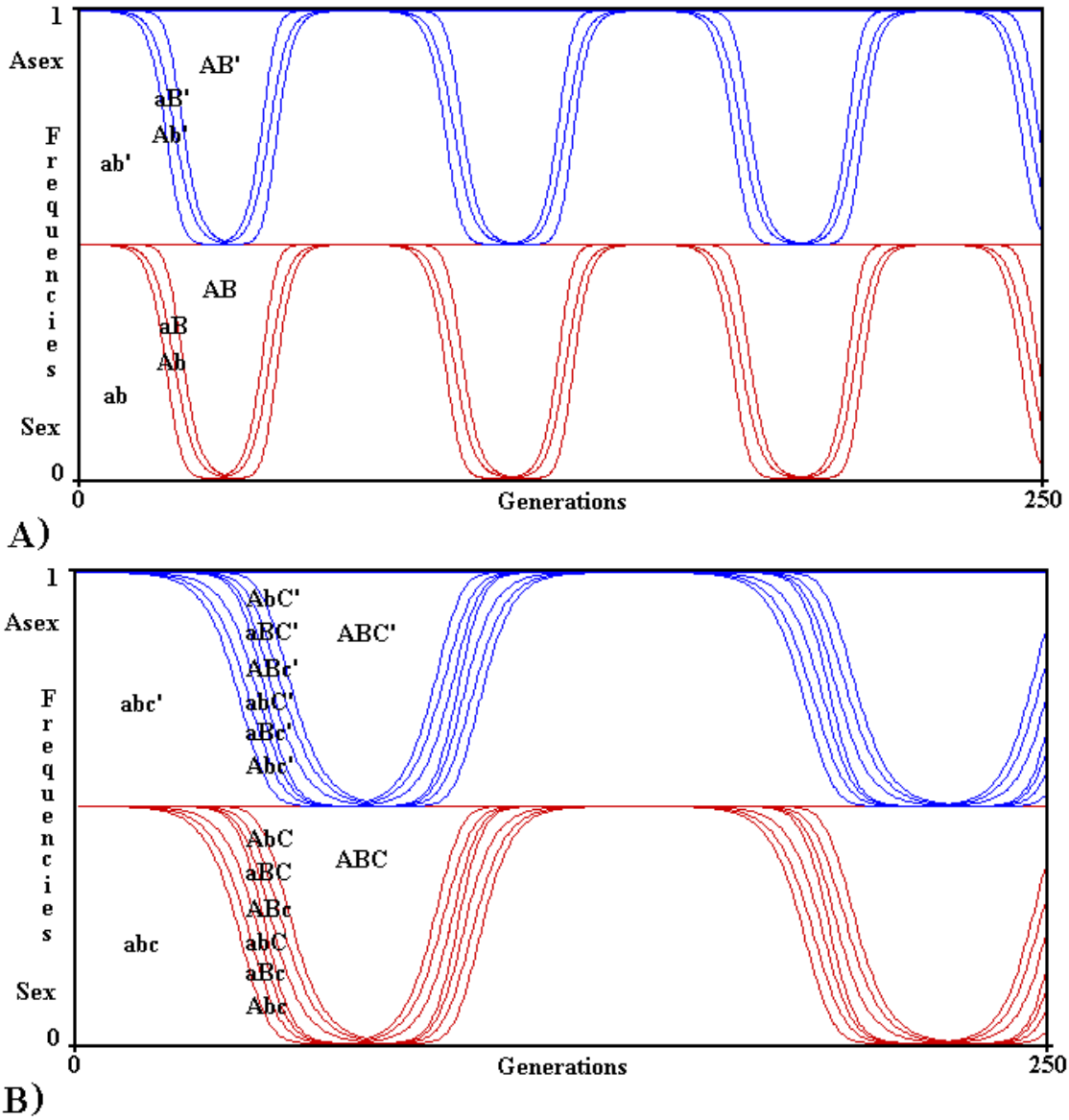


Fig. 5. Effects of the oscillations of s. A) Two genes case; B) Three genes case. In the simulations, *s* value oscillates from –0.1 to +0.1 every 150 generations.

The model shows that in infinite populations any oscillating value of advantages cannot be sufficient to justify sex.

The results for finite populations (see subsequent section) show that sex is advantageous but this in relation to the finiteness and discreteness of real populations and not to the biotic or physical character of selective pressures or to the condition of oscillating values of advantages/disadvantages. This should by no means be interpreted as a rejection or diminution of the Red Queen concept but as a theoretical argument against the Red Queen hypothesis.

If $k > 1$ (positive epistasis), sex is disadvantageous, while, on the other hand, if $k < 1$ (negative epistasis), sex is advantageous (Fig. 6).

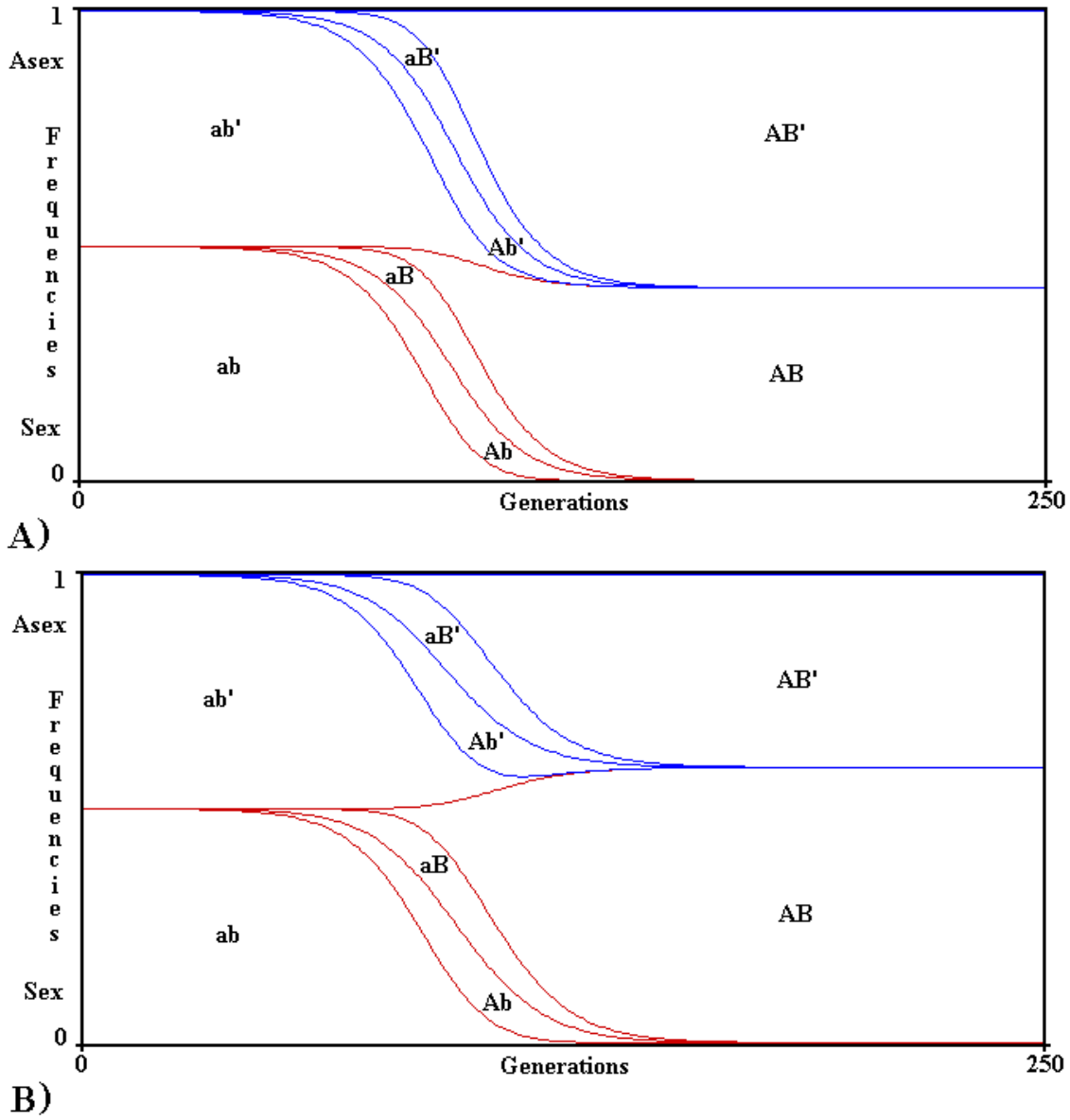


Fig. 6. Effects of the variations of *k*. Two genes case. A) $k = 1.03$ (positive epistasis): sex is disadvantageous; B) $k = 0.97$ (negative epistasis): sex is advantageous. If the absolute value of $1-k$ is greater, the disadvantage / advantage of sex increases proportionally.

With positive linkage disequilibrium sex is disadvantageous, while with negative linkage disequilibrium sex is advantaged (Fig. 7).

In an infinite population, the results of simulations confirm considerations obtained through analytical arguments by other AA. (Felsenstein, 1965; Maynard Smith, 1968; Eshel and Feldman, 1970; Karlin, 1973).
However, a justification of sex as caused by prevailing conditions of negative epistasis or of negative linkage disequilibrium is unlikely and undocumented.

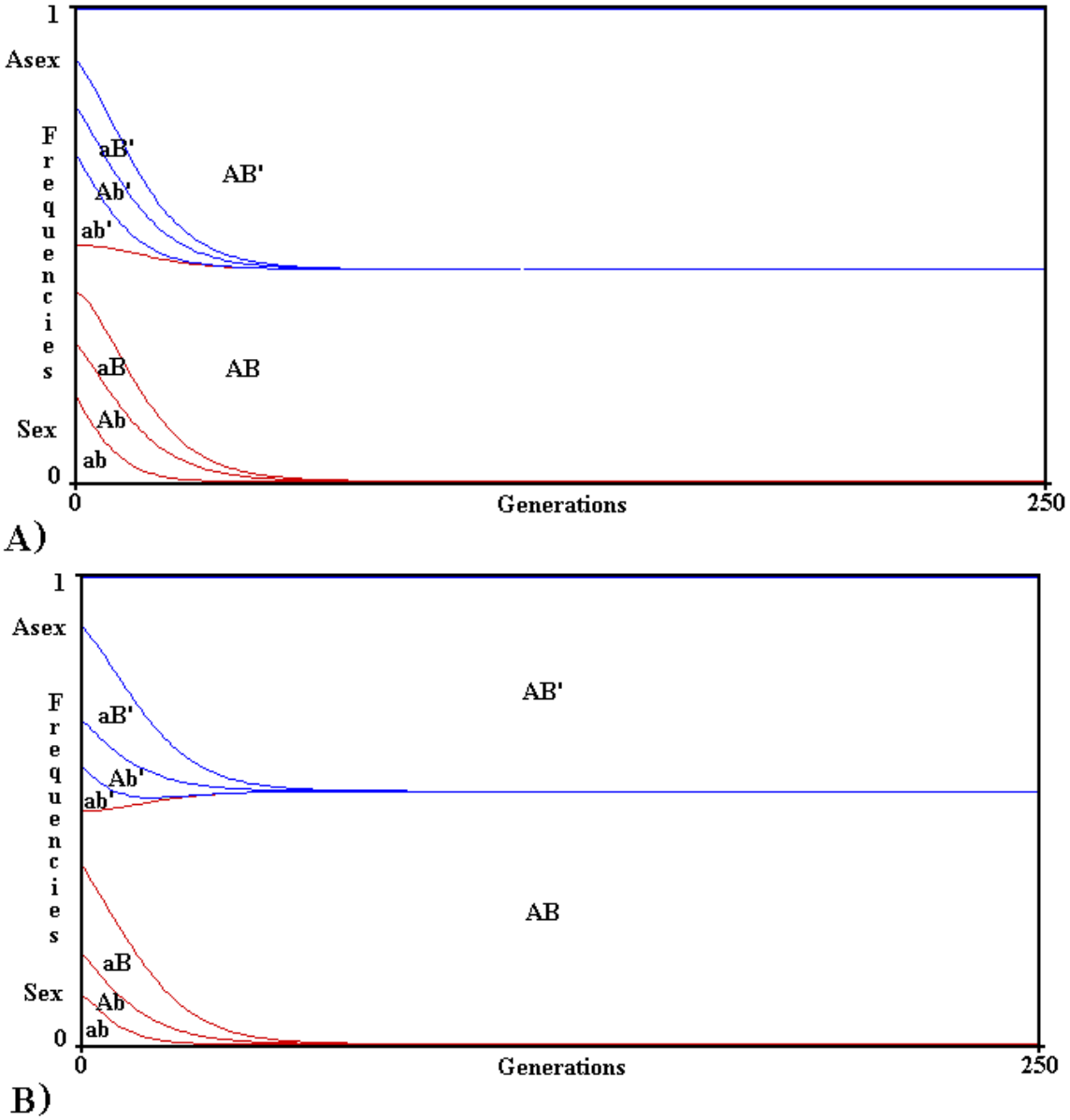
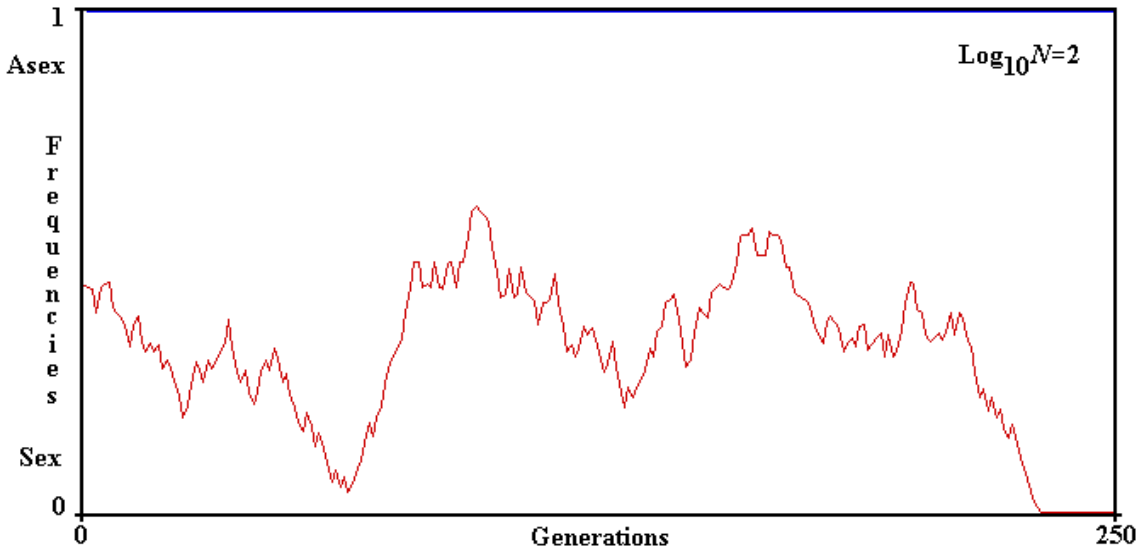


Fig. 7. Effects of the variations of *D*. Two genes case. A) *D* = +0.04 (positive linkage disequilibrium): sex is disadvantageous; B) *D* = –0.04 (negative linkage disequilibrium): sex is advantageous. If the absolute value of *D* is greater, the disadvantage / advantage of sex increases proportionally.

Results for a finite population

Examples of single simulations are illustrated in Fig. 8. With small values of N, the contemporary appearance of two advantageous mutations is rare and sex cannot be favoured: prevalence of R+ or R- is determined only by genetic drift. With intermediate values of N, sex is generally favoured, though sometimes it loses. With greater values of N, sex is almost always favoured but the advantage (difference between $P_{R+,250}$ and 0.5) becomes progressively smaller.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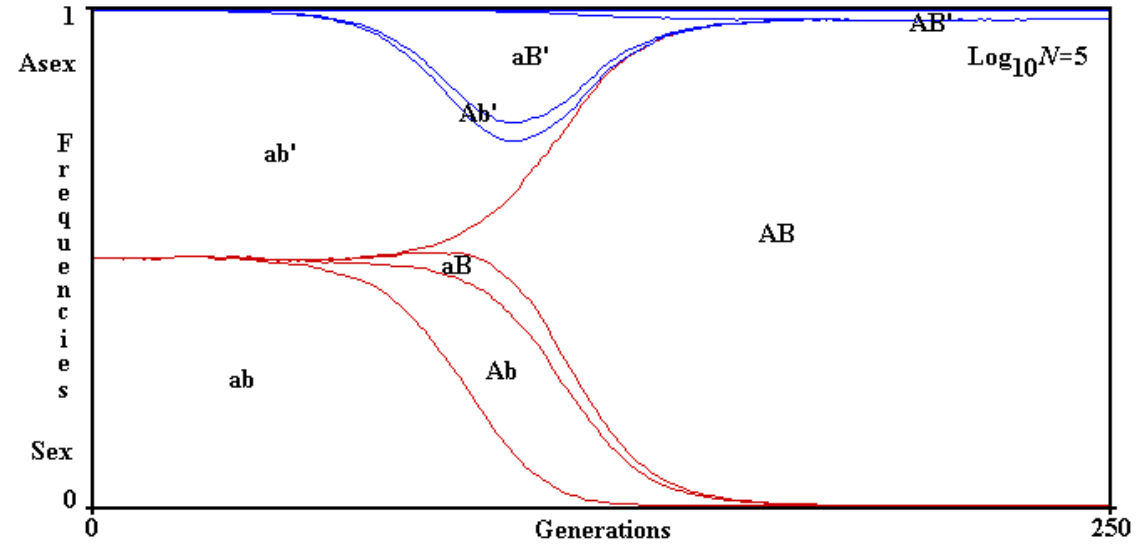
Asex
Frequencies
Sex
0
Log10N=2
0
Generations
250

A)


1
Asex
Frequencies
Sex
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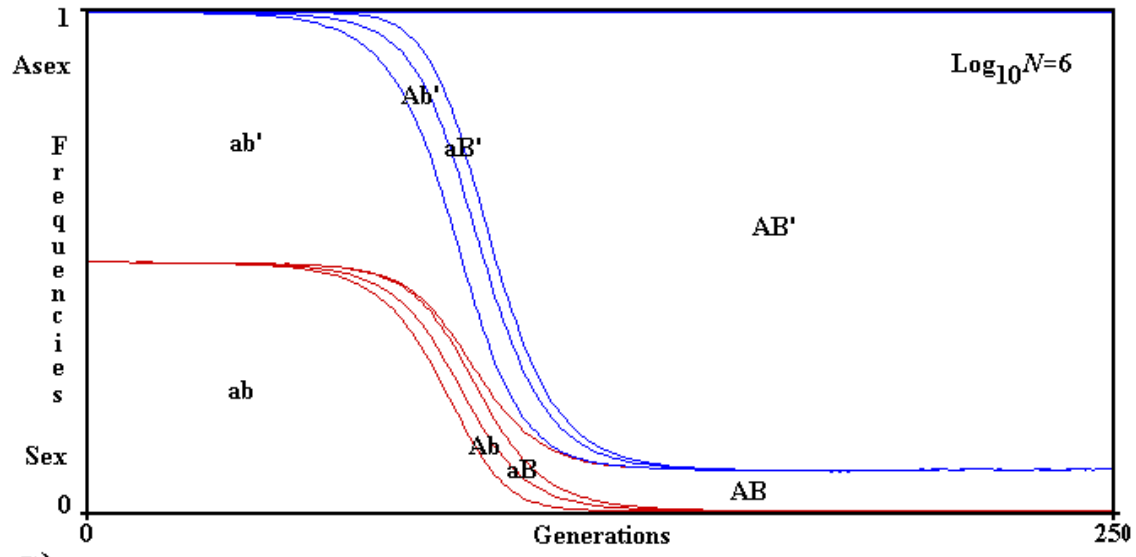
Log10N=5
aB'
AB'
Ab'
ab'
AB
aB
Ab
ab
0
Generations
250

B)


1
Asex
Frequencies
Sex
0
Log10N=6
Ab'
aB'
ab'
AB'
ab
Ab
aB
AB
0
Generations
250

C)

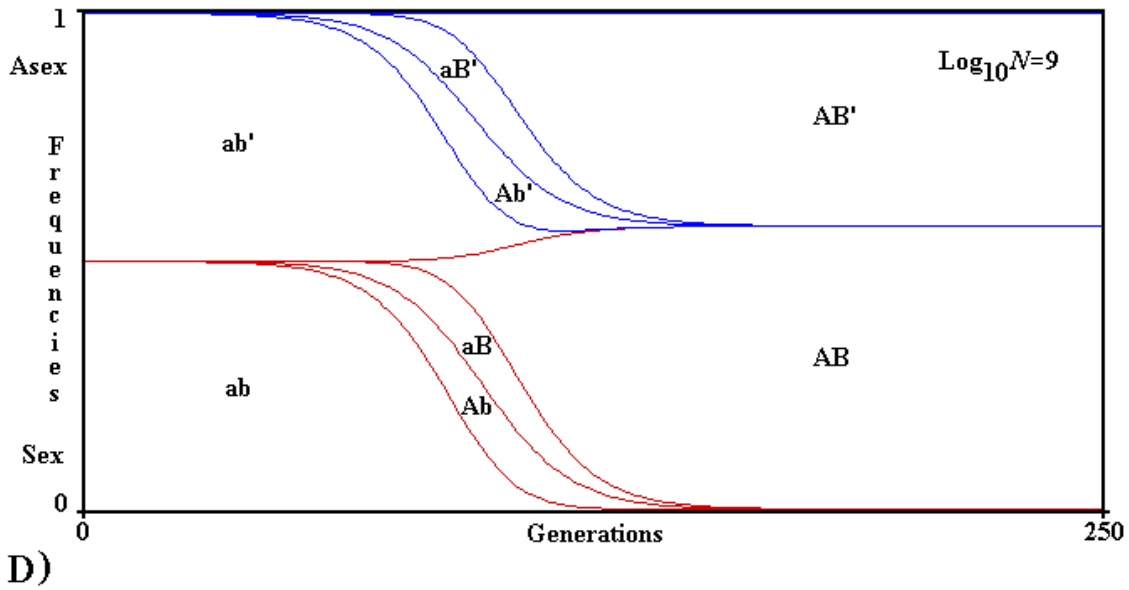


Fig. 8. Two genes case, single simulations in finite populations. A) $\log_{10}N = 2$; B) $\log_{10}N = 5$; C) $\log_{10}N = 6$; D) $\log_{10}N = 9$. In case A, only genetic drift determines the fluctuation of R+ and R- values. In cases B, C, D, the prevalence of R+ or R- is determined by the antecedence of mutation onset in R+ or R-.

Fig. 9 illustrates a series of simulations (1,000 for each point) with log10N varying from 1 to 12 step 0.5. Mean (indicated by a square) and S.D. are reported for each point and compared with another series of simulations (indicated by symbol x) where R+ individuals are not allowed to recombine, each point marked with an asterisk if the results are significantly different ($p < 0.001$, with t-test for two unpaired groups of data [Armitage et al., 2001]).

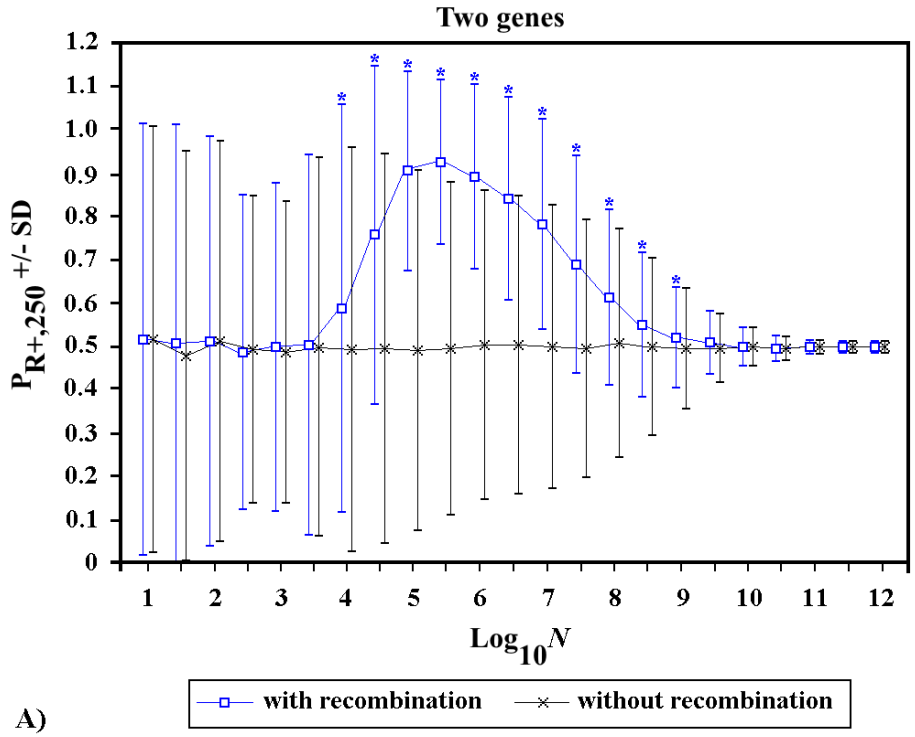
In Fig. 10, the same series of simulations of the preceding figure is compared with two other simulations where, to a fraction z of R- individuals, recombination is allowed (in Appendix, the modifications of equations (10-15), necessary when $z > 0$, are illustrated). Even with small values of z the advantage of R+ over R- individuals fades.

In Fig. 11, a variation of u modifies the curve of sex advantage. In particular the left side is shifted to the left by an increase of u, and vice versa, in proportion to u (sex advantage is conditioned by mutation onset, which is proportional to u). The right side is shifted to the right / left in proportion to u^2 in the two genes case and to u^3 in the three genes case (sex advantage fades when two – in the two genes case – or three – in the three genes case – mutations arise at the same time and these events are proportional to u^2 and u^3, respectively).

In Fig. 12, a variation of s modifies, in proportion, only the right side of the curve of sex advantage.

In Fig. 13, the population (now defined as metapopulation) is divided in d demes each made up of by N individuals, with an interdemic interchange of individuals (f) equal to 0.1 per generation. The results show that for the advantage of sex a metapopulation is equivalent to a single population of $d \cdot N$ individuals.

In Fig. 14, it is shown that a contemporary variation of d and u have multiplicative effects and, so, with many demes and high values of u sex is advantageous even with small values of N. In these figures, as in Fig. 12, an increase of d shifts both sides of the advantage curves of sex to the left in proportion to $\mathrm{Log}_{10}\Delta d$. For the three genes case, sex results advantageous even for values of $\log_{10}N = 1$.



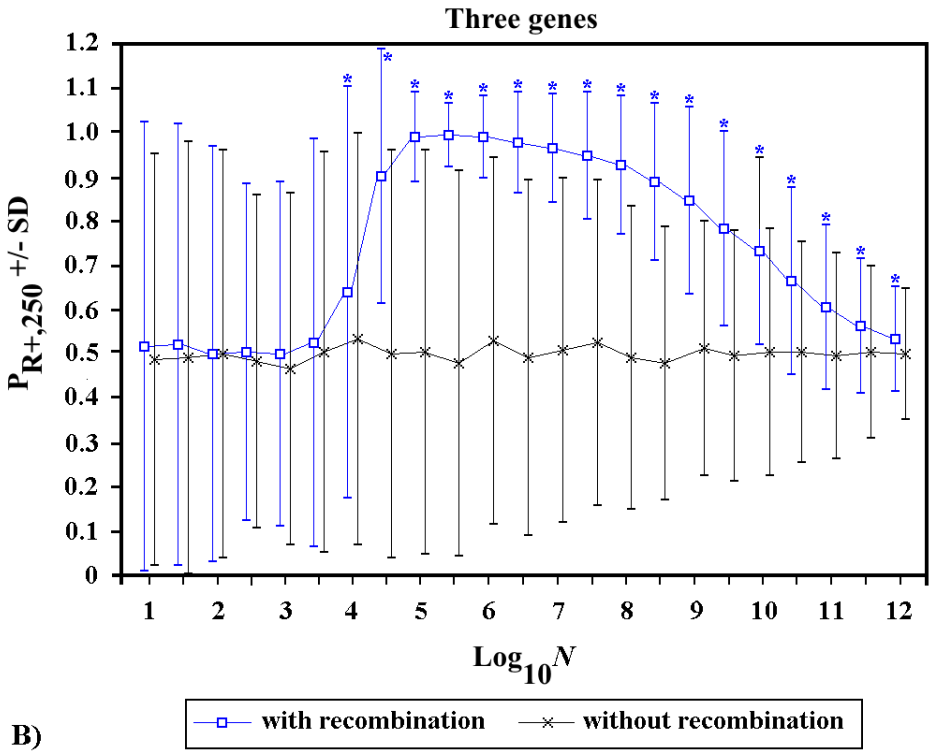
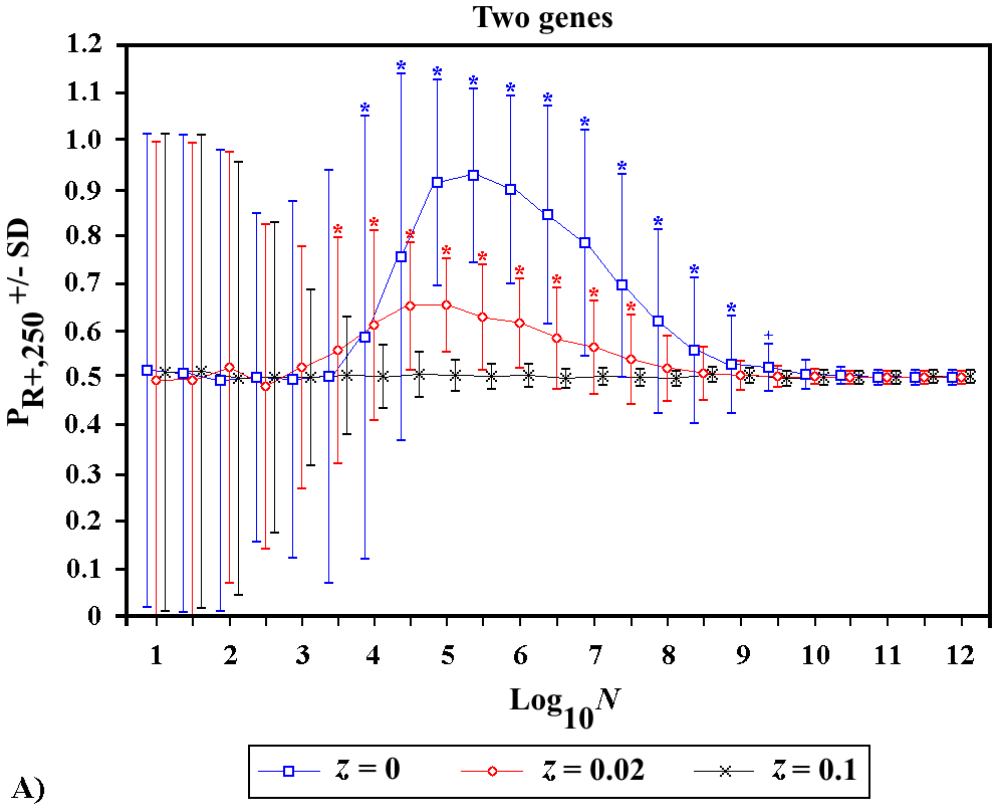
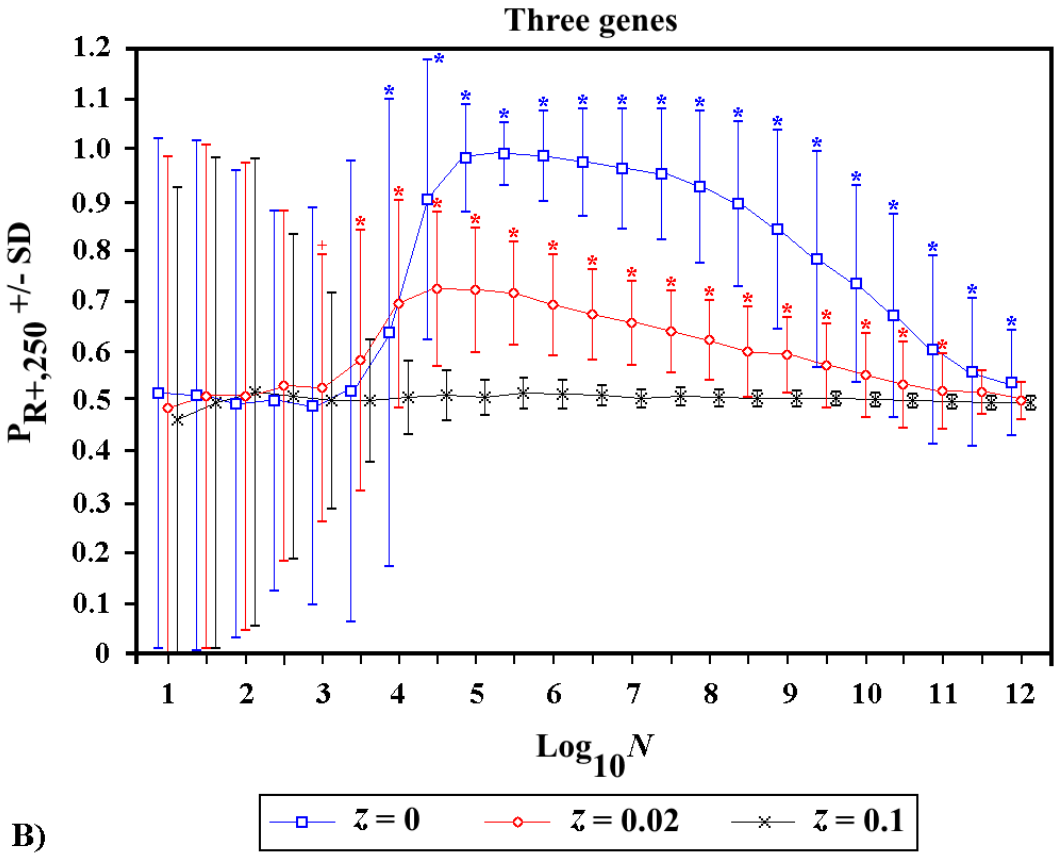


Fig. 9. Effects of recombination in finite populations. A) Two genes case; B) Three genes case. In these and in the following figures, if not specified otherwise: $u = w = 0.00001$; $s = 0.1$; $k = 1$; $D = 0$. Mean and standard deviation (SD) are reported for each point. For the series of simulations with recombination, an asterisk indicates a significant difference ($p < 0.001$) for each point with the corresponding point of simulations without recombination. In this and in the following figures: a) to avoid the superimposition of SD bars, the symbols of the first and of the last series have been shifted a little to the left and to the right, respectively; b) the results are always those obtained with the first run of simulations. Repetitions of the simulation runs for each series have given results equivalent to those of the first runs and these have not been used to substitute them.



A)



B)

Fig. 10. Effects of the variations of *z*. A) Two genes case; B) Three genes case. The two series with $z = 0$ are the same as in Fig. 11 with recombination. With $z = 0.02$ the advantage for R+ individuals is greatly reduced and with $z = 0.1$ is practically cancelled. In these and in the following figures, an asterisk or a cross indicate a significant difference ($p < 0.001$ and $p < 0.01$, respectively) for each point versus the corresponding point of simulations without recombination in figures 11-A and 11-B.

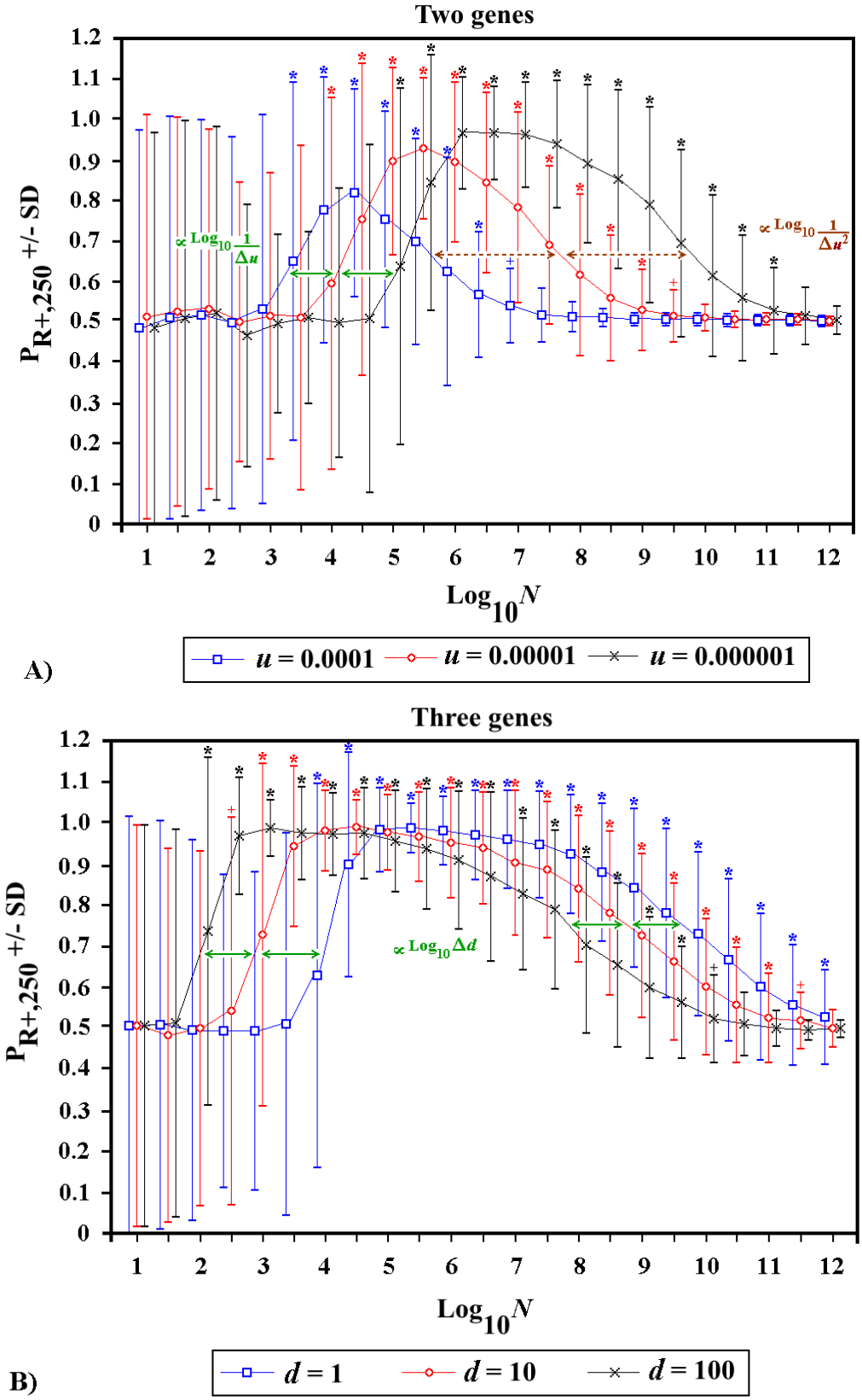
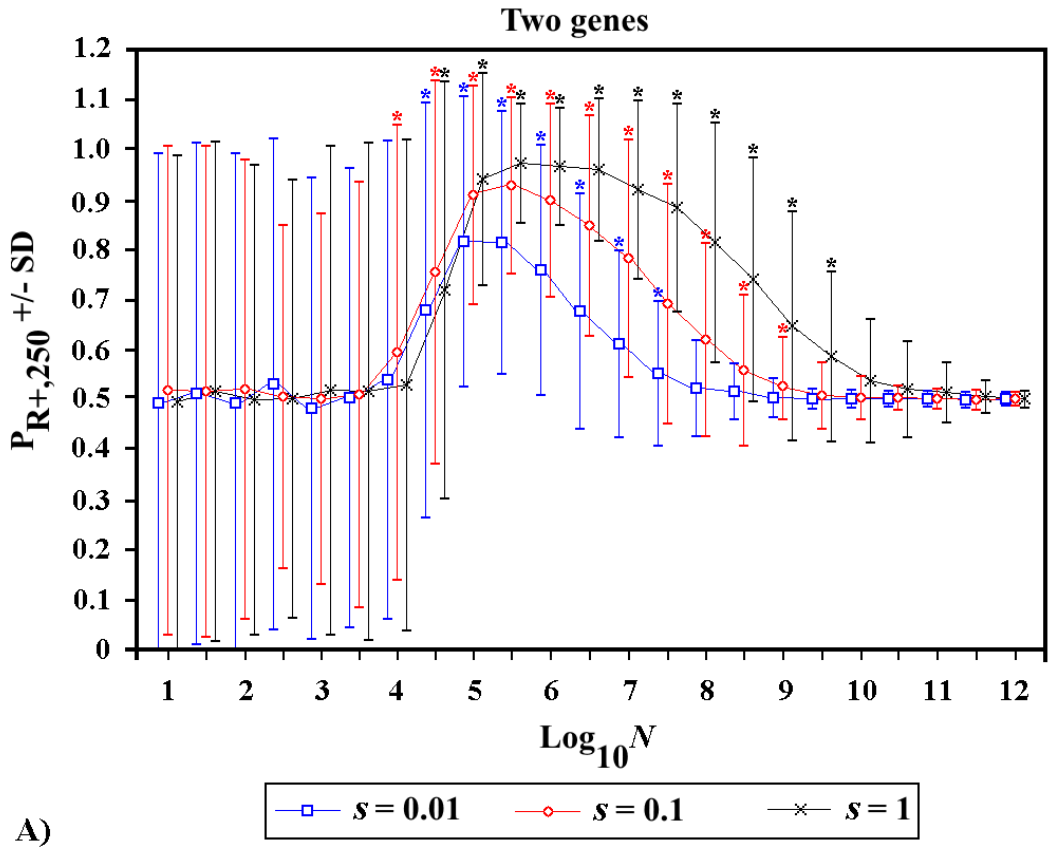


Fig. 11. Effects of the variations of u. A) Two genes case; B) Three genes case. The distance between the left sides of the curves is proportional to $\mathrm{Log}_{10}(1/\Delta u)$, while for the right sides the distance is proportional to $\mathrm{Log}_{10}(1/\Delta u_2)$ in A and to $\mathrm{Log}_{10}(1/\Delta u_3)$ in B.



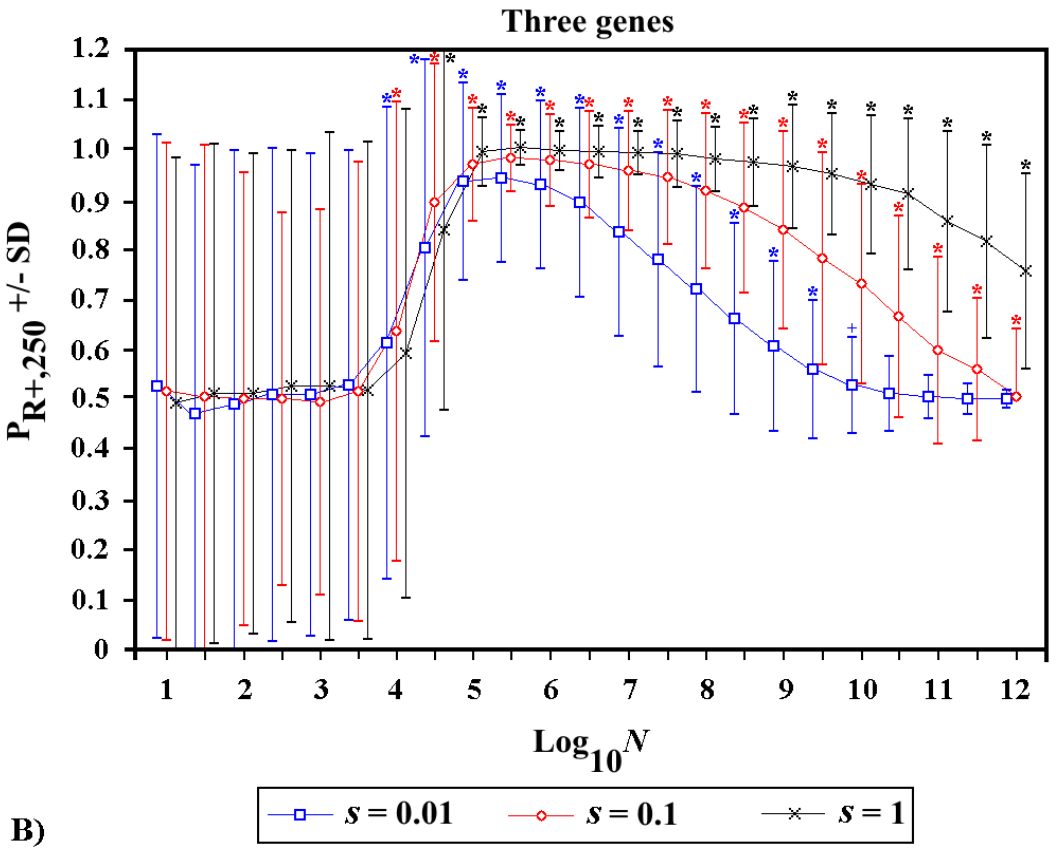


Fig. 12. Effects of the variations of *s*. A) Two genes case; B) Three genes case. With *s* = 0.01, simulations have been extended to 2,000 generations.

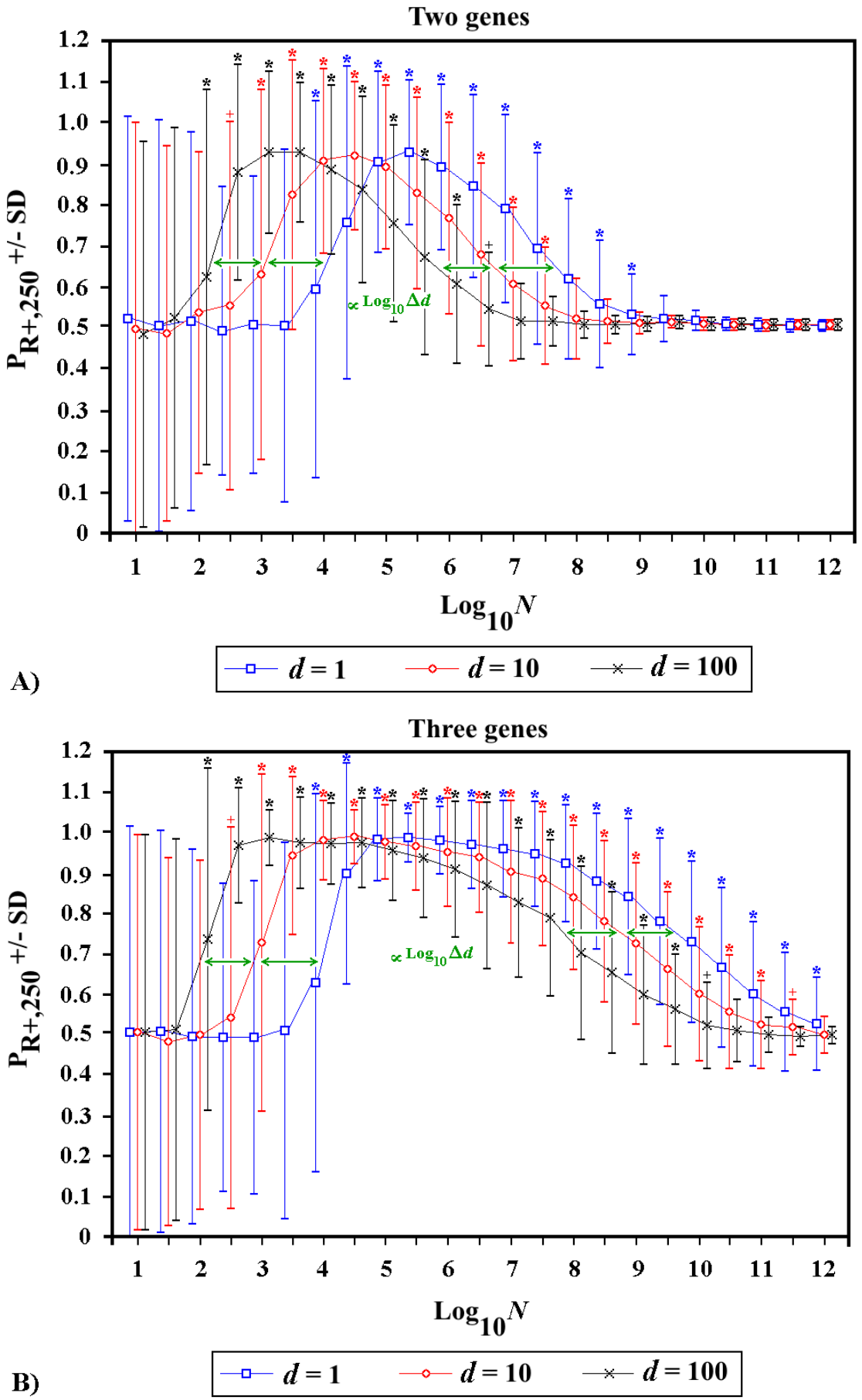
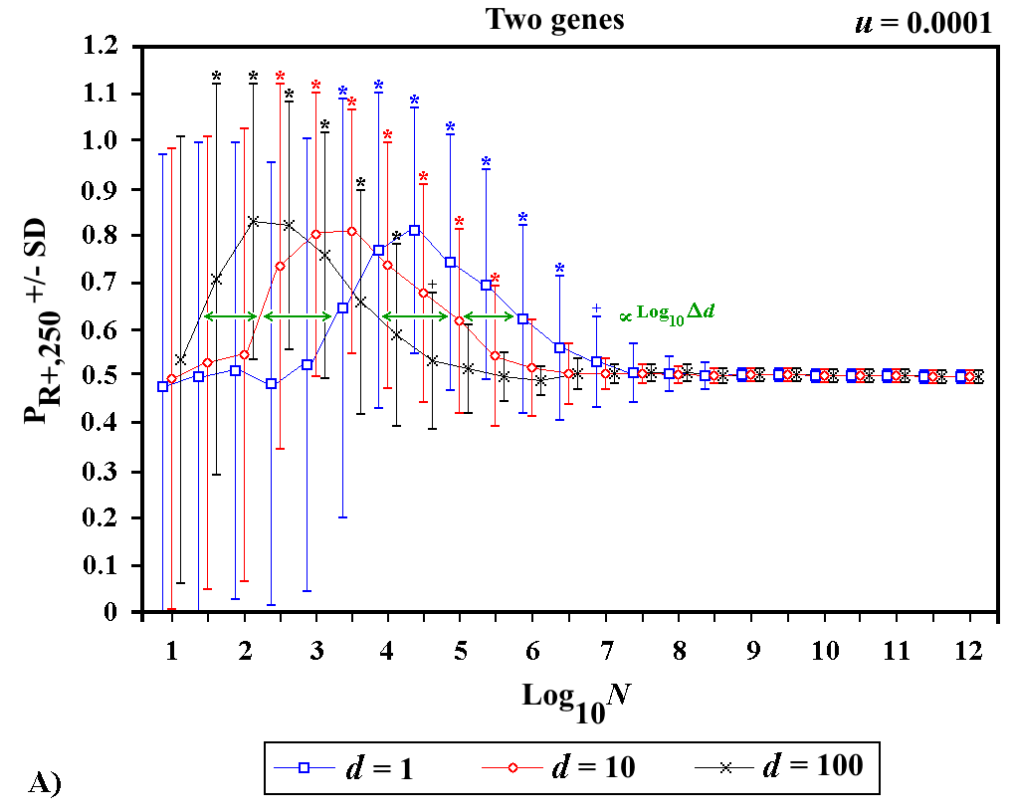


Fig. 13. Effects of the variations of *d*. A) Two genes case; B) Three genes case. An increase of *d* shifts both sides of the advantage curves of sex to the left in proportion to $\mathrm{Log}_{10}\Delta d$.



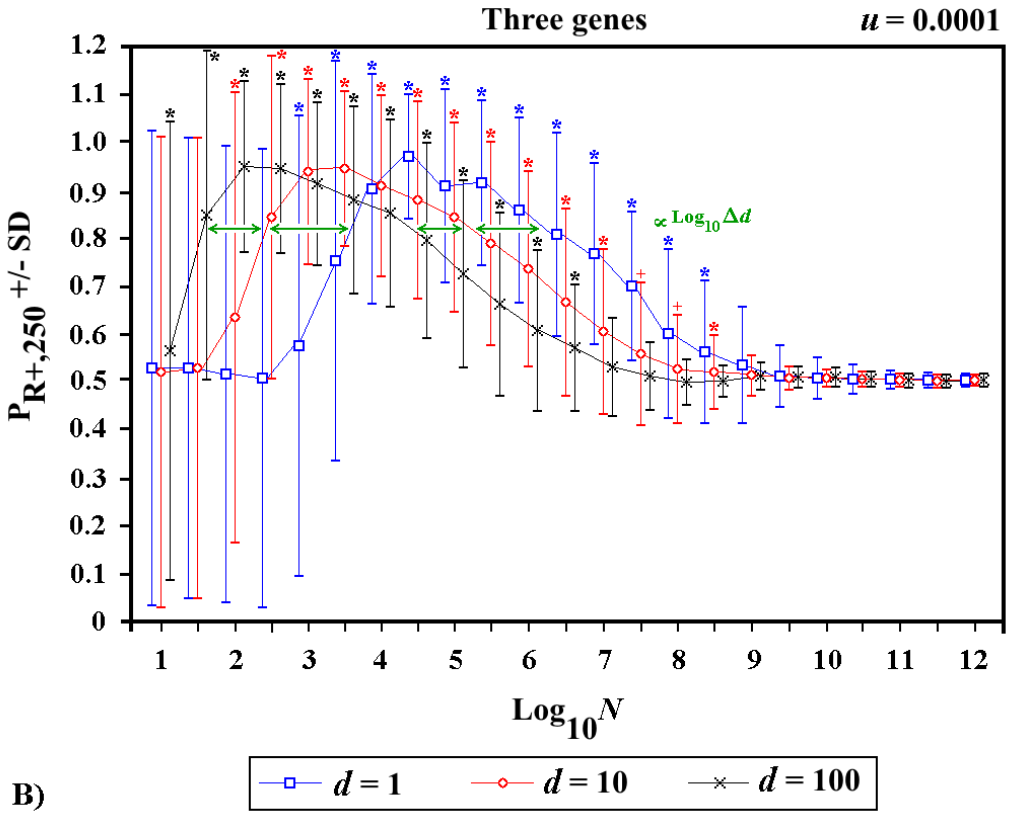


Fig. 14. Effects of the combined variations of *u* and *d*. A) Two genes case; B) Three genes case. The same conditions as in the previous figure, but the value of *u* is 0.0001 instead of 0.00001 and the curves are shifted to the left by a logarithmic unity. In these figures too, an increase of *d* shifts both sides of the advantage curves of sex to the left in proportion to $\mathrm{Log}_{10}\Delta d$. For the three genes case, sex results advantageous even for values of $\log_{10} N = 1$.

Disadvantage of sex

The simple fact that "a copy of a given gene is certain to be present in any asexual egg, but has only a 50 per cent chance of occurring in any given sexual ovum" (Bell, 1982), has been described as "cost of sex" (Maynard Smith, 1971) or "cost of meiosis" (Williams, 1975) or "twofold selective advantage" of parthenogenesis (Maynard Smith, 1978). But, as an equally simple counter-argument, in the case of an isogamous species, if m is the optimal size of a zygote, the production of a single asexual zygote of m size has a cost proportional to m. This cost is equal to the cost of two sexual gametes of size $m/2$ that, when coupled with two other gametes of the same size obtains the optimal size m for two zygotes. In both cases, a gene has the same probability of being present in a zygote (1 in the first case; $0.5 \cdot 2 = 1$ in the second case). This is perfectly true if the relation between zygote size and viability is linear. In fact, if we symbolize survival with s, the relationship between zygote size and its viability can be expressed as $m = A\, s^B$, where A and B are constants and, in the model of some Authors (Parker et al., 1972; Bell, 1978; Charlesworth, 1978), in isogamous species, with B=1 (linear relation between zygote size and viability) the overall cost of sex is zero, with $B < 1$ the cost of sex is > 0, and with $B > 1$ the cost of sex is < 0 (Bell, 1982). This means that for isogamous species in particular conditions only ($B<1$) there is a cost of sex and that in other conditions ($B>=1$) the cost of sex is an advantage or is inexistent.

Moreover, if in the evolution from isogamy to anisogamy there are advantages / disadvantages caused by the second condition, selection should favour / contrast anisogamy and not sex in itself.

For these considerations, in an attempt to predict the trends of sex diffusion among the various species, as an alternative to asexual reproduction, or to predict the occurrence of sexual phases for species alternating sexual and asexual phases, I have disregarded the so-called "cost of sex".

On the contrary, I deem it absolutely necessary to consider for sexual individuals the disadvantages deriving from the search of a mate and connected to the coupling. In this paper, I maintain that the counterbalance to the advantage of sex is intrinsic to the patterns of sex expression, as expressed by Bell (Bell, 1982): "Amphimicts have one ... handicap: they must be able to find a mate, and this may be an expensive, risky and time consuming process." (p. 357). Moreover, courtship and copulation take up more precious time. For the sake of brevity, I will call this set of handicaps the "disadvantage of sex" (DS).

Gerritson (Gerritson, 1980) maintains that DS is greater in conditions of low population density. On the contrary, I think that DS will be critically greater in severely disturbed habitats and in conditions of r-selection. Indeed, in severely disturbed habitats the search for a mate is too expensive and risky. Likewise, in conditions of r-selection (and in phases of exponential growth of population) the crucial factor is reproduction swiftness, and sex, a "time consuming process" (Bell, 1982), is highly disadvantageous. Given these considerations, I do not share the consequence of Gerritson's opinion that "reproduction following long-distance dispersal should be parthenogenetic" (Bell, 1982, p. 357), because there is no severely disturbed habitat. Also in contrast with Gerritson's opinion: "parthenogenetics insects .... very often live in small patches of high local population density" (*ibidem*), which is a condition of r-selection.

A comparative and experimental critique of the theories (Empirical evidence for various theories)

As a theory is sound or unsound according to whether predictions are confirmed or falsified by empirical data, it is necessary to verify whether predictions of the "classic" hypothesis about sex evolutionary advantage are confirmed or refuted by data from natural observation. Moreover, according to the scientific method, a theory refuted by empirical data must be considered as untenable and not presented as a valid hypothesis until its contradictions with empirical data have been explained or somehow resolved.

I have drawn a table (Table 3) in which predictions of the "classic" hypothesis on the evolutionary meaning of sex, along with those of three other theories (Best-Man, Tangled Bank and Red Queen)

concerning the expected trends of the distribution in the nature of sex and related phenomena are compared with empirical evidence from natural observation.

Table 3. Comparison between predictions of four hypotheses on the evolutionary meaning of sex and data from natural observation. (Expected trends of prevalence of sex / asexual forms). Page numbers refer to Bell's book (Bell, 1982).

	PREDICTIONS OF				
	Best-Man hypothesis	Tangled-Bank hypothesis	Red Queen hypothesis	Classic hypothesis (Fisher-Muller)	Data from natural observation
PART 1: INTERSPECIFIC COMPARISON					
Correlation with different habitats (pp. 359-365)					
Freshwater, Higher latitudes, Severely disturbed environments, r-selection, Ecological periphery of a species range, Novel habitats, Recently glaciated areas, Xeric environments	Sexual (p. 359, 364)	Asexual (p. 359, 364)	Asexual[1]	Asexual[2]	Asexual (p. 359)
Ocean, Lower latitudes, Constant environments, K-selection, Ecological center of a species range, Ancient habitats, Unglaciated areas, Non xeric environments	Asexual (p. 359, 364)	Sexual (p. 359, 364)	Sexual[3]	Sexual[4]	Sexual (p. 359)
Other conditions (pp. 378-383 and 364)					
Parasitism	The same as observed in nature (p. 378-383)	The same as observed in nature but thelitoky is expected not rare (p. 378-383)	The same as observed in nature (p. 378-383)	The same as observed in nature[5]	Sexual whenever possible. Thelitoky extremely rare, more common in free-living form (p. 378-383)
Very small size of soma	Sexual (p. 364)	-	Asexual[1]	Asexual[2]	Asexual (p. 364)
Large size of soma	Asexual p. 364)	-	Sexual[3]	Sexual[4]	Sexual (p. 364)
Recombination (pp. 411-436)					
Correlation between achiasmy and Ocean, Lower latitudes, constant environment, K-selection, etc.	Expected negative (p. 433)	Expected positive (p. 433)	Expected positive (p. 433)	Not expected[6]	Not found (p. 411-35)
Correlation between chromosome number and sexual reproduction	Expected negative (p. 433)	Expected positive (p. 433)	Expected positive (p. 433)	Not expected[6]	Not found (p. 411-35)
Correlation between crossing over frequency and sexual reproduction	Expected negative (p. 433)	Expected positive (p. 433)	Expected positive (p. 433)	Not expected[6]	Not found (p. 411-35)
PART 2: INTRASPECIFIC COMPARISON					
Intermittent sexuality (pp. 365-370)					
During growing season (exponential growth of population)	Asexual (p. 365)	- (p. 367)	-	Asexual[2]	Asexual (p. 368)
Before climatic changes	Sexual (p. 365-366)	- (p. 367)	-	-	Not related (p. 367)
At times of minimal population density	Sexual (p. 368)	Asexual (p. 367)	Asexual[1]	Asexual[2]	Asexual (p. 367)
At times of high population density	Asexual (p. 368)	Sexual (p. 367)	Sexual[3]	Sexual[4]	Sexual (p. 367)
Elicitation of sex in laboratory (pp. 370-371)					

Signals of a change in environment	Sex elicited (p. 370)	-	-	-	Not related (p. 370-371)
Crowding and starvation in constant conditions	-	Sex elicited (p. 371)	Sex elicited[3]	Sex elicited[4]	Sex elicited (p. 370-371)
Dispersal and dormancy (pp. 371-777)					
Actively dispersing stage	Sexual (p. 371)	Sexual (with some reservation) (p. 371)	-	Sexual[7]	Sexual (p. 373)
Dormant stage	Sexual (for most Best-Man models) (p. 377)	Sexual / Asexual (p. 377)	-	Sexual[7] (Asexual if the change of environment conditions is abrupt[8])	Sexual / Asexual (p. 371-377)

Note:
*[1] Because of a smaller interspecific competition;
*[2] Because of a greater DS;
*[3] Because of a greater interspecific competition;
*[4] Because of a smaller DS;
*[5] As DS is likely to be small in parasitic phase and great in free-living phase;
*[6] As there is no likely related DS difference;
*[7] There is no particular reason to suppose a greater DS;
*[8] With an abrupt change of environment conditions a greater DS is likely;

Summary

	Best-Man hypothesis	Tangled-Bank hypothesis	Red Queen hypothesis	Classic hypothesis
Differences	12	4	3	0
Concordances	3	7	8	14
No prediction	1	5	5	2

This paragraph has the same name as chapter 4 of Bell's book (Bell, 1982) and has its aims, methods and predictions for the Best-Man, Tangled-Bank and Red Queen hypotheses and references to data from natural observation, in common with it. Predictions for the aforesaid hypotheses are identical to those expounded by Bell, but in some cases, in the absence of Bell's predictions, I have attempted a prediction explained in an appropriate note.
I have also formulated predictions of the "classic" hypothesis with one simple criterion: as the theory and the simulation model of this paper maintain and show that sex – disregarding DS - is always advantageous except in small and isolated populations, sex is predicted to be always favoured except for the above-mentioned populations and when DS is important (severely disturbed environments, r-selection, phases of exponential growth of population, etc.). Moreover, because DS does not exist as regards recombination, no correlation between certain phenomena of recombination (achiasmy, chromosome number, crossing over frequency) and amphimixis or parthenogenesis is expected.
In various cases, predictions of the "classic" hypothesis and those of other hypotheses coincide but the motivations are different (e.g., predictions of the "classic" hypothesis and those of the Red Queen for Correlation with different habitats).
The noteworthy result, in my judgement, is an almost total correspondence between predictions of the "classic" hypothesis and data from natural observation.
The utter failure of the Best-Man hypothesis is remarkable and I share Bell's negative opinion on this theory which, in Table 3, has the only function of showing a plain example of a hypothesis in almost constant contradiction with data from natural observation.
For the Tangled-Bank and the Red Queen hypotheses, there are the wrong predictions of correlation between certain phenomena of recombination and amphimixis/parthenogenesis ("Amphimixis is to parthenogenesis as high rates of recombination are to low; the correlates of low levels of recombination will therefore be the same as the correlates of parthenogenesis." (Bell, 1982)), a

significant contradiction described and underlined by Bell in ch. 5.2 (Bell 1982). On the other hand, as for such phenomena as achiasmy, frequency of crossing over and number of chromosomes intrinsically DS does not exist, a correlation between these phenomena and parthenogenesis is not predicted by the "classic" hypothesis, in accordance with data from natural observation (Bell, 1982).
Moreover, for the Tangled-Bank hypothesis the prediction for parasitism is not completely adequate, as the Bell, himself, underlines (Bell, 1982).
As regards other theories not considered in the table:
- Muller's Ratchet hypothesis. This could justify sex only for small populations as "Muller's ratchet operates only in small or asexual populations ... harmful mutations are unlikely to become fixed in sexual populations unless the effective population size is very small." (Keightley and Otto, 2006). Therefore, this theory, which is not contradicted by the results of this paper, could integrate the "classic" theory.
- Historical hypothesis. This theory, which does not justify sex existence, is refuted by the evidence that sexual or asexual reproduction is influenced by many conditions. However, if it is considered not as a theory explaining sex but as an inertial factor restraining a free passage from sexual to asexual reproduction, or vice versa, it should deserve a certain amount of attention.
- Hitch-hiker hypothesis. A R+ gene could be described as a gene that is advantaged because it hitchhikes favourable genes that are better spread because of by its action. The hitch-hiker hypothesis could, therefore, be defined as a different and indirect way of expounding the "classic" theory.
- Hypothesis that sex is advantageous because it slows down evolution and excessive specialisation. This theory makes no prediction.

Conclusion

Williams proclaimed (Williams, 1975): "... the unlikelihood of anyone ever finding a sufficiently powerful advantage in sexual reproduction with broadly applicable models that use only such general properties as mutation rates, population sizes, selection coefficients, etc." (p. 14), and Ridley wrote (Ridley, 1993): "I asked John Maynard Smith, one of the first people to pose the question 'Why sex?', whether he still thought some new explanation was needed. 'No. We have the answers. We cannot agree on them, that is all.' " (p. 29).
I think that Williams' unlikelihood is now a likelihood and that the uncertainty of Maynard Smith has been solved: with theoretical arguments, the advantage of sex has been rationally explained by the "classic" theory in terms of individual selection and using only the "general properties ..." that Williams insisted on (Williams, 1975). Moreover, if we consider the disadvantage of sex, it is possible to formulate predictions about the trends of its diffusion in nature that are confirmed by data from natural observation.
For small populations, Muller's Ratchet hypothesis, if confirmed, could reinforce and integrate the "classic" theory. Historical hypothesis deserves attention as an inertial factor in the prediction of trends of diffusion of sex and related phenomena.
The correct concept that biotic factors – often with oscillating *s* values - are quantitatively more important than physical factors as selective forces in determining evolution (Red Queen concept), which is the pivotal idea at the roots of the Red Queen theory, is not at all against the "classic" theory, although it is insufficient in itself to explain sex, and should be considered an argument that reinforces this hypothesis.
Somehow, the "pluralist approach to sex and recombination" (West et al., 1999) seem to be the correct solution, but with this specification: "classic" theory is the trunk with the main branches and other theories complete the tree.

Supplementary documents

From the Internet address "http://www.r-site.org/ageing/sex_model.zip", it is possible to obtain an Excel© file with the raw data of figures 9-14 and the executable file of the simulation program.
A technical note for the program is necessary. With the option:
Loop with $Log_{10}N$ = [...] to [...] step .5 *No. iterations (from 1 to 10000) [...]*
if the number of iterations is not small, the graphic display of simulations may disappear after some simulations (as a consequence of PC power limits) and program commands freeze. This does not mean that the program is blocked: it continues to run till the end. Please, await the end and then see the results in ReportFile2.txt (result of each simulation) and ReportFile3.txt (mean and SD for each group of simulation).

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