Asexuals, Polyploids, Evolutionary Opportunists...: The Population Genetics of Positive but Deteriorating Mutations

Bengt O. Bengtsson[1]
Department of Biology, Evolutionary Genetics, Lund University, SE-223 62 Lund, Sweden

ABSTRACT Some genetic phenomena originate as mutations that are initially advantageous but decline in fitness until they become distinctly deleterious. Here I give the condition for a mutation–selection balance to form and describe some of the properties of the resulting equilibrium population. A characterization is also given of the fixation probabilities for such mutations.

MUTATIONS that change the normal genetic system of an organism may well have an initial selective advantage, but an advantage that deteriorates with time and later transforms into a disadvantage. Polyploids lose chromosomes and become unbalanced, asexuals miss out on the advantage of recombination, mutants that spend less energy on repair find themselves loaded with bad mutations, and so on. How can such mutations be studied and their evolutionary effects understood?

Haldane (1927) showed that an organism that suffers regular mutations with fixed deleterious effects evolves toward a stable mutation–selection balance. Wright and Dobzhansky (1946) introduced the study of nonfixed fitnesses and considered the effects of frequency-dependent fitness values, while Kimura and Ohta (1970) studied advantageous mutations (inversions) that gradually lose their fitness advantage. Here I present results for the population genetics of positive mutations that with time become truly deleterious.

The inheritance system for the considered organism is haploid, but the model is relevant also for the formation of reproductively separated clones of asexuals and polyploids at any ploidy level. Assumptions are kept at a minimum to find general conclusions for the considered class of mutations. Some additional derivations, examples, tables, and figures are given as supporting information.

It is my hope that these results will inspire further study of this type of contradictory but relevant mutations, their expected evolutionary behavior, and how they can be empirically recognized in nature.

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[1]Address for correspondence: Department of Biology, Evolutionary Genetics, Lund University, Sölvegatan 35, SE-223 62 Lund, Sweden. E-mail: bengt_olle.bengtsson@biol.lu.se

General model

Consider an infinitely large population of haploids. In each generation the standard type, A_0, changes to the mutant type, A_1, with probability μ ($0 < \mu < \frac{1}{2}$). The relative fitness of A_0 is 1 and of A_1 $1 + s$, where s is strictly greater than 0. In general, the mutant type t generations after production is denoted A_t and its fitness is $(1 + s)f_t$. To make this a model of deteriorating mutants, it is assumed that $f_t \geq f_{t+1}$ for $t \geq 1$. All f-values are positive and we define f_1 as 1.

In a particular generation, let the standard type (A_0) have a frequency of x_0, and let mutants of age-class t (A_t) have a frequency of x_t. The recursion equations describing the relationship between these frequencies can then be written

$$\begin{aligned} x_0' &= (1-\mu)x_0/\,W, \\ x_1' &= \mu\, x_0/\,W, \\ x_{t+1}' &= (1+s)f_t\, x_t/\,W \text{ for all } t \geq 1, \end{aligned} \tag{1}$$

where

$$W = x_0 + (1+s)\sum_{t=1}^{\infty} f_t\, x_t \tag{2}$$

equals the mean relative fitness of the population.

If this dynamic system goes to an equilibrium state (*i.e.*, a state where $x_t' = x_t$ for $t \geq 0$), then the first of the equations tells us immediately that

$$W = 1 - \mu \tag{3}$$

and then, in combination with the other two equations, that the equilibrium frequencies must be

$$\begin{aligned} x_0 &= (1-\mu)/[1+\mu A] \\ x_t &= \mu(1+s)^{t-1} f_1 f_2 \ldots f_{t-1}/(1-\mu)^{t-1}[1+\mu A] \text{ for all } t \geq 1, \end{aligned} \tag{4}$$

where

$$\begin{aligned} A &= \left[\frac{1+s}{1-\mu}\right] f_1 + \left[\frac{1+s}{1-\mu}\right]^2 f_1 f_2 + \left[\frac{1+s}{1-\mu}\right]^3 f_1 f_2 f_3 + \ldots \\ &= \sum_{t=1}^{\infty} \left[\frac{1+s}{1-\mu}\right]^t \prod_{k=1}^{t} f_k \end{aligned} \tag{5}$$

(from now on all x-values denote equilibrium frequencies).

The equilibrium frequencies are valid if and only if A takes a positive, limited value, and the necessary and sufficient condition for this is that there is a positive number T such that

$$f_T < (1-\mu)/(1+s). \tag{6}$$

(If there is no such value, then the sum A will not converge to a limited value and there will be no stable equilibrium state; when condition 6 is fulfilled, on the other hand, the equilibrium frequencies given by 4 are always valid.) The fitness of mutants in age-class t is $(1 + s)f_t$, so another way to express this equilibrium condition is to say that the fitness of the mutant should be smaller than $1 - \mu$ within a limited number of generations after it has been produced. Note that this condition is independent of how strong the initial fitness advantage is and for how long the favorable phase lasts.

The mutational load is, as seen from (3) above, equal to μ, just as in the standard mutation–selection balance for haploids. The average degree of selection against the mutant in the equilibrium population (denoted σ) can be shown to be (see supporting information, section S1, File S1)

$$\sigma = (1 + \mu A)/(1 + A). \tag{7}$$

It follows also that

$$\sum_{t=1}^{\infty} x_t = 1 - x_0 = \mu/\sigma. \tag{8}$$

We have thereby reached the following important result: The population will go to a state where the frequency of the mutant type equals the ratio between the frequency with which mutants recurrently are formed and the average degree of selection against mutants in the population. The difference relative to the standard Haldane-type mutation–selection balance is that in this case mutants of different ages are favored or disfavored differently by selection. Thus, the strength of selection against the mutants is not given by a constant but by an average over the different mutant age-classes in the equilibrium population.

The equilibrium distribution of mutant age-classes can be characterized as follows: In "the young mutant phase," lasting for as long as $f_t > (1 - \mu)/(1 + s)$, subsequent age-classes increase in relative frequency. Then, when $f_t = (1 - \mu)/(1 + s)$, the frequencies of the age-classes remain unchanged between generations. Finally, in "the old mutant phase," for which $f_t < (1 - \mu)/(1 + s)$, the age-classes decline in frequency toward zero. The first two of these phases may be long or short or even missing, but they must be finite in length and they do not intercalate.

Since fitness is $1 - \mu$ during the second mutant phase (if it exists), it follows that for all reasonably smooth distributions of f-values the most common mutant age-class(es) will have a fitness that is close to—in many situations indistinguishable from—the fitness of the standard, nonmutant type.

One-step fitness drop model

So far, the assumptions of the model have been very general. Let us now consider a specific example, built on the idea that newly formed mutations have a high fitness but that this drops drastically after a specified time (a second example based on the idea of a continuous deterioration of fitness is found in section S4, File S1). Or in more formal terms: Let the mutant type retain fitness $1 + s$ until and including generation $T - 1$, when fitness falls to $1 - z$ for all consecutive generations ($z > \mu$). In addition, assume that the mutation rate is very small and that $(1 + s)^{T-1}$ can be approximated by $1 + (T - 1)s$. Then the average strength of selection against the mutant type becomes

$$\sigma = z/[(T-1)(s+z)+1]. \tag{9}$$

This expression is relatively unaffected by the size of s, as long as s is small relative to z. Indeed, if the positive effect of the new mutation is not very great and stays fixed for many generations before fitness plunges to a strongly deleterious state, then the mean selection coefficient (9) becomes close to T^{-1}. In this situation, the time structure of the model rather than the relationship between s and z determines the properties of the equilibrium population. A numerical example of this effect is given as supporting information (see section S2, File S1; and Table S1).

A key assumption in the general model, and also in this investigated special case, is that all changes in mutant fitness occur deterministically in time. The importance of this assumption is shown by the following model extension: Let the time to fitness drop, T, be a random variable with a geometric distribution. Denote the mean of the distribution $E(T)$; this value then equals the inverse of the probability for fitness to drop per generation.

Now the condition for the population to move to a mutation–selection balance becomes

$$E(T) < \frac{1+s}{s+\mu} \tag{10}$$

(see section S3, File S1 for derivation). There is an interesting structural difference between this result, where the mean time to fitness drop must be smaller than a certain value given by μ and s, and the earlier derived condition for stability that is independent of the quantitative relationship between these parameters and requires only that the drop occurs in finite time. The reason for this discrepancy is that the rate with which mutants drop to their deleterious state in the stochastic case must be large enough to keep pace with their constantly growing number, while no such condition is necessary in the deterministic situation, where *all* positive mutations—irrespective of their number—become deleterious at a specific moment in time. For $\mu \ll s \ll 1$ condition (10) becomes $E(T) < s^{-1}$, which supports this interpretation.

On probabilities of fixation and fitness estimates

So far the analysis has been made under the assumption of an infinite population size. The important new factor that a finite population size brings to our investigation is the possibility that a mutation of the considered kind may go to fixation. Using simulations I have studied the probability of this occurring. The results can be summarized as follows (see also Table S2 and Table S3): Barring very rare events, a mutation of the considered kind will go to fixation only if it manages to do so before its fitness falls below the normal fitness value. The fixation probability of a new positive mutation is approximately $2s$ (Haldane 1927, based on Fisher 1922), with the mean time to fixation being strongly related to the inverse strength of selection, s^{-1}. Thus, mutations of the kind studied here are most likely to become fixed if their initial advantage is strong and this advantage lasts for a sufficiently long time. As expected, in the one-step fitness drop example this implies that the size of s becomes much more important for the probability of fixation than the size of z (see section S5, File S1; and Figure S1).

In general, positive but deteriorating mutations will be difficult to recognize as such in nature. Above is shown that the most common class of mutants will have fitness close to normal. In addition, the fixation simulations demonstrated that the mean fitness of mutants that ultimately become lost due to genetic drift is not only close to normal but often greater than normal (see section S5, File S1).

However, from expression (8) above is seen that the mean coefficient of selection against mutants can be estimated from the relative frequency of new mutations among mutant newborn (among N newborn, μN are new mutants among a total number of $(\mu/\sigma)N$ mutant newborn; from this follows that their proportion is σ). Thus, given that parental relationships can be established, this method may function as a way to comprehend more complex fitness relationships for recurrent mutations.

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File S1

Supporting Material

Here I describe some more technical details relating to the analysis of positive but deteriorating mutations. Whenever possible, a direct reference is in the main text given to the relevant section below.

The first section provides a derivation of results (7) and (8) in the main text. The next section introduces Table S1 summarizing numerical examples of equilibrium populations. In section S3, a formal model is described, similar to the general model in the main text, but where the abrupt drop in fitness occurs stochastically and not at a fixed moment in time. It leads to result (10) in the main text. Another model for the decline in fitness is described next (section S4); here the decline in fitness occurs gradually over time at a constant rate. Finally, in section S5, details of the numerical simulations analyzing the fixation properties of positive but deteriorating mutations are given. Some of the fixation results discussed are summarized and illustrated in Tables S2 and S3, as well as in Figure S1.

S1: Additional derivation

Since at equilibrium for the general model the fitness of the standard type is 1 and the population mean fitness is $1 - \mu$, the arithmetic mean fitness of the mutant type of all age-classes, which we denote $1 - \sigma$, can be found from the simple equation

$$1 \cdot x_0 + (1 - \sigma) \cdot (1 - x_0) = 1 - \mu.$$

This implies that the mean fitness of the mutant type is

$$1 - \sigma = 1 - \mu/(1 - x_0) = (1 - \mu)\, A / (1 + A)$$

and that the average degree of selection against the mutant in the equilibrium population is

$$\sigma = (1 + \mu A)/(1 + A),$$

which – as expected – always falls between 0 and 1. From this expression follows (7) and (8) in the main text.

S2: Equilibrium population

In Table S1 is described a numerical example of an equilibrium distribution for the one-step fitness drop model; the parameters have been chosen so that they strengthen some of the interesting effects. The importance of even a brief positive spell for mutations before they become disadvantageous is clearly illustrated. Only five generations with a positive effect makes, for example, the frequency of the normal type 0.658, compared to 0.929 which this frequency would take if the mutation were immediately deleterious (calculated as $1 - 0.05/0.7$). In accordance with the result given in the section discussing the general model in the main text, it can also be noted that the most common mutant age-class is the one immediately after the mutational fitness has fallen to its low value. Indeed, 69% of the mutants have fitness above 1 and only 31% below. In this case, the parameters are far from the values assumed in the approximations used in the main text, but the average strength of selection against the mutation in the equilibrium population, 15%, is nevertheless very close to the inverse of the time to fitness drop, $1/6 \approx 17\%$.

S3: Stochastic fitness drop

The situation with a stochastic drop in fitness is best studied as a separate model, where two kinds of mutations occur: from normal to positive, and from positive to negative.

Consider an infinitely large population where the standard type, A_0, has fitness 1. In every generation there is a probability μ ($0 < \mu < ½$) that it mutates to type A_p. The fitness of type A_p is $1 + s$, where s is strictly greater than zero. So far the assumptions are as before. Now, however, assume that the drop in fitness follows itself a mutational process, *i.e.* that in every generation there is a second probability, ν , that type A_p mutates to type A_n. The A_n type has fitness $1 - z$, where z is positive and strictly greater than μ. This model corresponds to the model of a drastic fitness drop at generation T introduced above, except that the time for how long the mutant remains positive is now determined by a geometric distribution with parameter ν. The mean time to the drop in fitness is thus $1/\nu$.

Let the frequencies of the three genetic types be x_0, x_p and x_n and use standard notations. The recursion system for the model is then given by

$$x_0' = (1 - \mu)\, x_0 / W ,$$

$$x_p' = \mu x_0 / W + (1 - \nu)(1 + s)x_p/W$$

$$x_n' = (1 - z)x_n/W + \nu(1 + s)x_p/W,$$

where $W = 1 + sx_p - zx_n$.

It is easy to show that if there is an internal equilibrium to the system then the equilibrium frequencies for the mutant types are given by

$$x_p = \frac{\mu x_0}{(1-\mu) - (1-\nu)(1+s)}$$

$$x_n = \frac{\mu\nu(1+s)x_0}{\left[(1-\mu) - (1-\nu)(1+s)\right](z-\mu)}$$

Thus, two conditions must be fulfilled for there to be an internal equilibrium to the system. The first is trivial and part of the assumptions: z must be strictly greater than μ. The second is much more interesting. It is that

$$1 - \mu > (1-\nu)(1+s),$$

which also can be written

$$1/\nu < \frac{1+s}{s+\mu}.$$

This result is presented as expression (10) in the main text.

S4: A second example: Model of gradual fitness decay

The one-step fitness drop example discussed in the main text reduces the richness allowed in the general case with infinitely many *f*-values to a system where only two parameters are

needed: T and z (in addition to the defining parameters μ and s). The following model is formally even simpler, since here only one parameter is used to describe the decay in fitness.

In this model the decrease in fitness between generations for the mutated type is assumed to occur as a constant decay, *i.e.* that

$$f_t = (1 - \alpha s)^{t-1} \quad \text{for } t \geq 1,$$

where α is a strictly positive value not greater than s^{-1} .

This model always leads to an equilibrium, since whatever parameter values used there is always a T such that $f_T < (1 - \mu)/(1 + s)$. This occurs for

$$T_{crit} > 1 + [\ln(1 - \mu) - \ln(1 + s)] / \ln(1 - \alpha s).$$

For small values on μ and αs it is easy to show that this value is approximated by $1 + \alpha^{-1}$. This generation is, in addition, the one where the equilibrium frequency of mutant age-classes reaches its maximum.

Also this model is numerically illustrated with an example in Table S1. The initial positive fitness is the same in the two models, as is the time when fitness falls below 1 – μ. But here the drop in fitness is more gradual and slow, which is reflected in the much higher chance to find older age-classes of the mutation. The effect on the normal type is drastic: its frequency is reduced to about a half. The mutant distribution has its maximum at generation 6, as expected, and 26% of the mutants have fitness above 1. (The approximation for T_{crit} given in the main text is not valid due to the large value of μ.)

S5: Probability of fixation

A constantly recurring non-lethal mutation that does not back-mutate will always go to fixation in a population of finite size – by drift, selection, or a combination thereof. The process will go quickly if the mutation is positive and slowly if it is deleterious. So, what happens to a mutation that starts positive but turns deleterious with time? This has been investigated by studying the fixation properties of single individual mutations with numerical simulations. A summary of the results is given in the main text, and a simple illustration of the major results is provided by Figure S1. It should be remembered that in all simulation runs

no recurrent mutation occurs; it is the fate of a single, initial mutation in an otherwise normal population that is studied.

For the runs on which Figure S1 is based, the mean fitness of mutants in runs that did not end in mutant fixation was calculated. The value ranged between 0.999 and 1.100 in the 16 cases; the highest value was reached when the mutant started as very positive, since almost all ended runs were then due to the loss of mutants that had not experienced any fitness drop. This result gives the basis for the claim in the main text that measuring the fitness of a segregating mutation of the present kind may not tell about its variability in fitness over time; in many cases it will be thought of as being advantageous through and through.

The following more detailed description and discussion of the simulation runs is based on the assumption that the population consists of 1,000 haploid individuals and that there is exactly one new mutant in the first generation; all other members of the population are of the standard genetic type and no more mutants are formed during the studied process. Unless otherwise noted 10,000 independent runs were made for each parameter set. The fitness scheme follows either the one-step fitness model presented in the main text or the gradual fitness decay model presented above.

Results for the fixation probabilities of positive mutations with an abrupt fall in fitness are given in Table S2. When the drop in fitness comes early, then the probability of fixation is negligible. When the drop comes late, then the probability of fixation is close to 2s (in this case 2%), the expected value for a mutant with fitness advantage s (Haldane 1927).

The mean time to fixation in the model setup, but with a mutation that never drops in fitness, is 707 generations (with standard deviation 203; data based on 1,927 runs leading to fixation out of 100,000). This result makes the values in Table S2 easily understandable: the reported fixations are almost exclusively due to mutations that in the interplay between selection and drift happened to reach fixation or at least a very high frequency before they dropped in fitness. Thus, in the table is seen that the mean time to fixation is on average smaller for smaller values on T, the time for the drop in fitness. In addition, the mean time to loss – and in particular the standard deviation of this time – is on average larger for smaller values on T, reflecting that many of these mutations would first have increased in frequency before they experienced the fitness drop and were selectively removed.

The effect of the size of s and z can be summarized as follow. A sharper drop in fitness ($z = 0.1$; other parameters unchanged, including $s = 0.01$) decreased the probability of fixation of the new mutation, but only slightly. For example with T equals 700, out of 10,000

runs 104 ended with fixation rather than 131 as recorded for $z = 0.01$ in Table S2. The results given above on time to fixation and loss held even more clearly in this case. The effect of a sharper drop in fitness is thus to make the dominant logic more distinct: mutations with an insufficiently high frequency at the time of the fitness drop will almost always be lost.

A stronger advantage during the positive phase ($s = 0.02$, $z = 0.01$) had a much stronger effect. If there were no drop in fitness, then the probability of fixation is 0.04 and the mean time to fixation is 427 generations with a standard deviation of 99 (calculated from 3,964 fixations out of 100,000 runs). In accordance with this result, a drop in generation 700 caused no weakening of the effect on the probability of fixation (419 fixations out of 10,000 runs). Even with a drop as early as generation 300, there was a reasonable probability of fixation (80 out of 10,000; compare to only 3 for $s = 0.01$ as given in Table S2). The interplay between s and z is illustrated with an example in Figure S1.

Results for the fixation probabilities of positive mutations with a gradual loss in fitness are given in Table S3. In the table is included T_{crit}, the value for which mutant fitness becomes equal to 1; it is seen that this value, as found above, is very close the inverse of α. It is also seen that the probability of fixation was small when s equaled 0.01, unless the rate of decline in fitness was *very* small. The result is not primarily due to the deleterious effect of the mutation after generation T_{crit}, but to the relatively short time the mutation was distinctly selectively favored.

The importance of a strong initial positive effect of the mutation was seen when s was taken to be 0.02. For α equals 0.001, the number of positive generation was still close to 1000 (991 to be exact), but the number of fixations among 10,000 runs became 348 compared to only 104 for $s = 0.01$ (see Table S3).

Table S1 The frequency of the normal type and the different age-classes of mutants under two sets of assumptions. In Model 1 an initially high fitness ($1 + s = 1.1$) is abruptly changed into a low fitness ($[1 + s]f_t = 0.3$ for $t \geq 6$), while in Model 2 the decline in fitness towards 0 occurs continuously with a constant rate ($\alpha = 3\%$). The mutation frequency (μ) equals 0.05 in the two models. In both cases mutant fitness goes below the critical value ($1 - \mu = 0.95$) by generation 6.

	Model 1		Model 2	
t	*fitness* $(1 + s)f_t$	x_t	*fitness* $(1 + s)f_t$	x_t
0	1	0.658	1	0.505
1	1.1	0.035	1.1	0.027
2	1.1	0.040	1.067	0.031
3	1.1	0.046	1.035	0.035
4	1.1	0.054	1.004	0.038
5	1.1	0.062	0.974	0.040
6	0.3	0.072	0.945	0.041[a]
7	0.3	0.023	0.916	0.041[b]
8	0.3	0.007	0.889	0.039
9	0.3	0.002	0.862	0.037
10	0.3	0.001	0.836	0.033
11–20	0.3	0.000	–	0.132
21–	0.3	0.000	–	0.004

[a] With four rounded digits: 0.0408

[b] With four rounded digits: 0.0405

Table S2 Fixation properties of initially positive mutations that suddenly drops in fitness at time T, based on 10,000 independent runs. Every run starts with one mutation with fitness 1+*s* in a haploid population of size 1000 and continues to fixation. The fitness of the mutant is changed to 1 – *z* after T generations. In all reported runs, $s = z = 0.01$.

T	Runs ending in substitution	Time to loss (mean, SD)	substitution (mean, SD)
200	0	16.2, 67.5	
300	2	22.8, 102.3	541.5, 635.7
400	27	23.4, 115.3	475.5, 158.9
500	56	20.3, 114.7	506.5, 122.4
600	91	19.5, 118.0	546.2, 112.8
700	131	16.4, 102.7	608.7, 149.5
800	156	12.8, 86.4	645.1, 157.6
900	183	9.6, 51.7	670.1, 156.7
1000	192	10.1, 64.9	666.2, 168.4
1100	217	8.7, 41.9	683.2, 190.9
1200	183	8.8, 38.6	689.7, 198.8

Table S3 Fixation properties of initially positive mutations that gradually decline in fitness, based on 10,000 independent runs. Every run starts with one mutation with fitness $1+s$ in a haploid population of size 1000 and continues to fixation. The fitness of the mutant in generation T is $(1 + s)\ (1 - \alpha s)^{T-1}$. T_{crit} is the value for which mutant fitness is close to 1. In all reported runs, $s = 0.01$.

α	T_{crit}	Runs ending in substitution	Time to loss (mean, SD)	substitution (mean, SD)
0	–	184	8.2, 23.9	687.5, 198.6
0.0005	1991	204	10.1, 74.8	863.2, 370.3
0.001	996	104	20.9, 144.7	798.4, 293.4
0.002	499	13	23.1, 122.7	653.0, 212.5
0.003	333	2	19.7, 91.5	521.0, 521.8

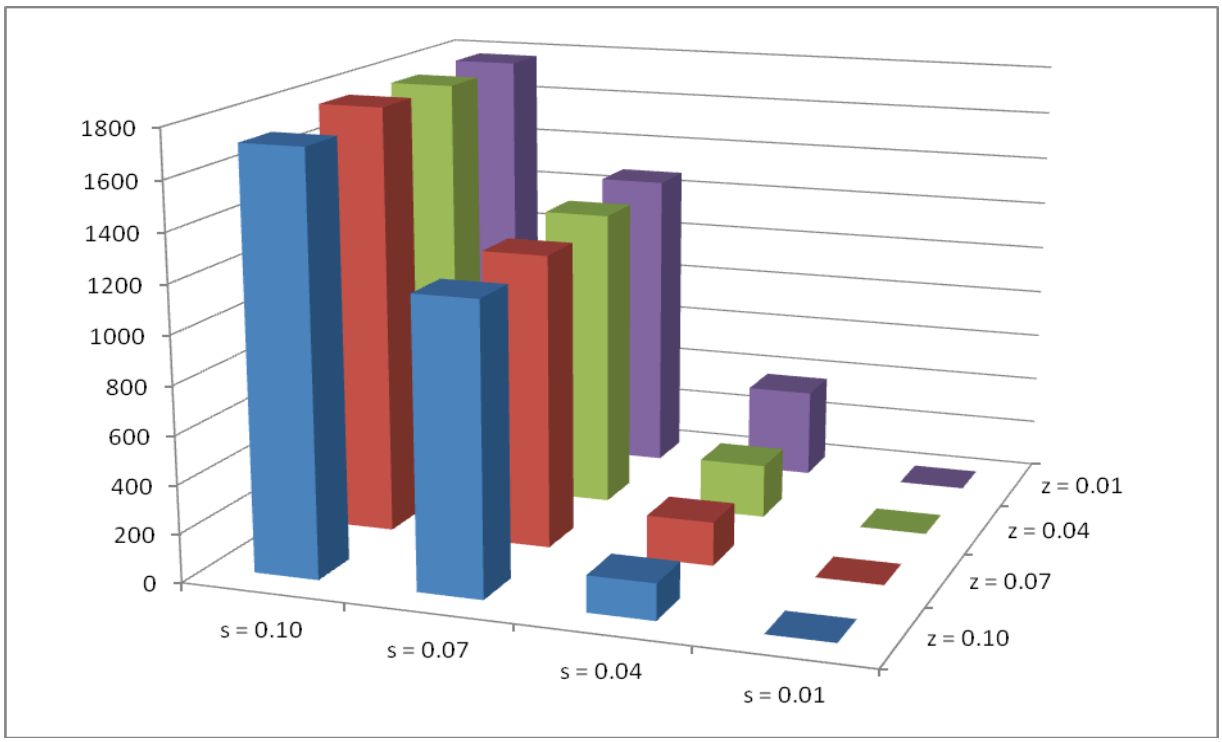

Figure S1 The number of fixations (vertical axis) out of 10.000 simulated runs with the one-step fitness drop model. Every run is started with only one recently formed mutation. The population size is 1000 and the drop in fitness occurs in generation 200. The strong effect of *s* is seen, as is the relatively weak effect of *z*.