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What is the difference between models of error thresholds and Muller's ratchet?

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Abstract. Two independently derived theories predict upper limits to the mutation rate beyond which evolution cannot be controlled by natural selection. One is the theory of Muller's ratchet, explaining the low phylogenetic age of parthenogenetic clones, the other one is the theory of error thresholds, predicting the maximal information content of selfreplicating molecules in prebiotic evolution. Both theories are based on similiar mathematical models but reach qualitatively different conclusions. Muller's ratchet only works in finite populations, while error thresholds are a deterministic phenomenon. In this paper it is shown that this discrepancy is due to different assumptions about the fitness values the selfreplicative units are allowed to assume. If no lower limit for the fitness values is assumed then the deterministic equilibrium frequency of the currently best genotype is strictly positive, no matter how strong mutation is, and random drift is required to cause its extinction (Muller's ratchet). On the other hand, positive lower limits for the fitness values lead to zero equilibrium frequencies in the deterministic description provided the mutation rate is high enough and no back mutations occur.

Key words: Mutation – Selection – Random drift – Muller's ratchet

Introduction

With frequency-independent fitness differences and without recombination, mutation and selection are opposing forces. In general, selection tends to increase the frequency of the genotype with the highest fitness, while mutation tends, to lower it. It is intuitively obvious that there must be an upper limit to the rate of mutation that can be tolerated by the population. Beyond this limit selection cannot compensate the influx of mutations any more. Mutation becomes the dominating force governing the composition of the population and genetic deterioration and eventually extinction may result.

Theories on mutation rate limits have been developed independently in the area of poly-nucleotide chemistry, called error thresholds (Eigen and Schuster 1979, Swetina and Schuster 1982), and in population genetics, called Muller's ratchet (Muller 1964). These theories play fundamental rôles in evolutionary theory in general, as they may explain the evolutionary significance of genetic recombination (Felsenstein 1974, Maynard-Smith 1978, Bell 1988, Chao 1990), the origin of Y-chromosomes (Charlesworth 1978) and the evolution of first replicative systems (Eigen 1971).

Both theories, Muller's ratchet as well as the theory of error thresholds, are based on mutation-selection equations of basically identical structure. At least from a mathematical point of view, it is disturbing that qualitatively different results have been obtained, calling into question the fundamental similarity of the phenomena (Nowak and Schuster 1989).

Muller's ratchet only works in finite populations. It is a mechanism that requires random drift. However, the error threshold is primarily a deterministic theory without reference to random drift, although a finite population size version exists (Demetrius et al. 1985). In the models for error thresholds the equilibrium frequency of the best genotype becomes zero if back mutations are ignored. This, however, cannot happen in the Felsenstein-Maynard-Smith model (FMS) for Muller's ratchet, since the deterministic equilibrium frequency of the best genotype is always strictly positive regardless of the mutation rate and the relative fitness of the first order mutations (Haigh 1978). Hence, random drift is required to eliminate the best genotype as its frequency becomes small to set Muller's ratchet into action.

In this paper it is shown that the differences of the two models are due to one assumption regarding the possible fitness values of the mutants. Whenever the fitness of the mutants is bounded below then there exists a mutation rate less than 1 beyond which the equilibrium frequency of the best genotype is equal to zero. This condition is met in all models of Eigen and Schuster. On the other hand, if there is no positive lower limit to the fitness of mutants, the frequency of the best genotype can never be zero at equilibrium in the deterministic model, no matter how high the mutation rate is. This is the case, e.g., in the FMS model of Muller's ratchet.

The model

Throughout this paper an infinite chain of possible genotypes

$$G_0, G_1, G_2, G_3, \ldots$$

is considered. Each genotype G_i reproduces asexually and mutates with a certain rate u to the successor genotype G_{i+1}. Let w_i be the relative Wrightian fitness of genotype G_i; then the mutation-selection equation reads:

$$p'_0 = (1-u)\,p_0/\bar{w} \tag{1}$$

for the genotype at the left hand end of the chain, and:

$$p'_i = p'_i w_i (1-u)/\bar{w} + u\,p_{i-1} \tag{2}$$

for genotype G_i, where $\bar{w}$ is the mean fitness. This equation describes the dynamics where selection and mutation act independently at the same time. We will give the proof of the main result for this simplified model first, since it gives a clearer picture of the result (Proof I). However, the same result can be proved within the standard model, where mutation and selection act at different stages of the life cycle, and we will give this proof, too (Proof II). In this case eq. (2) has to be replaced by:

$$p_i' = (p_i w_i (1 - u) + p_{i-1} w_{i-1} u)/\bar{w} \,. \tag{3}$$

Equation (2) can also be considered as a weak-selection approximation of eq. (3).

In addition, the fitness of genotypes is assumed to be strictly decreasing; if $i < j$ then $w_i > w_j$. Consequently the genotype G_0 is the fittest in the population. Note that in the discrete time model the fitness values are chosen from the closed interval $[0, 1]$. Since the evolution equations are invariant to linear transformation of the fitness scale, $w_0 = 1$ is assumed without loss of generality. No other restrictions are necessary to give the following results.

Results

First a simple lemma is considered that explains why the frequency of the best G_0 can become zero.

Lemma 1 *If there is a value e, $0 < e < 1$, such that $w_i > e$ for all i, then there exists a mutation rate $u' < 1$ such that for all mutation rates $u > u'$ the frequency of G_0 at equilibrium is zero, $\hat{p}_0 = 0$.*

Proof. According to the assumptions, all fitness values are between 0 and 1. Consequently also the mean fitness remains within these limits. Then there exists a real u' such that u' is strictly less than 1 and $1 - u' < e$ and consequently for all u such that $1 > u > u'$: $1 - u < e$.

Therefrom we obtain immediately that the ratio

$$(*) \qquad (1 - u)/e < 1$$

is strictly less than 1 for all u with $1 > u > u'$.

As the mean fitness $\bar{w}$ will always remain between 1 and e, we always have $1 > \bar{w} > e$ and consequently $1/\bar{w} < 1/e$.

Combining this inequality with $(*)$ for all u, $1 > u > u'$ we can conclude $(1 - u)/\bar{w} < (1 - u)/e < 1$ for all possible values of mean fitness.

Together with the mutation-selection eq. (1) for genotype G_0 we obtain

$$p_0' = p_0(1 - u)/\bar{w} \leqq p_0(1 - u)/e$$

for all u, $1 > u > u'$ and all possible values for the mean fitness $\bar{w}$.

Thus for the frequency of G_0 in the n-th generation we have

$$p_0 \leqq [(1 - u)/e]^n$$

and as the ratio $(1 - u)/e < 1$ is strictly less than 1, this means that the frequency of G_0 will become arbitrarily small. So, if there is non-zero lower bound e for the fitness values, a positive real u' exists, such that u' is strictly less than 1 and for all mutation rates u with $1 > u > u'$ we have $\hat{p}_0 = 0$ where $\hat{p}_0$ is the limit towards which the frequency of G_0 converges. Note that, if fitness of mutations is bounded by some non-zero real e, then for mutation rates u, such that $(1 - u) < e$ there is no equilibrium distribution of frequencies.

Result The following two statements are equivalent:

(a) The sequence w_i has no positive lower limit.

(b) For all mutation rates u, such that u is strictly less than 1, an equilibrium exists and the frequency of the best genotype at equilibrium is greater than zero.

Proof I (For the simplified model, as given by eqs. (1) and (2)).

(a)→(b) From eq. (1) it follows that, if the frequency of genotype G_0 is in equilibrium, $p'_0 = p_0 = \hat{p}_0$, then the mean fitness must be $\bar{w} = 1 - u$. Hence, at equilibrium the equation for the other genotypes simplifies to

$$\hat{p}_i = w_i \hat{p}_i + u \hat{p}_{i-1} .$$

This leads to a simple recursion equation for the frequencies of genotypes G_i, $i > 0$ at equilibrium

$$\hat{p}_i = u \hat{p}_{i-1}/(1 - w_i) .$$

This equation can be iterated to give the frequency of G_i at equilibrium as a function of $\hat{p}_0$

$$\hat{p}_i = \hat{p}_0 * \frac{u^i}{\prod_{j=1}^{i} (1 - w_j)} , \tag{$*$}$$

and the mean fitness at equilibrium is proportional to p_0

$$\hat{\bar{w}} = \hat{p}_0 (K + 1)$$

with

$$K = \sum_{i=1}^{\infty} \frac{u^i w_i}{\prod_{j=1}^{i} (1 - w_j)} . \tag{4}$$

This leads to an equation for the frequency of the best genotype at equilibrium

$$\hat{p}_0 = (1 - u)/(1 + K) , \tag{$**$}$$

Under the assumptions of the model, the values w_i are not bounded below by any other value than zero, i.e. for all mutation rates u, $u < 1$, there are only finitely many w_i, such that $u > (1 - w_i)$. Thus the series K always converges (see Appendix I). Therefore an equilibrium for the whole population indeed exists, the frequencies at equilibrium being defined by eqs. (**) and (*). (b)→(a) The inverse implication is equivalent to the former lemma.

Idea of proof II. This is the proof for the standard model with selection and mutation acting at different times during the life-cycle. Since this proof is somewhat technical, we will outline its main idea in advance:

The first step will be to prove that for every sequence of genotypes $G_0, G_1, G_2, \ldots$ with strictly decreasing fitness values $w_0 > w_1 > w_2, \ldots$, for every mutation rate u, $u < 1$ for every finite initial sequence $G_0, G_1, \ldots, G_k$ of genotypes there is a function φ, such that φ assigns a strictly positive real $\varphi(r)$ to every strictly positive real r and

$$p_0 + p_1 + \cdots + p_k \geqq r \rightarrow p_0 \geqq \varphi(r) \tag{$*$}$$

is valid in every generation. So, the proportion of G_0 in the part of the population consisting only of genotypes $G_0, G_1, \ldots, G_k$ cannot become arbitrarly low. This is consequence of Lemma 4 (the preceeding lemmas prepare for the proof of Lemma 4).

Now, assume $G_0, G_1, G_2, \ldots$ is an arbitrary but fixed sequence of genotypes with strictly decreasing fitness values such that no positive lower bound exists for these fitness values. Let u be an arbitrary mutation rate strictly less than 1. Then there is a u^* such that $u < u^* < 1$. (e.g. $u + (1 - u)/2$). Since there is no positive lower bound, there is a finite index $\xi(u^*)$ such that $w_i \leqq u^*$ for all $i \geqq \xi(u^*)$. If the sum of frequencies of genotypes G_i with index $i \leqq \xi(u^*)$ becomes arbitrary small then the mean fitness becomes less than $1 - u$. So there is some real $\rho(u)$ such that

$$p_0 + p_1 + \cdots + p_{\xi(u^*)} < \rho(u) \rightarrow \bar{w} < 1 - u \ .$$

Together with (*) we can conclude that there is a strictly positive real $\varphi(\rho(u))$ such that

$$p_0 < \varphi(\rho(u)) \rightarrow \bar{w} < 1 - u \ .$$

Since the frequency of G_0 can no longer decrease if the mean fitness falls below $1 - u$ it is straightforward that a strictly positive lower bound for the frequency of G_0 exists.

Proof II. It is useful to introduce notations for frequencies before and after selection. We will do so by writing p_i^w for the frequency of genotype p_i after selection. Furthermore the frequency of G_0 will be assumed to be 1 in the first generation. The sequence of frequencies during evolution reads as

$$1 = p_0, p_0^w, p_0', p_0'^w, p_0'', \ldots$$

for G_0 and

$$0 = p_i, p_i^w, p_i', p_i'^w, p_i'', \ldots$$

for genotypes G_i, $i > 0$.

Consequently the mutation-selection eq. (3) can be split into equations

$$p_0^w = p_0/\bar{w} \ , \tag{5}$$

$$p_0' = p_0^w(1 - u) \tag{6}$$

for G_0, and

$$p_i^w = p_i\, w_i/\bar{w} \ , \tag{7}$$

$$p_i' = p_i^w(1 - u) + p_{i-1}^w u \tag{8}$$

for G_i, $i > 0$.

We will start by proving a lemma, saying that for all G_i there is a non-zero positive real r_i, such that the ratio of the frequencies of G_i and G_{i+1} never will exceed r_i after the $t + 1$-th generation if it did not exceed this ratio r_i after the t-th generation. Together with the assumption that $p_0 = 1$ for $t = 0$, this lemma yields that this ratio never will be exceeded throughout the evolution of the population.

Lemma 2 *For all G_i there is a fixed real r_i such that*

$$r_i p_i^w \geqq p_{i+1}^w$$

is valid in every generation.

Proof. By induction on the number of generations, First we define

$$r_i := \frac{1}{\left[\frac{w_i}{w_{i+1}} - 1\right](1-u)}$$

for all G_i.

Since $(1-u) > 0$ and $w_i > w_{i+1}$ for all G_i this clearly is a well-defined positive number for all G_i. For the first generation the relation

$$r_i p_i^w \geqq p_{i+1}^w$$

clearly holds for all p_i^w, since

$$r_0 p_0^w = r_0 1 \geqq 0 = p_1^w ,$$

and for all $G_i, i > 0$:

$$r_i p_i^w = r_i 0 \geqq 0 = p_{i+1}^w$$

holds due to the assumption of $p_0 = 1$. Now we assume as induction hypothesis

(i.-hy) $$r_i p_i^w \geqq p_{i+1}^w ,$$

and we prove:

$$r_i p_i^w \geqq p_{i+1}^w \rightarrow r_i p_i'^w \geqq p_{i+1}'^w .$$

We start by combining the two mutation-selection equations. For G_0 the sequence of frequencies after selection is given by

$$p_0'^w = p_0^w (1-u) \frac{w_0}{\bar{w}} .$$

For G_i, $i \neq 0$ we have

$$p_i'^w = [p_i^w(1-u) + p_{i-1}^w u] \frac{w_i}{\bar{w}} , \tag{9}$$

as an immediate consequence we obtain for all G_i.

$$p_i'^w \geqq p_i^w(1-u) \frac{w_i}{\bar{w}} . \tag{10}$$

From the assumptions $u < 1, w_i > w_{i+1}$ and the definition of r_i, by purely algebraic transformation (see Appendix II) we obtain:

$$\frac{w_i}{w_{i+1}}(1-u)r_i > (1-u)r_i + u .$$

Multiplication with p_i^w on both sides yields

$$\frac{w_i}{w_{i+1}}(1-u)r_i p_i^w > (1-u)r_i p_i^w + u p_i^w .$$

By induction hypothesis we have

$$r_i p_i^w \geqq p_{i+1}^w .$$

Thus we can transform the former inequality into

$$\frac{w_i}{w_{i+1}}(1-u)r_i p_i^w > (1-u)p_{i+1}^w + u\, p_i^w$$

which is equivalent with

$$\frac{w_i}{\bar{w}}(1-u)r_i p_i^w > \frac{w_{i+1}}{\bar{w}}\left[(1-u)\,p_{i+1}^w + u\, p_i^w\right].$$

Thus, together with inequality (10)

$$r_i p_i'^w > \frac{w_{i+1}}{\bar{w}}\left[(1-u)\,p_{i+1}^w + u\, p_i^w\right].$$

The right side of this inequality is equal to $p_{i+1}'^w$ according to eq. (9). Thus we have

$$r_i p_i'^w > p_{i+1}'^w \tag{11}$$

which completes the proof of the lemma.

The next lemma extends the assertion of Lemma 2 to ratios of frequencies of genotypes G_i and sums of frequencies of genotypes $G_i, G_{i+1}, \dots, G_{i+k}$. That is: Let $G_i, \dots, G_{i+k}$ be an arbitrary finite segment of the sequence of genotypes $G_1, G_2, G_3, \dots$. Then there is a fixed real $\tilde{r}_{i,k'}$ such that the proportion of G_i within the part of the population consisting of genotypes $G_i, \dots, G_{i+k}$ will never fall below $\tilde{r}_{i,k}$.

Lemma 3 *For each genotype G_i and each integer k there exists a number $\tilde{r}_{i,k'}$ such that*

$$\tilde{r}_{i,k}\, p_i^w \geqq \sum_{j=1}^{i+k} p_j^w$$

will hold in every generation.

Proof (by induction on k). For the case of $k = 0$ the proof is trivial since

$$\sum_{j=1}^{i+0} p_j^w = p_i^w \leqq p_1^w .$$

Thus $\tilde{r}_{i,0} := 1$ for all G_i will do.

Now we will assume as induction hypothesis the above statement to be true for a fixed k, that is:

$$\text{(i. hy)} \qquad \tilde{r}_{i,k}\, p_i^w \geqq \sum_{j=1}^{i+k} p_j^w$$

in every generation.

From Lemma 2 we know that there is a r_{i+k}, such that

$$r_{i+k}\, p_{i+k}^w \geqq p_{i+k+1}^w$$

will hold in every generation. As all frequencies are positive, we can conclude that

$$r_{i+k} \sum_{j=1}^{i+k} p_j^w \geqq p_{j+k+1}^w$$

holds in every generation. Combining this with the induction hypothesis yields

$$\tilde{r}_{i,k} r_{i+k} p_i^w \geqq p_{j+k+1}^w$$

and, using the induction hypothesis again, we conclude

$$\tilde{r}_{i,k} p_i^w (1 + r_{i+k}) \geqq \left[p_{i+k+1}^w + \sum_{j=1}^{i+k} p_j^w \right] = \sum_{j=i}^{i+k+1} p_j^w \, .$$

So we can complete the proof of the lemma, defining inductively:

$$\tilde{r}_{i,0} := 1$$

$$\tilde{r}_{i,k+1} := \tilde{r}_{i,k} * (1 + r_{i+k}) \, .$$

Lemma 4 *For every genotype G_i and every integer k there is a real $\tilde{r}^*_{i,k}$, such that in every generation*

$$\tilde{r}^*_{i,k} p_i \geqq \sum_{j=i}^{i+k} p_j$$

holds. This statement is analogous to that of Lemma 3, *for frequencies before selection.*

Proof. According to Lemma 3 we are justified to assume that

$$\tilde{r}^*_{i,k} p_i^w \geqq \sum_{j=1}^{i+k} p_j^w$$

holds for every genotype G_i in every generation for $\tilde{r}_{i,k}$ being defined as in Lemma 3. We can immediately conclude

$$\left[\tilde{r}_{i,k} \frac{1}{1-u} \right] \left[(1-u) p_i^w \right] \geqq \sum_{j=1}^{i+k} p_j^w$$

and, together with $p_i' \geqq (1-u) p_i^w$

$$\tilde{r}_{i,k} \frac{1}{1-u} p_i' \geqq \sum_{j=1}^{i+k} p_j^w \, . \qquad (*)$$

As mutations change genotype G_i to G_{i+1} we can calculate the sum of frequencies of genotypes $p_{i+1}' + \cdots + p_{i+k}'$ after mutation and before selection as

$$\sum_{j=i+1}^{i+k} p_j' = u p_i^w + \sum_{j=i+1}^{i+k} p_j^w - u p_{i+k}^w \, .$$

As u is less than 1 and p_{i+k} is non-negative, we conclude

$$\sum_{j=i+1}^{i+k} p_j' \leqq \left[u p_i^w + \sum_{j=i+1}^{i+k} p_j^w \right] \leqq \sum_{j=1}^{i+k} p_j^w \, .$$

this yields together with (*)

$$\tilde{r}_{i,k} \frac{1}{1-u} p_i' \geqq \sum_{j=i+1}^{i+k} p_j' \, .$$

Adding p' on both sides of the inequality we obtain

$$\left[1 + \tilde{r}_{i,k}\frac{1}{1-u}\right]p'_i \geqq \sum_{j=1}^{i+k} p'_j\,.$$

We complete the proof of the lemma by defining

$$\tilde{r}^*_{i,k} := 1 + \tilde{r}_{i,k}\frac{1}{1-u}\,.$$

Proof of the main result. As we have assumed no strictly positive lower limit to exist for fitness values, for all mutation rates u, such that u is strictly less than 1, a genotype G_x must exist such that w_{x+k} is strictly less than $(1-u)$ for all $k \geqq 0$.

Thus there is some strictly positive δ_u, such that

$$\delta_u + (1-\delta_u)w_x < (1-u)\,, \tag{12}$$

Now, suppose p_0 to be strictly less than $\delta_u/\tilde{r}^*_{0,x}$, $\tilde{r}^*_{0,x}$ being defined as in Lemma 4. Then, according to Lemma 4, we have

$$\sum_{i=0}^{x} p_i \leqq \delta_u\,. \tag{13}$$

As $1 \geqq w_i > w_{i+1}$ holds for all i, $i \geqq 0$, we have

$$\sum_{i=0}^{\infty} p_i w_i < \sum_{i=0}^{x} p_i + \sum_{i=x+1}^{\infty} p_i w_x = \sum_{i=0}^{x} p_i + \left[1 - \sum_{i=0}^{x} p_i\right] * w_x\,.$$

With inequalities (12) and (13) we obtain

$$\sum_{i=0}^{\infty} p_i w_i < \delta_u + (1-\delta_u)w_x < (1-u)\,.$$

Therefore, under the assumptions of the model, for all u strictly less than 1 there is a strictly positive δ_u and a real $\tilde{r}^*_{0,x}$ with:

$$p_0 \leqq \delta_u/\tilde{r}^*_{0,x} \rightarrow \bar{w} < (1-u)\,.$$

With eq. (1) we can conclude

$$p_0 \leqq \delta_u/\tilde{r}^*_{0,x} \rightarrow p'_0 \geqq p_0\,.$$

The existence of a lower bound for the smallest value that can be reached from p_0 can be derived.

Assume p'_0 to be the smallest value the frequency of G_0 reached during an arbitrary number n of generations. Then, according to the former result, the frequency of G_0 in the immediately preceeding generation cannot have been less than $\delta_u/\tilde{r}^*_{0,x}$. On the other hand, if p_0 was not less than $\delta_u/\tilde{r}^*_{0,x}$ then p'_0 cannot be less than $\delta_u(1-u)/\tilde{r}^*_{0,x}$. Since δ_u and $(1-u)$ are strictly positive and $\tilde{r}^*_{0,x}$ is positive. This yields a non-zero lower bound for the frequency of G_0. Thus, under the assumptions of the model, i.e., absence of a lower bound for the fitness-values, for all mutation rates u, u being strictly less than 1, there is a strictly positive lower bound for the frequency of G_0.

A simple corollary to the above result is, that the existence of non-zero lower limits for the fitness is equivalent with the existence of mutation rates u, strictly less than 1, which lead to extinction of the best genotype from the population in the deterministic model.

Conclusions

The above result shows that the assumption of lower limits of the fitness of mutants is a necessary and sufficient condition for the existence of mutation rates that drive the best genotype to extinction, even in the deterministic model. On the other hand it is necessary and sufficient for the existence of non-zero equilibrium frequencies of the fittest genotype for all mutation rates less than one, to have no strictly positive lower limit of fitness of the mutants. The best genotype cannot go to extinction in infinite populations under these conditions. Only random drift can cause it to vanish.

In the theory of error thresholds a lower limit to the fitness values is explicitly assumed. This is motivated by the fact that the theory of error thresholds is based on continuous time, where unbounded fitness values would imply infinitely large negative rates. In the continuous time approach fitness is defined as the difference in production and degradation rates. The production rate can vanish, as it does indeed in the case of a lethal variant. Thus fitness can take negative values. The degradation rate, however, has to remain finite by the nature of the process – infinite reaction rates occur only in exceptional cases, for example with autocatalytic chain reaction and then result in explosions. Consequently, infinitely large negative rate have been excluded by Eigen and Schuster.

However, in the discrete time model zero fitness values are not unreasonable, as they simply represent a lethal genotype. Using the usual transformation between discrete and continuous time models the logarithm of the Wrightian fitness should be the Malthusian fitness, which is used in continous time models (Crow and Kimura 1970). Zero Wrightian fitness would thus correspond to Malthusian fitness, minus infinity, which seems to be excluded by physical plausibility. With very small Wrightian fitness values the analogy between Wrightian and Malthusian fitness seems to break down.

Based on discrete time models, the formal differences between error thresholds and Muller's ratchet are due to assumptions about the fitness the mutants can assume. Therefore the predictions by the theories of error thresholds and Muller's ratchet about population behaviour will differ. The error threshold is essentially a delocalization phenomenon, that does not necessarily lead to arbitrarily low mean fitness. The distribution of genotypes will approach the mutation distribution (for details see Eigen 1989). In the case described by the theory of Muller's ratchet no sudden delocalization occurs, because the best genotype never gets lost in a sufficiently large population. Only random drift will finally drive the population to infinitely small fitness, as long as back mutations do not play any rôle. With compensatory mutations an equilibrium is reached even in small populations (Wagner and Gabriel 1990).

While zero fitness values are completely plausible in biological models, it may be noteworthy that the strong condition that no non-zero lower limit e for the fitness values must exist in order to prevent the best genotype from vanishing, can be weakened if some upper limit $u_{\max} < 1$ for the rate of mutation is assumed. The condition for the optimum genotype vanishing in equilibrium for any given mutation rate u is that no genotype G_i of fitness $w_i < (1 - u)$ exists. So, if mutation rate is assumed to be bounded by some $u_{\max} < 1$, the best genotype will not vanish from a population even if a non-zero lower bound e for the fitness values exists, provided the greatest lower bound for the mutant's fitness values is less than $1 - u_{\max}$.

Appendix I

Since $w_i < 1$ for all i, the series (3) can be bounded by some F:

$$K < F = \sum_{i=1}^{\infty} f_i$$

with

$$f_i = f_{i-1}\, u/(1 - w_i) \qquad \text{and} \qquad f_1 = u/(1 - w_i)\ .$$

Because the sequence w_i is strictly decreasing there exists a finite number k, such that for all m, $m > 0$:

$$u/(1 - w_{k+m}) < u/(1 - w_k) < 1\ . \tag{A1}$$

Thus F may be decomposed into two terms:

$$F = F_k + F_{k+}$$

where F_k is the sum of terms from $i = 1$ to $i = k$, and $F_{k+} = F - F_k$. Using (A1) one can see that F_k is less than

$$F_{k+} < f_k * \sum_{i=1}^{\infty} [u/(1 - w_k)]^i$$

which is less than infinity. This proves the convergence of K.

Appendix II

We will use the equation

$$x\frac{k}{(k-1)x} = x\frac{1}{(k-1)x} + 1, \quad k \neq 1\ . \tag{A2}$$

Substitution of w_i/w_{i+1} for k and $(1 - u)$ for x in eq. (A2) yields:

$$\frac{w_i}{w_{i+1}}(1-u)\frac{1}{\left[\dfrac{w_i}{w_{i+1}} - 1\right](1-u)} = (1-u)\frac{1}{\left[\dfrac{w_i}{w_{i+1}} - 1\right](1-u)} + 1$$

and therefrom, since $u < 1$:

$$\frac{w_i}{w_{i+1}}(1-u)\frac{1}{\left[\dfrac{w_i}{w_{i+1}} - 1\right](1-u)} > (1-u)\frac{1}{\left[\dfrac{w_i}{w_{i+1}} - 1\right](1-u)} + u\ .$$

By definition of r_i this can be written as:

$$\frac{w_i}{w_{i+1}}(1-u)\,r_i > (1-u)\,r_i + u\,.$$

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