

## Does Muller's ratchet work with selfing?

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### SUMMARY

The accumulation of deleterious mutations in a finite diploid selfing population is investigated. It is shown that the conditions for accumulation are very similar to those for the accumulation of mutations in an asexual population by 'Muller's ratchet'. The ratchet is likely to operate in both types of population if there is a large class of slightly deleterious mutations.

### 1. INTRODUCTION

Muller (1964) pointed out that in a finite asexual population there is a tendency for deleterious mutations to accumulate, despite contrary selection. The reason is as follows. The members of a population can be classified according to whether they carry 0, 1 . . .  $i$  . . . deleterious mutations. Let the numbers in each class be  $n_0, n_1 \dots n_i \dots$ . The fittest individuals would be the members of the 0 class, carrying no harmful mutations. In a finite population, however,  $n_0$  may be a small number, and hence there is a possibility that no members of the 0 class will leave offspring. The 1 class would then be the fittest. Muller's essential point was that there is no way (except by back mutation, which can be shown to be unimportant) in which the original optimal class can be reconstituted. In contrast, in a sexual population, two members of the 1 class can produce offspring with no mutations by recombination.

Hence, in the absence of recombination, successive optimal classes may be lost, and mutations may accumulate. This 'ratchet' mechanism has been investigated quantitatively by Felsenstein (1974), Felsenstein & Yokoyama (1976) and Haigh (1978).

In this paper we investigate a similar process which may occur in a finite diploid selfing population. Now, individuals can be homozygous for 0, 1 . . .  $i$  . . . deleterious mutations, and may also be heterozygous for varying numbers of mutations. No ratchet operates on the heterozygous loci, because by selfing a heterozygote can give rise to a normal homozygote. However, a ratchet does

operate for the homozygous loci, because an individual homozygous for  $i$  mutations cannot, by selfing, produce offspring homozygous for fewer mutations.

It turns out that the ratchet will operate in selfing populations under the same conditions as Haigh (1978) has shown to be necessary in asexual populations. The procedure we adopt is as follows. We consider an infinite selfing population, and seek the frequencies  $x_0, x_1 \dots x_i \dots$  of individuals homozygous for  $0, 1 \dots i \dots$  deleterious mutations, at equilibrium between mutation and selection. We then argue that in a finite population of size  $N$ , the expected number of individuals in the optimal class is  $n_0 = Nx_0$ . Provided that  $n_0$  is large, this expectation will be approximately realized. However, if  $n_0$  is small, the optimal class will, sooner or later, be lost, and the ratchet will operate. Hence everything depends on the magnitude of  $n_0 = Nx_0$ .

2. THE MODEL

Consider an infinite diploid selfing population with non-overlapping generations. Each individual suffers deleterious mutations at a rate  $\mu$  per genome per generation. The fraction of individuals carrying  $i$  homozygous and  $j$  heterozygous mutations is  $x_{ij}$ . For an individual in the class  $x_{ij}$  the fitness is  $(1 - \sigma)^i(1 - \tau)^j$ . It is assumed that  $\sigma > 0$  and  $\tau \geq 0$ .

For simplicity of mathematical treatment, we make the following assumptions:

(i) The number of mutations within one individual does not affect the mutation rate for the rest of the genome. This is a reasonable assumption provided the number of mutable loci is large compared to the number of loci at which mutations are already present.

(ii) Mutation from the heterozygous to the homozygous condition is ignored, because it is of negligible importance compared to selfing in producing homozygotes.

(iii) Back mutations are ignored. It is shown later that this is a safe assumption in conditions in which the ratchet might operate.

We shall now prove that there exists an equilibrium frequency distribution with

$$\sum_{0 \leq j} x_{0j} > 0$$

given by:

$$x_{ij} = \frac{1}{i!} \left[ \frac{\mu(1-\tau)}{2\sigma(1+\tau)} \right]^i \cdot \exp \left[ -\frac{\mu(1-\tau)}{2\sigma(1+\tau)} \right] \cdot \frac{1}{j!} \left[ \frac{2\mu}{1+\tau} \right]^j \cdot \exp \left[ -\frac{2\mu}{1+\tau} \right], \tag{1}$$

$i, j = 0, 1, 2 \dots$ . Thus  $x_{ij}$ :  $i, j = 0, 1, 2 \dots$  form a bivariate Poisson distribution

$$P \left( \frac{\mu(1-\tau)}{2\sigma(1+\tau)}, \frac{2\mu}{1+\tau}, 0 \right).$$

We define  $\alpha = \mu(1-\tau)/2\sigma(1+\tau)$  and  $\beta = 2\mu/(1+\tau)$ .

In the initial population, the  $x_{ij}$  are given as by (1). Then the mean fitness of the population is given by:

$$\exp(-\beta\tau - \sigma\alpha).$$

After selection and segregation have taken place, the fractions  $x_{ij}$  have changed to

$$\begin{aligned}
 x'_{ij} &= e^{+\beta\tau+\sigma\alpha} \cdot \sum_{0 \leq n \leq i} \sum_{i+j-n \leq m} \frac{m!}{(i-n)! j! (m+n-i-j)!} \\
 &\quad \times \left(\frac{1}{2}\right)^{i-n} \left(\frac{1}{2}\right)^j \left(\frac{1}{2}\right)^{m+n-i-j} \cdot (1-\sigma)^n (1-\tau)^m x_{nm}, \\
 &= e^{-\beta(1-\tau)-\alpha(1-\sigma)} \cdot \frac{1}{j!} \left(\frac{1}{2}\right)^j \sum_{0 \leq n \leq i} \frac{\alpha^n (1-\sigma)^n}{(i-n)! n!} \left(\frac{1}{2}\right)^{i-n} \\
 &\quad \times \sum_{i+j-n \leq m} \left(\frac{1}{2}\right)^{m+n-i-j} \cdot \frac{\beta^m (1-\tau)^m}{(m+n-i-j)!}.
 \end{aligned}$$

Since the second sum is

$$[\beta(1-\tau)]^{i+j-n} \cdot \sum_{0 \leq k} \left(\frac{1}{2}\right)^k \frac{\beta^k (1-\tau)^k}{k!} = [\beta(1-\tau)]^{i+j-n} \cdot e^{\beta(1-\tau)/4},$$

we obtain

$$x'_{ij} = e^{-\frac{3}{2}\beta(1-\tau)-\alpha(1-\sigma)} \frac{1}{j!} \left(\frac{1}{2}\right)^j \cdot \sum_{0 \leq n \leq i} \frac{\alpha^n (1-\sigma)^n}{(i-n)! n!} \left(\frac{1}{2}\right)^{i-n} [\beta(1-\tau)]^{i+j-n}.$$

After mutation, the fractions have changed to

$$\begin{aligned}
 x''_{ij} &= \sum_{0 \leq m \leq j} \frac{\mu^{j-m}}{(j-m)!} \cdot e^{-\mu} \cdot x_{ij} \\
 &= e^{-\frac{3}{2}\beta(1-\tau)-\alpha(1-\sigma)-\mu} \sum_{0 \leq m \leq j} \frac{1}{(j-m)! m!} \cdot \mu^{j-m} \left[\frac{1}{2}\beta(1-\tau)\right]^m \\
 &\quad \times \sum_{0 \leq n \leq i} \frac{\alpha^n (1-\sigma)^n}{(i-n)! n!} \left(\frac{1}{2}\right)^{i-n} [\beta(1-\tau)]^{i-n}.
 \end{aligned}$$

Since  $(a+b)^i = \sum_{0 \leq n \leq i} \binom{i}{n} \cdot a^n \cdot b^{i-n}$ ,

it turns out that

$$\begin{aligned}
 x''_{ij} &= e^{-\frac{3}{2}\beta(1-\tau)-\alpha(1-\sigma)-\mu} \cdot \sum_{0 \leq m \leq j} \frac{1}{(j-m)! m!} \mu^{j-m} \cdot \left[\frac{\beta}{2}(1-\tau)\right]^m \\
 &\quad \times \frac{1}{i!} \left[\alpha(1-\sigma) + \frac{\beta}{4}(1-\tau)\right]^i, \\
 &= e^{+\frac{1}{2}\beta(1-\tau)+\beta\tau+\sigma\alpha-\mu} \cdot \frac{1}{j!} \left[\mu + \frac{\beta}{2}(1-\tau)\right]^j \cdot e^{-\beta} \\
 &\quad \times \frac{1}{i!} \left[\alpha(1-\sigma) + \frac{\beta}{4}(1-\tau)\right]^i \cdot e^{-\alpha}.
 \end{aligned}$$

Since

$$\mu + \frac{\beta}{2}(1-\tau) = \beta, \quad \alpha(1-\sigma) + \frac{\beta}{4}(1-\tau) = \alpha \quad \text{and} \quad e^{+\frac{1}{2}\beta(1-\tau)+\beta\tau+\sigma\alpha-\mu} = 1,$$

we have shown that the frequency distribution (1) reproduces itself exactly after selection, segregation and mutation.

Distribution (1) is not the only possible frequency distribution. Thus if

$$\sum_{0 \leq n \leq k-1} \sum_{0 \leq m} x_{nm} = 0$$

for some  $k > 0$ , there exists a self reproducing frequency distribution given by

$$y_{ij} = \begin{cases} 0 & (i < k) \\ \frac{\alpha^{i-k}}{(i-k)!} \cdot \frac{\beta^j}{j!} \cdot \exp(-\alpha-\beta) & (i > k). \end{cases} \tag{2}$$

This differs from (1) only in that every individual has at least  $k$  homozygous loci, so that the fitnesses and the frequencies of the classes, relative to the most fit class, remain the same (compare Haigh, 1978). Thus the  $y_{ij}$  give the expected frequencies when the ratchet has clicked round  $k$  notches.

Computer simulations suggest that (1) and (2) are *the only possible stable equilibria*.

### 3. DISCUSSION

Assuming a population of constant size  $N$ , the expected number of individuals in the optimal class is

$$K_0 = N \cdot \sum_{0 \leq j} x_{0j}. \tag{3}$$

The magnitude of  $K_0$  will determine the ratchet's speed. For fully recessive mutations ( $\tau = 0$ ), (3) reduces to

$$K_0 = N \cdot e^{-\mu/2\sigma}. \tag{4}$$

The corresponding formula obtained by Haigh (in press) for a haploid asexual population was

$$K_0 = N \cdot e^{-\mu/\sigma}.$$

Since, other things being equal, the mutation rate for a diploid will be twice that of a haploid, it follows that the values of population size, mutation rate and selective disadvantage causing the ratchet to operate are identical for haploid asexual and for diploid selfing populations. 'Mutation rate' is here taken to mean the rate of deleterious mutations effective in the haploid, or in homozygous condition in the diploid.

If the mutations are not completely recessive ( $\tau > 0$ ), this makes only a small difference to the value of  $K_0$  and hence to the operation of the ratchet.

It was stated earlier that back mutation can be ignored. The justification is as follows. The ratchet operates only if  $n_0$  is of the order of 100 or less. With  $n_0 = 100$ , simulation shows that it takes of the order of 100 generations for the loss of an optimal class. Back mutation would be relevant only if, during that 100 generations, there was a reasonable chance of a back mutation taking place in a member of the optimal class. Since only of the order  $100 \times 100 = 10^4$  members of an optimal class exist, between the moment it became optimal to the time of extinction, the chance of a specific back mutation occurring is negligible.

Consideration of (4) shows that, in a selfing population, as in an asexual one,

there are values of  $N$ ,  $\mu$  and  $\sigma$  for which deleterious mutations would accumulate, although they would not do so in a sexual one. Very approximately:

- if  $\mu/\sigma \leq 1$ , the ratchet does not operate;
- $\mu/\sigma \simeq 10$ , the ratchet operates in any but very large populations;
- $\mu/\sigma \simeq 20$ , the ratchet operates.

A sexual population is unlikely to have a deleterious mutation rate substantially greater than 1. It follows that the ratchet is likely to be important in selfing or parthenogenetic populations descended from sexual ones if there is a large class of mildly deleterious mutants, for which  $\sigma \ll 1$ . However, the work of Mukai *et al.* (1972) makes it clear that such a class does exist.

There are two modifications to the model which are biologically plausible but which we have not investigated. The first, which is also relevant for the asexual case, is the effect of non-multiplicative effects on fitness between loci. The second is the effect of occasional outcrossing in a selfing population (Allard, Kahler & Clegg, 1977).

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