



# Letter to the Editor

## On the Speed of Muller's Ratchet

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WHILE asexual populations can suffer from an effectively irreversible accumulation of mildly deleterious mutations, sexual populations are essentially immune to it. This remarkable difference between the absence and the presence of recombination was first put into words by Muller, who defined what later was named Muller's ratchet (MULLER 1964; FELSENSTEIN 1974). Since then, Muller's ratchet has been proposed as a potential explanation for the advantage of recombination, the extinction of asexual populations, a limit to the genome size of asexual organisms, and the degeneration of Y chromosomes (CHARLESWORTH 1978; MAYNARD SMITH 1978; LYNCH *et al.* 1993; CHARLESWORTH and CHARLESWORTH 1997; GESSLER and XU 1999). In its classical formulation, the ratchet is portrayed as a process of successive losses of the least-loaded classes of individuals (the class with the minimum number of mutations at any one time) due to genetic drift. One important question concerns the speed with which it operates, usually defined as the mean time for one turn of the ratchet. This was first examined by HAIGH (1978), who identified the following relevant parameters for its quantification: the population size ( $N$ ), the mutation rate ( $u$ ), the selective effect of a single mutation ( $s$ ), and the size of the least-loaded class at mutation-selection equilibrium  $n_0 = N \exp(-u/s)$ , assuming multiplicative fitnesses.

Although a general expression for the speed of this process remains to be obtained, we have recently provided an expression for quantifying the mean time between turns of the ratchet that appeared to be a good approximation for moderate values of  $s$  and for  $n_0 \gg 1$  (GORDO and CHARLESWORTH 2000). While this approximation seems to work reasonably well for values of  $s$  consistent with the classical estimates from mutation-accumulation experiments (of the order 1–2%; CROW 1993), it underestimates the time with much smaller values of  $s$  (see Figure 8 of GORDO and CHARLESWORTH

2000). Since it has recently been proposed that there may be a large class of mildly deleterious mutations with selection coefficients  $\ll 2\%$  (KEIGHTLEY and EYRE-WALKER 1999), we need to have an approximation to the speed of the process for this parameter range.

Here we reexamine our previous approximation and suggest a more robust prediction that seems to work better over a wider range of parameters. As in previous investigations (STEPHAN *et al.* 1993; CHARLESWORTH and CHARLESWORTH 1997), we have tried to determine the speed of Muller's ratchet by modeling the ratchet as a one-dimensional diffusion process for which we calculate the mean time to absorption of the frequency of the least-loaded class (GORDO and CHARLESWORTH 2000). To derive the diffusion coefficient, we assume a Wright-Fisher model; for the drift coefficient, we assume small perturbations around the equilibrium under deterministic mutation-selection balance. For the latter, we also assume that, just after a turn of the ratchet, the size of the new least-loaded class would rapidly approach a value close to  $1.6 n_0$  [as suggested by the corollary to HAIGH's (1978) Theorem 1]. When  $s$  is intermediate, this is likely to be true, but the smaller the value of  $s$ , the longer the time it takes to approach this value. In particular, when  $n_0$  and  $s$  are small, then this relaxation time becomes the main determinant of the total time to absorption (HAIGH 1978; STEPHAN *et al.* 1993). It is this additional time ( $T_a$ ), which we previously assumed to be effectively zero, that we must add to get a better prediction.

We can approximate  $T_a$  by the time it takes to get from the size of the new least-loaded class immediately after one turn (which at this point has an approximate value of  $n_1 = n_0 u/s$ ) to  $1.6 n_0$ , using Haigh's Theorem 1 or Equation 3 in STEPHAN *et al.* (1993). This is approximately

$$T_a \approx \frac{1}{s} \left( 1 - \frac{1.6s}{u} \right). \quad (1)$$

Therefore, the mean time for a turn of the ratchet is  $T(N, u, s) = T_a + T_{0,x_0} + T_{x_0,1}$ , where  $T_{0,x_0}$  is the time spent in the frequency interval  $[0, x_0]$  and  $T_{x_0,1}$  is the

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TABLE 1  
Comparison of the mean time between turns of the ratchet between simulations,  
 $T$  (with 2 SE), and the analytical expression,  $T(N, u, s)$

$N$	$u$	$s$	$n_0$	$T$ (2 SE)	$T(N, u, s)$	$\bar{w}/\bar{w}_i^a$	No. of fixations <sup>b</sup>
275	0.06	0.015	5	63 (5)	66	$8.06 \times 10^{-53}$	7,937
565	0.1	0.03	20	119 (2)	101	$3.29 \times 10^{-55}$	4,119
1,000	0.04	0.01	18	169 (39)	144	$1.22 \times 10^{-13}$	2,959
3,000	0.0075	0.0015	20	489 (42)	571	$2.15 \times 10^{-1}$	1,023
3,000	0.1	0.02	20	135 (14)	120	$3.19 \times 10^{-33}$	3,704
5,000	0.04	0.01	92	514 (99)	442	$5.68 \times 10^{-5}$	973
6,065	0.03	0.005	15	215 (25)	225	$8.66 \times 10^{-6}$	2,326
10,000	0.075	0.01	5.5	126 (12)	109	$4.78 \times 10^{-18}$	3,968
13,500	0.075	0.02	317	4,574 (1,913)	4,712	$1.10 \times 10^{-1}$	109
30,000	0.005	0.001	202	1,743 (225)	1,601	$6.98 \times 10^{-1}$	359
30,000	0.01	0.002	202	1,225 (272)	1,200	$4.42 \times 10^{-1}$	408
30,000	0.1	0.02	202	1,543 (275)	1,521	$1.44 \times 10^{-3}$	324
30,000	0.175	0.035	202	4,890 (454)	3,860	$2.62 \times 10^{-2}$	102
50,000	0.04	0.01	918	45,922 (26,244)	38,957	$8.96 \times 10^{-1}$	11
500,000	0.015	0.0025	1,239	4,924 (764)	7,785	$7.76 \times 10^{-1}$	102
500,000	0.015	0.0015	23	732 (66)	1,343	$3.59 \times 10^{-1}$	683
500,000	0.03	0.003	23	490 (114)	716	$4.66 \times 10^{-2}$	1,020
500,000	0.3	0.03	23	167 (79)	139	$4.29 \times 10^{-38}$	2,994
500,000	0.03	0.005	1,239	12,819 (5,681)	17,625	$8.22 \times 10^{-1}$	39
500,000	0.04	0.004	23	371 (86)	570	$4.51 \times 10^{-3}$	1,348
500,000	0.04	0.005	168	940 (106)	1,018	$6.95 \times 10^{-2}$	532
500,000	0.04	0.006	636	3,868 (322)	4,657	$4.59 \times 10^{-1}$	129
500,000	0.04	0.0065	1,063	13,381 (6,210)	19,225	$7.84 \times 10^{-1}$	37
500,000	0.05	0.0075	636	3,912 (369)	5,910	$3.82 \times 10^{-1}$	128
500,000	0.056	0.008	456	2,420 (303)	3,219	$1.90 \times 10^{-1}$	207
500,000	0.065	0.01	752	9,310 (1,306)	16,934	$5.83 \times 10^{-1}$	54
500,000	0.07	0.01	456	2,711 (411)	4,022	$1.57 \times 10^{-1}$	184
500,000	0.08	0.01	168	812 (113)	915	$2.05 \times 10^{-3}$	616

<sup>a</sup> The expected ratio of the mean fitness of the population and the initial mean fitness after 500,000 generations.

<sup>b</sup> Expected number of fixations of deleterious mutations after 500,000 generations.

time spent in the interval  $[x_0, 1]$ , given by Equations 3a and 3b in GORDO and CHARLESWORTH (2000).

While  $T_a$  is the deterministic time for the frequency to approach a state close to the new mutation-selection balance, the other terms represent the mean time of the stochastic process leading to absorption. For a given  $N$  and  $u$ , small values of  $n_0$  correspond to small values of  $s$ , and  $T_a$  dominates the other terms; as  $s$  increases, so does  $n_0$ , and the value of  $T_a$  becomes less relevant compared with the other terms.

In Table 1 we compare the results of this formulation with those obtained by simulations. The simulation method is as described in GORDO and CHARLESWORTH (2000), *i.e.*, we assume the sequence of events: mutation, reproduction and selection, a constant population size, and multiplicative fitness effects of mutations at different loci. The parameter values were chosen as follows. The large values of  $N$  in Table 1 are of considerable biological importance, since we want to analyze the role of Muller's ratchet in the degeneration of  $Y$  and neo- $Y$  chromosomes in systems such as *Drosophila miranda*, for which the effective population size is thought to be in

the order of hundreds of thousands or millions (YI and CHARLESWORTH 2000). A  $Y$  or neo- $Y$  chromosome behaves like a haploid asexual population, for which  $N$  is the number of breeding males, the selection coefficient is the effect of a mutation when heterozygous, and the mutation rate is the fraction of the total haploid deleterious mutation rate corresponding to the size of that chromosome (CHARLESWORTH 1978). The values of the deleterious mutation rate were chosen to cover a region that is reasonable in the light of various mutation-accumulation experiments (KEIGHTLEY and EYRE-WALKER 1999). All the parameters are constrained to the condition  $n_0 \geq 1$ , because, if this condition is not met, the assumption of the existence of a state characterized by the deterministic mutation-selection balance is invalid [see GESSLER (1995) for results on the case of  $n_0 < 1$ ]. For all the simulation results reported previously (GORDO and CHARLESWORTH 2000) and other parameters that we tested, the new expression performs better.

In Figure 1 we show, as an example, the dynamics of the size of the least-loaded class over time intervals of

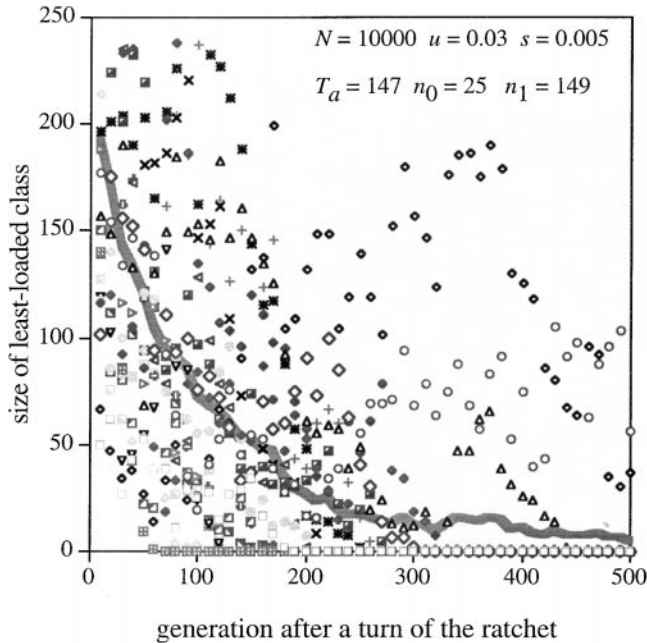


FIGURE 1.—Changes in the size of the least-loaded class after the first turn of the ratchet has occurred for different simulation runs (corresponding to different symbols). The thick line is the average value.

10 generations after a turn of the ratchet, taken from several simulation runs. The parameter values are  $N = 10,000$ ,  $u = 0.03$ , and  $s = 0.005$ . With these parameters,  $n_0 = 25$ ,  $1.6 n_0 = 40$ , and  $n_1 = 149$ . Although there is an enormous variance in the behavior of the changes in size of the least-loaded class, on average (thick line in the figure) the behavior is close to what we have assumed. Immediately after a turn of the ratchet, the mean size of the least-loaded class is close to  $n_1$ , and then it approaches a value close to  $n_0$  over 100–200 generations. This pattern is essentially the same for other parameter values. One fact is probably worth noting: although we can, with a single expression, estimate reasonably well the time between turns of the ratchet (for very different values of  $N$ ,  $u$ , and  $s$ ), when  $s$  is large ( $>0.04$ ) our expression underestimates the time obtained in the simulations. In this range, none of the diffusion approximations is accurate, as expected from the conditions for diffusion theory to be reliable (EWENS 1979, Chap. 4).

Under this model, under which each mutation causes an identical and independent deleterious effect on fitness, the decline in the logarithm of mean fitness is

$$\frac{\partial \ln \bar{w}}{\partial t} = \frac{\ln(1 - s)}{T} \approx -\frac{s}{T}, \quad (2)$$

where  $T$  is the mean time for a turn of the ratchet.

Clearly, deleterious mutations with larger effects cause a bigger decline in log mean fitness per turn but take more time to accumulate, while weaker deleterious mutations will accumulate faster but cause a smaller

decline in log mean fitness (as noted before by LYNCH *et al.* 1993). Therefore there is a value of  $s$ , say  $s_{\max}$ , that maximizes the decline in log mean fitness. The partial derivation of  $s/T$  with respect to  $s$  will be zero at this point. We can easily calculate the approximate value of  $s_{\max}$ , using our approximation. This value is obviously a function of  $N$  and  $u$ . For example, in the case of a population of a *Drosophila Y* or neo-*Y* chromosome,  $N$  is likely to be of the order of 500,000 if we assume an effective population size for *Drosophila* of  $\sim 1$  million and a 1:1 sex ratio (YI and CHARLESWORTH 2000). If the mutation rate is 0.04, then mutations whose effect is  $\sim 0.004$  are expected to cause the biggest decline in log mean fitness ( $s/T \approx 1.3 \times 10^{-5}$ ). If  $u$  is smaller, say 0.02, then weaker mutations will correspond to the maximum rate of decline but cause a much lower rate of decline ( $s/T \approx 3.7 \times 10^{-6}$ ) than in the first case. From (2), we can calculate the ratio of the mean fitness at any time to the initial mean fitness of the population,  $\bar{w}/\bar{w}_0$ . We display this ratio after 500,000 generations in Table 1. We also show the expected number of fixed deleterious mutations at this time, since it is known that, in the long run, the rate of the ratchet is the rate of fixation of deleterious mutations (CHARLESWORTH and CHARLESWORTH 1997).

For large populations, the average time between turns of the ratchet, for mutations that cause a considerable decline in log mean fitness of the population per turn ( $0.005 < s < 0.01$ ), is on the order of thousands of generations (see Table 1) for values of  $u$  that are possibly reasonable for large nonrecombining segments of the genome (such as the *Y* chromosome) in real populations of this size. The neo-*Y* chromosome of *D. miranda* results from a fusion between an autosome and the *Y* chromosome, and the estimated time of origin of the rearrangement is  $\sim 1$  million years ago (YI and CHARLESWORTH 2000). Since there are  $\sim 13,600$  genes in *Drosophila* (RUBIN *et al.* 2000) and the neo-*Y* constitutes about one-fifth of the genome, we expect  $\sim 2700$  genes on the neo-*Y*. This means that, if the ratchet is operating approximately as in our model, we expect hundreds of fixations of mildly deleterious mutations in about one-tenth of the total lifetime of the neo-*Y*. Contrary to the suggestion of CHARLESWORTH (1996), the ratchet thus seems to be a viable mechanism for the degeneration of the neo-*Y* if the great majority of deleterious mutations have selection coefficients  $\leq 2\%$ . Of course this process is not incompatible with the operation of other processes (as discussed in CHARLESWORTH 1996).

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