Finite genome size can halt Muller’s ratchet

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Abstract: We study the accumulation of deleterious mutations in a haploid, asexually reproducing population, using analytical models and computer simulations. We find that Muller’s ratchet can come to a halt in small populations as a consequence of a finite genome size only, in the complete absence of backward or compensatory mutations, epistasis, or recombination. The origin of this effect lies in the fact that the number of loci at which mutations can create considerable damage decreases with every turn of the ratchet, while the total number of mutations per genome and generation remains constant. Whether the ratchet will come to a halt eventually depends on the ratio of the per-locus deleterious mutation rate \( u \) and the selection strength \( s \). For sufficiently small \( u/s \), the ratchet halts after only a few clicks. We discuss the implications of our results for bacterial and virus evolution.

Keywords: Muller’s ratchet, mutation accumulation, population bottlenecks, RNA viruses, compensatory mutations

A major evolutionary pressure that distinguishes finite asexual from sexual populations experience is Muller’s ratchet, i.e., the continual loss of those individuals from the population that carry the smallest load of mutations (Muller 1964; Felsenstein 1974). Sexual populations can regenerate individuals with reduced number of mutations through recombination, while asexual populations cannot. This may be one of the main advantages of sexual recombination (Felsenstein 1974; Maynard Smith 1978; Takahata 82; Pamilo et al. 1987; Antezana and Hudson 1997). Besides its importance for theories of the evolution and maintenance of sex, Muller’s ratchet may also play a significant role in bacterial or viral dynamics, where host to host transmission often creates severe bottlenecks (Chao 1990; Andersson and Hughes 1996). Conventional wisdom says that Muller’s ratchet proceeds at a constant rate, as a result of which an asexual population may eventually go extinct (Lynch and Gabriel 1990; Gabriel et al. 1993). The main assumptions that enter the classic ratchet model are a vanishing probability of back mutations, a genome with an infinite number of loci, and mutations that do not interact. When epistatic interactions are taken into account, Muller’s ratchet will slow down over time (Charlesworth et al. 1993; Kondrashov 1994), though it will not necessarily come to a halt (Butcher 1995). On the other hand, if back mutations are assumed to be frequent and the genome is finite, then the ratcheting process will always stop eventually, even in the absence of epistatic interactions (Woodcock and Higgs 1990; Prügel-Bennett 1997). A similar result can be found if there is sufficient supply of compensatory mutations (Wagner and Gabriel 1990). However, since the majority of studies focuses on the classic model with infinite genome (Haigh 1978; Pamilo et al. 1987; Stephan et al. 1993; Higgs and Woodcock 1995; Gessler 1995; Charlesworth and Charlesworth 1997; Gordo and Charlesworth 2000a; Gordo and Charlesworth 2000b), it is not entirely clear how Muller’s ratchet affects bacteria or viruses, which contain at most a couple of hundred genes.

Here, we investigate the selection-mutation balance for a finite number of loci, and we also consider arbitrary forward and back mutation rates. Perhaps not so surprisingly, we find that if the back mutation rate is small but non-zero, selection-mutation balance stabilizes the population before the genome is com-
completely deteriorated. More importantly, however, the assumption of a finite number of loci alone guarantees that even in the complete absence of back mutations, Muller’s ratchet can come to a complete halt within a biologically relevant time frame if selection is sufficiently strong.

INFINITE POPULATION SIZE

As in the case of an infinitely long genome, the deterministic mutation-selection balance of an infinite population is a useful basis for the subsequent analysis of finite population effects (Haigh 1978). We therefore give a brief treatment of the infinite population case, and discuss the influence of various rates of back mutations on the equilibrium distribution of deleterious mutations.

The deterministic mutation-selection equilibrium can be calculated straightforwardly from the eigenvector corresponding to the largest eigenvalue of the transition matrix $W$ (Eigen et al. 1988). The transition matrix contains the rates at which genotypes are produced as offspring of other genotypes, i.e., an entry $w_{ij}$ in the transition matrix is given by the fitness of genotype $j$ times the probability that genotype $j$ mutates into genotype $i$. In the present case, the analysis can be simplified because we disregard epistatic interactions, in which case it is sufficient to calculate the equilibrium point for a single locus. The generalization to a finite number of loci $L$ is trivial (Rumschitzki 1987).

We assume a single locus with two alleles, '+' and '−'. The '+' allele carries a fitness of 1, and the '−' allele carries a fitness of 1 − $s$. Mutations from '+' to '−' may occur with a rate $u$ per locus. We call these mutations forward (or deleterious) mutations. Conversely, mutations from '−' to '+' occur with a rate $v$, and we call these mutations back mutations. The transition matrix for this single-locus, two-allele model is given by

$$W = \begin{pmatrix} 1-u & (1-s)v \\ u & (1-s)(1-v) \end{pmatrix}. \quad (1)$$

From diagonalization, we find that the '−' allele is present in the population at a concentration of

$$a = \frac{1}{2} \left[ 1 - v + \frac{u+v}{s} - \sqrt{\left(1-v+\frac{u+v}{s}\right)^2 - \frac{4uv}{s}} \right]. \quad (2)$$

The concentration of the '+' allele is correspondingly $1-a$. In the case of $L$ loci, this result generalizes to

$$x_k = \left(\frac{L}{k}\right)^{a^k(1-a)^{L-k}}, \quad (3)$$

where $x_k$ is the concentration of genomes that carry $k$ alleles of the '−' type (we will in the following simply say that these genomes carry $k$ mutations). From (3), the average number of mutations $\langle k \rangle$ in the population follows as $\langle k \rangle = aL$.

If we set the back mutation rate to $v = 0$, we find the simple expression

$$\frac{\langle k \rangle}{L} = a = \begin{cases} 1 & \text{for } u > s \\ \frac{u}{s} & \text{for } u \leq s. \end{cases} \quad (4)$$

We learn that the fate of an infinite population without back mutations is determined by the ratio between the rate of deleterious mutations per locus $u$ and the selection strength $s$. When $u$ is of the order of $s$ or larger, then $\langle k \rangle = L$, which means that the population will eventually consist exclusively of individuals that have been hit by mutations at all loci. For $u$ smaller than $s$, on the other hand, the majority of individuals in the population will accumulate only a small number of mutations.

In Fig. 1, we show the average fraction of mutated loci in the population, $\langle k \rangle/L$, as a function of the forward mutation rate $u$ and for various back mutation rates $v$. Note the sharpness of the transition at $u/s = 1$. If $u$ is only a factor of 10 smaller than $s$, then on average each individual carries mutations in only 10% of the loci. We observe further that the ratio of $u/s$ plays a more important role in determining the equilibrium point of the population than the back mutation rate $v$. Unless $v$ is of the order of $u$, the deviations from the case of $v = 0$ are small.

It is worth mentioning that if we substitute $a = u/s$ into (3) and take the limit $L \to \infty$ while keeping the genomic mutation rate $U = uL$ constant, we recover the Poisson distribution of mutants that is normally assumed in models of Muller’s ratchet with infinite genome size (Haigh 1978).

FINITE POPULATION SIZE

Simulation methods

All simulation results reported in this work were obtained in the following manner. We keep track of
In this section, we focus on the case of no back mutations, $v = 0$. From a mathematical point of view, a finite population without back mutations will always hit the absorbing boundary at $\langle k \rangle = L$ eventually, i.e., it will always lose all '+' alleles as time $t \to \infty$. Therefore, we know that any set of equations aimed at finding the true equilibrium point of such a system is bound to yield $\langle k \rangle = L$. However, this solution has no biological significance if the waiting time to arrive at $\langle k \rangle = L$ is extremely large, e.g., of the order of millions of generations or larger. Consequently, we must try to find a description for the increase in waiting times between successive clicks, and may assume that the ratchet has stopped once the waiting times exceed a biologically relevant time scale. Below follows a mathematical description for the waiting times that, while being too simplistic to yield accurate quantitative results for very small $N$, describes well the qualitative behavior that we see in simulations, and gives valuable insight into the nature of Muller’s ratchet in finite genomes.

We assume that the number of sequences in the least loaded class $n_0$ is given by the infinite population concentration times the population size $N$, and that loss of the least loaded class occurs if all individuals in that class do either fail to reproduce or give birth to mutated offspring. The situation of a population with a least loaded class having $k_{\text{min}}$ mutations is equivalent to one in which the least loaded class has zero mutations, but the genome is of length $L - k_{\text{min}}$. In the following, we will therefore refer to $L - k_{\text{min}}$ as the effective genome size, and to the model that we describe now as the “effective genome size model”.

From (B), we find

\[ n_0 = N(1 - a)^{L - k_{\text{min}}} \quad \text{(5a)} \]
\[ \approx Ne^{a(k_{\text{min}} - L)} \quad \text{(5b)} \]
The probability $\xi$ that an organism in the next generation is an offspring of one of the $n_0$ organisms in the least loaded class is given by [with $x_i$ as defined in (3)]

$$\xi = \frac{(n_0/N)(1-s)^{k_{\text{min}}}}{\sum_{i=k_{\text{min}}}^{L} x_i (1-s)^i}.$$  \hspace{1cm} (6)

The probability that there will be $j$ descendants of the least loaded class in the next generation can be expressed in terms of $\xi$ as

$$p_{\text{birth}}(j) = \binom{N}{j} \xi^j (1-\xi)^{N-j}. \hspace{1cm} (7)$$

The probability that all these $j$ organisms carry at least one additional mutation is given by

$$p_{\text{mut}}(j) = [1-(1-u)^{L-k_{\text{min}}}]^j. \hspace{1cm} (8)$$

The total probability of a ratchet event then follows as

$$p_{\text{ratchet}} = \sum_{j=0}^{N} p_{\text{mut}}(j)p_{\text{birth}}(j) = [1-\xi(1-u)^{L-k_{\text{min}}}]^N \hspace{1cm} (9a)$$

$$\approx \exp[-N\xi(1-u)^{L-k_{\text{min}}}] \hspace{1cm} (9b)$$

We find that $p_{\text{ratchet}}$ decays exponentially with the two quantities $N\xi$ and $(1-u)^{L-k_{\text{min}}}$. The latter quantity grows exponentially with every turn of the ratchet, i.e., $(1-u)^{L-k_{\text{min}}}$ increases exponentially as the effective genome length $L - k_{\text{min}}$ decreases. Moreover, $N\xi$ is proportional to $n_0$, which again increases exponentially with decreasing effective genome length. As a result, $p_{\text{ratchet}}$ decays superexponentially as the ratchet turns. This implies that the ratchet will turn at a relatively high rate initially, but can suddenly reach a point where the waiting time exceeds any biologically relevant time scale. This is dramatically illustrated in Fig. 4. Note the logarithmic time scale. Within the first 1000 generations, 70% of the genes were lost, while during the next $10^5$ generations, only an additional 10% of the genes were lost. Moreover, in the final 50000 generations, we observed hardly any clicks of the ratchet at all.

Figure 4 gives also a comparison between simulation results and our theoretical model. The theoretical prediction was derived from (3) by assuming that the average waiting time till the next ratcheting event is given by the inverse of $p_{\text{ratchet}}$, so that the time until a certain $k_{\text{min}}$ is reached is simply given by the sum of the inverse ratchet probabilities from the first ratchet event until the $(k_{\text{min}} - 1)$th ratchet event. When comparing the results thus obtained to the simulation results, we find that although the model predicts a too early slowdown of the ratchet, the qualitative form of the predicted curve agrees well with the one from the simulations. This demonstrates that our main reasoning about the increase in waiting times between successive ratchet events is correct, even though the microscopic details are somewhat incorrect. The origin of the deviations between model and simulations is clear. At the beginning of the simulation, we initialize all sequences to the wild type with zero mutations, while the model always assumes a fully developed mutation-selection equilibrium. The population in the simulation thus retains at early times a larger fraction of individuals in the least loaded classes than what the model assumes, and the model overestimates the transition probabilities. For later times, the model underestimates the transition probabilities, because it disregards cases in which the loss of the least loaded class happens in more than one step, for example, cases in which the number of individuals in the least loaded class first fluctuates to an unusually low value before the currently least loaded class disappears completely.

In Fig. 4, we show another comparison between our model and the simulation results. There, we consider the average number of mutations in the population, $\langle k \rangle$, instead of the number of mutations in the least loaded class, $k_{\text{min}}$, so that we can compare our results to the moment expansion as well. In the effective genome size model, we calculated $\langle k \rangle$ from $k_{\text{min}}$ with the formula $\langle k \rangle = (L - k_{\text{min}})a$. Both the effective genome size model and the moment expansion agree on the mutation rate at which Muller’s ratchet starts to slow down. However, the form of the transition to a mutation free population is significantly misrepresented by the moment expansion, while the effective genome size model predicts the qualitative form of the transition well. In addition, the moment expansion does not yield any insights into the temporal change of the ratchet rate. The effective genome size model is therefore the more useful one, despite
its mathematical simplicity.

Simulation results

For population sizes below about one hundred, the effective genome size model consistently predicts too low ratchet rates. This is not surprising, as our model suffers from the same limitations that infinite genome models do when \( n_0 \lesssim 1 \) (Gessler 1995), namely insufficient equilibration of the least loaded class. We therefore have to resort to simulation results for very small population sizes. Fig. 4 shows the simulation data from Fig. 3 for \( N = 500 \), and in addition results for \( N = 50 \) and \( N = 10 \). All three cases show a very similar behavior, but shifted to smaller and smaller mutation rates. For sufficiently small mutation rates, Muller’s ratchet stops after the first few clicks. In a transition region that covers roughly one order of magnitude in the mutation rate, Muller’s ratchet stops at intermediate points, with a good fraction of genes lost, but another large fraction of genes retained. When the mutation rate is too high, all genes are lost within a biologically relevant time scale.

In our analytical model presented above, we have assumed that in order to predict the probability of the next click of the ratchet, it is sufficient to know the effective length \( L - k_{\text{min}} \), while the absolute values of \( L \) and \( k_{\text{min}} \) do not enter the calculation. If this assumption is correct, then for any given mutation rate \( u \), the value of \( L - k_{\text{min}} \) at which the ratchet stops should be independent of \( L \). In other words, the per-locus mutation rate \( u \) determines how many loci can at most be retained unmutated, and the genomic mutation rate \( uL \) is largely irrelevant. Fig. 3 demonstrates that this reasoning is consistent with our simulation results. When we plot the difference between the length \( L \) and the average number of mutations \( \langle k \rangle \) as a function of \( u \), the results for widely differing lengths lie right on top of each other in the regime in which substantial mutation accumulation occurs.

We have also performed a number of simulations with a non-zero rate of back mutations \( v \) (data not shown). The main result is similar to the case of an infinite population, as depicted in Fig. 4. Unless the back mutation rate is of the same order of magnitude as the forward mutation rate, back mutations do not have a large effect on the rate at which mutations accumulate. The ratio \( u/s \) and the population size \( N \) are the main determinants of whether genomes accumulate a fair amount of mutations, or stay largely mutation free.

Discussion

Two main differences between Muller’s ratchet in infinite and in finite genomes emerge from our study. First, the ratchet rate is constant for infinite genomes, whereas the rate decays with every turn of the ratchet in a finite genome. The slowdown of the ratchet rate is so dramatic that the ratchet can stop completely, even in the absence of epistasis or compensatory mutations. Second, in an infinite genome, the main parameter that governs the ratchet rate, besides the population size, is the ratio \( \theta \) between the genomic deleterious mutation rate and the selection strength (Haigh 1978). In a finite genome, on the other hand, it is not the genomic but the per locus deleterious mutation rate that we have to compare to the selection strength. As a consequence, Muller’s ratchet is not as important a limiting factor in the evolution of large genomes as was previously thought (Maynard Smith 1978). An additional consequence is that we can expect organisms with longer genomes and more sophisticated error correction to be less prone to mutation accumulation than organisms with shorter genomes, even if the mutation rates per genome are comparable.

Backwards or compensatory mutations result in an additional slowdown of the ratchet. However, unless they occur at a rate comparable to the forward rate, they do not play a significant role in determining whether the ratchet stops early, or continues until a large proportion of the genome is deteriorated. It is therefore adequate to neglect them for order of magnitude estimates of the ratchet rate. Nevertheless, a complete theoretical description of the ratchet rate, including a finite genome size and variable forward and back mutation rates, is certainly desirable but completely lacking at this point.

The range of parameters that case Muller’s ratchet to halt early is certainly biologically plausible. For example, Andersson and Hughes (1996) estimate the mutation rate in Salmonella typhimurium to 0.0014–0.0072 mutations per genome per generation, in a genome of about 200 genes (Riley 1993). Andersson and Hughes do not estimate the selection strength \( s \).
However, selection is certainly not weak, considering that out of the five lineages in which fitness loss was observed, two experienced a doubling of their generation time, while the other three had an increase in generation time of about 10–15%. Given the low mutation rate and the number of bottlenecks of only 60, we can estimate that this loss in fitness was probably due to only a small number of mutations, maybe between one and three. Of course, a more accurate estimate of the selection strength in this system would be desirable. In any case, the parameters of the simulations in Fig. 3 (s = 0.1 and L = 100) are probably of the right order of magnitude, and hence we find that while bottlenecks of size one will lead to Muller’s ratchet, bottleneck sizes above 10 or 50 will not lead to persistent genome deterioration. Therefore, if the bottlenecks encountered during transmission from one host to another are typically between 10 to 100 individuals, bacterial populations may not suffer significantly from mutation accumulation over time.

In the case of RNA viruses, where mutation rates are much higher, it seems that the risk of mutation accumulation should be higher as well. Since sufficiently large virus populations can exist without loss in fitness, however, we can assume that \( u/s \ll 1 \), so that Muller’s ratchet becomes important only for very small populations. Most experimental work focuses on bottleneck sizes of one (Chao 1990; Duarte et al. 1992; Elena et al. 1996; de la Peña et al. 2000), in which case loss of fitness is readily observed after a couple of serial transfers. However, these works do not address intermediate bottleneck sizes between 10 and 100, or the change in fitness over time. Therefore, they do not allow a full assessment of the importance of Muller’s ratchet in virus evolution. An important step towards more conclusive experimental results has been presented in recent work by Chao and coworkers (Chao 1997; Burch and Chao 1999; Burch and Chao 2000). There, a wide range of population sizes has been investigated, and in particular in Burch and Chao (1999), fitness measurements have been performed after every bottleneck. Propagation of lineages of a strain with impaired fitness showed recovery back to the original fitness level for bottleneck sizes of \( N = 33 \) or larger (Fig. 3 of Burch and Chao 1999). For \( N = 10 \), the original fitness could not be regained within 100 generations. However, Burch and Chao did not observe a further decline in fitness at \( N = 10 \) either, instead they observed a slight fitness increase. Burch and Chao’s results for large bottlenecks demonstrate that compensatory mutations are readily available for sufficiently large population sizes, so that a virus population can easily recover a short sequence of extreme bottlenecks if later it is allowed to expand again. Their results for \( N = 10 \) suggest two alternative interpretations. On the one hand, compensatory and deleterious mutations may cancel each other almost exactly, so that the net result is a small fitness increase. On the other hand, the impaired virus strain may already have reached the point at which Muller’s ratchet stops to operate for \( N = 10 \). In that case, the lineage is protected from further mutation accumulation, and can safely exist until some compensatory mutations occur eventually. We believe that the second explanation is the more accurate one, but the current data does not allow to reject one of the two scenarios conclusively. More data at small bottleneck sizes (between one and 10) and for longer times should allow a more accurate assessment of these issues.

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Appendix

The following calculation is directly analogous to the one presented by Woodcock and Higgs (1996). We refer to their work for a more complete description of the necessary steps.

Assume that an individual \(i\) carries \(k_i\) deleterious mutations and creates an offspring with \(j = k_i + m_i\) deleterious mutations. The probability that an offspring carries exactly \(j\) mutations is given by the transition matrix

\[
M_{jk} = \sum_{i = \max(0,k-j)}^{\min(k,l-j)} \binom{k}{i} \binom{l-k}{j-i} v^i u^{j-i} \times (1-v)^{k-i}(1-u)^{l-j-i}.
\]

The expectation values of \(m_i\) and \(m_i^2\) are

\[
E(m_i) = \sum_j (j - k_i) M_{jk} = u(l - k) - v k, \tag{11}
\]

\[
E(m_i^2) = \sum_j (j - k_i)^2 M_{jk} = k^2(u + v)^2 + k[-u^2 - v^2 + (v - u) + 2u^2 - 2uL(u+v)] + u(1-u)L + u^2L^2. \tag{12}
\]

Both results reduce to the ones found by Woodcock and Higgs if we set \(v = u\). Now consider two individuals \(i\) and \(j\) with fitnesses \(w_i = (1-s)k_i\) and \(w_j = (1-s)k_j\) that have \(n_i\) and \(n_j\) offspring in the next generation. The expected values of \(n_i\), \(n_i^2\), and \(n_in_j\) have been calculated by Woodcock and Higgs, and we only state the final result for completeness:

\[
E(n_i) \approx 1 - s(k_i - \langle k \rangle), \tag{13}
\]

\[
E(n_i^2) \approx 2 - 1/N - 3s(k_i - \langle k \rangle), \tag{14}
\]

\[
E(n_in_j) \approx 1 - 1/N - s(k_i - \langle k \rangle) - s(k_j - \langle k \rangle). \tag{15}
\]

In what follows, we have to distinguish between averages over a population, denoted by \(\langle ... \rangle\), and averages over an ensemble of independent evolutionary histories, denoted by \(\ldots\). The ensemble-averaged moments of the distribution of \(k_i\) are defined as

\[
M_n = \frac{1}{N} \sum_{i=1}^{N} (k_i - \langle k \rangle)^n, \tag{16}
\]

For the second moment, we will in the following use the symbol \(V\) instead of \(M_2\).

Now, write

\[
\langle k \rangle_{t+1} = \frac{1}{N} \sum_i n_i(k_i + m_i). \tag{17}
\]

With (11) and (13), and the equilibrium condition \(\langle k \rangle_{t+1} = \langle k \rangle_{t+1} = \langle k \rangle\), we find

\[
(u+v)\langle k \rangle + [1-(u+v)]sV = uL. \tag{18}
\]

Similarly, from

\[
\langle k^2 \rangle_{t+1} = \frac{1}{N^2} \sum_i \sum_j n_in_j(k_i + m_i)(k_j + m_j) \tag{19}
\]

and

\[
\langle k^2 \rangle_{t+1} = \frac{1}{N^2} \sum_i \sum_j n_in_j(k_i + m_i)(k_j + m_j) \tag{20}
\]

we find in equilibrium, using (11)–(13),

\[
V = [1-(u+v)]^2[(1-1/N)V - sM_3]
+ [u(u-1) - v(v-1)] \times [(1-1/N)\langle k \rangle - sV]
+ u(1-u)L(1-1/N). \tag{21}
\]

These two equations contain three variables, and in general every equation of higher order will contain correspondingly higher moments, so that the set of equations can never be solved. This problem can be avoided with a suitable closure approximation. Following Woodcock and Higgs, we use

\[
M_3 = V(1 - 2\langle k \rangle / L), \tag{22}
\]

which is the expression for the third moment in an infinite population. With (18), (21), and (22), \(\langle k \rangle\) is uniquely determined, and we find

\[
\frac{\langle k \rangle}{L} = \alpha \frac{4}{\beta} \left[ \frac{\alpha}{2} - \frac{\sqrt{\alpha^2 - \beta}}{2} \right], \tag{23}
\]

with

\[
\alpha = \frac{3u+v-2}{u+v-1} + \frac{1}{sN} + \frac{2(u+v)-(u+v)^2}{s(u+v-1)^2} + \frac{u-v}{N(u+v)}, \tag{24}
\]

\[
\beta = \frac{2u}{u+v} \left[ \frac{2(u+v)-(u+v)^2}{s(u+v-1)^2} + \frac{1}{sN} + \frac{u}{u+v-1} \right] + \frac{1}{N(u+v-1)}. \tag{25}
\]
Figure 1: Average fraction of mutations in an infinite population as a function of $u/s$ for various back mutation rates $v$.

Figure 2: Average number of mutations $\langle k \rangle$ vs. the back mutation rate $v$, for $N = 100$, and $s = u = 0.01$. Solid lines represent the analytic prediction based on (9), points represent simulation results, averaged over 5 replicates. The errors in the simulation are of the order of the symbol size.

Figure 3: Number of mutations in the least loaded class as a function of time, for $N = 1000$, $L = 100$, $s = 0.1$, $u = 0.01$, and $v = 0$. The thin solid lines represent simulation results, the thick dashed line represents the theoretical prediction obtained from (9).

Figure 4: Average number of mutations in the population vs. genomic mutation rate, for $N = 500$, $L = 100$, $s = 0.1$, and $v = 0$. The individual points represent results from simulation results, averaged over 5 replicates. The errors are of the order of the symbol size. The solid line represents the theoretical prediction obtained from (9), and the dashed line represents the moment expansion result (23). The simulation results and equation (9) were evaluated after $t = 10^5$ generations. The moment expansion predicts an equilibrium point, so time does not enter this equation.

Figure 5: Average number of mutations in the population vs. genomic mutation rate, for various population sizes $N$, and $L = 100$, $s = 0.1$, $v = 0$. The individual points represent results from simulation results, averaged over 5 replicates. The errors are of the order of the symbol size.

Figure 6: Average number of mutation-free loci $L - \langle k \rangle$ vs. mutation rate $u$, for various length $L$ and $N = 50$, $s = 0.1$, $v = 0$. The individual points represent results from simulation results, averaged over 5 replicates. The errors are of the order of the symbol size.
Figure 1: Graph showing the relationship between $\langle k \rangle / L$ and $u/s$. The graph includes curves for different values of $v$: $v = 0$, $v = 0.01u$, $v = 0.1u$, and $v = u$.
Figure 2.

Average number of mutations ($k$) vs. Back mutation rate $v$ for different values of $L$: $L = 200$, $L = 100$, and $L = 40$.
Figure 4.
Figure 5.
Figure 6.

The figure shows a graph with the x-axis labeled as "Mutation rate $u$" and the y-axis labeled as "$L - \langle k \rangle$". The graph includes different markers for different values of $L$: $L = 1000$ (triangle), $L = 500$ (diamond), $L = 200$ (square), and $L = 100$ (circle). The data points suggest a trend that $L - \langle k \rangle$ decreases as the mutation rate $u$ increases.