J. theor. Biol. (1996) **179,** 61–73

Population Evolution on a Multiplicative Single-Peak Fitness Landscape

GLENN WOODCOCK AND PAUL G. HIGGS†

Department of Physics, University of Sheffield, Hounsfield Road, Sheffield S3 7RH, U.K.

(*Received on* 31 *March* 1995, *Accepted in revised form on* 26 *October* 1995)

A theory for evolution of either gene sequences or molecular sequences must take into account that a population consists of a finite number of individuals with related sequences. Such a population will not behave in the deterministic way expected for an infinite population, nor will it behave as in adaptive walk models, where the whole of the population is represented by a single sequence. Here we study a model for evolution of population in a fitness landscape with a single fitness peak. This landscape is simple enough for finite size population effects to be studied in detail. Each of the N individuals in the population is represented by a sequence of L genes which may either be advantageous or disadvantageous. The fitness of an individual with k disadvantageous genes is $w_k = (1-s)^k$, where s determines the strength of selection. In the limit $L \to \infty$, the model reduces to the problem of Muller's Ratchet: the population moves away from the fitness peak at a constant rate due to the accumulation of disadvantageous mutations. For finite length sequences, a population placed initially at the fitness peak will evolve away from the peak until a balance is reached between mutation and selection. From then on the population will wander through a spherical shell in sequence space at a constant mean Hamming distance $\langle \overline{k} \rangle$ from the optimum sequence. We give an approximate theory for the way $\langle \overline{k} \rangle$ depends on N, L, s, and the mutation rate u. This is found to agree well with numerical simulation. Selection is less effective on small populations, so $\langle \overline{k} \rangle$ increases as N decreases. Our simulations also show that the mean overlap between gene sequences separated by a time of t generations is of the form $Q(t) = Q_\infty + (Q_0 - Q_\infty)\exp(-2ut)$, which means that the rate of evolution within the spherical shell is independent of the selection strength. We give a simplified model which can be solved exactly for which $Q(t)$ has precisely this form. We then consider the limit $L \to \infty$ keeping $U = uL$ constant. We suppose that each mutation may be favourable with probability p, or unfavourable with probability $1-p$. We show that for p less than a critical value p_c, the population decreases in fitness for all values of U, whereas for $p_c < p < 1/2$, the population increases in fitness for small U and decreases in fitness for large U. In this case there is an optimum non-zero value of U at which the fitness increases most rapidly, and natural selection will favour species with non-zero mutation rates.

1. Introduction

The ideas of fitness landscapes and sequence spaces in models of evolution are now familiar (Eigen *et al.*, 1989; Fontana *et al.*, 1993; Kauffman, 1993). We may be considering the space of all possible proteins of length L composed of 20 types of amino acids, or the space of all possible length L sequences of DNA composed of four types of bases, or a chromosome with L loci where a very large number of alternative alleles may exist for each locus. The fitness landscape determines the multiplication rate of each sequence, which is either the mean number of offspring of an individual with a given gene sequence in a biological population, or the replication rate of a given chemical sequence in a model for molecular evolution. There has been much interest in the structure of these fitness landscapes: in particular in the number and sizes of the local optima in such landscapes, and the correlation in fitness between neighbouring sequences (Kauffman & Levin, 1987; Kauffman & Weinberger, 1989; Weinberger, 1991; Weinberger & Stadler, 1993).

†Author to whom correspondence should be addressed at his permanent address: School of Biological Sciences, University of Manchester, 2-205 Stopford Building, Oxford Road, Manchester M13 9PT.

If the population size is assumed to be infinite then deterministic equations can be obtained for the relative frequencies of sequences with different fitnesses within the population (Schuster, 1986; Eigen *et al*., 1989; Tarazona, 1992; Higgs, 1994; Wiehe *et al*., 1995). If the mutation rate (or replication error rate) is not too large then the population tends to cluster about the fittest sequence. The distribution of frequencies converges to a stationary state known as the quasi-species. For simple landscapes the quasi-species distribution can be calculated exactly. Other studies have emphasized the ruggedness of fitness landscapes, and have modelled evolution as an adaptive walk (Macken *et al*., 1991; Flyvbjerg & Lautrup, 1992; Kauffman, 1993). The population is represented by a single point in sequence space which moves due to mutations, to neighbouring fitter sequences until a local optimum is reached.

Both these types of model neglect the important feature that the population is of finite size and that stochastic effects may be extremely large. One cannot assume that there is a finite concentration of copies of each sequence, since the number of possible sequences of a given length increases exponentially with the length, and may be far larger than the total number of individuals in the population. Neither can one assume that the population is just a single point in sequence space. The real population is a cluster of related sequences in a given region of sequence space. It is important that there is a range of sequences and of fitnesses within the population, otherwise natural selection has nothing to work on. If the landscape is flat (i.e. neutral evolution) the population will wander at random through sequence space (Derrida & Peliti, 1991; Higgs & Derrida, 1991, 1992). If the landscape is not flat then selection will tend to drag the population towards regions of higher than average fitness. However, natural selection is rather inefficient. It is by no means true that a population always evolves relentlessly uphill towards the nearest local fitness maximum, as in the adaptive walk models. The fitness of a population can often decrease due to stochastic effects.

The archetypal model which demonstrates this is Muller's ratchet (Haigh, 1978; Lynch & Gabriel, 1990; Wagner & Gabriel, 1990; Charlesworth *et al*., 1993; Lynch *et al*., 1993; Gabriel *et al*., 1993; Stephan *et al*., 1993; Wagner & Krall, 1993; Higgs & Woodcock, 1995). Here one considers a gene sequence of effectively infinite length, initially composed of favourable genes. Unfavourable mutations occur at rate U which each reduce the fitness of the individual by a factor $(1-s)$. Although selection acts against these unfavourable mutations, it is powerless to stop them accumulating, and the fitness therefore decreases indefinitely until the population is no longer viable. Lynch *et al*. (1993) call this "mutational meltdown". The Muller's ratchet model assumes that all mutations are bad, and that there is no possibility of back mutation. This is entirely reasonable if the sequence is very long and is already very close to an optimum. If the sequence has only a moderate fitness and is not close to a fitness peak then there is a considerable chance of a mutation leading to an increase in fitness. Evolution will thus lead toward higher fitness sequences, but will never manage to get right to the top of the fitness peaks, since Muller's ratchet will set in. The population will evolve toward a steady state with constant fitness, where there is a balance between selection and unfavourable mutations. This steady state is a dynamic one in which the sequence can continue to evolve even though the mean fitness remains constant. It is therefore not equivalent to the steady state quasi-species distribution in the infinite population model. Finite size population effects in similar models to this have been considered by Nowak & Schuster (1989) and Bonhoeffer & Stadler (1993).

It is useful to borrow an image from Kauffman (1993, Chapter 3). If the fitness landscape is viewed as a mountain range, then the population is likely to be found hanging like a layer of cloud below the mountain peaks but above ground level. The main aim of this article is to determine how high are the clouds.

2. Description of the Model

We suppose that each individual has a sequence of L genes, and that each gene may be either of two possible alleles. Each individual will be represented by a sequence $\sigma_1\sigma_2\cdots\sigma_L$ where each of the σ_i may be $+1$ or -1. Each $+1$ represents a favourable allele having a relative fitness of 1, and each -1 represents an unfavourable allele having a relative fitness $1-s$. The fitness of an individual with k unfavourable alleles is $(1-s)^k$, i.e. we have assumed that the contributions to the fitness from different loci are independent, and therefore multiplicative. The fitness landscape thus has a single optimum sequence, and the fitness of a sequence depends only on its Hamming distance from the optimum. Any landscape with this property might be called a "single-peak" landscape. The term "single-peak landscape" is sometimes used to indicate the case where there is one high fitness sequence (or Master sequence) in an otherwise flat landscape, which is not the model which we study here. In the

title we use the term "multiplicative single-peak" to distinguish from the other case.

In our model there are N individuals in the population at each generation. Individuals reproduce asexually with a reproduction rate proportional to their fitness. For each individual in a new generation, an individual is selected to be its parent from the previous generation with a probability proportional to the fitness of the parent. In this way the mean number of offspring of a given parent individual i is $w_i/\langle w\rangle$, where w_i is the fitness of individual i, and $\langle w\rangle$ is the mean fitness in the parent generation. The probability that individual i has n_i offspring is

$$p(n_i) = x_i^{n_i}(1 - x_i)^{N - n_i}\binom{N}{n_i}, \qquad (1)$$

where $x_i = w_i/(N\langle w\rangle)$. After choosing the parent for each of the new individuals the gene sequences are copied from the parents to the offspring with a small probability u of mutation occurring at each gene. Hence, $\sigma_i^{\text{offspring}} = \sigma_i^{\text{parent}}$ with probability $1 - u$, and $\sigma_i^{\text{offspring}} = -\sigma_i^{\text{parent}}$ with probability u, where typically $u \ll 1$.

When simulating this model we began by setting all individuals to be identical to the optimum sequence ($\sigma_i = 1$ for all i, and for all individuals). Initially almost all mutations are unfavourable, therefore the population moves away from the optimum sequence, and the number k of -1 genes in the sequence increases. As k increases the chance of a favourable mutation increases. After a certain time a steady state is reached where the occurrence of new unfavourable mutations is balanced by the action of selection plus the occurrence of favourable mutations. Figure 1 shows the mean number $\langle\overline{k}\rangle$ of unfavourable genes per individual in the steady state as a function of u. This is just the mean Hamming distance of the population from the optimum sequence. Note that two separate averages are necessary here: the angular brackets indicate an average over all individuals in the population at one moment in time, and the overbar indicates a time average over many generations after the steady state has been reached.

The expected value of $\langle\overline{k}\rangle$ is known in several limits. Firstly, in the neutral evolution limit, where $s = 0$, all sequences have an equal probability of occurring. On average half the genes will be -1, and therefore $\langle\overline{k}\rangle = L/2$. Secondly, if s is non-zero, and $u \to 0$ only the optimum sequence will remain in the population, so that $\langle\overline{k}\rangle \to 0$. If $u \to 1/2$, on the other hand, the offspring sequences will have no correlation

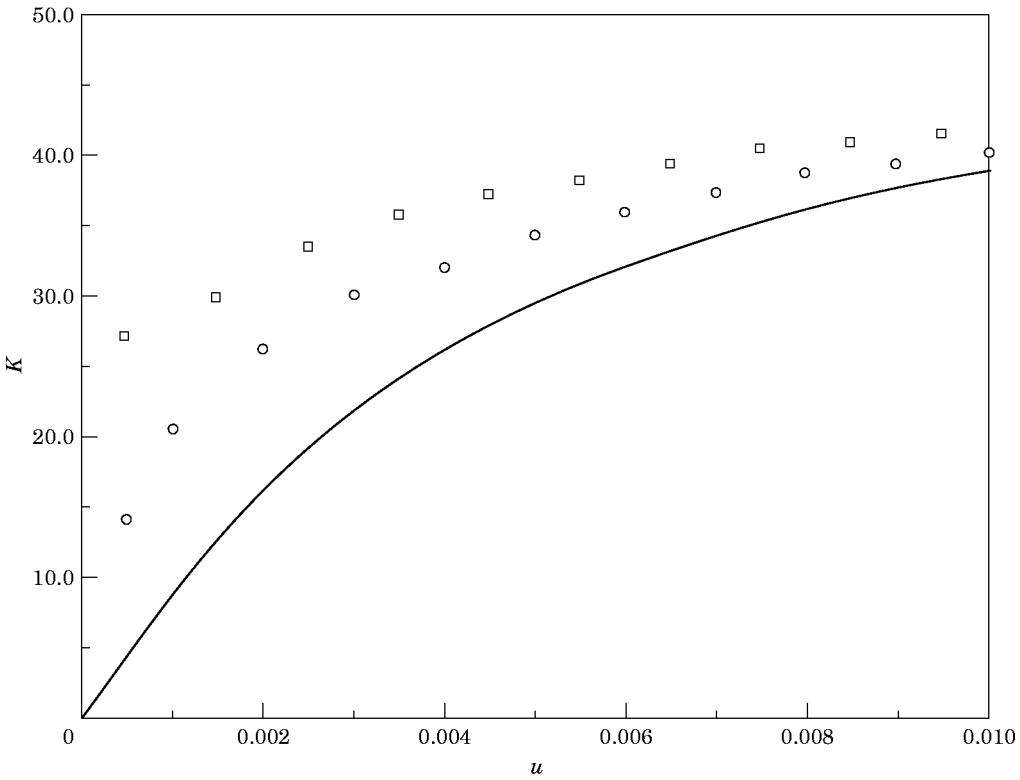

FIG. 1. Mean Hamming distance $\langle\overline{k}\rangle$ from the optimum sequence as a function of mutation rate u, for $L = 100$ and $s = 0.01$. The solid line shows the exact result for the infinite population. Symbols indicate simulation results. Circles $N = 384$, Squares $N = 96$.

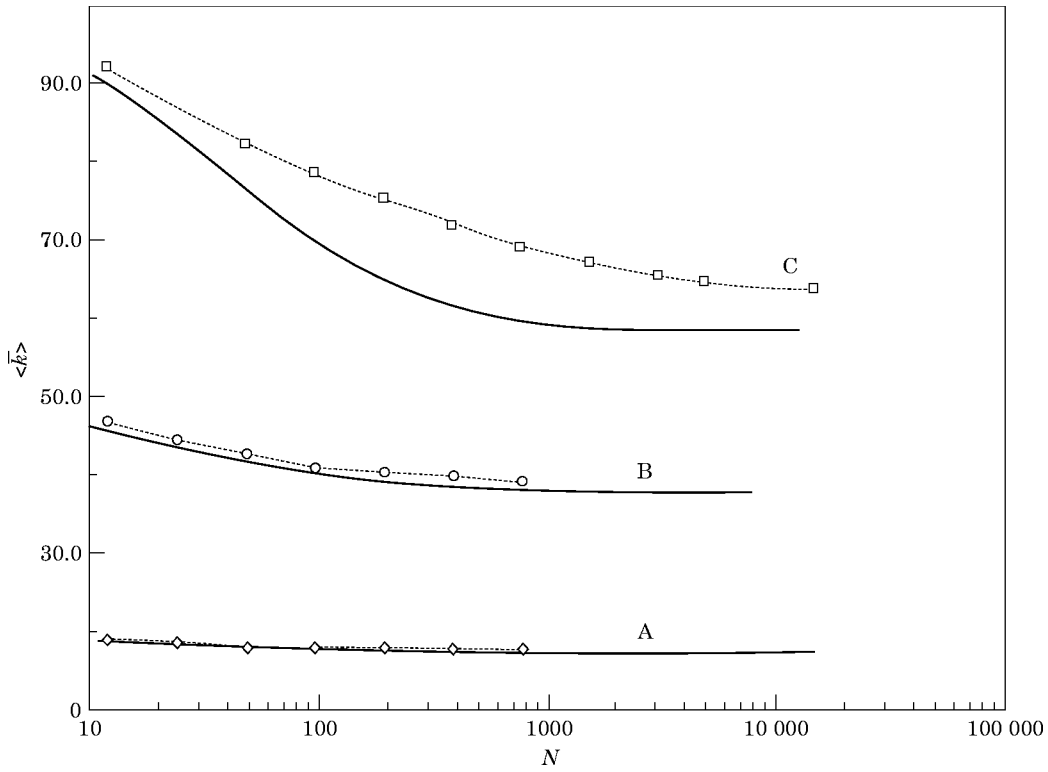

FIG. 2. Mean Hamming distance $\langle \overline{k} \rangle$ from the optimum sequence as a function of population size N, for $U = uL = 1.0$ and $s = 0.01$. Solid lines show the result of an approximate theory, and symbols show simulation results. (A) $L = 40$, (B) $L = 100$, (C) $L = 200$.

with their parent sequences, and again $\langle \overline{k} \rangle \to L/2$. In general we know that $\langle \overline{k} \rangle$ is an increasing function of u and a decreasing function of s, and we would like a theory to predict $\langle \overline{k} \rangle$ for any values of u and s.

The other important variable in the problem is the population size N. Selection can only work if there is a range of fitnesses in the population. If N is small all the sequences will be very similar, since they can all be traced back to a common ancestor at a time of order N generations in the past. The spread of fitnesses within the population will therefore be small if N is small, and hence selection will be less effective. We therefore expect that $\langle \overline{k} \rangle$ will increase if we decrease the size of the population. This is seen to be the case in Fig. 2, where we show $\langle \overline{k} \rangle$ as a function of N for three different values of L. We have chosen u so that $uL = 1$ in each case.

When $N \to \infty$ the problem becomes a deterministic one. The fraction C_j of the population having j unfavourable genes satisfies the following equation in the stationary state:

$$C_j = \frac{1}{W} \sum_{k=0}^{L} M_{jk}(1-s)^k C_k, \tag{2}$$

where the mean fitness W is given by

$$W = \sum_{k=0}^{L} (1-s)^k C_k, \tag{3}$$

and the probability of mutation from a sequence with k unfavourable genes to a sequence with j unfavourable genes is

$$M_{jk} = \sum_{i_{\min}}^{i_{\max}} \binom{k}{i} \binom{L-k}{j-k+i} u^{j-k+2i} (1-u)^{L-j+k-2i}. \tag{4}$$

In eqn (4) the index i represents the number of mutations from -1 to $+1$ genes, and the limits are $i_{\min} = \max(0, k-j)$, and $i_{\max} = \min(k, L-j)$. Equation (2) can be solved exactly by making the ansatz that C_k is a binomial distribution:

$$C_k = \binom{L}{k} a^k (1-a)^{L-k}. \tag{5}$$

By substituting into (2) we find that this is the correct solution, with the value of a given by

$$a = \tfrac{1}{2}((1-u+2u/s) - \sqrt{(1-u+2u/s)^2 - 4u/s}). \tag{6}$$

Examples of stationary C_k distributions in other fitness landscapes are given by Higgs (1994). For general choices of fitness landscapes it is usually necessary to solve the equivalent eqn (2) by numerical iteration. The particular choice of the multiplicative landscape makes an analytical solution possible.

From (5), the mean Hamming distance from the optimum sequence is $\langle \bar{k} \rangle = \Sigma\, kC_k = aL$, and the mean fitness is $W = (1 - as)^L$. If we suppose that $s \ll 1$, and $u \ll 1$, but that u/s may be of order 1, then the u terms in (6) are negligible, and a is just a function of u/s. If, in addition, $u/s \ll 1$, then $a \approx u/s$. If we take the limit $u \ll 1$, and $L \gg 1$, keeping $U = uL$ constant, then (5) becomes a Poisson distribution with $\langle \bar{k} \rangle = U/s$. The solution in this limit has already been given by several authors (Kimura & Maruyama, 1966; Haigh, 1978; Higgs, 1994). The other limit of (5) which is of interest is when $u = 1/2$, i.e. the replication procedure is completely random. In this case $a = 1/2$ independent of s, as is expected.

3. The Moments Equations

Having found an exact solution for $\langle \bar{k} \rangle$ for the infinite population, we will now obtain an approximate solution for finite N. The mean Hamming distance from the optimum sequence at a given generation is

$$\langle k \rangle = \frac{1}{N} \sum_i k_i, \tag{7}$$

where the sum is over all individuals in that generation, and k_i is the number of -1 genes in the ith individual. We may now define the time averaged values of the moments M_n of the distribution of the k_i as

$$M_n = \frac{1}{N} \overline{\sum_{i=1}^{N} (k_i - \langle k \rangle)^n}, \tag{8}$$

where the time average is to be taken after the ensemble average. We will use V for the variance of the distribution synonymously with M_2. It is possible to derive a set of equations relating each moment to the moment of next higher order. We have already given several of these equations for the problem of Muller's ratchet (Higgs & Woodcock, 1995). In the present case we require only the first two:

$$u(L - 2\langle \bar{k} \rangle) = (1 - 2u)sV, \tag{9}$$

$$sM_3 + (4u + 1/N)V = uL. \tag{10}$$

A derivation of these equations is given in the Appendix. It has been assumed that u, s and $1/N$ are all much less than 1. Here we have only two equations with three unknown quantities, $\langle \bar{k} \rangle$, V and M_3. Each higher order equation for the moments introduces a further unknown, so that no matter how many of these equations we calculate, we will always be forced to introduce an approximation to close the set of equations. One suitable closure approximation is the following. We know that in the limit $N \to \infty$, the distribution is binomial with $\langle \bar{k} \rangle = aL$, $V = a(1 - a)L$, and $M_3 = a(1 - a)(1 - 2a)L$. Hence for the infinite population we know that

$$M_3 = V(1 - 2\langle \bar{k} \rangle / L). \tag{11}$$

We will suppose that (11) is approximately true for finite N. Combination of (9), (10) and (11) gives a quadratic equation for $\langle \bar{k} \rangle$ which has the solution

$$\frac{\langle \bar{k} \rangle}{L} = \frac{1}{2}\left(\left(1 + \frac{2u}{s} + \frac{1}{2sN}\right) - \sqrt{\left(1 + \frac{2u}{s}\frac{1}{2sN}\right)^2 - \frac{4u}{s} - \frac{1}{sN}}\right). \tag{12}$$

We have neglected terms of small order in derivation of (9), (10) and (12), so that only ratios of small parameters appear in (12). If we take the limit $N \to \infty$, we obtain the result of (6), except that the u term is not given correctly, since we have already neglected terms of this order.

The prediction of eqn (12) is given in Fig. 2, in comparison to the simulation results. The agreement is not too bad for most cases, although the measured values for $L = 200$ are substantially higher than the prediction. We see from (12) that a finite population will behave like an infinite one only if $sN \gg 1$. If sN is of order one then $\langle \bar{k} \rangle$ is larger for the finite population that for the infinite one, and the mean fitness will be lower. This confirms what we stated qualitatively above: selection is less effective in small size populations, and the mean fitness decreases as the population size decreases.

4. The Strong Selection Limit

In deriving the moments equations it was assumed that selection was weak, i.e. $s \ll 1$. Figure 3 shows the simulation results of $\langle \bar{k} \rangle$ as a function of u for larger s values. It can be seen that as $s \to 1$, the curves tend to a limiting form. Suppose that $k_{\min}$ is the number of unfavourable genes on the sequence which has the

highest fitness within the population at a given generation. There will typically be more than one individual with $k_{\min}$ unfavourable genes, but the sequences of these individuals may differ, even though they have the same fitness. In the strong selection limit the fitness of these individuals will be so much larger than that of individuals with a higher k that only these individuals will have offspring. Let us suppose that $k_{\min} = 0$, i.e. that there is at least one individual with the optimum sequence. All individuals at the next generation will be descended from parents which had the optimum sequence. Hence the expected number of individuals N_k with k unfavourable genes is

$$N_k = N\binom{L}{k}u^k(1-u)^{L-k}. \tag{13}$$

Note that the expected values of the N_k at the next generation are independent of the value of N_0 at the parent generation, provided N_0 is at least 1. As long as $N(1-u)^L > 1$, N_0 will almost always be at least 1, and it is valid to assume that $k_{\min} = 0$. In this case from (13) we obtain $\langle \overline{k} \rangle = uL$. In Fig. 3 the data for the large s values are seen to lie on this straight line at small u values. At higher u, $\langle \overline{k} \rangle$ increases above this line, and there is a bend in the curve close to the value $u = u_c$, where $N(1-u_c)^L = 1$. For $u > u_c$ the optimum sequence is not always present in the population. This argument is very similar to that given by Bonhoeffer & Stadler (1993), in their discussion of error thresholds in finite populations. For finite populations, however, there is no true singularity in the curve of $\langle \overline{k} \rangle$ vs. u, and hence u_c is not defined precisely. We prefer only to use the term error threshold for infinite population models where there is a singularity (e.g. Eigen *et al*., 1989; Higgs, 1994). Nevertheless, we see that there are two types of behaviour in this model with finite N. At small u the optimum sequence is almost always present, and at larger u the fittest sequence varies from one generation to the next, and is usually not the optimum sequence.

Let $f(k_{\min})$ be the probability that the fittest individual at any given generation has $k_{\min}$ unfavourable genes. In the strong selection limit all the

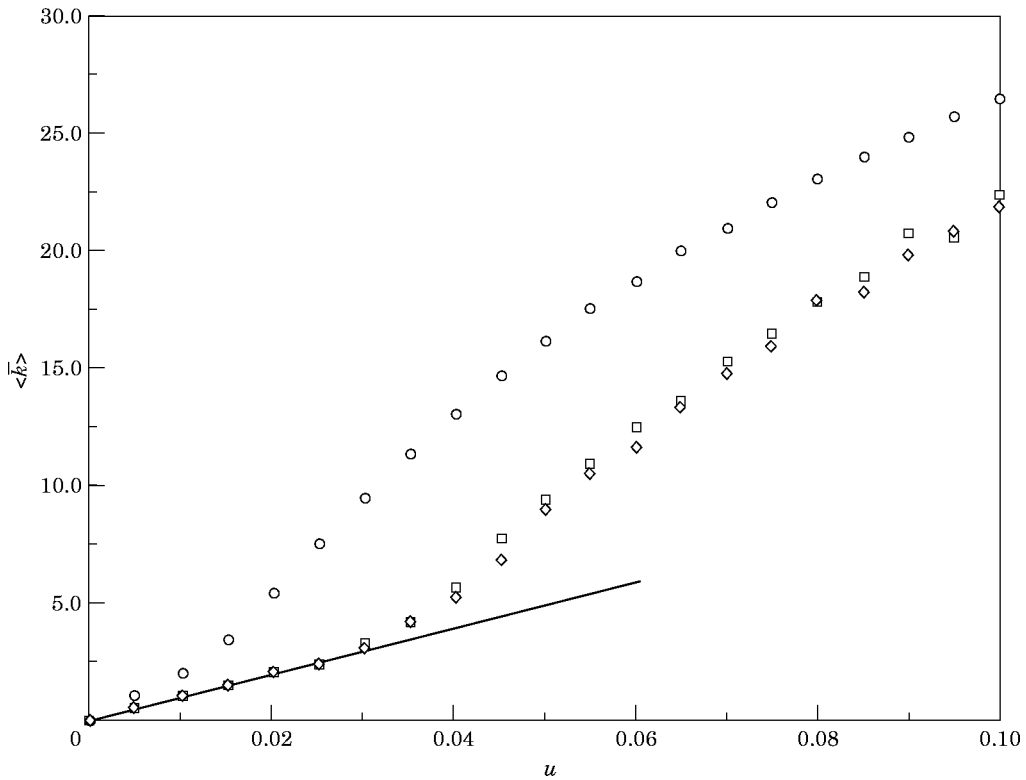

FIG. 3. Mean Hamming distance $\langle \overline{k} \rangle$ from the optimum sequence as a function of mutation rate u, for $N = 100$, and $L = 100$. Symbols indicate simulation results. Circles $s = 0.5$, Squares $s = 0.95$, Diamonds $s = 0.99966$. The curves tend to a limit as s tends to 1. The limiting curve lies on the line $\langle \overline{k} \rangle = uL$ for u less than $u_c \approx 0.03$, indicating that the population is localized close to the optimum sequence for $u \leqslant u_c$.

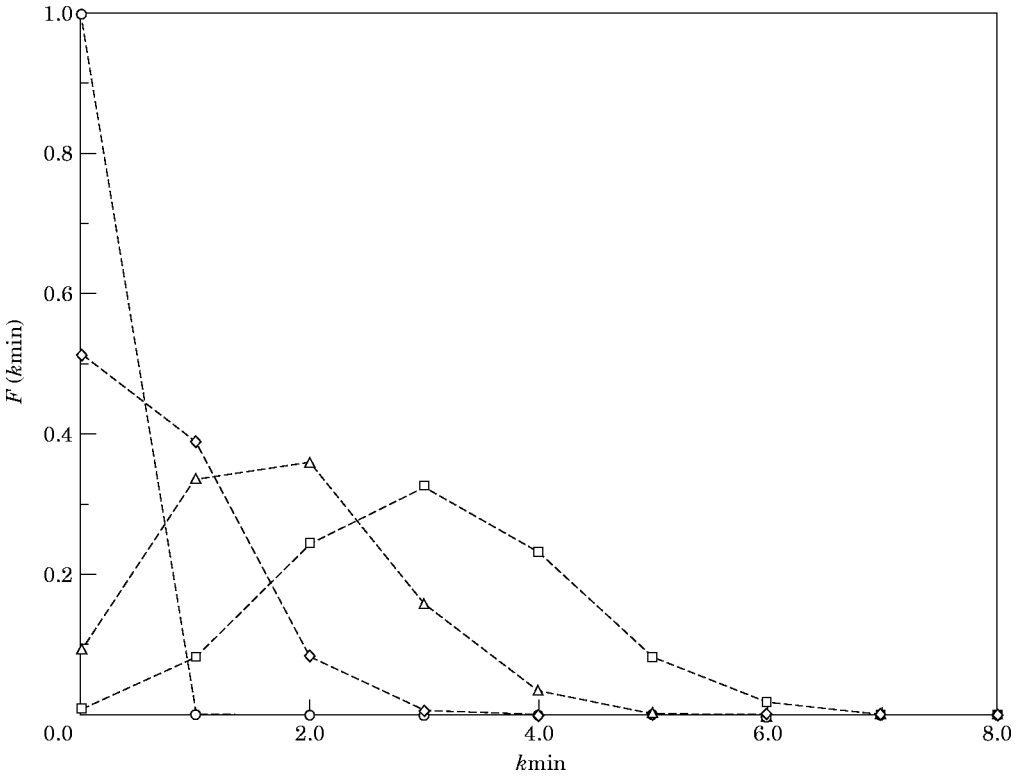

FIG. 4. The probability $F(k_{\min})$ that the fittest individual in the population has $k_{\min}$ unfavourable genes, calculated for $N = 100$ and $L = 100$, in the limit s tends to 1. Circles $u = 0.025$, Diamonds $u = 0.035$, Triangles $u = 0.04$, Squares $u = 0.045$. At $u = 0.025$ the optimum sequence is almost always present, and at $u = 0.045$ it is almost never present.

parents have $k = k_{\min}$, hence the mean value of k in the next generation will be

$$\sum_{k=0}^{L} kM_{k,k_{\min}} = k_{\min} + u(L - 2k_{\min}). \tag{14}$$

The mutation matrix $M_{k,k_{\min}}$ is that given in eqn (4). The time averaged value $\langle \bar{k} \rangle$ is therefore given by

$$\langle \bar{k} \rangle = \sum_{k_{\min}=0}^{L} f(k_{\min})(k_{\min} + u(L - 2k_{\min})), \tag{15}$$

and it just remains to calculate $f(k_{\min})$. The probability $P(k, j_{\min})$ that an individual has at least k unfavourable genes in the sequence, given that its parent had $j_{\min}$ unfavourable genes is

$$P(k, j_{\min}) = \sum_{i=k}^{L} M_{i,j_{\min}}. \tag{16}$$

The probability that all the individuals in the new generation have at least k unfavourable genes is therefore $P(k, j_{\min})^N$, and the probability that the fittest individual in the new generation has exactly $k_{\min}$ unfavourable genes is

$$A_{k_{\min}, j_{\min}} = P(k_{\min}, j_{\min})^N - P(k_{\min} + 1, j_{\min})^N. \tag{17}$$

The distribution of $k_{\min}$ must satisfy

$$f(k_{\min}) = \sum_{j_{\min}} A_{k_{\min}, j_{\min}} f(j_{\min}). \tag{18}$$

We have now reduced the original stochastic problem to a deterministic problem: that of finding the stationary solution of (18). We have found $f(k_{\min})$ numerically by iterating the equation until the distribution converges. Having done this $\langle \bar{k} \rangle$ is obtained from (15). We have checked that the curve of $\langle \bar{k} \rangle$ against u obtained by this method is the same as that obtained by simulation of the original model in the strong selection limit.

The approximate argument above suggests that u_c is the solution of $N(1 - u_c)L = 1$. For $N = 100$ and $L = 100$ gives $u_c = 0.045$. The data in Fig. 3 seem to move away from the straight line slightly before this ($u = 0.03$–0.035). In Fig. 4 we show the calculated curves $f(k_{\min})$ for four values of u in this range. We see that for $u = 0.025$ the optimum sequence is almost always present, and at $u = 0.045$ it is almost never

present. For intermediate values the optimum sequence is present some of the time. The population thus gradually escapes from the optimum over a range of u values.

5. Time Correlation of Gene Sequences

If σ_i^α represents the i^{th} gene on individual α (which may be either $+1$ or -1), then one way of measuring the correlation between two individuals α and β is to use the overlap $q^{\alpha\beta} = 1/L \sum_i \sigma_i^\alpha \sigma_i^\beta$. Two identical sequences have $q^{\alpha\beta} = 1$, whilst two completely uncorrelated sequences have $q^{\alpha\beta} = 0$. In this section we are interested in the mean overlap $Q(t)$ between sequences at a given generation and sequences t generations later.

$$Q(t) = \frac{1}{N^2 L} \overline{\sum_\alpha \sum_\beta \sum_i \sigma_i^\alpha(t') \sigma_i^\beta(t+t')} \qquad (19)$$

Here, the sum over α represents a sum over all individuals at a time t', and the sum over β represents a sum over all individuals at a time $t' + t$. The overbar indicates a time average over all t'. We assume that the population has reached the steady state and that the correlation between two generations only depends on the time t between them.

In the neutral limit, $s = 0$, it is easy to show that $Q(t) = Q_0(1-2u)^t$ (which is approximately $Q_0 \exp(-2ut)$ for small u), where the mean overlap between two individuals at the same generation is $Q_0 = 1/(1+4uN)$ (see Derrida & Peliti, 1991; Higgs & Derrida, 1991, 1992). We have measured $Q(t)$ by simulation for non zero s. Figure 5 shows that the results may be well fitted by a function of the form

$$Q(t) = Q_\infty + (Q_0 - Q_\infty)\exp(-2ut). \qquad (20)$$

It can be seen that although both Q_0 and Q_∞ change with s, the rate of decay appears to be equal to $2u$ independent of s. The value of Q_∞ is easy to calculate. Suppose that individuals α and β have k_α and k_β -1s in their sequences. If the two individuals are widely separated in time then the positions of the -1s within the sequence will not be correlated, so that $q^{\alpha\beta} = (1/L^2)(k_\alpha k_\beta + (L-k_\alpha)(L-k_\beta) - k_\alpha(1-k_\beta) - k_\beta(1-k_\alpha))$. Taking an average of this equation gives

$$Q_\infty = 1 - 4\frac{\langle k \rangle}{L}\left(1 - \frac{\langle k \rangle}{L}\right). \qquad (21)$$

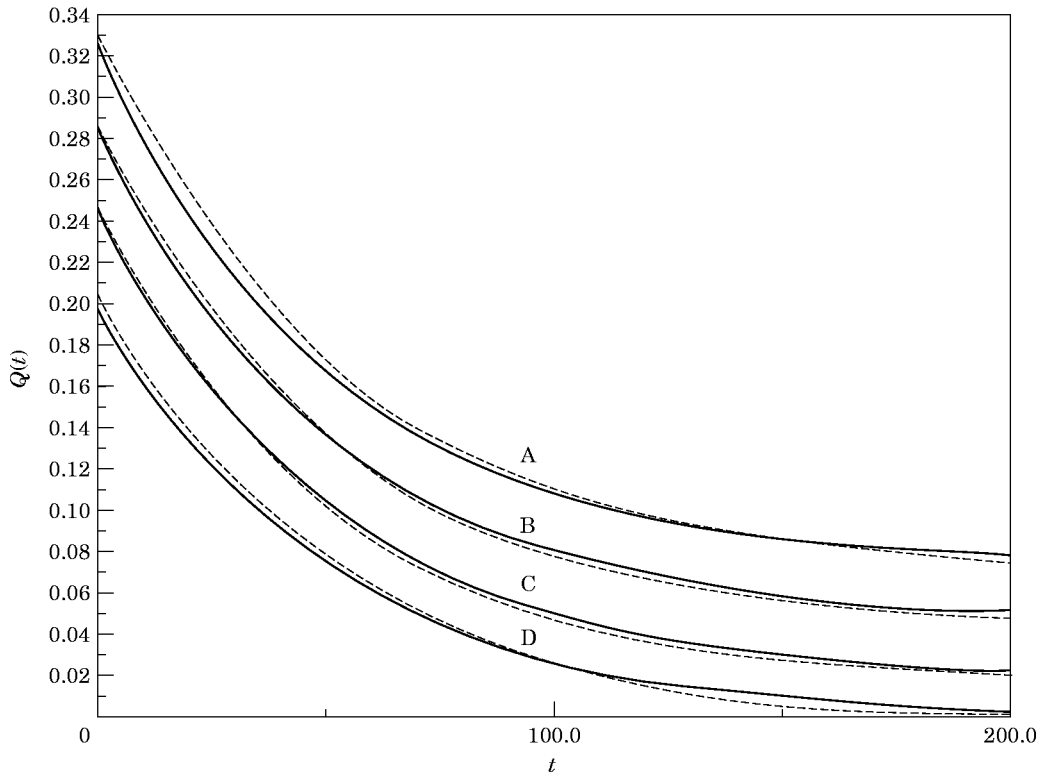

FIG. 5. The overlap function $Q(t)$ shown for $N = 100$, $L = 100$, and $u = 0.01$. Dashed lines show simulation results, and solid lines show best fits of the data to the exponential formula given in the text. (A) $s = 0.02$, (B) $s = 0.014$, (C) $s = 0.01$, (D) $s = 0.0$.

Thus Q_∞ depends only on the already known value of $\langle \overline{k} \rangle$.

If the population is in the steady state and u is sufficiently large so that the population has moved away from the optimum, most of the individuals have k close to $\langle \overline{k} \rangle$. The population is thus to be found within a spherical shell at Hamming distance $\langle \overline{k} \rangle$ from the optimum sequence. Since the population is finite, and since all individuals are related by common ancestry, not all of the sequences at this Hamming distance from the optimum will be found. The whole of the population will be clustered together on "one side" of the optimum. The population will wander around the shell at random. Q_∞ is just the overlap between two randomly chosen points on this spherical shell. In the neutral case $\langle \overline{k} \rangle = L/2$, therefore $Q_\infty = 0$.

We have not found a simple argument for Q_0. This is the mean overlap between two individuals at the same generation. As s is increased the probability that two individuals have a common ancestor in a recent generation increases, and the mean time since any two individuals had a common ancestor decreases. This means that the overlap will increase, as is seen in the simulations. The problem can be solved exactly for the neutral case (Derrida & Peliti, 1991; Higgs & Derrida, 1991, 1992; Higgs, 1995), but when selection is present an analytical solution is much more difficult. We have studied the distribution of times since the existence of common ancestors in more detail for the problem of Muller's ratchet (Higgs & Woodcock, 1995), and we expect a similar type of behaviour in this problem.

We have seen that the rate of the exponential decay in (20) appears to be independent of s. In other words, the rate of evolution within the spherical shell in sequence space does not depend on the radius of the shell. Although we have no strong argument as to why this is the case, we will now discuss a simplified toy model where $Q(t)$ can be calculated exactly, and shown to be of the form (20).

In the toy model there is just one sequence at each moment in time, and this has exactly $K = \langle \overline{k} \rangle$ genes which are -1 and L–K genes which are $+1$. Time proceeds by iterations. At each iteration two genes are picked at random on the sequence and their values are interchanged. If a given gene is $+1$, the probability that it changes to -1 is the probability that it is picked, and that the other gene picked is a -1. Thus the probability that it changes is $2K/L(L-1)$. If a gene is -1 the probability that it changes is $2(L-K)/L(L-1)$. If both the genes picked have the same sign then there is no change to the sequence on that iteration. Let $p^{++}(n)$ be the probability that a gene is $+1$ at iteration n, given that it was $+1$ initially, and let $p^{+-}(n)$ be the probability that it is -1 at iteration n, given that it was $+1$ initially. These probabilities satisfy the recursion

$$\begin{pmatrix} p^{++}(n+1) \\ p^{+-}(n+1) \end{pmatrix} = \begin{pmatrix} 1 - \dfrac{2K}{L(L-1)} & \dfrac{2(L-K)}{L(L-1)} \\ \dfrac{2K}{L(L-1)} & 1 - \dfrac{2(L-K)}{L(L-1)} \end{pmatrix} \times \begin{pmatrix} p^{++}(n) \\ p^{+-}(n) \end{pmatrix}. \quad (22)$$

This matrix has eigenvalues 1 and $1 - 2/(L-1)$. Using the initial condition $p^{++}(0) = 1$, we obtain the solution

$$\begin{pmatrix} p^{++}(n) \\ p^{+-}(n) \end{pmatrix} = \begin{pmatrix} (L-K)/L \\ K/L \end{pmatrix} + (1 - 2/(L-1))^n \begin{pmatrix} K/L \\ -K/L \end{pmatrix}. \quad (23)$$

In a similar way we can calculate the functions $p^{-+}(n)$ and $p^{--}(n)$, which are the probabilities of a gene being $+1$ or -1, given that it was -1 initially. The mean overlap between the sequence at iteration n and the initial sequence is

$$\begin{aligned} \mathbf{Q}(n) &= (1 - K/L)(p^{+}{+}(n) - p^{+-}(n)) \\ &\quad + K/L(p^{--}(n) - p^{-+}(n)) \\ &= 1 - \frac{4K}{L}\left(1 - \frac{K}{L}\right) \\ &\quad + (1 - 2/(L-1))^n \frac{4K}{L}\left(1 - \frac{K}{L}\right). \end{aligned} \quad (24)$$

If $L \gg 1$ then $(1 - 2/(L-1))^n \approx \exp(-2n/L)$. We now wish to equate the time represented by one iteration in the toy model to the mean time between mutations in the real model. Since there are an average of uL mutations per generation per sequence in the real model, the mean time between mutations is $1/uL$. Hence $\exp(-2n/L) = \exp(-2ut)$, and (24) is exactly of the form (20) which was found for the real model. In the toy model $Q_0 = 1$ since there is only one sequence, whereas for the real model $Q_0 < 1$. Q_∞ is the same in both models. In the toy model the eigenvalues of the matrix are not dependent on K, and this means that the exponential decay rate is independent of Q_0 and Q_∞ as observed in the real model. This was our

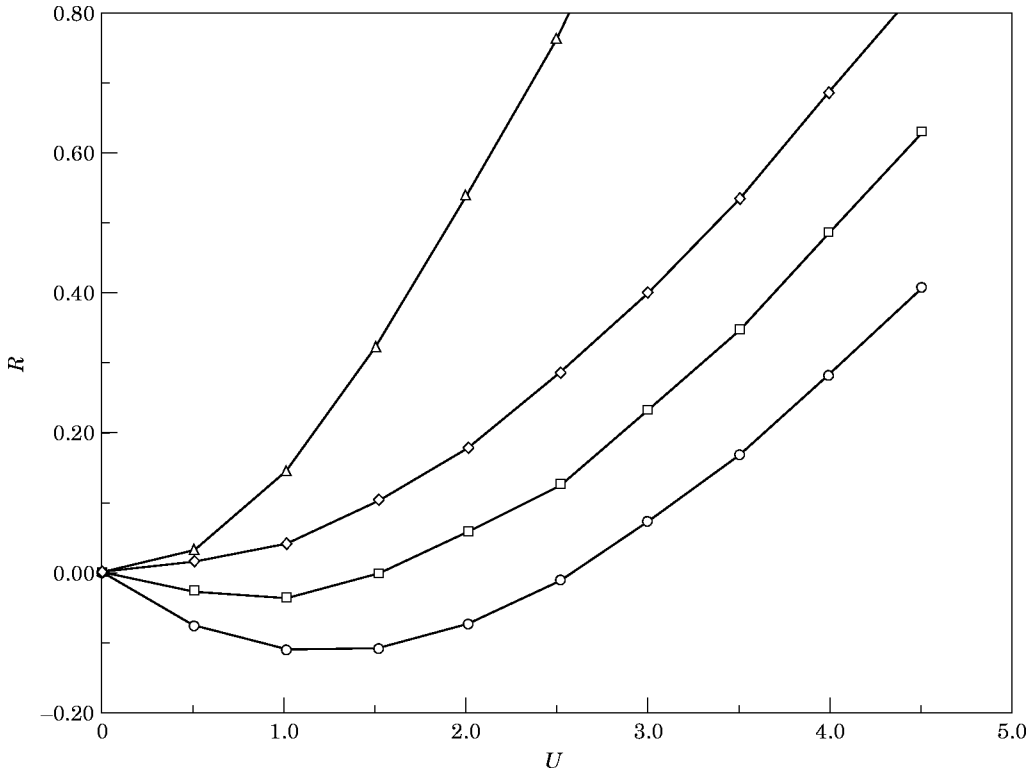

FIG. 6. The rate of accumulation of mutations R shown as a function of U for several values the fraction p of favourable mutations. Positive R means decreasing fitness, and negative R means increasing fitness. R is always positive for $p < p_c$, whilst for $p > p_c$ R is negative at small U. These curves are simulation results with $N = 100$ and $s = 0.2$. The values of p are 0.0 (triangles), 0.1 (diamonds), 0.12 (squares) and 0.14 (circles). The critical value p_c lies between 0.1 and 0.12.

main reason for introducing the toy model in this section.

6. Behaviour of the Model far from Equilibrium

Up to now we have mostly been studying properties of the model in the steady state. In this section we will consider the rate of approach of $\langle k \rangle$ towards its equilibrium steady state value, beginning at a value far from equilibrium. We will simplify the model slightly by assuming that $L \gg 1$, and that $U = uL$ is a constant of order 1. In this way L drops out of the problem. Suppose that the mean Hamming distance from the origin is $\langle k \rangle$ at a given time. The probability that a mutation leads to an increase in fitness is $p = \langle k \rangle / L$. The probability that m mutations occur in one generation is a Poisson distribution $U^m / m! \exp(-U)$, and each mutation either decreases k by one with probability p, or increases k by one with probability $1 - p$. If $p = 0$ then we have the familiar model for Muller's ratchet (Higgs & Woodcock, 1995). This model is much easier to simulate than the original model for finite L, since we do not need to store the whole gene sequence for an individual. It is sufficient to store a value k for each individual in order to calculate the fitness of an individual relative to the other members of the population, and hence to determine the multiplication rates of the different individuals. When doing simulations of this model we suppose that $\langle k \rangle$ and L are so large that $\langle k \rangle$ may change without altering p significantly. This means that $\langle k \rangle$ will change at a constant rate for a given p. (If L were finite then the rate of change of $\langle k \rangle$ would decrease as $\langle k \rangle$ approached its steady state value).

Thus, in the simplified model with infinite L, the relevant parameters are U, p, s and N, and we wish to calculate $R = d\langle k \rangle / dt$ as a function of these parameters. Positive R means that the population is moving away from the optimum, and decreasing in fitness, as in the usual model of Muller's ratchet, whilst negative R means that the population is increasing in fitness. Figure 6 shows values of R measured by simulation as a function of U for several different values of p (with s and N kept constant). This figure is reminiscent of a second order phase transition. For p less than a critical value p_c, R is positive for all U, and R increases with U. In this example p_c is close to 0.11, but it will vary with N and s. For $p_c < p < 1/2$, R is negative at small values of U, passes through a minimum at an intermediate

value of U, and becomes positive at large U. For $p > 1/2$, R is always negative.

The region $p > 1/2$ makes little sense, since this would mean that the population was actually less fit than a random sequence. There is no reason why a population should ever have got into this situation. The other two cases are more realistic. If $p < p_c$ the population is already rather close to the fitness maximum, and most mutations are unfavourable. It therefore pays to have as few mutations as possible. In this case natural selection will tend to cause a reduction in the mutation rate, and to favour species with lower mutation rates. On the other hand, if $p_c < p < 1/2$, there is an optimum mutation rate at which the fitness increases most rapidly, and natural selection will tend to cause an increase in the mutation rate if it is too small.

7. Discussion

When discussing the theory of evolution in a given fitness landscape it is important to remember that evolution works with populations of a finite number of individuals. At any one time the population "sees" only a small fraction of the fitness landscape. Natural selection can only act upon the sequences which are present in the population. Since all sequences in an asexual population can eventually be traced back to a single common ancestor, all the sequences are related to each other. The whole population is clustered together in a particular region of sequence space. The cluster increases in size as the population size increases, so that there is a larger spread of fitness values in a larger population. Larger populations therefore tend to respond more rapidly to selective pressure, and to achieve higher mean fitnesses in the steady state. Another way of saying this is that random drift in sequence space is less important for larger populations.

We wish to emphasize that finite and infinite populations can behave qualitatively differently. For the case $L \to \infty$ there is a perfectly stable concentration distribution C_k if the population is infinite, but for a finite population Muller's ratchet sets in, and the fitness decreases indefinitely. For finite L, both finite and infinite populations reach a steady state. Equation (12) shows that the mean Hamming distance from the origin for a finite population may only be slightly higher than for an infinite one if sN is quite large. Hence the mean fitness may only be slightly lower. However, the two situations are qualitatively different. The total frequency of all sequences at Hamming distance k from the optimum sequence is given in (5) for the infinite population. The frequency of each individual sequence is therefore $a^k(1-a)^{L-k}$. Since $a < 1/2$, the single sequence with the highest frequency is always the optimum sequence, even if $\langle \bar{k} \rangle \gg 1$. For a finite population with $\langle \bar{k} \rangle \gg 1$, the optimum sequence will typically not be present at all, and the sequence with the highest frequency will have k close to $\langle \bar{k} \rangle$. In an infinite population the frequency of each sequence remains constant once a steady state is reached. For a finite population the steady state is dynamic, and evolution of the sequence continues to occur. In the multiplicative landscape the population becomes confined to a spherical shell in sequence space at Hamming distance close to $\langle \bar{k} \rangle$ from the optimum. The behaviour of the overlap function $Q(t)$ shows that the population wanders at random around this spherical shell. Wagner & Krall (1993) have also highlighted the difference between finite and infinite populations. Other studies of models where the finite population size is important include Nowak & Schuster (1989), Bonhoeffer & Stadler (1994), and Wiehe *et al*. (1995).

Section 6 of this article makes the link between the model studied here and our previous work on Muller's ratchet. The fraction p of mutations which are favourable depends on the distance of the population from the fitness peak. A population initially very close to the optimum will move away from it, whilst a population initially far from the optimum will approach it. In our simplification, we took p to be constant, and hence the rate of change of k was constant. We saw that for certain values of p there is an optimum value of U for which the rate of increase of fitness is largest. The question therefore arises as to whether it is better to have as small a mutation rate as possible, or whether there is some non-zero mutation rate which is preferable.

Clearly, if the fitness landscape is unchanging, and if the population is already close to the optimum in the landscape, then it is preferable to reduce the mutation rate as much as possible. In general the steady state mean fitness is higher for smaller u, whatever the shape of the landscape. In the simple single peaked landscape studied here, it is easy for the population to find the optimum sequence, since selection is always acting towards the optimum. For a general rugged landscape, however, there may be many local optima. A population with a small mutation rate is likely to become trapped in a rather poor local optimum, whereas a population with a higher mutation rate may avoid becoming trapped on the lower peaks, and might find a local optimum with a higher fitness. If the mutation rate is extremely low then the population will almost all be clustered on a

single sequence. The population will therefore behave like an adaptive walk (Kauffman & Levin, 1987; Macken *et al*., 1991; Flyvbjerg & Lautrup, 1992). It is known that adaptive walks usually end up on local optima far below the global optimum. For reasonable values of u there will always be a substantial degree of variation within the population, and hence real populations will probably be far from the adaptive walk limit.

The fitness landscape of a real biological species is likely to change over time, either due to changes in the environment or due to co-evolution of other interacting species. If the fitness landscape is changing in time, the population may not succeed in finding the high fitness regions, even in a relatively smooth fitness landscape. The population for ever tries to climb uphill, but it never succeeds in increasing its fitness, since although new favourable mutations are continually occurring, other genes which were previously advantageous are becoming disadvantageous. In a changing landscape it is clearly an advantage to have a non-zero mutation rate, in order to keep up with the changes. If the landscape is very rugged, the problem of trapping in local optima may be less severe if the landscape changes with time: what was a peak will eventually become a hillside, and the population will escape. Thus there are both advantages and disadvantages for the population if the landscape is changing.

In finite populations, stochastic effects must be taken into account. This makes the problem much more difficult to treat mathematically than for infinite populations. We have used a very simple smooth single-peaked landscape here, so that at least an approximate analytical theory can be given. This is a starting point for a theory of the evolution of finite populations in rugged fitness landscapes. We have seen that in this case the population remains within a spherical shell in sequence space once the steady state is reached. Evolution within this shell is effectively neutral since the mean fitness of the sequence does not change. In a rugged landscape we might expect something similar to occur. The population is likely to remain in a band of sequence space at a certain distance below the peaks, and evolve in a quasi neutral fashion within this band. The long-term behaviour will depend on whether these regions are percolating through the whole of sequence space or confined to isolated islands (see Kauffman, 1993 Chapter 3, and Amitrano *et al*., 1989). To obtain a mathematical theory of this behaviour is an important goal for future work.

REFERENCES

Amitrano, C., Peliti, L. & Saber, M. (1989). Population dynamics in a spin-glass model of chemical evolution. *J. Mol. Evol*. **29,** 513.

Bonhoeffer, S. & Stadler, P. F. (1993). Error thresholds on correlated fitness landscapes. *J. theor. Biol*. **164,** 359–372.

Charlesworth, D., Morgan, M. T. & Charlesworth, B. (1993). Mutation accumulation in finite outbreeding and inbreeding populations. *Genet. Res. (Camb)*. **61,** 39–56.

Derrida, B. & Peliti, L. (1991). Evolution in a flat fitness landscape. *Bull. Math. Biol*. **53,** 355–382.

Eigen, M., McCaskill, J. & Schuster, P. (1989). The molecular quasispecies. *Adv. Chem. Phys*. **75,** 149–263.

Flyvbjerg, H. & Lautrup, B. (1992). Evolution in a rugged fitness landscape. *Phys. Rev. A*. **46,** 6714–6718.

Fontana, W., Stadler, P. F., Bornberg-Bauer, E. G., Griesmacher, T., Hofacker, I. L., Tacker, M., *et al*. (1993). RNA folding and combinatory landscapes. *Phys. Rev. E* **47,** 2083–2099.

Gabriel, W., Lynch, M. & Bürger, R. (1993). Muller's ratchet and mutational meltdowns. *Evolution* **47,** 1744–1757.

Haigh, J. (1978). The accumulation of deleterious genes in a population—Muller's ratchet. *Theor. Pop. Biol*. **14,** 251–267.

Higgs, P. G. (1994). Error thresholds and stationary mutant distributions in multi-locus diploid genetics models. *Genet. Res. (Camb)* **63,** 63–78.

Higgs, P. G. (1995). Frequency distributions in population genetics parallel to those in statistical physics. *Phys. Rev. E*. **51,** 95–101.

Higgs, P. G. & Derrida, B. (1991). Stochastic models for species formation in evolving populations. *J. Phys. A (Math. & Gen.)* **24,** L985–L991.

Higgs, P. G. & Derrida, B. (1992). Genetic distance and species formation in evolving populations. *J. Mol. Evol*. **35,** 454–465.

Higgs, P. G. & Woodcock, G. (1995). The accumulation of mutations in asexual populations and the structure of genealogical trees in the presence of selection. *J. Math. Biol*. **33,** 677–702.

Kauffman, S. A. (1993). *The Origins of Order*. Oxford: Oxford University Press.

Kauffman, S. A. & Levin, S. (1987). Towards a general theory of adaptive walks on rugged landscapes. *J. theor. Biol*. **128,** 11–45.

Kauffman, S. A. & Weinberger, E. D. (1989). The NK model of rugged fitness landscapes and its application to maturation of the immune response. *J. theor. Biol*. **141,** 211–245.

Kimura, M. & Maruyama, T. (1966). The mutational load with epistatic gene interactions in fitness. *Genetics* **54,** 1337–1351.

Lynch, M. & Gabriel, W. (1990). Mutation load and the survival of small populations. *Evolution* **44,** 1725–1737.

Lynch, M., Bürger, R., Butcher, D. & Gabriel, W. (1993). The mutational meltdown in asexual populations. *J. Hered*. **84,** 339–344.

Macken, C. A., Hagan, P. S. & Perelson, A. S. (1991). Evolutionary walks on rugged landscapes. *SIAM J. Appl. Math*. **51,** 799–827.

Maynard Smith, J. (1978). *The Evolution of Sex*. Cambridge: Cambridge University Press.

Nowak, M. & Schuster, P. (1989). Error thresholds of replication in finite populations, mutation frequencies, and the onset of Muller's ratchet. *J. theor. Biol*. **137,** 375–395.

Schuster, P. (1986). Dynamics of molecular evolution. *Physica D* **22,** 100–119.

Stephan, W., Chao, L. & Smale, J. G. (1993). The advance of Muller's ratchet in a haploid asexual population: approximate solutions based on diffusion theory. *Genet. Res. (Camb)* **61,** 225–231.

Tarazona, P. (1992). Error thresholds for molecular quasispecies as phase transitions: From simple landscapes to spin-glass models. *Phys. Rev. A*. **45,** 6038–6050.

WAGNER, G. P. & GABRIEL, W. (1990). Quantitative variation in finite parthenogenic populations: what stops Muller's ratchet in the absence of recombination? *Evolution* **44,** 715–731.
WAGNER, G. P. & KRALL, P. (1993). What is the difference between models of error thresholds and Muller's ratchet. *J. Math. Biol.* **32,** 33–44.
WEINBERGER, E. D. (1991). Local properties of Kauffman's NK model: A tunably rugged landscape. *Phys. Rev. A* **44,** 6399–6413.
WEINBERGER, E. D. & STADLER, P. (1993). Why some fitness landscapes are fractal. *J. theor. Biol.* **163,** 255–275.
WIEHE, T., BAAKE, E. & SCHUSTER, P. (1995). Error propagation in reproduction of diploid organisms. *J. theor. Biol.* **177,** 1–15.

APPENDIX

Here we will derive the moments equations used in Section 3. Consider an individual i with k_i unfavourable genes. Suppose that its offspring has $j = k_i + m_i$ unfavourable genes. The expectation values of m_i and m_i^2 are

$$E(m_i) = \sum_j (j - k_i) M_{j,k_i} = u(L - 2k_i), \quad \text{(A. 1)}$$

$$E(m_i^2) = \sum_j (j - k_i)^2 M_{j,k_i} = u(1-u)L + u^2(L - 2k_i)^2. \quad \text{(A. 2)}$$

Now consider two individuals i and j having fitnesses w_i and w_j. The probability that these individuals have n_i and n_j offspring in the next generation is

$$(n_i, n_j) = \frac{N!}{n_i! n_j! (N - n_i - n)!} \times x_i^{n_i} x_j^{n_i} (1 - x_i - x_j)^{N - n_i - n_j}, \quad \text{(A. 3)}$$

where $x_i = w_i / N\langle w \rangle$, and $\langle w \rangle$ is the mean fitness of the population at that generation. From this we obtain

$$E(n_i) = N x_i \approx 1 - s(k_i - \langle k \rangle), \quad \text{(A. 4)}$$

$$E(n_i^2) = N^2 x_i^2 + N x_i (1 - x_i) \approx 2 - 1/N - 3s(k_i - \langle k \rangle), \quad \text{(A. 5)}$$

$$E(n_i n_j) = N(N-1) x_i x_j \approx 1 - 1/N - s(k_i - \langle k \rangle) - s(k_j - \langle k \rangle). \quad \text{(A. 6)}$$

Here we assume that $s \ll 1$, and only work to first order is s, so that $\langle w \rangle \approx 1 - s\langle k \rangle$. Suppose j is an individual at generation $t+1$, and $G(j)$ is its parent at generation t; then clearly $k_j = k_{G(j)} + m_{G(j)}$, where $m_{G(j)}$ is the number of new mutations in individual j. Averaging this equation gives

$$\overline{\langle k \rangle_{t+1}} = \frac{1}{N} \overline{\sum_j k_{G(j)} + m_{G(j)}} = \frac{1}{N} \overline{\sum_i n_i (k_i + m_i)}. \quad \text{(A. 7)}$$

The sum over j indicates the average of the parents of generation $t+1$. This has been replaced by a sum over i, representing a sum over individuals in generation t, and we count each one n_i times. In this model the k_i and the m_i are correlated as in (A. 1) and (A. 2). In our previous derivation of these equations for the Muller's ratchet problem (Higgs & Woodcock, 1995) this was not the case. Now making use of (A. 1) and (A. 4) we have

$$\overline{\langle k \rangle_{t+1}} = \frac{1}{N} \overline{\sum_i (k_i + u(L - 2k_i))(1 - s(k_i - \langle k \rangle))} = uL + (1 - 2u)(\overline{\langle k \rangle_t} - sV). \quad \text{(A. 8)}$$

In the stationary state $\langle \overline{k} \rangle$ is independent of time, and (A. 8) becomes equation (9). To obtain the second of the moments equations we need to evaluate

$$\overline{\langle k^2 \rangle_{t+1}} = \frac{1}{N} \overline{\sum_i n_i (k_i + m_i)^2} \quad \text{(A. 9)}$$

and

$$\overline{\langle k \rangle_{t+1}^2} = \frac{1}{N^2} \overline{\sum_i \sum_j n_i n_j (k_i + m_i)(k_j + m_j)}, \quad \text{(A. 10)}$$

which can be done using (A. 1)–(A. 6). Finally, subtracting these gives V, and assuming that we are in the stationary state gives eqn (10).