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Evolution on a Smooth Landscape: The Role of Bias

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The role of mutational bias in evolution on a smooth landscape is investigated. We consider both a finite-length genome where the bias increases linearly with the fitness, and an infinite genome with a fixed bias. We present simulations of finite populations in a waiting time model, showing both the nonequilibrium dynamics and the equilibrium fitness distributions that are reached. We compute the equilibrium analytically in several cases, using approximate direct solution of the master equations and truncated hierarchies.

KEY WORDS: Evolution; birth/death processes; mean-field; population dynamics.

1. INTRODUCTION

Motivated by results on RNA virus evolution in a controlled laboratory setting,[1] we recently introduced a simple model of evolution on a smooth fitness landscape.[2, 3] Specifically, we studied a continuous time Markov process involving birth events (proportional to an individual's fitness), a compensating uniform death rate and mutations which change the fitness of descendants by ± 1. In addition to naturally explaining some of the striking experimental findings, this model also offers some important insights on appropriate analytic strategies for dealing with evolutionary dynamics. The essential observation is the complete breakdown of mean field theory (aka the Eigen–Schuster[4] reaction kinetics approach) at any finite value of the population size N. Instead, the dynamics is controlled by fluctuations near the "leading-edge," as mutants with improved fitness must rely on chance to become fixed in the population before being killed.

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In this work, we extend our previous analysis to include the effects of bias in the mutation process. By bias, we mean the fact that it might be more likely for the aforementioned mutational event to change the fitness in one direction as opposed to the other. Bias can arise from two different causes. First, it might be the case that it is easier to damage a gene (for example) then to improve it. So, if we interpret the fitness change in our model as being due to an allele change in one gene (contributing in an additive fashion), any *intrinsic* bias in gene improvement versus gene degradation shows up as *fitness-independent* bias in our model.

There is a second possible source of bias in a fitness-space model. To see this, let us focus on the concrete example of a "genome" consisting of L "genes" taking the values 0 or 1, with fitness taken to be just the sum of those values. Intrinsic bias would mean that the probability of flipping any specific "bit" from 0 to 1 is different than from 1 to 0. Even if this is not the case, however, as we vary the fitness, the overall probabilities of going up and down in *fitness* are not the same. In the extreme case of having $L-1$ bits equal to 1 and one bit equal to 0, there is a much greater chance that a random bit flip will lower fitness as opposed to raise it. This *fitness-dependent* bias is sometimes referred to as Muller's Ratchet;[5] it is an entropic effect corresponding to the relative smallness of genome space volume near regions of fitness maxima. Formally, one can recover the constant bias case in the $L \to \infty$ limit. In this limit, finite changes in fitness make only infinitesimal changes to the overall percentage of "1" genes and hence do not alter the bias.

We will show that in the presence of any (negative) bias, the mean fitness of the population eventually stops increasing and the Markov process reaches an equilibrium state. This result is obtained first by direct simulation of the stochastic evolution rules and is then explained via analytic solutions of the model in a variety of accessible limits. Just as in our previous work, we investigate to what extent mean field approaches can correctly capture the behavior at finite N. What we will see is that in the *fitness-dependent* case there is a crossover from a fluctuation-dominated equilibrium state to a (nearly) mean-field one as N is increased at fixed L. Even when the equilibrium is correctly described by mean field theory, however, the dynamics of starting from an arbitrary *compact* initial population and evolving towards the equilibrium remains dominated by fluctuations.

The outline of the rest of this paper is as follows. In the next section, we define our smooth landscape model and demonstrate computationally that the mean fitness saturates at long times. Subsequently, we solve the master equations in the limit of small mutation rate μ to analytically investigate the nature of the equilibrium state; these results are compared

to simulations in this limit. In particular, for the finite L problem, we find that there are two very different regimes, one for $N \ll L$ and the other for $L \ll N$. In the case $N \ll L$, the selection pressure is insufficient to overcome the entropy effect which drives the system to the most probable (in the absence of selection effects) state with $L/2$ 0's and $L/2$ 1's, and the equilibrium population remains relatively close to this state. In the opposite limit, $L \ll N$, the system succeeds in getting close to the maximally fit state with all 1's. We show in Section 4 that the resulting equilibrium state is well described in this limit by the mean-field treatment, which we solve analytically. In Section 5, we turn to an analysis of the hierarchy of equations for moments of the probability distribution. Finally, our results are summarized in Section 6, and where we also discuss future research directions.

2. CONTINUOUS-TIME EVOLUTION MODEL

We consider a population of fixed size, each individual of which reproduces at a characteristic rate in a standard Poisson process. We identify this rate as the individual's fitness. To keep the population fixed, an individual selected randomly from the existing population is killed whenever a new individual is born, a kind of competition which forms the sole interaction between members of the population.[6] The newly born individual has the same fitness as its parent, except for some fraction of cases where a mutation occurs, which changes the fitness by ± 1.

To complete the model, we need to specify the probabilities of positive and negative mutations. One case we consider consists of a fixed length genome with a finite length L, consisting of individual genes which may be either functional or deficient. Functional genes are assumed to contribute some fixed amount to the overall fitness, deficient genes nothing, giving a smooth fitness landscape with discrete fitnesses. We set μ equal to the total probability of mutation, which if we wish may be considered as arising from a constant mutation probability per generation per site. What is important is that we take the probabilities of flipping an individual functional gene into a deficient state or vice versa to be the same. Hence, the probability of moving up during a mutation, p_x, is proportional to the number of deficient genes which could flip, $1 - x/L$, where x is the fitness of the mutating individual. Here, the bias is clearly fitness-dependent as it arises from the location of the individual genome in relation to the overall fitness maximum where all genes are functional.

The other case we study is that of constant bias. As we noted above, this can be thought of as the limit of infinite genome length. We take the mutation rate per gene, u, to zero in this limit, keeping the overall probability of mutation $\mu = uL$ to fixed. The probability of a mutation being

detrimental is no longer x dependent, as in the finite L case, as our overall location in the genome is effectively constant in the large L limit. Thus we pick a constant probability p of a mutation being beneficial; this proportional can arise either from our location x/L or from an intrinsic bias in the rates of flipping up or down; in either case, the bias is fitness-independent. Our previous paper was concerned with this infinite genome limit in the special case of $p = 1/2$, i.e. with no overall bias either up or down.

We simulate the continuous time population evolution by using a waiting time algorithm. The rate for every process in the system (here all the various possible births) is summed, giving a total rate τ. The waiting time until the next event is picked as a stochastic variable from the distribution $P(\Delta t) = \exp(-\Delta t/\tau)/\tau$. The simulation time is updated, and the particular process which occurred is chosen randomly according to its weight in the overall rate. The new baby is a mutant with probability μ, and its fitness is increased by one with probability p, which may or may not depend on x as discussed above. Mutations to the zero fitness state are disallowed. The system is updated, and the cycle is repeated.

Statistics of the system are taken at regular intervals. One consequence of our continuum-time modeling of each birth event is that as the overall fitness of the population increases, the amount of computer time required to simulate a fixed amount of simulation time increases in line with the overall fitness increase of the population. This is very different than what occurs in any discrete-time model; here the mean birth (and death) rate speeds up as fitness increases.

In Fig. 1, we show a typical simulation result for the mean fitness of a population evolving with a variety of (fixed) negative values of the bias;

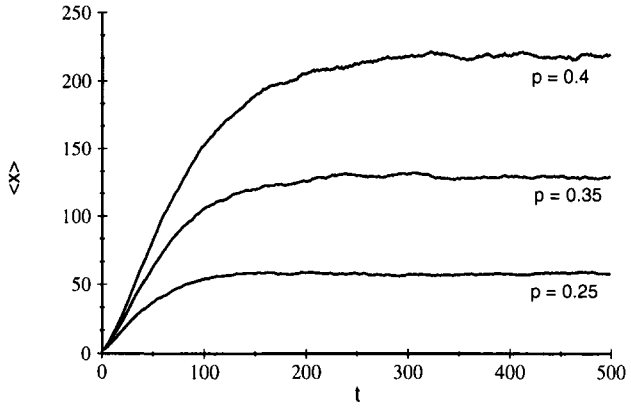

Fig. 1. Fitness vs. time, various constant $p < 1/2$. $N = 100$, $\mu = 0.1$, $p = 0.4, 0.35, 0.25$; averaged over 100 realizations.

i.e., $p < 1/2$. Note that there is equilibrium state which is reached, which we found to be independent of initial conditions. This situation is very different from that which obtains in the model of Woodcock and Higgs,[7] with which our model shares many features. Woodcock and Higgs also study a model with our simple single-peak landscape, in the presence of an overall mutational bias. The crucial difference between the models is in the dynamics. W-H use a discrete time updating scheme. In their scheme, only relative fitness differences are meaningful; they replace the entire population at fixed time intervals and only the relative number of babies of each individual determine the makeup of the succeeding generation. This leads to translation invariance in fitness space and hence to a constant rate of fitness change of the population. Unless one is working with a population with an explicitly synchronous birthing cycle, our model is more similar to typical real birth-death processes and hence our finding should be more relevant to the actual behavior one might expect.

For the case of $p > 0.5$, the fitness increases at an extremely rapid rate. This is shown in Fig. 2. In any real-world scenario, such a rapid increase in fitness would quickly bring the system to a region of genome space which lacks the positive bias, and hence this explosive growth should be seen for only rather limited periods of time.

Next, we turn to equilibrium fitness distribution in the finite-L, continuous time model. Again, the average fitness approaches an equilibrium value independent of the initial conditions, as seen in Fig. 3. Here the situation is much closer to that of the aforementioned work of Woodcock and Higgs.[7] Later, we will study the dependence of mean fitness on population size and mutation rate and discuss the correspondence in more detail.

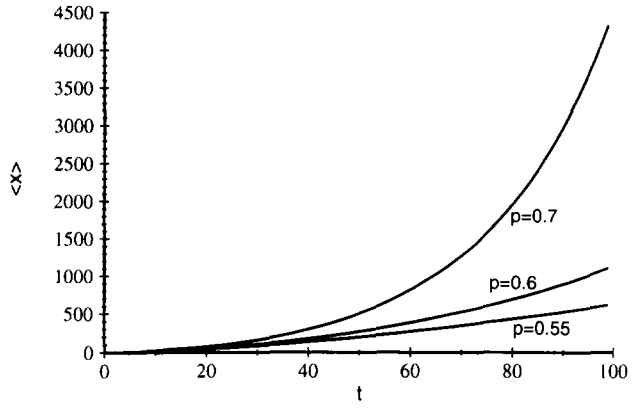

Fig. 2. Fitness vs. t, various constant $p > 1/2$. $N = 100$, $\mu = 0.1$, average of 100 realizations.

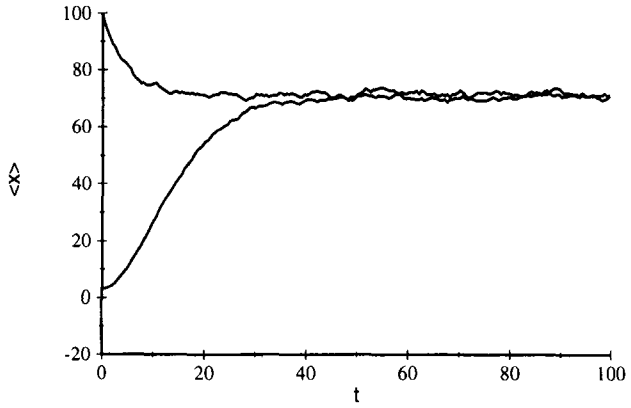

Fig. 3. Equilibrium in finite-L, $p_x = 1 - x/L$ model. $L = 100$, $N = 100$, $\mu = 0.001$. Average of 10 realizations. Initial fitnesses are 3 and 100, showing that the equilibrium fitness is independent of initial conditions.

3. THE SMALL μ LIMIT

We now turn to an analytic treatment of our model in the small μ limit. We work this out first for the case of two individuals. As discussed in ref. 3, in the small μ limit, either both individuals will have the same fitness, or they will have adjacent fitnesses. Call f_x the probability that we have two individuals at x, and g_x the probability that we have adjacent individuals at x and $x+1$. We may then write an explicit master equation

$$\frac{d}{dt} f_x = \frac{x}{2} g_x + \frac{x}{2} g_{x-1} - 2\mu x f_x \tag{1}$$

$$\frac{d}{dt} g_x = -\frac{x}{2} g_x - \frac{(x+1)}{2} g_x \tag{2}$$

$$+ 2\mu p_x x f_x + 2\mu(1 - p_{x+1})(x+1) f_{x+1} \tag{3}$$

where we have ignored mutations from g as being lower order in μ. We may solve this explicitly for the equilibrium solution. Setting the time derivatives to 0, and adding the second equation to the first equation (shifted in x by 1) we get

$$0 = \Delta_+ \left\{ -2\mu p_x x f_x + \frac{x}{2} g_x \right\} \tag{4}$$

where Δ_+ is the discrete forward-difference operator: $\Delta_+\{h(x)\} \equiv h(x+1) - h(x)$ for any function $h(x)$. This is a continuity equation and is a byproduct of the conservation of the number of individuals. Thus the bracketed term is a constant function, and in fact is zero, since f and g vanish at the origin. Thus, we find

$$g_x = 4\mu p_x f_x \tag{5}$$

Plugging this into the (shifted) equation of motion for f above yields at equilibrium

$$f_{x+1} = \frac{p_x}{1 - p_{x+1}} f_x \tag{6}$$

We can now consider our two cases. In the case of *constant* p, infinite L, we have that f is a geometric distribution

$$f_x = Ar^x \tag{7}$$

where $r \equiv p/(1-p)$ and A is a normalization constant, fixed by the requirement that $\sum_{x=1}^{\infty} f_x = 1$ (the contribution of g to the normalization is of order μ and so is negligible). We see that the negative bias swamps the selection pressure, and the most probable state is that of minimal fitness, namely that of fitness 1. We compare the predicted density to the result of simulations in Fig. 4, and note that the agreement is excellent as expected.

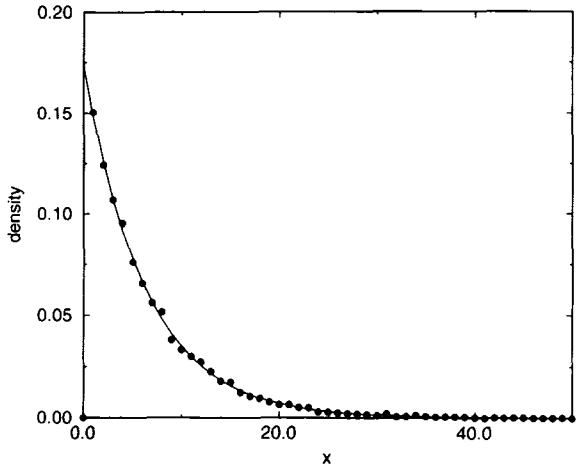

Fig. 4. The density distribution at $t = 2000$; here $p = 0.46$, $\mu = 0.05$. The line is from Eq. 7.

The (ensemble) average value of the mean fitness, $\bar{x}$, is given to leading order in μ by

$$\langle \bar{x} \rangle = \sum_{x=1}^{\infty} x f_x = \frac{1}{1-r} = \frac{1-p}{1-2p} \tag{8}$$

In Figure 5, we compare this result to those of simulation. Again the agreement is excellent, showing that for small μ, the simulations are well described by truncation to f and g.

In the case of *finite* L, with a variable $p_x = 1 - x/L$, we have $f_{x+1} = ((L-x)/(x+1))\, f_x$ with the solution

$$f_x = A \binom{L}{x} \tag{9}$$

with again A being a (different) normalization factor. In other words, f is in this case a binomial distribution, so that the maximum is at $L/2$. Here again the selection pressure is unable to overcome the bias, here induced by the entropy effect, and the state with maximal entropy is the most probable. The predicted distribution is compared with simulation in Fig. 6, again with good agreement. The ensemble average mean fitness is clearly $L/2$ in this case.

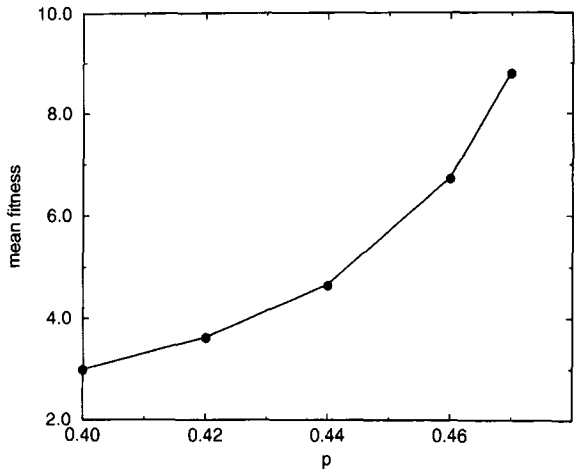

Fig. 5. Equilibrium fitness vs. p, fixed bias. $\mu = 0.05$, $N = 2$. The line is the theoretical prediction from Eq. 8.

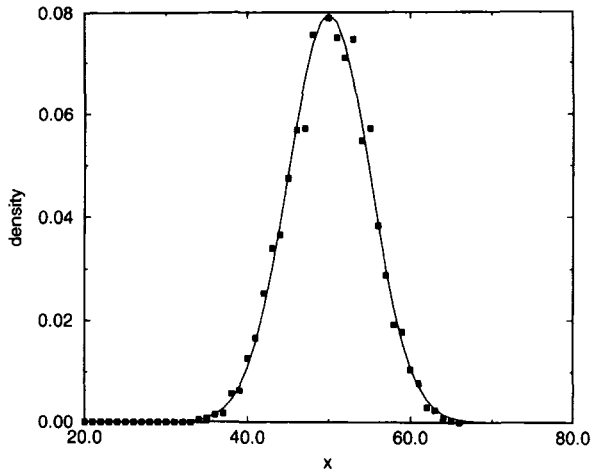

Fig. 6. The function f_x for $L=100$, $N=2$, $\mu=0.1$. Average over 4000 realizations at time $t=50$. The line is the theoretical prediction, Eq. 9.

These small μ results are easily extended to arbitrary N. As in ref. 3, the relevant states are those where the individuals are distributed among at most 2 adjacent fitnesses. As above, the probability of being in any of these states can be exactly related to the probability f_x of having all the individuals having the same fitness x. Doing this, we find that f_x satisfies the equation

$$f_{x+1}=\frac{p_x}{1-p_{x+1}}\left(\frac{x+1}{x}\right)^{N-2} f_x \tag{10}$$

In the constant bias case, then, f_x is given by

$$f_x = Ar^x x^{N-2} \tag{11}$$

The second factor has the effect of pushing the distribution out to larger x's, an effect which increases with N. Thus, the average mean fitness increases monotonically with N. We can compute this average mean fitness for large N using Laplace's method for sums.[8] We find that

$$\langle \bar{x} \rangle \sim \frac{N}{\ln(1/r)} \tag{12}$$

Thus, asymptotically, the mean fitness increases linearly with N. We show simulation results, together with a numerical calculation of $\langle \bar{x} \rangle$ for

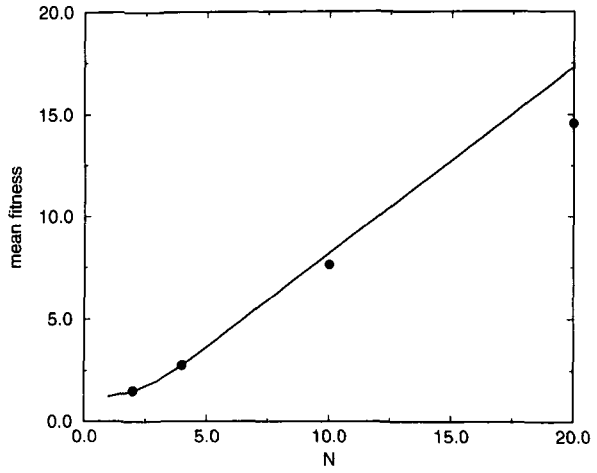

Fig. 7. Equilibrium fitness as a function of population size, with $\mu = 0.1$, $L = \infty$, $p = 0.25$; curve comes from the small μ theory, Eq. (11).

$p = 0.25$ in Fig. 7. We see that the asymptotic result of a linear N dependence sets in quite rapidly, but the agreement of the theory with simulation data begins to slip at around $N = 10$. This is because of the fact, already discussed in ref. 3, that the small μ limit is not uniform in N and the corrections are of order μN. The effect of finite μ is to decrease the equilibrium fitness.

For the finite L case with $p_x = 1 - x/L$, the solution is similarly seen to be

$$f_x = A \binom{L}{x} x^{N-2} \tag{13}$$

Again, the increased selection pressure for larger N pushes the distribution out to higher fitnesses. When analyzing this result for large N, we immediately see that there are two different asymptotic regimes. For $1 \ll N \ll L$, the maximum is pushed up by an amount of order N from $L/2$. For sufficiently large N of order L, the maximum hits the highest possible fitness $x = L$ (for infinitesimally small μ). The distribution is then completely one-sided, falling as the fitness decreases away from the maximum. This effect is demonstrated in Fig. 8, where we show the population density for various N.

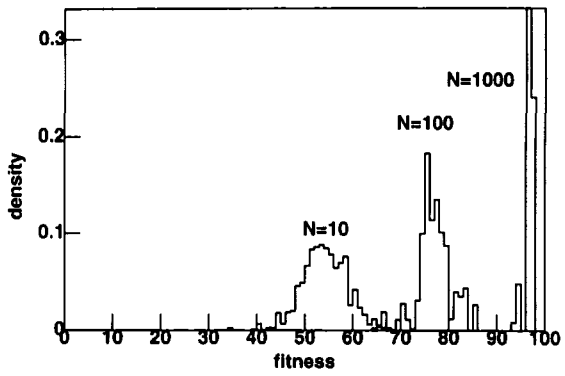

Fig. 8. $N - L$ crossover. For $N \ll L$, we have the behavior already seen in Fig. 6 for the case $N = 2$, while for $N \gg L$ we have mean-field type behavior. This figure shows the asymptotic population density (normalized to one) for $N = 10, 100, 1000$, $\mu = 0.01$.

More precisely, for $1 \ll N \ll L$, again using Laplace's method,

$$\langle \bar{x} \rangle \sim \frac{L}{2} + \frac{N-2}{2} \tag{14}$$

A comparison of this prediction with simulations is shown in Fig. 9. Again, finite mutation rate lowers the mean fitness by an amount of order μN.

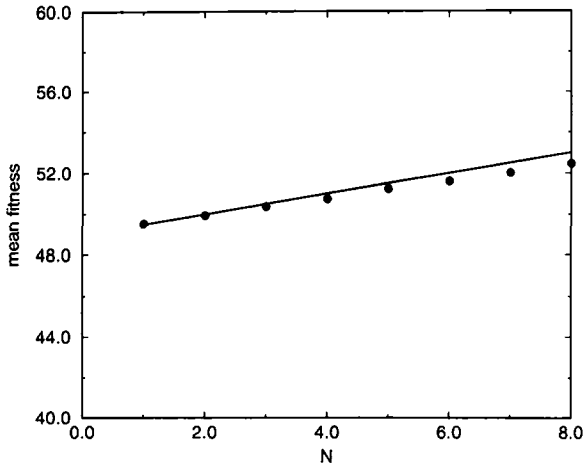

Fig. 9. Equilibrium value of $\langle x \rangle$ vs. N. Here $L = 100$, $\mu = 0.05$. The straight line is $50 + (N-2)/2$.

For $L \ll N$, the fall-off away from $x = L$ is extremely rapid for very small μ, and μ plays a vital role in smoothing the distribution. To analyze this situation, we turn in the next section to mean-field theory.

4. $N \gg L$: MEAN FIELD THEORY

As N becomes much larger than L, one can turn to mean field theory. The point is that in the equilibrium state, at sufficiently large N all the high-fitness states are occupied by many individuals and so a mean-field treatment is valid. While the low-fitness states are vacant, they are irrelevant for the behavior of the system. Now, one of the most important results in our previous work was the utter failure of mean field theory to properly describe the dynamics at any finite value of the population size. This was attributed to the fact that outlying more fit mutants are quite often eliminated by death before they dominate the population. This fact remains true at finite L and hence the *dynamics* can not be dealt with via the mean-field equations, for times less than that required to occupy all the high-fitness states with a large number of individuals. This crossover time, however, which depends on the initial conditions, cannot be predicted from the mean-field theory.

The mean-field equation consists of a deterministic temporal evolution equation for the population P at each fitness x;

$$\dot{P}_x = (x - \bar{x})\, P_x + \mu((x+1)(1 - p_{x+1})\, P_{x+1} + (x-1)\, p_{x-1} P_{x-1} - x P_x) \tag{15}$$

For large L, we write $x = L - y$, with $y \ll L$. To leading order in L, we find, for the time-independent state, the simple recurrence relation

$$P_y = \frac{\mu L}{\mu L + y - \bar{y}}\, P_{y-1} \tag{16}$$

It is immediately apparent from this that the relevant parameter in this case is μL. N has dropped out of the problem, as we are in the $N \to \infty$ limit. The solution to this recursion relation is clearly

$$P_y = A \frac{(\mu L)^y}{\Gamma(\mu L + y - \bar{y} + 1)} \tag{17}$$

The mean value $\bar{y}$ needs to be determined by the nonlinear relation

$$\sum_{y=0}^{L} (y - \bar{y})\, P_y = 0 \tag{18}$$

It is easy to verify that this relation is satisfied (up to exponentially small corrections in L) by the solution $\bar{y} = \mu L$. In this case

$$P_y = A \frac{(\mu L)^y}{y!} \tag{19}$$

Then, $\sum P_y = A \exp(\mu L)$ and $\sum y P_y = A \mu L \exp(\mu L) = A \bar{y} \sum P_y$ and the condition on $\bar{y}$ is satisfied. It is also important to note that this solution is consistent with the equation for $P(y=0)$, which, since there is no state at $L+1$, reads to leading order

$$0 = \bar{y} P(y=0) + \mu(-LP(y=0)) \tag{20}$$

This means that no boundary layer is necessary to leading order for P, which in principle might have been necessary since the leading order equation is only a first-order difference equation. We see then that the mean-field distribution $P(y)$ has the form of a Poisson distribution, with a maximum at the mean value $\bar{y} = pL$, or in other words $\bar{x} = (1-\mu)L$. A similar result was obtained in Woodcock and Higgs[7] in the limit of small μ.

How well does the mean field prediction agree with the model results? Figs. 10 and 11 show a comparison between large N simulations and the corresponding mean field theory solution. In Fig. 10, the mean-field prediction is quite satisfactory; however, for the larger μL case shown in Fig. 11, the agreement is fairly poor, even at these rather large values of N. Essentially, the population density at the highest fitness states is still too low for

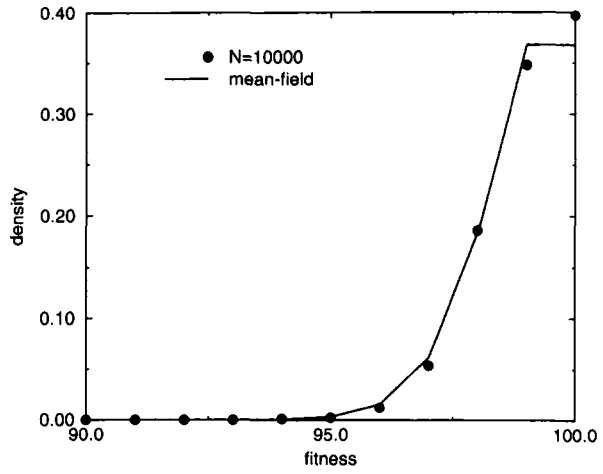

Fig. 10. Average of 4 density snapshots in the equilibrium state for $N = 10000$, compared to mean field theory; $L = 100$, $\mu = 0.01$.

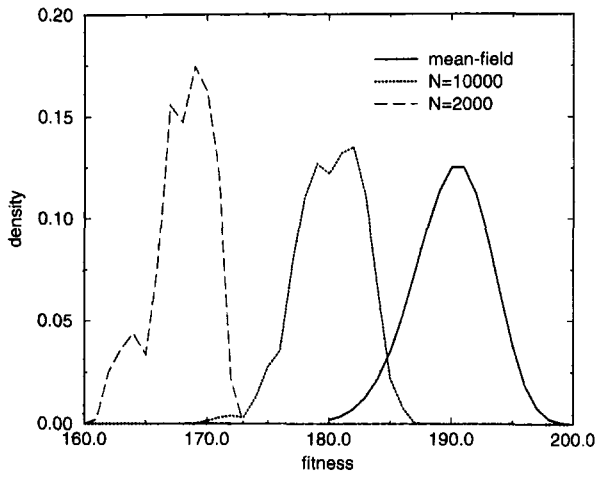

Fig. 11. Density snapshots in the equilibrium state, compared to mean field theory; $L = 200$, $\mu = 0.05$.

the fluctuations to be ignored. If we were to hold μL fixed, one might imagine that eventually the number of people at the state L, which is roughly $Ne^{-\mu L}$, will be large enough for mean-field theory to be quantitatively valid. So, at small μL, one gets reasonably good agreement at moderate N; as μL increases, this critical population size grows exponentially.

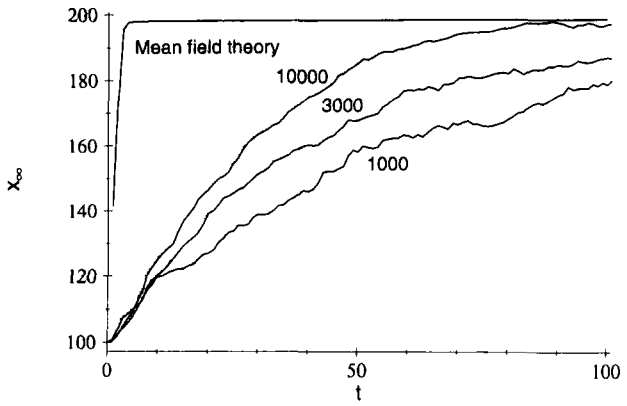

Fig. 12. Kinetics of approach to equilibrium: mean field theory contrasted with simulations. Although large populations reach the same equilibrium value as mean field theory, the rate at which they do so is much slower. Populations $N = 1000, 3000, 10000$, $\mu = 0.01$, $L = 200$. The initial condition is for all members of the population to have fitness 100.

As already mentioned, the dynamics is not mean-field like even when the final state can be described by this approach. In Fig. 12, the kinetics of the approach to equilibrium is shown for some large populations and also for infinite population. For these populations of order a few thousand individuals or more, the asymptotic distribution is essentially indistinguishable from the mean field theory distribution. Nevertheless, the real system has a quite different behavior in terms of its approach to equilibrium. This is natural: once the population has reached the areas of high fitness where it finds equilibrium, mean field theory and the finite population are controlled by the same strong negative bias. However, in the approach to equilibrium, the time scale for a finite population is set by how long it takes the luckiest individual to mutate to the top. While this may be quite rapid for a large population, it is much slower than in mean field theory, which has infinitely lucky individuals among its infinite population. Due to this effect, mean field theory will not be even approximately valid for the dynamics of *any* finite size population.

5. MOMENT HIERARCHY APPROACH

To complete our understanding it is useful to consider our program via the moment hierarchy. We saw in ref. 3 that the moment equations can provide much useful insight. In this section, we derive the first equations in this hierarchy and relate them to the results obtained in the previous sections.

In the language of chemical reactions, the master equations for our model are

$$A_x + A_{x'} \xrightarrow{x} 2A_x \tag{21}$$

$$A_x \xrightarrow{\mu x p} A_{x+1} \tag{22}$$

$$A_x \xrightarrow{\mu x(1-p)} A_{x-1} \tag{23}$$

where the first equation is the basic equation of reproduction and selection. The other two are, respectively, beneficial and detrimental mutations. (Here, the correlation between reproduction events and mutation events is ignored. We have checked the validity of this by doing simulations with uncorrelated reproduction and mutation, and found equivalent results.)

It is convenient to write the master equations in operator form, along the lines of refs. 9, 10. Probability distributions are vectors $|\psi\}$, (using the notation of [9], where the standard angle-bracket notation denotes an alternate Hilbert space) and the operators are constructed in terms of

raising and lowering operators $a^\dagger$ and a, observables are operators, and the master equation is written in terms of a time evolution operator L. This time evolution operator L may be broken into separate parts, one for each "fundamental reaction" composing it. The first such reaction corresponds to reproduction and selection. This corresponds to an operator

$$L_s = \frac{1}{N} \sum_{xx'} x a_x^\dagger (a_x^\dagger - a_{x'}^\dagger)\, a_x a'_x \tag{24}$$

with the mutation piece being

$$L_\mu = \mu \sum_x x\{ p_x a_{x+1}^\dagger + (1 - p_x)\, a_{x-1}^\dagger - a_x^\dagger \}\, a_x \tag{25}$$

This formalism is convenient for computing moment equation hierarchies. The moments are given by matrix elements of powers of a between the state $\{0|$ and $|\psi\}$. (It should be noted that in this formalism, the action of $a^\dagger$ on the bra state $\{0|$ is given by $\{0|\, a^\dagger = \{0|$ which is of course very different from the rules in second-quantized quantum mechanics.) For example, the ensemble-average mean fitness is given by the appropriate matrix element of the operator $\bar{X} \equiv 1/N \sum_x x a_x$. Then, $d/dt\langle \bar{x} \rangle = \{0|\, \bar{X} L\, |\psi\}$. First we compute the effects of the selection term,

$$\{0|\, \bar{X} L_s\, |\psi\} = \{0| \frac{1}{N^2} \sum_{x_1 x_2 x_3} x_1 x_2 a_{x_1} a_{x_2}^\dagger (a_{x_2}^\dagger - a_{x_3}^\dagger)\, a_{x_2} a_{x_3}\, |\psi\} \tag{26}$$

$$= \frac{1}{N^2} \sum_{x_2 x_3} x_2 (x_2 - x_3) \{0|\, a_{x_2} a_{x_3}\, |\psi\} \tag{27}$$

$$\equiv \{0|\, \Omega\, |\psi\} \tag{28}$$

where the matrix element of the operator Ω is the ensemble average of ω, the variance of the fitness. Turning now to the mutation term, we have

$$\{0|\, \bar{x} L_\mu\, |\psi\} = \{0| \frac{\mu}{N} \sum_{x_1 x_2} x_1 x_2 a_1 (p_{x_2} a_{x_2+1}^\dagger + (1 - p_{x_2})\, a_{x_2-1}^\dagger - a_{x_2}^\dagger)\, a_{x_2}\, |\psi\} \tag{29}$$

$$= \frac{\mu}{N} \sum_{x_1} x_1 (2p_{x_1} - 1) \{0|\, a_{x_1}\, |\psi\} \tag{30}$$

Combining these two results, we get

$$\frac{d}{dt} \langle \bar{x} \rangle = \mu \langle (2p_x - 1) x \rangle + \langle \omega \rangle \tag{31}$$

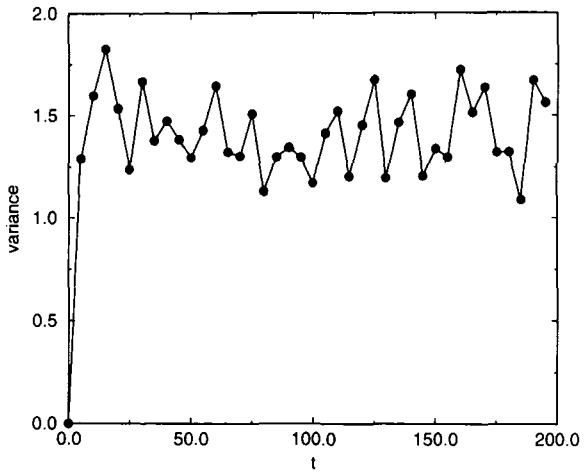

Fig. 13. Variance versus time for $N = 5000$, $\mu = 0.01$, $L = 200$. The initial condition is for all members of the population to have fitness 100.

Comparing this to the analogous result in ref. 3, we see that the bias introduces an additional term in the velocity equation. It is this additional term that for negative bias leads to an equilibrium state. The point is, since the bias is mutation-driven and the mutation rate is proportional to the (increasing) birth rate, the bias becomes increasingly important as the population climbs the landscape. This continues until equilibrium is attained. Without the bias term, this equation is a statement of Fisher's "fundamental theorem of natural selection",[11] which states that the rate of change of fitness is equal to the variance of the population. As such, increases of fitness feed off of the variance of the population as supplied by mutations. To Fisher, this statement captured Darwin's essential insight into the process of natural selection, hence the name. However, the "theorem" clearly does not allow the achievement of equilibrium, as in equilibrium the variance remains finite, but the velocity vanishes. The presence of the bias term in Eq. (31) repairs this defect.

We can use the result to obtain a rough estimate of the velocity during the transient phase during which fitness is increasing to its final equilibrium value. For $N \gg L$, the width ω saturates fairly quickly at a value close to its equilibrium value of μL, as found by mean-field theory; this can be seen by looking at the variance versus time for a single run with $N = 5000$ shown in Fig. 13. Then, the instantaneous velocity should be given by

$$\frac{d}{dt}\langle \bar{x} \rangle = \mu\left(1 - \frac{2\bar{x}}{L}\right) + \mu L \tag{32}$$

This result agrees roughly with the results of Fig. 12. Mean-field dynamics, on the other hand, predicts a width that drastically overshoots its equilibrium value and thereby gets the velocity wrong by a large factor and achieves equilibrium on times of order 1 as opposed to order $1/\mu$.

To compute the equilibrium state, we need to know the width $\langle \omega \rangle$. To this end, we compute its time derivative. We first need the contribution of L_μ to $d/dt\langle \omega \rangle$:

$$\{0|\, \Omega L_\mu \,|\psi\} = \{0| \left[\frac{1}{N^2} \sum_{12} x_1(x_1 - x_2)\, a_{x_1} a_{x_2} \right] \times \left[\mu \sum_3 x_3 \{ p_{x_3} a^\dagger_{x_3+1} + (1 - p_{x_3})\, a^\dagger_{x_3-1} - a^\dagger_{x_3} \}\, a_{x_3} \right] |\psi\} \tag{33}$$

After some tedious algebra, we arrive at

$$\{0|\, \Omega L_\mu \,|\psi\} = \frac{\mu(N-1)}{N^2} \sum_3 x_3 \{0|\, a_{x_3} \,|\psi\} - 2\frac{\mu}{N^2} \sum_{23} (1 - 2p_{x_3})\, x_3(x_3 - x_2) \{0|\, a_{x_2} a_{x_3} \,|\psi\} \tag{34}$$

where we have pulled out the sum $\sum_{x_2} a_{x_2}$, and set it equal to $N-1$ (as there is one destruction operator to its right).

This term for the time evolution of the variance needs to be added to the selection piece which was already calculated in ref. (3). This leads to

$$\frac{d}{dt}\langle \omega \rangle = \mu(1 - 1/N)\langle \bar{x} \rangle + 2\mu \langle \overline{(2p_x - 1)(x - \bar{x})^2} \rangle - \frac{2\langle \bar{x} \rangle \langle \omega \rangle}{N} + \langle S \rangle \tag{35}$$

where S is the skewness defined as

$$S \equiv \overline{(x - \bar{x})^3} \tag{36}$$

We now investigate these equations for the two cases of constant bias or a gradient bias. As opposed to the unbiased case, here the skewness, as well as the connected component $\langle \bar{x}\omega \rangle - \langle \bar{x} \rangle \langle \omega \rangle$, does not vanish at large times, in general. However, these quantities are negligible if p is close to 1/2, so that the equilibrium fitness is large. To leading order in $(p - 1/2)$, we easily find

$$\langle \bar{x} \rangle = \frac{N-1}{2(1-2p)} \tag{37}$$

This formula agrees with our previous formula, Eq. 12, in the same limit. Notice that the mutation rate μ makes a negligible change to the fitness in this limit.

We now turn to the finite L case. To get a feeling for the answer, we note that if we neglect the bias term in the variance equation Eq. (35) and again drop the skewness and use the factorization of $\langle \bar{x}\omega \rangle$, we recover the simple result

$$\langle \omega \rangle = \mu(N-1)/2 \tag{38}$$

At small N (i.e. $N \ll L$), this is small. Hence in the $\langle \bar{x} \rangle$ equation, $\bar{x}$ must remain close to $L/2$ so that $p_x \simeq 1/2$; it cannot be less than $L/2$, because the resultant *positive* bias would rapidly drive the system to higher fitness. This then suggests the qualitative prediction that $\langle \bar{x} \rangle = L/2 + O(N)$. This result then justifies a posteriori the previous assumptions about the neglect of the bias term in the variance equation, as well as the irrelevance of the skewness and connected piece, since these are all small for $p_x \simeq 1/2$. This is consistent with the results derived Section 3 using the small μ expansion. Unfortunately, it appears difficult to go beyond this qualitative discussion, as the aforementioned assumptions break down as soon as we go beyond these leading order estimates.

6. CONCLUSION

In this paper, we have extended our previous study of evolution on a smooth landscape to the case where there is a bias in whether a mutation increases or decreases an individual's fitness. This bias emerges naturally whenever we take into account the finite size of the genome with a concomitant absolute maximum for fitness. In this case the bias varies with fitness; states close to the fitness peak are guaranteed to have a large negative bias. We have also studied the constant bias situation.

The results we have found are as follows. For small numbers of individuals in the population and small mutation rate, analytic methods allow us to find the final equilibrium distribution of fitness. In these cases, the equilibrium state cannot be described by mean field theory, aka the Eigen–Schuster equations. For very large N compared to the genome size L, mean-field theory does correctly predict the final state but still utterly fails to describe the non-equilibrium dynamics which determines how long it takes to get to this state starting from typical initial data.

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