PHYS 320 Problem Set 4
Mutation-selection balance

1 Background

At the beginning of the course we used a continuum approximation to describe diffusion of a biological molecule randomly moving in one dimension (Lectures 4-5), leading to the diffusion equation for the probability $p(x,t)$ of finding the molecule at position x at time t:

$$\frac{\partial}{\partial t}p(x,t) = D\frac{\partial^2}{\partial x^2}p(x,t). \tag{1}$$

Here the diffusion constant D was related to the discrete hopping model via $D = wa^2$, where $w\delta t$ was the probability to move one step either left or right in time step δt, and a was the length of the step. If there were a bias in the hopping, where the rate of going right, w^+, is different from the rate of going left, w^-, then the same continuum approach would give the Fokker-Planck equation:

$$\frac{\partial}{\partial t}p(x,t) = -v\frac{\partial}{\partial x}p(x,t) + D\frac{\partial^2}{\partial x^2}p(x,t), \tag{2}$$

where $v \equiv (w^+ - w^-)a$ and $D \equiv \frac{1}{2}(w^+ + w^-)a^2$. In the limit of equal rates, $w^+ = w^- = w$, we see that Eq. (2) reduces to Eq. (1). We can view Eq. (2) as a biased diffusion equation, with the D term ("diffusion") describing the spreading of the probability distribution through random motion, and the v term ("drift" or "advection") introducing an overall rightward ($v > 0$) or leftward ($v < 0$) movement of the mean position.

It turns out that the mathematics of biased diffusion is also quite useful in a completely different biological area: modeling the random dynamics of a mutant genetic variant competing in a population of non-mutants ("wild-types"). In Lecture 36 we introduced the Moran model to capture these dynamics. Here we will try to understand the long-term behavior of the Moran model in the presence of both natural selection and constant mutations back and forth between the wild-type and mutant variants. (We assume that back mutation is possible, taking the wild-type back to the mutant.) Rather than the mutant going extinct or taking over (fixing) in the population, we will observe a new phenomenon: an equilibrium between the forces of selection and mutation that allows for a mixed population of mutants and wild-types to persist indefinitely. Under the right conditions it may be a factor in maintaining genetic diversity in nature.

This phenomenon of *mutation-selection balance* was mathematically modeled in a classic 1955 paper from Motoo Kimura, one of the founders of the field of theoretical population genetics. In this problem set we will reproduce the main argument of the paper, and derive a very interesting "phase transition" as a function of mutation rate. Kimura's diffusion approach can be used on many microscopic models of evolution, but the Moran model turns out to be a convenient starting point, making the derivation relatively straightforward. By combining diffusion with evolution, we come full circle with the course, demonstrating how the same theoretical framework can describe biological processes at both the smallest and largest scales.

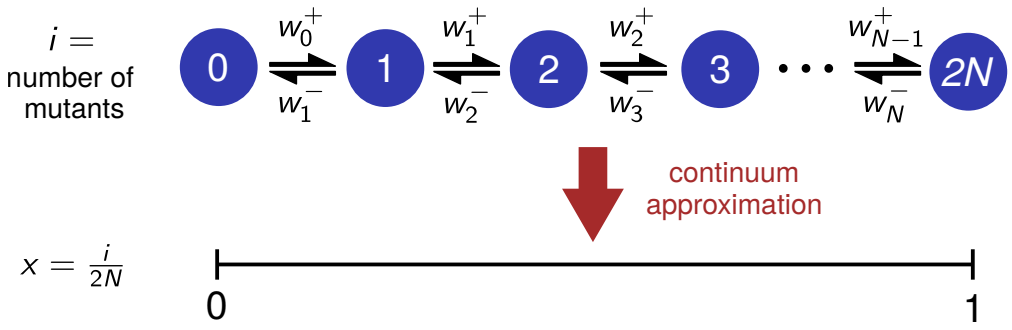

Figure 1: Top: the states and transition rates in the discrete Moran model. Bottom: the continuum approximation, where $x = i/2N$ is the fraction of mutants in the population.

2 Details of the model

Let us first summarize the main aspects of the Moran model. We have a total population of $2N$ alleles, and at any given time a number i of them are mutants, while the remainder $2N - i$ are wild-type. At each time step one allele at random dies, and one allele makes a copy of itself (possibly with a mutation, as described below). These dynamics ensure that the total population remains always at $2N$. We use i to denote the state of the system, so we can imagine a discrete network of states (Figure 1) with transition rates between neighboring states. If we are currently in state i we denote w_i^+ as the probability to go to $i+1$ (gain a mutant) and w_i^- as the probability to go to $i-1$ (lose a mutant).

As described in Lecture 36, there are four main probabilities to consider in the original Moran model:

$$\begin{aligned}
&\text{probability of choosing a wild-type to die:} \quad d_i^w = \frac{2N-i}{2N} \\
&\text{probability of choosing a mutant to die:} \quad d_i^m = \frac{i}{2N} \\
&\text{probability of choosing a wild-type to copy itself:} \quad b_i^w = \frac{g(2N-i)}{fi+g(2N-i)} \\
&\text{probability of choosing a mutant to copy itself:} \quad b_i^m = \frac{fi}{fi+g(2N-i)}
\end{aligned} \tag{3}$$

Here g is the fitness of the wild-type and f the fitness of the mutant. If $f = g$ the copying probabilities b_i^w and b_i^m just reflect that proportions of wild-type and mutant in the population. But if $f > g$ or $f < g$ the mutant has a greater (or lesser) chance of reproducing than the baseline expectation, reflecting the influence of natural selection. We will quantify this bias via the selection coefficient $s = f/g - 1$.

We now add one additional component to the model: at every copying event there is a mutation probability μ that the copy will switch types (a wild-type copy becoming a mutant, or vice versa). As a consequence the probability rates of gaining or adding a mutant in the population during one time step are as follows:

$$w_i^+ = d_i^w(b_i^m(1-\mu) + b_i^w\mu), \qquad w_i^- = d_i^m(b_i^w(1-\mu) + b_i^m\mu). \tag{4}$$

The rationale for these rates are as follows. In order to gain a mutant (w_i^+) we need one wild-type to die (probability d_i^w) and either one of two options: a mutant to copy itself and *not* switch types (probability $b_i^m(1-\mu)$) or a wild-type to copy itself and switch types (probability $b_i^w\mu$). The expression for w_i^- can be understood in a similar way. When $\mu = 0$ we recover the original model from lecture without mutation.

At first glance the overall picture is very similar to the discrete diffusion models from the first part of the course, except that the transition rates w_i^+ and w_i^- depend on the state i. Similar to the approach in Lectures 4-5, we introduce a variable $x = i/(2N)$, the fraction of mutants in the population, and a step size $a = 1/(2N)$ (corresponding to a microscopic change in x when i changes by 1). In the continuum limit of small a (large N), the expressions in Eq. (4) become continuous functions $w^+(x)$ and $w^-(x)$. Using the continuum approximation as in Lectures 4-5, the corresponding Fokker-Planck equation turns out to be:

$$\frac{\partial}{\partial t}p(x,t) = -\frac{\partial}{\partial x}\left(v(x)p(x,t)\right) + \frac{\partial^2}{\partial x^2}\left(D(x)p(x,t)\right), \tag{5}$$

where $v(x) \equiv (w^+(x) - w^-(x))a$ and $D(x) \equiv \frac{1}{2}(w^+(x) + w^-(x))a^2$. Note that x must be in the range $0 \leq x \leq 1$, so the probability satisfies the normalization condition $\int_0^1 dx\, p(x,t) = 1$. Our goal in the problem set is to analyze this evolutionary Fokker-Planck equation and derive the behavior of $p(x,t)$ in the limit $t \to \infty$.

Before starting the derivation, note that Eq. (5) has the structure of a continuity (conservation of probability) equation. We can see this by rewriting it as:

$$\frac{\partial}{\partial t}p(x,t) = -\frac{\partial}{\partial x}J(x,t), \tag{6}$$

where

$$J(x,t) \equiv v(x)p(x,t) - \frac{\partial}{\partial x}\left(D(x)p(x,t)\right) \tag{7}$$

is called the probability current, with $J(x,t) > 0$ corresponding to net probability flow to the right (toward higher x). If we were to integrate both sides of Eq. (6) over a region $a \leq x \leq b$, we would get:

$$\frac{d}{dt}\int_a^b dx\, p(x,t) = J(a,t) - J(b,t). \tag{8}$$

Hence the rate of change in the total probability between a and b is just the probability current flowing into the region, $J(a,t)$, minus the probability current flowing out, $J(b,t)$.

References

[1] Kimura, M. Stochastic processes and distribution of gene frequencies under natural selection. *Cold Spring Harb. Symp. Quant. Biol.* **20**, 33–53 (1955).

3 Questions

a) The first step is to write down simplified expressions for $v(x)$ and $D(x)$. Plug $i = 2Nx$ and $f = g(1+s)$ into the expressions from Eqs. (3), and then simplify the resulting rates in Eq. (4) so that $w^+(x)$ and $w^-(x)$ depend only on x, μ, and s. In most biological scenarios both selection coefficients and mutation rates are small, $|s| \ll 1$, $\mu \ll 1$. Taylor expand $v(x)$ and $D(x)$ to the smallest non-vanishing order in s and μ, and show that:

$$v(x) \approx \frac{1}{2N}\left((1-2x)\mu + sx(1-x)\right), \qquad D(x) \approx \frac{x(1-x)}{4N^2}. \tag{9}$$

For $v(x)$ we have ignored second-order terms ($\propto \mu s, s^2$, or μ^2) and higher. For $D(x)$ there is a non-vanishing zeroth order term, so we ignore first-order and higher. Show that based on the form of $v(x)$ and $D(x)$ we know that the integral $\int_0^1 p(x,t)$ does not change in time: the Fokker-Planck equation preserves the normalization of $p(x,t)$ over time.

b) In the limit $t \to \infty$, the solution $p(x,t)$ of a Fokker-Planck equation with time-independent $v(x)$ and $D(x)$ goes to an equilibrium distribution, $p(x,t) \to p^{\text{eq}}(x)$. This corresponds to the left-hand side of Eq. (6) going to zero. There is a special case where finding $p^{\text{eq}}(x)$ is particularly simple: assume that $v(x)$ takes the form $v(x) = -D(x)\partial\Phi(x)/\partial x$ for some function $\Phi(x)$. For now do not try to find the specific expression for $\Phi(x)$ in our model, since we will do so in the next part. Prove that under this assumption the equilibrium distribution has a Boltzmann-like form, $p^{\text{eq}}(x) = A\exp(-U(x))$, where $U(x) = \Phi(x) + \ln D(x)$ and A is a normalization constant (which we will not worry about in this derivation). *Hint:* show that $J(x,t) = 0$ when you plug in the equilibrium distribution. This guarantees that the left-hand side of Eq. (6) is zero.

c) Show that $v(x) = -D(x)\partial\Phi(x)/\partial x$ is indeed valid for our model, by finding an expression for $\Phi(x)$. *Hint:* you may find the following integral useful: $\int dx\, \frac{1-2x}{(1-x)x} = \ln(x(1-x))$.

d) Test out whether your answer makes intuitive sense by plotting $U(x)$ for several cases. First try out $N = 1000$, $\mu = 0.01$ and three different s values: $s = -0.05$, 0, 0.05. You should see that $U(x)$ in these cases has a minimum at some value of x between 0 and 1, which corresponds to the maximum of $p^{\text{eq}}(x)$: the most likely value of x in the long-time limit. The minimum of $U(x)$ is at $x = 1/2$ for $s = 0$, since in the neutral case there should be roughly the same number of mutants as wild-types in the population. It is shifted to the right or left respectively for $s > 0$ and $s < 0$, reflecting the selective bias when the mutant has greater or lower fitness than the wild-type. But note that the minimum does not reach $x = 0$ or 1. This is precisely the phenomenon of mutation-selection balance: even when $s > 0$ and the minimum is shifted close to 1 (all mutants), there is always mutation replenishing the wild-types and keeping them from entirely disappearing. Similarly for $s < 0$: mutation prevents the mutants from going entirely extinct, and the minimum stays above 0.

e) The model has one more surprise in store: repeat the plots of part d), but make the mutation probability much smaller: $\mu = 0.0001$. You should notice a strange behavior: $U(x)$ flips upside down, becoming concave instead of convex. Now the minimum of $U(x)$ occurs either at $x = 0$ (for $s < 0$), $x = 1$ (for $s > 0$), or there are equal minima at both $x = 0$ and $x = 1$ (for $s = 0$).

To explain this behavior, find an expression for $\partial^2 U(x)/\partial x^2$. Show that the second derivative is positive at all x for $\mu > \mu_c$, where μ_c is some threshold value, and negative for $\mu < \mu_c$. Find an expression for μ_c. *Hint:* you will see that our old friend, the effective population size N, plays an important role.

Thus the model shows that mutation-selection balance depends on the strength of μ. If mutations are infrequent enough ($\mu < \mu_c$) selection dominates, and the population will spend most of the time either with no mutants ($x = 0$) or mutants fixed ($x = 1$). Only when μ gets above a certain threshold will it be competitive with natural selection. This is particularly relevant to evolving populations with high mutation rates (for example viruses).