Chapter 7

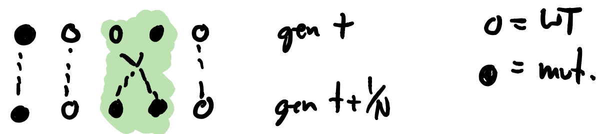
Dynamics of linear branching processes

The previous chapter showed that some of the most interesting dynamics of a new mutation occur while it is still at a low frequency in the population ($f \ll 1$). In this limit, the single-locus model in Eq. (6.1) reduces to the linear SDE,

$$\frac{\partial f}{\partial t} = \underbrace{sf}_{\text{selection}} + \underbrace{\mu - \nu f}_{\text{mutation}} + \underbrace{\sqrt{\frac{f}{N}} \cdot \eta(t)}_{\text{genetic drift}} \tag{7.1}$$

also known as a ***linear branching process***.[1] The reasons for this linear behavior can be motivated by revisiting the microscopic Moran model from Chapter 5. When $f \ll 1$, most competitions involving the mutant occur against a wildtype individual, simply because the number of such pairs ($f \cdot 1$) is much larger than the number of mutant-mutant pairs ($f \cdot f \ll f \cdot 1$):

[1]Technically, it is a continuous-time, continuous-state branching process. Other versions exist that discretize the time and/or frequency dimensions. You will analyze one such example in Problem X of HW Y.



This suggests that selection and genetic drift can be approximated by assuming that the mutant is growing in an environment consisting *solely* of wildtype individuals. The descendants of any two mutant individuals must be independent in such a scenario, and the only way that this can occur is if the selection and drift terms in the SDE are linear functions of $f(t)$.

The independence assumption will clearly break down when the mutant reaches higher frequencies (e.g. 50%). For example, correlations between individuals are eventually critical for ensuring that the mutant frequency cannot exceed 100%. The linear model in Eq. (7.1), by contrast, allows the "frequency" to diverge to infinity. This unboundedness will not be an important feature for us here — we will always make sure to switch back to the full model in Eq. (6.1) long before the mutation reaches 50% frequency (see Section 7.3).

When the independence assumption is satisfied, the linear nature of Eq. (6.1) is simple enough that we will be able to gain a nearly complete picture of the ***temporal dynamics*** of mutations, in addition to the long-time limits (e.g. fixation probabilities and stationary distributions) that we explored Chapter 6. Understanding these dynamics will turn out to give us lots of useful intuition for thinking about evolutionary problems, and they will provide a natural starting point when we go on to consider more complicated scenarios later in the course. These temporal dynamics are also increasingly relevant for analyzing longitudinal data (e.g. ancient DNA, genomic surveillance of pathogens, laboratory evolution experiments, etc.), so a detailed understanding of this case will have useful practical benefits as well.

7.1 Dynamics of the mean and variance

For simplicity, we will first consider the case with no mutations ($\mu = \nu = 0$), where Eq. (7.1) reduces to

$$\frac{\partial f}{\partial t} = \underbrace{sf}_{\text{selection}} + \underbrace{\sqrt{\frac{f}{N}} \cdot \eta(t)}_{\text{genetic drift}} . \tag{7.2}$$

Since the selection term is now a linear function of $f(t)$, the moment equations no longer suffer from the "moment hell" that plagued our original model in Chapter 6. The mean frequency now satisfies the deterministic dynamics,

$$\frac{\partial \langle f(t) \rangle}{\partial t} = s \langle f(t) \rangle \,, \tag{7.3}$$

whose solution is a simple exponential growth function,

$$\langle f(t) \rangle = f_0 e^{st} \,. \tag{7.4}$$

Similar results can be obtained for higher moments as well. Repeating the steps in Chapter 6, one can show that the second moment now satisfies,

$$\frac{\langle f(t)^2 \rangle}{\partial t} = 2s \langle f(t)^2 \rangle + \frac{\langle f(t) \rangle}{N} \tag{7.5}$$

Since the mean is given by Eq. (7.4), we can integrate this linear ODE to obtain

$$\langle f(t)^2 \rangle = f_0^2 e^{2st} + \frac{f_0 e^{st} \left(e^{st} - 1 \right)}{Ns} \,. \tag{7.6}$$

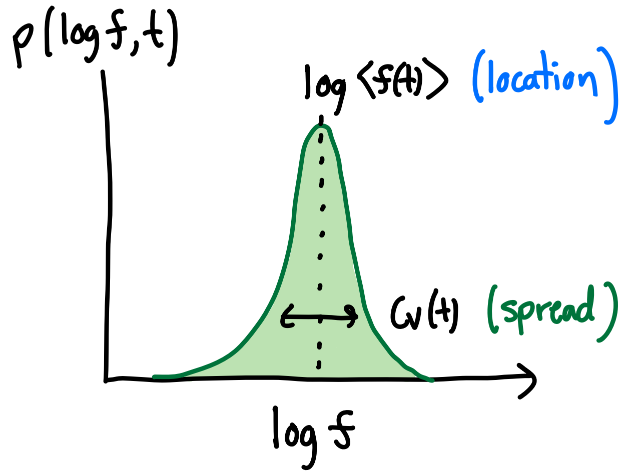
The first term corresponds to the deterministic expectation, $\langle f(t)^2 \rangle \approx \langle f(t) \rangle^2$, while the second term is a new contribution due to genetic drift. It will be useful to express this result in terms of the ***coefficient of variation (CV)***,

$$c_V^2(t) \equiv \frac{\mathrm{Var}(f(t))}{\langle f(t) \rangle^2} = \frac{1 - e^{-st}}{N s f_0} \,, \tag{7.7}$$

The coefficient of variation is useful for visualizing the spread of a distribution in log space (i.e. how uncertain are we at an order-of-magnitude level). For example, for a "Case 1" distribution with $x = \langle x \rangle \pm \sigma$, we have

$$\log x = \log\left(\langle x \rangle \pm \sigma\right) \approx \log\langle x \rangle \pm c_V \tag{7.8}$$

when $c_V \ll 1$. When the coefficient of variation starts to exceed one, the average becomes a poor approximation for actual value of the mutation frequency.



The coefficient of variation in Eq. (7.7) starts out with $c_V(0) \approx 0$, since we have assumed that the mutation begins at a fixed initial frequency. The behavior at later times strongly depends on the relative values of N, s, and f_0:

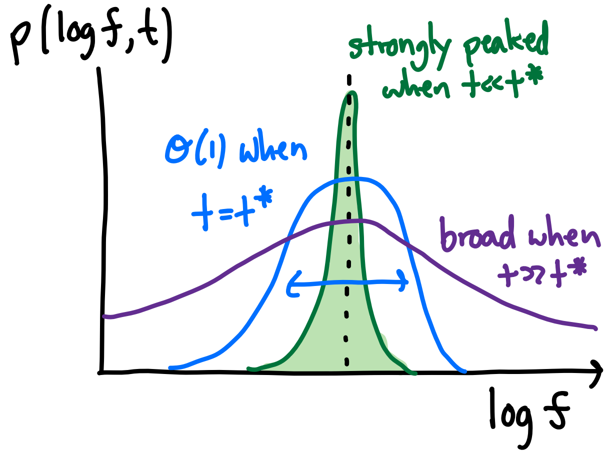
Case 1. For a positively selected mutation ($s > 0$), the coefficient of variation is bounded by its long-term value,

$$c_V^2(t) \leq \frac{1}{N s f_0} \tag{7.9}$$

Thus, if $f_0 \gg 1/Ns$, then $c_V(t) \ll 1$ for all times. This implies that the frequency of the mutation will be well-approximated by its average value, $\langle f(t) \rangle =$

$f_0 e^{st}$ when $f_0 \gg 1/Ns$ (i.e. the distribution will be of the "Case 1" form from Chapter 2). This is consistent with our fixation probability calculation from Chapter 6, which showed that beneficial mutations are guaranteed to fix when $f_0 \gg 1/Ns$.

Case 2. In all other cases (e.g. $f_0 \ll 1/Ns$, or $s \leq 0$), the mutation will start out with a small coefficient of variation, but will eventually reach a point where $c_V(t) \gg 1$. The location of this transition can be defined by the critical time t^* where $c_V(t^*) \approx 1$.



Solving for t^* yields

$$t^* \approx \begin{cases} \infty & \text{if } s > 0 \text{ and } f_0 \gg 1/Ns, \\ N f_0 & \text{if } f_0 \ll 1/N|s|, \\ \frac{1}{|s|}\log(N|s|f_0) & \text{if } s < 0 \text{ and } f_0 \gg 1/N|s|. \end{cases} \tag{7.10}$$

When $t \ll t^*$, the coefficient of variation is $\ll 1$, and frequency of the mutation can be well-approximated by its average value, $\langle f(t) \rangle = f_0 e^{st}$. In contrast, when $t \gtrsim t^*$, the distribution of $f(t)$ will become extremely broad, and will approach a "Case 2" form whose properties we will derive below.

7.2 Solving for the full distribution

One of the most useful features of the branching process model in Eq. (7.2) is that it allows us to solve for the full distribution of $f(t)$. We could in principle do this by solving the Fokker-Planck equation,

$$\frac{\partial p(f,t)}{\partial t} = -\frac{\partial}{\partial f}\left[sfp(f,t)\right] + \frac{\partial^2}{\partial f^2}\left[\frac{f}{N}\cdot p(f,t)\right] , \tag{7.11}$$

but the second derivative on the right-hand side makes this a difficult task (see the Appendix of Chapter 6). In this case, it will be much easier to work with the moment generating function of $f(t)$:

$$H(z,t) \equiv \langle e^{-zf(t)}\rangle \equiv \int e^{-zf} p(f,t)\, df , \tag{7.12}$$

which is governed by an analogous PDE,

$$\frac{\partial H}{\partial t} = \left[sz - \frac{z^2}{2N}\right]\frac{\partial H}{\partial z} . \tag{7.13}$$

subject to the initial condition $H(z,0) = e^{-zf_0}$. The main difference from our original model in Eq. (6.47) is that the branching process version contains only a single z derivative. PDEs of this form can be solved using a technique known as the ***method of characteristics***, which is a generalization of the trick that we used to solve for the fixation probability in Chapter 6. The details of this derivation are presented in the Appendix at the end of the chapter. For now, we will simply quote the final solution,

$$H(z,t) = \exp\left[\frac{-zf_0 e^{st}}{1+\frac{z}{2Ns}\left(e^{st}-1\right)}\right] . \tag{7.14}$$

Formally, it is possible to invert this expression to obtain the corresponding probability distribution $p(f,t)$. However, the details are somewhat complicated, and the resulting expressions can be difficult to interpret in the general case.[2] Instead, we will see that one can actually learn a lot about $p(f,t)$ by examining the generating function $H(z,t)$ directly.

For example, using our results for the mean and variance above, we can rewrite $H(z,t)$ in the convenient form,

$$H(z,t) = \exp\left[\frac{-z\langle f(t)\rangle}{1 + z\langle f(t)\rangle \cdot \frac{c_V^2(t)}{2}}\right] \tag{7.15}$$

By comparing this result to the generating function for a Gaussian random variable (Chapter 2),

$$\langle e^{-zx}\rangle = e^{-z\langle x\rangle + z^2\langle x\rangle^2 \cdot \frac{c_V^2}{2}} \tag{7.16}$$

we can see that $f(t)$ is *not* normally distributed in general, but becomes approximately normally distributed in the limit that $c_V(t) \ll 1$. Our results in Eq. (7.7) show that this will be a good approximation at short times, but it will eventually break down for $t \gtrsim t^*$ in Eq. (7.10), when $c_V(t) \gtrsim 1$. What can we say about the distribution of $f(t)$ in these cases?

Extinction and survival probabilities

When the variation in $f(t)$ is as large as its mean [$c_V(t) \gtrsim 1$], we must consider the possibility that the mutant has gone extinct [$f(t) = 0$]. The probability of this event can also be easily extracted from the generating function in Eq. (7.14). Recalling the definition of the generating function,

$$H(z,t) \equiv \int e^{-zf} p(f,t)\, df \tag{7.17}$$

we can see that the exponential factor acts like a crude version of a step function, approaching a uniform value for $f \ll 1/z$, and excluding contributions from

[2]The details of this inversion are presented in an appendix at the end of this chapter.

frequencies with $f \gg 1/z$. In the extreme limit where $z \to \infty$, the only values of f that will contribute to the generating function integral are those with $f = 0$; all of the nonzero frequencies will have $e^{-zf} \to 0$. This implies that

$$\lim_{z\to\infty} H(z,t) = 1 \cdot p_{\text{ext}}(t) + 0 \cdot [1 - p_{\text{ext}}(t)] = p_{\text{ext}}(t) \tag{7.18}$$

where $p_{\text{ext}}(t)$ is the ***time-dependent extinction probability*** of the mutation (i.e., the probability that it has gone extinct *by* time t). Using our expression for $H(z,t)$ in Eq. (7.14), we find that

$$p_{\text{ext}}(t) = \exp\left[\frac{-2Nsf_0}{e^{st}-1}\right] = \exp\left[\frac{-2}{c_V^2(t)}\right] . \tag{7.19}$$

We can also define a corresponding ***survival probability***

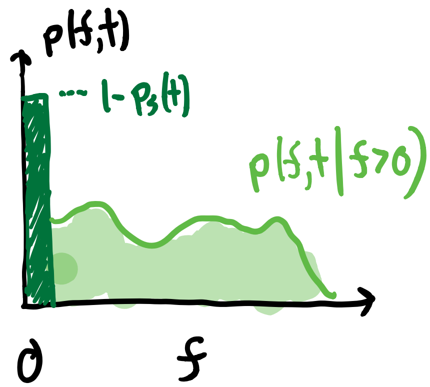
$$p_s(t) = 1 - p_{\text{ext}}(t) = 1 - \exp\left[\frac{-2Nsf_0}{1-e^{-st}}\right] , \tag{7.20}$$

which denotes the probability that the mutant is still alive at time t.

These two expressions show that the extinction and survival probabilities are intimately connected to the coefficient of variation in Eq. (7.7). At early times ($t \ll t^*$), the coefficient of variation is $\ll 1$, so there is a negligible chance of extinction (i.e., the survival probability is close to 100%). However, once $c_V(t) \gtrsim 1$, there is a decent chance that the mutant has now gone extinct. This implies that the crossover time t^* in Eq. (7.10) can also be interpreted as a characteristic ***extinction time*** — i.e. the time at which the survival probability starts to drop below 100%. For a beneficial mutation with $f_0 \gg 1/2Ns$, the survival probability in Eq. (7.20) remains close to 100% at all times. In all other cases, the survival probability eventually grows quite small [$p_s(t) \ll 1$], and there is a large chance that the mutant has gone extinct.

Conditioning on non-extinction

The results above suggest that when $t \gtrsim t^*$, the distribution of $f(t)$ will approach a "Case 2" form that contains a mixture of two different types of mutation trajectories: (i) ***extinct paths***, which have $f(t) = 0$, and (ii) ***non-extinct paths*** where $f(t) > 0$.



We can formalize this idea by writing $p(f, t)$ as a mixture of two components,

$$p(f,t) = \underbrace{[1 - p_s(t)]\,\delta(f)}_{\text{extinct paths}} + \underbrace{p_s(t) \cdot p(f,t|f>0)}_{\text{non-extinct paths}} \qquad (7.21)$$

where $p(f, t|f > 0)$ denotes the ***conditional distribution*** of $f(t)$, given that it has survived for a time t. Since $p_s(t)$ is known, this conditional distribution contains all the non-trivial features of the full distribution $p(f, t)$. What can we learn about the frequencies of these surviving lineages?

TODO: REFER BACK TO OLD VERSION OF NOTES.

7.3 Asymptotic matching at higher frequencies

7.4 Heuristic picture

7.5 Incorporating spontaneous mutations

7.6 Appendix

7.6.1 Exact solution using the method of characteristics

In this section, we show how to solve the partial differential equation for the generating function of the linear branching process using the ***method of characteristics***.

No mutations ($\mu = \nu = 0$)

We will start by considering the case without mutations ($\mu = \nu = 0$), where the mutant starts at an initial frequency $f(0) = f_0$. The generating function satisfies the PDE in Eq. (7.13),

$$\frac{\partial H}{\partial t} = \left[sz - \frac{z^2}{2N} \right] \frac{\partial H}{\partial t} \,, \tag{7.22}$$

subject to the initial condition $H(z, 0) = e^{-zf_0}$.

The method of characteristics is a generalization of the trick that we used to solve for the fixation probability of the full single-locus model in Chapter 6. Recall that in that case, we found a special value of $z^* = 2Ns$ for which $\partial_t H(z^*, t) = 0$. This allowed us to relate the values of $H(z^*, t)$ at long times (where $f = 0, 1$) with the initial value $H(z^*, 0)e^{-z^* f}$.

We can generalize this idea by searching for a ***family of curves***, $z^*(t)$, along which

$$\frac{d}{dt}\left[H(z^*(t),t)\right] = 0\,. \tag{7.23}$$

When this condition is satisfied, we can again relate the values of $H(z,t)$ between the initial timepoint and any later time,

$$H(z^*(t),t) = H(z^*(0),0) = e^{-z^*(0)f_0} \tag{7.24}$$

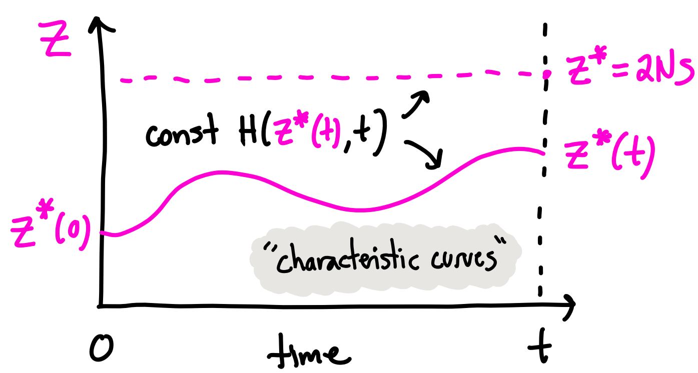
The line $z^*(t) = 2Ns$ is one such ***characteristic curve***, but there are infinitely many others. Using the chain rule on Eq. (7.23), we can write the total derivative as

$$\frac{dH(z^*(t),t)}{dt} = \frac{\partial H}{\partial t} + \frac{\partial H}{\partial z}\frac{dz^*}{dt} = \frac{\partial H}{\partial z}\left[sz^* - \frac{z^{*2}}{2N} + \frac{dz^*}{dt}\right]\,, \tag{7.25}$$

where we have used the equation of motion in Eq. (7.22) to replace $\partial H/\partial t$. This shows that if $z^*(t)$ satisfies the first order ODE,

$$\frac{dz^*}{dt} = -sz^* + \frac{z^{*2}}{2N} \tag{7.26}$$

then Eq. (7.24) will be satisfied. We can visualize this the following diagram:



The curve $z^*(t) = 2Ns$ is one possible solution Eq. (7.26) corresponding to the initial condition $z^*(0) = 2Ns$. However, Eq. (7.24) shows that this only allows us to evaluate the generating function at a special value of $z = z^*$. To obtain the full generating function $H(z,t)$, we want to be able to choose the value of z that we will use to evaluate $H(z,t)$ in the present. In other words, we need to find the initial value $z^*(0)$ that produces a characteristic curve with $z^*(t) = z$.

This is easiest to accomplish by defining a corresponding curve in ***reverse time*** (i.e. working back from the final time t). In particular, if we define a function,

$$\phi(t') = z^*(t - t') \tag{7.27}$$

then $\phi(t')$ must satisfy the initial value problem

$$\frac{\partial \phi}{\partial t'} = s\phi - \frac{\phi^2}{2N}\,, \tag{7.28}$$

with $\phi(0) = z$, and the generating function is given by

$$H(z,t) = e^{-\phi(t) f_0}\,. \tag{7.29}$$

In this case, the solution to Eq. (7.28) is a simple logistic function,

$$\phi(t) = \frac{z e^{st}}{1 + \frac{z}{2Ns}\left(e^{st} - 1\right)}\,, \tag{7.30}$$

so the generating function is given by

$$H(z,t) = \exp\left[\frac{-z f_0 e^{st}}{1 + \frac{z}{2Ns}\left(e^{st} - 1\right)}\right]\,. \tag{7.31}$$

Incorporating new mutations

TODO.