1.4 Backward Kolmogorov equation

When mutations are less likely, genetic drift dominates and the steady state distributions are peaked at $x = 0$ and 1. In the limit of $\mu_1 = 0$ (or $\mu_2 = 0$), Eq. (1.63) no longer corresponds to a well-defined probability distribution, as the $1/x$ (or $1/(1-x)$) divergence close to $x = 0$ (or $x = 1$) precludes normalization. This is the mathematical signal that our expression for the steady state is no longer valid in this limit. Indeed, in the absence of mutations a homogeneous population (all individuals A_1 or A_2) cannot change through random mating. In the parlance of dynamics these are *absorbing states*, where transitions are possible into the state but not away from it. In the presence of a single absorbing state, the steady state probability is one at this state, and zero for all other states. If there is more than one absorbing state, the steady state probability will be proportioned (split) among them.

In the absence of mutations, our models of reproducing populations have two absorbing states at $x = 0$ and $x = 1$. At long times, a population of fixed number either evolves to $x = 0$ with probability Π_0, or to $x = 1$ with probability $\Pi_1 = 1 - \Pi_0$. The value of Π_0 depends on the initial composition of the population that we shall denote by $0 < y < 1$, i.e. $p(x, t = 0) = \delta(x - y)$. Starting from this initial condition, we can follow the probability distribution $p(x, t)$ via the *forward Kolmogorov equation* (1.35). For purposes of finding the long-time behavior with absorbing states it is actually more convenient to express this as a *conditional probability* $p(x, t|y)$ that starting from a state y at $t = 0$, we move to state x at time t. Note that in any realization the variable $x(t)$ evolves from one time step to the next following the transition rates, but irrespective of its previous history. This type of process with no memory is called *Markovian,* after the Russian mathematician Andrey Andreyevich Markov (1856-1922). We can use this probability to construct evolution equations for the probability by focusing on the change of position for the last step (as we did before in deriving Eq. (1.35)), or the first step. From the latter perspective, we can write

$$p(x, t + dt|y) = \int d\delta_y \, R(\delta_y, y)dt \times p(x, t|y + \delta_y) + \left(1 - \int d\delta_y \, R(\delta_y, y)dt\right) p(x, t|y) \, , \quad (1.65)$$

where we employ the same parameterization of the reaction rates as in Eq. (1.30), with δ_y denoting the change in position. (The second term is the probability that the particle does not move in the initial dt.) The above equation merely states that the probability to arrive at x from y in time $t + dt$ is the same as that of first moving away from y by δ_y in the initial interval of dt, and then proceeding from $y + \delta_y$ to x in the remaining time t (first term). The second term corresponds to staying in place in the initial interval dt. (Naturally we have to integrate over all allowed intermediate positions.) Expanding both sides of Eq. (1.65) gives

$$\begin{aligned} p(x, t|y) + dt\frac{\partial p(x, t|y)}{\partial t} &= p(x, t|y) + \left(\int d\delta_y \, R(\delta_y, y)dt - \int d\delta_y \, R(\delta_y, y)dt\right) p(x, t|y) \\ &+ \left(\int d\delta_y \, \delta_y R(\delta_y, y)dt\right) \frac{\partial p(x, t|y)}{\partial y} \\ &+ \frac{1}{2}\left(\int d\delta_y \, \delta_y^2 R(\delta_y, y)dt\right) \frac{\partial^2 p(x, t|y)}{\partial y^2} + \cdots \, . \end{aligned} \quad (1.66)$$

Using the normalization condition for $R(\delta y, y)$ and the definitions of drift and diffusion coefficients from Eqs. (1.36) and (1.37), we obtain

$$\frac{\partial p(x,t|y)}{\partial t} = v(y)\frac{\partial p}{\partial y} + D(y)\frac{\partial^2 p}{\partial y^2}\,, \tag{1.67}$$

which is known as the *backward Kolmogorov equation.* If the drift velocity and the diffusion coefficient are independent of position, the forward and backward equations are the same-more generally one is the *adjoint* of the other.

1.4.1 Fixation probability

Let us denote by $\Pi^*(x_a, y)$, the probability that starting a starting composition y is at long time *fixed* to absorbing state x_a, i.e. $\Pi(x_a, y) = \lim_{t\to\infty} p(x_a, t|y)$. For our problem, we have two such states with $\Pi_0(y) \equiv \Pi^*(0, y)$ and $\Pi_1(y) \equiv \Pi^*(1, y)$, but keep the more general notation for the time being. These functions must correspond to steady state solutions to Eq. (1.67), and thus obey

$$v(y)\frac{d\Pi^*(y)}{dy} + D(y)\frac{d^2\Pi^*(y)}{dy^2} = 0\,. \tag{1.68}$$

After rearranging the above equation to

$$\frac{\Pi^*(y)''}{\Pi^*(y)'} = \frac{d}{dy}\log\frac{d\Pi^*(y)}{dy} = -\frac{v(y)}{D(y)}, \tag{1.69}$$

we can integrate it to

$$\log \Pi^*(y)' = -\int^y dy'\frac{v(y')}{D(y')} = -\ln\left(D(y)p^*(y)\right)\,. \tag{1.70}$$

The result of the above integration is related to an intermediate step in calculation of the steady state solution p^* of the forward Kolmogorov equation in (1.59). However, as we noted already, in the context of absorbing states the function p^* is not normalizable and thus cannot be regarded as a probability. Nonetheless, we can express the results in terms of this function. For example, the *probability of fixation*, i.e. $\Pi_1(y)$ is obtained with the boundary conditions $\Pi_1(0) = 0$ and $\Pi_1(1) = 1$, as

$$\Pi_1(y) = \frac{\int_0^y dy'[D(y)p^*(y')]^{-1}}{\int_0^1 dy'[D(y)p^*(y')]^{-1}}\,. \tag{1.71}$$

When there is selection, but no mutation, Eq. (1.54) implies

$$\log \Pi^*(y)' = -\int^y dy'\frac{v(y')}{D(y')} = -2\int^y (Ns) = -2Nsy + \text{constant}. \tag{1.72}$$

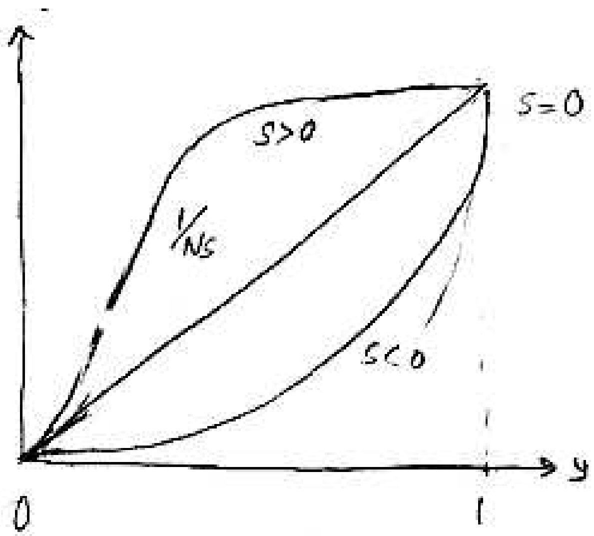

Figure 1: Fixation probability

Integrating $\Pi^*(y)'$ and adjusting the constants of proportionality by the boundary conditions $\Pi_1(0) = 0$ and $\Pi_1(1) = 1$, then leads to the fixation probability of

$$\Pi_1(y) = \frac{1 - e^{-2Nsy}}{1 - e^{-2Ns}} \,. \tag{1.73}$$

The fixation probability of a neutral allele is obtained from the above expression in the limit of $s \to 0$ as $\Pi_1(y) = y$.

When a mutation first appears in a diploid population, it is present in one copy and hence $y = 1/(2N)$. The probability that this mutation is fixed is $\Pi_1 = 1/(2N)$ as long as it is approximately neutral (if $2sN \ll 1$). If it is advantageous ($2sN \gg 1$) it will be fixed with probability $\Pi_1 = 1 - e^{-s}$ irrespective of the population size! If it is deleterious ($2sN \ll -1$) it will have a very hard time getting fixed, with a probability that decays with population size as $\Pi_1 = e^{-(2N-1)|s|}$. The *probability of loss* of the mutation is simply $\Pi_0 = 1 - \Pi_1$.

1.4.2 Mean times to fixation/loss

When there is an absorbing state in the dynamics, we can ask how long it takes for the process to terminate at such a state. In the context of random walks, this is known as the *first passage time*, and can be visualized as the time it takes for a random walker to fall into a trap. Actually, since the process is stochastic, the *time to fixation* (or loss) is itself a random quantity with a probability distribution. Here we shall compute an easier quantity, the mean of this distribution, as an indicator of a typical time scale.

Let us consider an absorbing state at x_a, and the difference $p(x_a, t + dt|y) - p(x_a, t|y) = dt\partial p(x_a, t|y)/\partial t$. Clearly the probability to be at x_a only changes due to absorption of particles, and thus $\partial p(x_a, t|y)/\partial t$ is proportional to the *probability density function (PDF) for fixation* at time t. *The conditional PDF* that the process terminates at x_a must be properly normalized, and we have to divide by the integral $\int_0^\infty dt \partial p(x_a, t|y)/\partial t$, which is simply $\Pi^*(x_a, y)$. Thus the normalized conditional PDF for fixation at time t at x_a is

$$p_a(t|y) = \frac{1}{\Pi^*(x_a, y)} \frac{\partial p(x_a, t|y)}{\partial t} \,. \tag{1.74}$$

The *mean fixation time* is now computed from

$$\langle \tau(y) \rangle_a = \int_0^\infty dt\, t\, p_a(t|y) = \frac{1}{\Pi^*(x_a, y)} \int_0^\infty dt\, t\, \frac{\partial p(x_a, t|y)}{\partial t} \,. \tag{1.75}$$

Following Kimura and Ohta (1968)[3], we first examine the numerator of the above expression, defined as

$$T_a(y) = \lim_{T\to\infty} \int_0^T dt\, t\, \frac{\partial p(x_a, t|y)}{\partial t} \,. \tag{1.76}$$

(Writing $\lim_{T\to\infty} \int_0^T$ rather than simply $\int_0^\infty$ is for later convenience.) We can integrate this equation by parts to get

$$\begin{aligned} T_a(y) &= \lim_{T\to\infty} \left[T p(x_a, T|y) - \int_0^T dt\, p(x_a, t|y) \right] \\ &= \lim_{T\to\infty} T\Pi^*(x_a, y) - \int_0^\infty dt\, p(x_a, t|y) \,. \end{aligned} \tag{1.77}$$

Let us denote the operations involved on the right-hand side of the backward Kolmogorov equation by the short-hand $\mathcal{B}_y$, i.e.

$$\mathcal{B}_y F(y) \equiv v(y) \frac{\partial F(y)}{\partial y} + D(y) \frac{\partial^2 F(y)}{\partial y^2} \,. \tag{1.78}$$

Acting with $\mathcal{B}_y$ on both sides of Eq. (1.77), we find

$$\mathcal{B}_y T_a(y) = \lim_{T\to\infty} T \mathcal{B}_y \Pi^*(x_a, y) - \int_0^\infty dt\, \mathcal{B}_y p(x_a, t|y) \,. \tag{1.79}$$

But $\mathcal{B}_y \Pi^*(x_a, y) = 0$ according to Eq. (1.68), while $\mathcal{B}_y p(x_a, t|y) = \partial p(x_a, t|y)/\partial t$ from Eq. (1.67). Integrating the latter over time leads to

$$\mathcal{B}_y T_a(y) = -p(x_a, \infty|y) = -\Pi^*(x_a, y) \,. \tag{1.80}$$

For example, let us consider a population with no selection ($s = 0$), for which the probability to lose a mutation is $\Pi_0 = (1 - y)$. In this case, Eq. (1.80) reduces to

$$\frac{y(1-y)}{4N} \frac{\partial^2 T_0}{\partial y^2} = -(1-y) \;\Rightarrow\; \quad \frac{\partial^2 T_0}{\partial y^2} = -\frac{4N}{y} \,. \tag{1.81}$$

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[3] M. Kimura and T. Ohta, Genetics **61**, 763 (1969).

After two integrations we obtains

$$T_0(y) = -4Ny\,(\ln y - 1) + c_1 y + c_2 = -4Ny \ln y\,, \tag{1.82}$$

where the constants of integration are set by the boundary conditions $T_0(0) = T_0(1) = 0$, which follow from Eq. (1.76). From Eq. (1.75), we then obtain the mean time to loss of a mutation as

$$\langle \tau(y) \rangle_0 = -4N \frac{y \ln y}{1-y}\,. \tag{1.83}$$

A single mutation appearing in a diploid population corresponds to $y = 1/(2N)$, for which the mean number of generations to loss is $\langle \tau(y) \rangle_0 \approx 2\ln(2N)$. The mean time to fixation is obtained simply by replacing y with $(1-y)$ in Eq. (1.83) as

$$\langle \tau(y) \rangle_1 = -4N \frac{(1-y)\ln(1-y)}{y}\,. \tag{1.84}$$

The mean time for fixation of a newly appearing mutation ($y = 1/(2N)$) is thus $\langle \tau(y) \rangle_1 \approx (4N)$.

We can also examine the amount of time that the mutation survives in the population. The net probability that the mutation is still present at time t is

$$S(t|y) = \int_{0^+}^{1^-} dx p(x,t|y)\,, \tag{1.85}$$

where the integrations exclude the absorbing points at 0 and 1. Conversely, the PDF that the mutation disappears (by loss *or* fixation) at time t is

$$p_\times(t|y) = -\frac{dS(t|y)}{dt} = -\int_{0^+}^{1^-} dx \frac{dp(x,t|y)}{dt}\,. \tag{1.86}$$

(Note that the above PDF is properly normalized as $S(\infty) = 0$, while $S(0) = 1$.) The mean survival time is thus given by

$$\langle \tau(y) \rangle_\times = -\int_0^\infty dt\, t \int_{0^+}^{1^-} dx \frac{dp(x,t|y)}{dt} = \int_{0^+}^{1^-} dx \int_0^\infty dt\, p(x,t|y)\,, \tag{1.87}$$

where we have performed integration by parts and noted that the boundary terms are zero. Applying the backward Kolmogorov operator to both sides of the above equation gives

$$\begin{aligned} \mathcal{B}_y \langle \tau(y) \rangle_\times &= \int_{0^+}^{1^-} dx \int_0^\infty dt\, \mathcal{B}_y p(x,t|y) \\ &= \int_{0^+}^{1^-} dx \int_0^\infty dt \frac{dp(x,t|y)}{dt} \\ &= S(\infty|y) - S(0|y) = -1\,. \end{aligned} \tag{1.88}$$

In the absence of selection, we obtain

$$\frac{y(1-y)}{4N}\frac{\partial^2 \langle\tau(y)\rangle_\times}{\partial y^2} = -1 \;\Rightarrow\; \quad \frac{\partial^2 \langle\tau(y)\rangle_\times}{\partial y^2} = -4N\left(\frac{1}{y}+\frac{1}{1-y}\right) \; . \tag{1.89}$$

After two integrations we obtains

$$\langle\tau(y)\rangle_\times = -4Ny\left[y\ln y + (1-y)\ln(1-y)\right] \; , \tag{1.90}$$

where the constants of integration are set by the boundary conditions $\langle\tau(0)\rangle_\times = \langle\tau(1)\rangle_\times = 0$. Note the interesting relation

$$\langle\tau(y)\rangle_\times = \Pi_0(y)\,\langle\tau(y)\rangle_0 + \Pi_1(y)\,\langle\tau(y)\rangle_1 \; . \tag{1.91}$$

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