1.3.4 Fitness Landscape

Members of a population with different genotypes are likely to reproduce (on average and not due to randomness) at different rates. This selective advantage is conferred at the level of the phenotype, not separate alleles, and quantified by a fitness parameter that indicates the expected number of off-spring in the next generation (after averaging and normalization).

To be precise, consider a population with a discrete number of phenotypes, labelled by $\alpha = 1, 2, \cdots, k$. The proportion of each phenotype (or quasi-species) in the population is labelled with $x_\alpha$, with $\sum_{\alpha=1}^{k} x_\alpha = 1$, and to each quasi-species we associate a fitness $f_\alpha$. The expected number of off-springs of phenotype $\alpha$ is proportional to $x_\alpha$ (number of reproducing individuals) and $f_\alpha$ (their relative fitness). After proper normalization, the proportion of quasi-species $\alpha$ in the next generation is given by

$$x'_\alpha = \frac{f_\alpha}{\bar{f}} x_\alpha,$$

where division by the mean-fitness

$$\bar{f} = \sum_{\alpha=1}^{k} x_\alpha f_\alpha,$$

ensures that $\sum_{\alpha=1}^{k} x'_\alpha = 1$.

Note that changes in proportions are related to the mean fitness by

$$x'_\alpha - x_\alpha = \frac{x_\alpha}{\bar{f}} (f_\alpha - \bar{f}) = x_\alpha \frac{\partial \bar{f}}{\partial x_\alpha} |_{\bar{f}} = x_\alpha \frac{\partial \ln \bar{f}}{\partial x_\alpha} |_{\bar{f}}.$$

(1.81)

Note that, $\frac{\partial \bar{f}}{\partial x_\alpha} |_{\bar{f}} = (f_\alpha - \bar{f})$, indicating that the partial derivative is taken under the condition $\sum_{\alpha=1}^{k} x_\alpha = 1$; the additional (Lagrange multiplier) $\bar{f}$ ensures this constraint. Equation (1.81) indicates that the proportions $x_\alpha$ change so as to increase the mean-fitness of the population; the gradient descent is somewhat reminiscent of the motion of an over-damped particle in a landscape of potential energy $-\ln \bar{f}(\{x_\alpha\})$. The change in fitness from one generation to next is given by

$$\bar{f}' - \bar{f} = \sum_{\alpha=1}^{k} (x'_\alpha - x_\alpha) f_\alpha = \sum_{\alpha=1}^{k} x_\alpha \frac{\partial \bar{f}}{\partial x_\alpha} |_{\bar{f}} = \sum_{\alpha=1}^{k} x_\alpha \frac{\partial \ln \bar{f}}{\partial x_\alpha} |_{\bar{f}},$$

(1.82)

where the last equality follows from $\sum_{\alpha=1}^{k} x_\alpha (f_\alpha - \bar{f}) = 0$. In the same way that we defined the mean fitness over the population, we can define its variance as

$$\text{var} f = \sum_{\alpha=1}^{k} x_\alpha (f_\alpha - \bar{f})^2,$$

(1.83)
in terms of which the change in fitness is given by

$$\overline{f}' - \overline{f} = \frac{\text{var}f}{\overline{f}}.$$  \hfill (1.84)

In the 1930’s, the biologist Ronald Fisher posited that “The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time,” known as Fisher’s fundamental theorem of natural selection.

Let us again consider a diploid population with variability of two alleles $A_1$ and $A_2$ at a single locus. The three phenotypes $A_1A_1$, $A_1A_2$ and $A_2A_2$ occur in proportions $x_{11}$, $x_{12}$ and $x_{22}$, and are assigned fitness values $f_{11}$, $f_{12}$ and $f_{22}$. Assuming Hardy–Weinberg equilibrium, the three proportions can be related to the frequency $x$ of allele $A_1$ in the population by $x_{11} = x^2$, $x_{12} = 2x(1-x)$ and $x_{22} = (1-x)^2$. The mean fitness can now be expressed in terms of the single parameter $x$ as

$$\overline{f}(x) = x^2f_{11} + 2x(1-x)f_{12} + (1-x)^2f_{22}.$$ \hfill (1.85)

The expected proportions of off-springs for the three genotypes are thus $x^2f_{11}/\overline{f}$, $2x(1-x)f_{12}/\overline{f}$ and $(1-x)^2f_{22}/\overline{f}$. Thus in the next generation, the frequency $x$ changes to

$$x' = \frac{f_{11}}{\overline{f}}x^2 + 2\frac{f_{12}}{\overline{f}}x(1-x).$$ \hfill (1.86)

The change in the proportion of the allele $A_1$ is thus given by

$$\Delta x \equiv x' - x = \frac{1}{\overline{f}} [f_{11}x^2 + f_{12}x(1-x) - \overline{f}x]$$

$$= \frac{1}{\overline{f}} [f_{11}x^2 + f_{12}x(1-x) - f_{11}x^3 - 2f_{12}x^2(1-x) - f_{22}x(1-x)^2]$$

$$= \frac{1}{\overline{f}} [f_{11}x^2(1-x) + f_{12}x(1-x)(1-2x) - f_{22}x(1-x)^2]$$

$$= \frac{x(1-x)}{\overline{f}} \left[ \frac{1}{2} \frac{d\overline{f}(x)}{dx} \right]$$

$$= \frac{x(1-x)}{2} \frac{d\ln \overline{f}}{dx}. \hfill (1.87)$$

We find that in this case, even from the perspective of the allele, the population changes so as to maximize the mean fitness function, or its logarithm $\ln \overline{f}(x)$. In the above context, this result is known as Wright’s equation.

There is some inconsistency is using Eq. (1.87) to describe the change in allele frequency in subsequent generations. The reason is that the derivation started with the assumption of Hardy–Weinberg equilibrium, requiring that the three phenotypes occur in proportions $x_{11} = x^2$, $x_{12} = 2x(1-x)$ and $x_{22} = (1-x)^2$. However, the proportions of off-springs, $x'_{11} = x^2f_{11}/\overline{f}$, $x'_{12} = 2x(1-x)f_{12}/\overline{f}$ and $x'_{22} = (1-x)^2f_{22}/\overline{f}$, do not satisfy the Hardy–Weinberg
condition, except in the special case of \(f_{11} = f_{22} = f_{12}^2\). A way to recover the result is two posit a two step generation cycle: The first step of reproduction/mating follows the Fisher–Wright process in which individuals are selected at random without any preference. This ensures that the chromosomes are mixed in the new population of ‘infants,’ satisfying the Hardy–Weinberg ratios. Selection acts in the maturation of ‘infants’ to ‘adults,’ with the fractions of surviving adults now proportioned as \(x^2 f_{11}/f\), \(2x(1 - x)f_{12}/f\) and \((1 - x)^2 f_{22}/f\). The subsequent random mating/reproduction of ‘adults’ will then ensure that the proportions of the ‘infant’ population satisfy \(x'_{11} = x'^2\), \(x'_{12} = 2x'(1 - x')\) and \(x'_{22} = (1 - x')^2\), with \(x'\) given by Eq. (1.86). The need to invoke a two-step reproduction process renders the Wright equation somewhat less satisfactory than Eq. (1.81). Nevertheless, it is commonly used in discussion of different forms of selection, as discussed next.

The relative fitness values of the above diploid phenotypes are typically labelled as follows: The “wild-type” \(A_2A_2\) is assigned fitness \(f_{22} = 1 - s\), while the homozygote mutant \(A_1A_1\) has fitness \(f_{11} = 1\). The selection coefficient \(s\) quantifies the increased (if \(s > 0\)) or decreased (when \(s < 0\)) fitness of this mutant. The fitness of the heterozygote \(A_1A_2\) is indicated by \(f_{12} = (1 - hs)\), leading to the mean fitness function

\[
\bar{f} = x^2 + 2x(1 - x)(1 - hs) + (1 - x)^2(1 - s) = (1 - s) + 2s(1 - h)x + s(2h - 1)x^2. \quad (1.88)
\]

Without loss of generality, we can assume \(s > 0\), so that the double mutant \((A_1A_1\) for \(x = 1\)) is more fit, and consider the role played by the parameter \(h\). For \(h = 1/2\), the fitness function varies linearly with \(x\), with each copy of the allele conferring an additive advantage (of \(s/2\)) to fitness. Following Eq. (1.87), the population advances monotonically towards the more fit phenotype. Similar monotonic increase of \(\bar{f}(x)\) appears for all \(0 \leq h \leq 1\) (as the fitness of heterozygote is intermediate between the homozygotes), and this behavior is dubbed directional selection. For the limiting values of \(h = 0\) and \(h = 1\), the heterozygote has the same fitness as one of the homozygotes, corresponding to cases where \(A_2\) is dominant or recessive, respectively.

Interesting, still parabolic, fitness landscapes occur when \(h\) is outside the interval \([0, 1]\). For \(h < 0\), the heterozygote is more fit than either homozygote, a condition referred to as overdominance. The mean fitness now displays a maximum at an intermediate value of \(x^* = (1 - h)/(1 - 2h) \geq 1/2\). In the resulting balanced selection, populations on either side of \(x^*\) evolve to this equilibrium value; the higher fitness of the heterozygote ensures that both alleles persist in steady state. It is worthwhile to note that the steady-state at finite \(x^*\) violates the result in Eq. (1.84). As no further change in fitness can occur in steady state, Eq. (1.84) implies that the variance of fitness over the population should vanish. A vanishing variance requires identical fitness for the entire population, such as when only one phenotype is present. However, the three phenotypes present at \(x^*\) manifestly have different fitness, leading to a positive variance. The resolution of this quandary is that, as discussed above, despite its superficial similarity to Eq. (1.81), Eq. (1.87) describes a different (two-step) reproduction process which is not subject to the same constraints.

Conversely, when \(h < 0\), the heterozygote is less fit than either homozygote (underdominance), the mean fitness encounters a minimum at \(x^*\). In such, so-called disruptive selection,
homozygotes are attractors of the population dynamics, and rare fluctuations are needed for the fixation of the more fit phenotype to occur (when starting from the less fit wild-type).

The role of fluctuations can be studied with the aid of the forward Kolmogorov Eq. (1.49). Including the contribution from fitness in Eq. (1.87), the drift velocity is

\[ v(x) = \mu_1(1 - x) - \mu_2 x + \frac{x(1 - x)}{2} \frac{d\ln f}{dx}, \]  

(1.89)

with \( D(x) = x(1 - x)/(4N) \) as before. The calculation of the steady-state profile in Eq. (1.77) is now modified to

\[
\log D(x)p^*(x) = \int_0^x \frac{v(x')}{D(x')} \, dx' \\
= 4N \int_0^x \left[ \frac{\mu_1}{x'} - \frac{\mu_2}{1 - x'} + \frac{1}{2} \frac{d\ln f}{dx'} \right] \, dx' \\
= 4N \left[ \mu_1 \ln x + \mu_2 \ln(1 - x) + \frac{1}{2} \ln f(x) \right] + \text{constant},
\]

resulting in

\[
p^*(x) \propto \frac{1}{x(1 - x)} \times x^{4N\mu_1} \times (1 - x)^{4N\mu_2} \times f(x)^{2N}.
\]  

(1.90)

The fitness profile appears as a multiplicative factor in the steady-state profile, raised to a large power of \( 2N \), greatly increasing the proportion of fit phenotypes in the population. To connect to the previous discussion of auto-catalytic reactions, consider the case of \( h = 1/2 \), and \( s \ll 1 \), where \( f = 1 - s + sx \approx \exp(-s + sx) \), leading to the result in Eq. (1.77). Indeed the role of selection in population genetics is frequently described by the single parameter \( s \), such that

\[ \Delta x = \frac{x(1 - x)}{2} s. \]  

(1.91)

We shall not consider more complex situations in which the fitness values \( f_\alpha \) (and hence \( s \)) are themselves functions of the composition \( \{x_\alpha\} \).
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. (1.77) 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, homogeneous populations correspond to 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 $\Pi_0$, or to $x = 1$ with probability $\Pi_1 = 1 - \Pi_0$. The value of $\Pi_0$ 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 (1.49). 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 property 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. (1.49)), or the first step. From the latter perspective, we can decompose the conditional probability after a time interval $t + dt$ as

$$p(x,t + dt|y) = \int d\delta_y R(\delta_y, y) dt \times p(x,t|y + \delta_y) + \left(1 - \int d\delta_y R(\delta_y, y) dt\right) p(x,t|y), \quad (1.92)$$

where we employ the same parameterization of the reaction rates as in Eq. (1.44), with $\delta_y$ denoting the change in position. 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 $\delta_y$ in the initial interval of $dt$, and then proceeding from $y + \delta_y$ to $x$ in the remaining time $t$ [the first term in Eq. (1.92)]. The second term corresponds to staying in place in the initial interval $dt$, and taking a trajectory that arrives at $x$ in the subsequent time interval $t$. (Naturally we have to integrate over all allowed intermediate positions.) Expanding the left hand side
of Eq. (1.92) in $dt$, and the right side in $\delta_y$ (assuming dominance of local changes), gives

$$p(x,t|y) + dt \frac{\partial p(x,t|y)}{\partial t} = p(x,t|y) + \left( \int d\delta_y R(\delta_y, y) dt - \int d\delta_y R(\delta_y, y) dt \right) p(x,t|y)$$

$$+ \left( \int d\delta_y \delta_y R(\delta_y, y) dt \right) \frac{\partial p(x,t|y)}{\partial y}$$

$$+ \frac{1}{2} \left( \int d\delta_y \delta_y^2 R(\delta_y, y) dt \right) \frac{\partial^2 p(x,t|y)}{\partial y^2} + \cdots.$$  (1.93)

Using the definitions of drift and diffusion coefficients from Eqs. (1.50) and (1.51), we obtain

$$\frac{\partial p(x,t|y)}{\partial t} = v(y) \frac{\partial p}{\partial y} + D(y) \frac{\partial^2 p}{\partial y^2},$$  (1.94)

which is known as the \textit{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 \textit{adjoint} of the other.