1.5 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_α, with $\sum_{\alpha=1}^{k} x_\alpha = 1$, and to each quasi-species we associate a fitness f_α. The expected number of off-springs of phenotype α is proportional to x_α (number of reproducing individuals) and f_α (their relative fitness). After proper normalization, the proportion of quasi-species α in the next generation is given by

$$x'_\alpha = \frac{f_\alpha}{\overline{f}} x_\alpha \,, \tag{1.79}$$

where division by the *mean-fitness*

$$\overline{f} = \sum_{\alpha=1}^{k} x_\alpha f_\alpha \,, \tag{1.80}$$

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

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

$$x'_\alpha - x_\alpha = \frac{x_\alpha}{\overline{f}} \left(f_\alpha - \overline{f} \right) = \frac{x_\alpha}{\overline{f}} \left. \frac{\partial \overline{f}}{\partial x_\alpha} \right|_* = x_\alpha \left. \frac{\partial \ln \overline{f}}{\partial x_\alpha} \right|_* \,. \tag{1.81}$$

Note that, $\frac{\partial \overline{f}}{\partial x_\alpha}|_* = (f_\alpha - \overline{f})$, indicating that the partial derivative is taken under the condition $\sum_{\alpha=1}^{k} x_\alpha = 1$; the additional (Lagrange multiplier) $\overline{f}$ ensures this constraint. Equation (1.81) indicates that the proportions x_α 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 $-\ln \overline{f}(\{x_\alpha\})$. The change in fitness from one generation to next is given by

$$\overline{f}' - \overline{f} = \sum_{\alpha=1}^{k} (x'_\alpha - x_\alpha) f_\alpha = \sum_{\alpha=1}^{k} \frac{x_\alpha}{\overline{f}} \left(f_\alpha - \overline{f} \right) f_\alpha = \sum_{\alpha=1}^{k} \frac{x_\alpha}{\overline{f}} \left(f_\alpha - \overline{f} \right) \left(f_\alpha - \overline{f} \right) \,, \tag{1.82}$$

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

$$\mathrm{var} f = \sum_{\alpha=1}^{k} x_\alpha \left(f_\alpha - \overline{f} \right)^2 \,, \tag{1.83}$$

in terms of which the change in fitness is given by

$$\overline{f}' - \overline{f} = \frac{\mathrm{var} f}{\overline{f}} \,. \tag{1.84}$$

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

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

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

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

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

$$\begin{aligned}
\Delta x \equiv x' - x &= \frac{1}{\overline{f}}\left[f_{11}x^2 + f_{12}x(1-x) - \overline{f}x\right] \\
&= \frac{1}{\overline{f}}\left[f_{11}x^2 + f_{12}x(1-x) - f_{11}x^3 - 2f_{12}x^2(1-x) - f_{22}x(1-x)^2\right] \\
&= \frac{1}{\overline{f}}\left[f_{11}x^2(1-x) + f_{12}x(1-x)(1-2x) - f_{22}x(1-x)^2\right] \\
&= \frac{x(1-x)}{\overline{f}}\left[\frac{1}{2}\frac{d\overline{f}(x)}{dx}\right] \\
&= \frac{x(1-x)}{2}\frac{d\ln\overline{f}}{dx} \,.
\end{aligned} \tag{1.87}$$

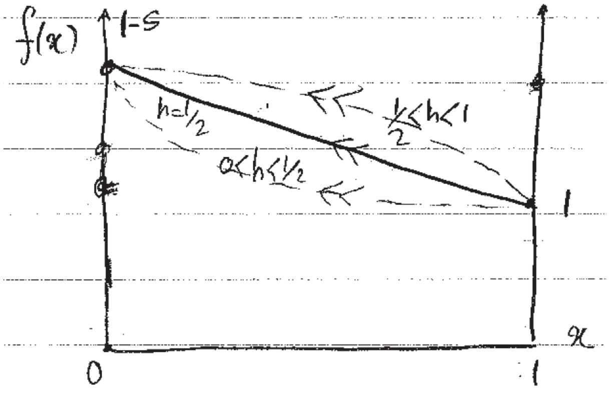
We find that in this case, even from the perspective of the allele, the population changes so as to maximize the mean fitness function, or its logarithm $\ln \overline{f}(x)$. In the above context, this result is known as *Wright's equation.*

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, $x'_{11} = x^2 f_{11}/\overline{f}$, $x'_{12} = 2x(1-x)f_{12}/\overline{f}$ and $x'_{22} = (1-x)^2 f_{22}/\overline{f}$, 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 $x^2 f_{11}/\overline{f}$, $2x(1-x)f_{12}/\overline{f}$ and $(1-x)^2 f_{22}/\overline{f}$. 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.

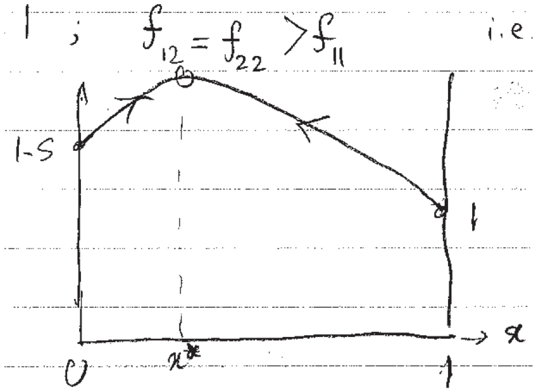
The relative fitness values of the above diploid phenotypes are typically labelled as follows: The "wild-type" A_2A_2 is assigned fitness $f_{22} = 1 - s$, while the homozygote mutant A_1A_1 has fitness $f_{11} = 1$. The *selection coefficient* s quantifies the increased (if $s > 0$) or decreased (when $s < 0$) 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

$$\overline{f} = x^2 + 2x(1-x)(1-hs) + (1-x)^2(1-s) = (1-s) + 2s(1-h)x + s(2h-1)x^2 \,. \quad (1.88)$$

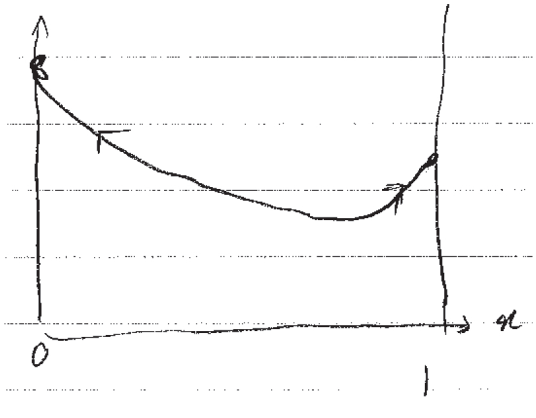
Without loss of generality, we can assume $s > 0$, so that the double mutant (A_1A_1 for $x = 1$) is more fit, and consider the role played by the parameter h. For $h = 1/2$, the fitness function varies linearly with x, with each copy of the allele conferring an additive advantage (of $s/2$) to fitness. Following Eq. (1.87), the population advances monotonically towards the more fit phenotype. Similar monotonic increase of $\overline{f}(x)$ 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. An example of such *heterozygote dominance* is provided by the hereditary disease sickle–cell anemia, which causes deformation of red blood cells. While the double mutant is unfit, the single mutant has some selective advantage as the disease also confers immunity to malaria. 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

$$v(x) = \mu_1(1-x) - \mu_2 x + \frac{x(1-x)}{2}\frac{d\ln \overline{f}}{dx}\,, \tag{1.89}$$

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

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

resulting in

$$p^*(x) \propto \frac{1}{x(1-x)} \times x^{4N\mu_1} \times (1-x)^{4N\mu_2} \times \overline{f}(x)^{2N}\,. \tag{1.90}$$

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-catylitic reactions, consider the case of $h = 1/2$, and $s \ll 1$, where $\overline{f} = 1 - s + sx \approx \exp(-s + sx)$, 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

$$\Delta x = \frac{x(1-x)}{2}s\,. \tag{1.91}$$

We shall not consider more complex situations in which the fitness values f_α (and hence s) are themselves functions of the composition $\{x_\alpha\}$.