

Mathematical Population Genetics

Lecture Notes

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Literature

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What is population genetics? – Basic concepts and definitions

Evolution describes the change in heritable characteristics of biological populations over time. Depending on the type of these characteristics, and depending on the time-scale of interest, we can distinguish different branches of evolutionary research.

- *Phylogenetics* is concerned with the construction of the *tree of life*, following Darwin's insight that all life on earth (and the fossil record) is connected via common ancestors. Changes in traits and characteristics among species, or the emergence of new traits happen over macroevolutionary time-scales, millions or billions of years. Differences among individuals within each species can usually be ignored relative to the differences among species. Each species is therefore generally only represented by a single data point, such as a consensus DNA sequence (“the” human genome).
- *Population genetics* and *quantitative genetics* are interested in the microevolutionary process within a population. Microevolution is concerned with heritable characteristics that differ among individuals in a population and describes how the distribution of these characteristics changes across generations. Going back to Darwin (again) and

to Wallace, the elementary forces that drive these changes are well-understood: mutation, selection, recombination, genetic drift, and gene flow/migration. In contrast to phylogenetics, which basically is a historical science, microevolution has a mechanistic basis that can be used to construct theoretical models and to make predictions for the future.

Genotype and phenotype

Each individual in a population can be characterized by a large number of morphological, physiological, and behavioral traits, which collectively define its *phenotype*. Individual phenotypes may be more or less adapted to the environmental conditions and influence the viability or reproductive success of its carrier. As a consequence, selection operates on phenotypes. Phenotypes themselves are not inherited, but phenotypic characteristics, such as body size, are influenced by heritable and non-heritable factors.

The part of an individual that is directly heritable is its *genotype*. The genotype of each individual is largely encoded in its *genome* and represented by its DNA (DeoxyriboNucleic Acid) sequence. DNA is a polymer consisting of four types of nucleotides, which differ in the *base* that they contain: adenine (A), guanine (G), thymine (T), and cytosine (C). The nucleotides are organized in two polynucleotide chains that form a double-helix with A-T and G-C base pairings. In eukaryotic cells (animals, plants, fungi), the cell nucleus contains several such DNA double strands, called *chromosomes*. In prokaryotic cells (bacteria and archaea), DNA typically forms a single ring (bacterial chromosome). Through development, the genotype determines (the heritable part of) the phenotype, but the connection is exceedingly complex for most phenotypic traits. The genotype naturally decomposes into *genes*, functional units of DNA that encode a single protein. Quantitative traits of interest (such as milk yield in cows) are usually affected by a large number of genes.

Due to the complexity of the genotype-phenotype map, all models of (micro)evolution must rely on simplifying assumptions. Models of quantitative genetics rely on phenotypic data, but often do not resolve individual genes. They rather infer heritable and non-heritable parts of phenotypic traits directly from trait measurements across generations. On the other hand, models of population genetics directly follow the frequencies of genotypes and variants of genes in a population. They often do not refer to phenotypes at all, but assume that selection acts directly on the genes, no matter where the selection pressure comes from and how it is transmitted via the genotype-phenotype map.

Genes, loci, and alleles

Population genetics is concerned with the evolutionary dynamics of genotypes. It follows the frequencies of genetic variants or *alleles* that differ between individuals. The complete genotype of each individual is given by its DNA sequence (≈ 3 billion base pairs in the human genome, ≈ 130 million in *Drosophila*). Usually however, one is only interested in changes at certain aspects of the genotype, such as the genomic positions, or *genetic loci*, that affect a phenotypic trait of interest. On the molecular level, a locus is the position of a

single base in the DNA. There are four alleles, corresponding to the four different bases, A, T, G, and C. Frequently, however, the term locus is used on a coarser level as the position of a gene (or some other significant stretch of sequence). It is always assumed that a locus is a “unit of recombination” that is not broken up during reproduction. There can be many different alleles at a single locus (4^n different alleles for a gene that is represented by a DNA sequence of fixed length n), but usually one considers classes of equivalent alleles. Many population genetic models only distinguish two classes: an ancestral *wildtype* and a *mutant* allele.

Genetic loci can have different levels of *ploidy*. Most simple life forms (bacteria, mosses, algae, fungi) have a single copy of each chromosome, they are *haploid*. For haploids, a single-locus genotype is determined by a single allele. Almost all higher plants and animals are *diploid*, i.e., most of their chromosomes (the so-called *autosomes* = non-sex-chromosomes) are represented twice in each adult cell. Some organisms (mostly plants) have even a higher ploidy level (e.g., *tetraploid* with a 4-fold set). Consequently, single-locus genotypes in diploids are given by a pair of alleles (4 alleles in tetraploids, etc).

Mathematical methods

The art of mathematical modeling is to choose the appropriate mathematical methods to address a scientific question. Since population genetics is concerned with the change of allele frequencies as a function of time, natural mathematical methods come from fields that describe such processes. Often, the main decision for a given problem is to decide whether a deterministic or a stochastic framework is appropriate.

- Deterministic models in population genetics use methods from the theory of dynamical systems and of differential equations (both ODE’s and PDE’s). On the biological side, this is appropriate if stochastic effects due to a finite population size (genetic drift) can be ignored. This is usually the case if selection is the dominant population genetic force and if the total number of individuals that carry a certain allele is not very small. The dynamics can be modeled in discrete time (using discrete dynamical systems) if a generation is a natural time unit in the biological system, like in annual plants. In other cases, a continuous-time dynamics (building on differential equations) is more appropriate. Since both type of models frequently lead to equivalent results, the choice is in practice also a matter of convenience.
- If genetic drift has a strong effect on the evolutionary process, stochastic models are needed. Basically all these models build on Markov processes (assuming that evolution is only affected by the present state of the population, not its entire history), typical examples being birth-death processes or branching processes. As in the deterministic case, they can proceed in discrete or in continuous time. Coalescent theory, in particular, is a stochastic process that proceeds in the reversed time direction, from the present to the past. It turns out that this is particularly appropriate if we want to explain observed patterns of diversity in data by past evolutionary processes. If population sizes are large and if selection is not too strong, allele frequencies can be

treated as a continuous random variable on the unit interval. This leads to diffusion processes as a model of evolutionary change. Indeed, parts of the theory of diffusions was developed in the early 20th century with applications in population genetics in mind.

1 Selection at a single locus

1.1 Selection at a single haploid locus

Consider a haploid population of size N . We characterize the genotype by the allelic type at a single locus. There are k alleles, denoted $\{A_1, \dots, A_k\}$. Generations are discrete and we assume that the population is sufficiently large that stochastic effects due to genetic drift can be ignored. Assume that there are initially n_i individuals with allele A_i . The frequency of A_i in the population is thus $p_i = n_i/N$. Reproduction is clonal, offspring inherit the genotype of their (single) parent, without any modification (no mutation). We are interested in the change of allele frequencies due to selection across a single generation.

Fitness

The fundamental property of individuals that leads to selection and drives adaptive evolution is their fitness. In population genetics, we assign fitness values directly to genotypes or alleles, as follows:

- The *viability* $v_i \geq 0$ measures the probability that a newborn A_i individual survives to reproductive age ($v_i = 0$ means that the individual is inviable).
- The *fecundity* $f_i \geq 0$ measures the expected number of offspring of an adult A_i individual ($f_i = 0$ means that the individual is sterile).
- Finally, the (*absolute*) *fitness* of allele A_i is defined as

$$w_i = v_i \cdot f_i.$$

$w_i \geq 0$ thus measures the *expected number of offspring of a newborn A_i individual*. Ignoring stochastic effects, we thus have $n'_i = w_i n_i$ for the number n'_i of A_i individuals in the next generation.

For the change in a single generation, we obtain

$$N' = \sum_i n'_i = \sum_i w_i n_i = \left(\sum_i w_i p_i \right) N =: \bar{w} N \quad (1.1)$$

where $\bar{w} = \sum_i p_i w_i$ is the *mean fitness* in the population. For the change in allele frequencies, the canonical selection equation for a single haploid locus follows as

$$p'_i = \frac{n'_i}{N'} = \frac{w_i n_i}{\bar{w} N} = \frac{w_i}{\bar{w}} p_i \quad \text{or:} \quad \Delta p_i = p'_i - p_i = \frac{w_i - \bar{w}}{\bar{w}} p_i. \quad (1.2)$$

We see that any fitness differences among alleles that are represented in the population ($w_i \neq w_j$ for $p_i, p_j > 0$) entails evolutionary change due to selection.

For allele frequency changes across multiple generations, we need to account for the fact that absolute fitness values, as defined above, are usually not constant across generations.

Indeed, $w_i = w_i(N, \mathbf{p}, t)$ is usually not only a function of the allelic type A_i , but also of the population size N (or density), the distribution of allele frequencies $\mathbf{p} = (p_1, \dots, p_k)$, and of generation time t .

- Imagine first that fitness does not depend on the population size (or density). We then have $n'_i = w_i(\mathbf{p}, t)n_i$ and usually obtain unlimited growth or decline of n_i over multiple generations. This is clearly unrealistic.
- Assume next that fitness does depend on density, but not on the allelic state. We then have $\bar{w}(N, \mathbf{p}, t) = w_i(N, \mathbf{p}, t) =: w(N, t)$ and thus

$$p'_i = p_i \quad ; \quad N' = w(N, t)N.$$

This means we have only changes in the population size (population dynamics), but no changes in the allele frequencies (population genetics) and thus no evolution. Pure population dynamics is a topic of theoretical ecology. With models like logistic growth ($w(N) = r - cN$), population sizes can be regulated and converge to a finite, non-zero value.

- To obtain a reasonable evolutionary model, we need to combine a model of population regulation with a model of evolutionary change. A canonical approach that is implicit to most models in population genetics is to assume that population size regulation is independent of selection. Absolute fitness values then decompose into two parts

$$w_i(N, \mathbf{p}, t) := w(N, t) \cdot w_i(\mathbf{p}, t).$$

This leads to

$$p'_i = \frac{w_i(N, \mathbf{p}, t)}{\bar{w}} p_i = \frac{w(N, t)w_i(\mathbf{p}, t)}{w(N, t) \sum_i w_i(\mathbf{p}, t)p_i} p_i = \frac{w_i(\mathbf{p}, t)}{\sum_i w_i(\mathbf{p}, t)p_i} p_i \quad (1.3)$$

and the density dependence drops out. Following this idea, population genetic models usually do not work with absolute fitness values, but only the *relative fitness* values. If population size regulation is independent of selection, relative fitnesses are density independent ($w_i = w_i(\mathbf{p}, t)$). We can then ignore changes in the population size in population genetic models and only follow the dynamics of allele frequencies. Note that we use the same symbol w_i for relative fitness. Since all fitness values in the following are *relative* fitness values, this should not lead to any confusion.

- Since any factor that is common to all fitness values w_i drops out of the selection equation, relative fitness values w_i are only defined up to a constant factor. We can use this freedom to normalize the fitness of some reference allele A_1 (often: the ancestral wildtype allele) to $w_1 = 1$.

- Following these leads, the easiest model of selection results if we assume constant *relative* fitness values for all alleles, $w_i = \text{const}$. We say that selection is time homogeneous and frequency-independent. The change in p_i across t generations follows as

$$p_i(t) = \frac{n_i(t)}{N} = \frac{w_i^t n_i(0)}{\sum_j w_j^t n_j(0)} = \frac{w_i^t p_i(0)}{\sum_j w_j^t p_j(0)}. \quad (1.4)$$

If $w_1 > w_j$, $j \geq 2$, we obtain

$$p_i(t) = \frac{p_i(0)}{\sum_j \left(\frac{w_j}{w_i}\right)^t \cdot p_j(0)} \xrightarrow{t \rightarrow \infty} \frac{p_i(0)}{p_1(0) \lim_{t \rightarrow \infty} \left(\frac{w_1}{w_i}\right)^t} = \delta_{1,i}.$$

We conclude that with time-homogeneous and frequency-independent selection in haploids only the fittest allele survives and fixes in the population. There is no genetic variation maintained.

1.2 Selection at a single diploid locus

Consider a diploid locus with two alleles (wildtype and mutant), A and a . In principle, there can be $2 \times 2 = 4$ genotypes at the locus, but if there is no *position effect* (i.e. it does not matter on which DNA strand an allele is located), there are only three: the two *homozygous* genotypes AA and aa and the *heterozygous* genotype Aa ($= aA$). Let x , y , and z be the frequencies of genotypes AA , Aa , and aa , respectively. We can express the frequencies $p = x + y/2$ of the A allele and $q = z + y/2$ of the a allele in terms of the genotype frequencies, but note that this is generally not possible vice-versa.

Random mating and Hardy-Weinberg proportions

To describe evolutionary dynamics in diploids, even without selection, we first need a model for the change in genotype frequencies under reproduction. Most diploids reproduce sexually. Under *Mendelian inheritance*, each newborn inherits a single allele from both parents at each autosomal locus. In general, the change of genotype frequencies across generations depends on the mating pattern. For example, males and females often prefer mating partners with similar phenotypic characteristics such as body size (assortative mating). However, the simplest mating scheme that is also used by *default* in population genetic models just assumes that matings are random. We also assume that sexes are equivalent and there are no differences in genotype frequencies among males and females in the population (this is necessarily true for monoecious species, where all individuals act in male and female roles). We can then summarize the offspring frequencies for each mating type in a table:

The third column of the table gives the probability of the mating pair under random mating and columns 4 to 6 the genotype frequencies in the offspring generation under Mendelian inheritance, conditioned on the mating pair. The total (unconditioned) genotype frequencies in the offspring generation derived by summing over all mating pairs. We observe:

♀	♂	mating prob.	x'	y'	z'
AA	AA	x^2	1	0	0
	Aa	xy	1/2	1/2	0
	aa	xz	0	1	0
Aa	AA	xy	1/2	1/2	0
	Aa	y^2	1/4	1/2	1/4
	aa	yz	0	1/2	1/2
aa	AA	xz	0	1	0
	Aa	yz	0	1/2	1/2
	aa	z^2	0	0	1

$$x' = 1 \cdot x^2 + 2 \frac{1}{2} xy + \frac{1}{4} y^2 = \left(x + \frac{y}{2}\right)^2 = p^2$$

$$y' = 2 \frac{1}{2} xy + 2 \frac{1}{2} yz + 2xz + \frac{1}{2} y^2 = 2\left(x + \frac{y}{2}\right)\left(z + \frac{y}{2}\right) = 2pq$$

$$z' = 1 \cdot z^2 + 2 \frac{1}{2} yz + \frac{1}{4} y^2 = \left(z + \frac{y}{2}\right)^2 = q^2$$

- The genotype frequencies after a single generation of random mating are determined by the allele frequencies, $(x', y', z') = (p^2, 2pq, q^2)$: *Hardy-Weinberg proportions*.
- The allele frequencies do not change under random mating

$$p' = x' + \frac{1}{2}y' = p \quad ; \quad q' = z' + \frac{1}{2}y' = q.$$

There is thus no loss of genetic variation under Mendelian inheritance.

- The so-called *Hardy-Weinberg law* states that, after a single generation of random mating, both the allele frequencies and the genotype frequencies remain invariant: They are in *Hardy-Weinberg equilibrium*.
- It is easy to extend the Hardy-Weinberg law to an arbitrary number of alleles $\{A_1, \dots, A_k\}$. Let $P_{ij} = P_{ji}$ denote the frequency of the genotype $A_i A_j$. The allele frequency of A_i is $p_i = P_{ii} + \frac{1}{2} \sum_{j \neq i} P_{ij}$. A straight-forward extension of the 2-allele derivation shows that $p'_i = p_i$, $P'_{ii} = p_i^2$ and, for $j \neq i$, $P'_{ij} = 2p_i p_j$.

The important consequence of the Hardy-Weinberg (HW) law for population genetic models is that it is sufficient to follow k allele frequencies, rather than the $k(k+1)/2$ frequencies of diploid genotypes. However, the law is only valid under a number of assumptions.

- Random mating: with other mating schemes (e.g. assortative mating or selfing), we obtain different equilibrium frequencies *and* generally only gradual (asymptotic) convergence to this equilibrium, rather than convergence in a single generation.
- Discrete Generations: Convergence to HW proportions is only asymptotic if generations are overlapping (individuals do not all reproduce and die at the same time).
- Equivalent sexes: If the initial allele frequencies in males and females differ, HW proportions are only reached in two generations of random mating.
- Autosomal loci: For X -linked loci (that are diploid in females, but haploid in males), HW proportions are only reached asymptotically.

- No selection, mutation, or drift: all evolutionary forces readily lead to deviations from HW proportions. However, as we will see below, we can often still make use of the HW law at certain stages of a diploid *life cycle*.

Viability selection at a single diploid locus

Consider a diploid population with discrete generations and equivalent sexes and a single locus with two alleles, A and a with frequencies p and q , respectively. We also assume that selection acts on the viability, the probability that newborn diploid individuals reach reproductive age (i.e., all fertilities are equal). We can then dissect the life-cycle of the population into two phases: a selection phase, during which juveniles grow up and a reproductive phase where adults mate and produce offspring. The key assumption is that selection and reproduction can be separated and occur at different stages.

- Consider the reproductive phase first. If reproduction works via random mating as described above, we can use the results of the HW law: Allele frequencies are conserved during the reproductive step and genotype frequencies will be in HW equilibrium directly after reproduction (at the stage of the *zygotes* = newly fertilized eukaryotic cell, not yet affected by selection).
- To model the change of allele and genotype frequencies during the selection phase, we assign fitness values w_{AA} , w_{Aa} , and w_{aa} to the three genotypes AA , Aa , and aa , respectively. The genotype frequencies are P_{AA} , P_{Aa} , and P_{aa} , and the allele frequencies are $p = P_{AA} + P_{Aa}/2$ and $q = P_{aa} + P_{Aa}/2$. The frequency of the genotypes after selection, denoted as \tilde{P}_{AA} , etc, is given by the usual single-generation selection equation,

$$\tilde{P}_{AA} = \frac{w_{AA}}{\bar{w}} = p^2 \frac{w_{AA}}{\bar{w}}; \quad \tilde{P}_{Aa} = \frac{w_{Aa}}{\bar{w}} = 2pq \frac{w_{Aa}}{\bar{w}}; \quad \tilde{P}_{aa} = \frac{w_{aa}}{\bar{w}} = q^2 \frac{w_{aa}}{\bar{w}}.$$

For the allele frequencies, we derive

$$\tilde{p} = p^2 \frac{w_{AA}}{\bar{w}} + \frac{1}{2} 2pq \frac{w_{Aa}}{\bar{w}} = p \frac{w_{AA}p + w_{Aa}q}{\bar{w}} = p \frac{w_A}{\bar{w}}; \quad \tilde{q} = q \frac{w_{aa}q + w_{Aa}p}{\bar{w}} = q \frac{w_a}{\bar{w}},$$

where

$$w_A = w_{AA}p + w_{Aa}q, \quad w_a = w_{aa}q + w_{Aa}p.$$

are the so-called *marginal fitness* values for the alleles A and a . The mean fitness can be expressed in terms of the marginal fitnesses as

$$\bar{w} = w_{AA}P_{AA} + w_{Aa}P_{Aa} + w_{aa}P_{aa} = w_A p + w_a q.$$

With these definitions, the changes in genotype and allele frequencies over a life cycle can be summarized in the following table.

	AA	Aa	aa	A	a
frequency after random mating	$P_{AA} = p^2$	$P_{Aa} = 2pq$	$P_{aa} = q^2$	p	q
frequency after selection	$\tilde{P}_{AA} = p^2 \frac{w_{AA}}{\bar{w}}$	$\tilde{P}_{Aa} = 2pq \frac{w_{Aa}}{\bar{w}}$	$\tilde{P}_{aa} = q^2 \frac{w_{aa}}{\bar{w}}$	$\tilde{p} = p \frac{w_A}{\bar{w}}$	$\tilde{q} = q \frac{w_a}{\bar{w}}$
next gener. frequency after random mating	$P'_{AA} = p'^2$	$P'_{Aa} = 2p'q'$	$P'_{aa} = q'^2$	$p' = \tilde{p}$	$q' = \tilde{q}$

Note that the diploid selection equation for the allele frequencies takes the same functional form as in the haploid case if we replace the allelic fitness value by the corresponding marginal fitness. Note that the marginal fitnesses are not constant, but change with the genetic composition of the population. In general, they depend on the full *genotype frequencies* and the equations on the level of *allele frequencies* do not form a closed dynamical system. However, in the special case of random mating and viability selection, however, we can express genotype frequencies as HW proportions and the dynamical system for the allele frequencies closes.

Selection scenarios

We have seen that viability selection on a single diploid locus with random mating leads to a selection equation that is formally equivalent to the haploid case. The difference is that the marginal fitness values for the alleles depend on the allele frequencies, even if the genotypic fitness values are constant. This leads to differences in the evolutionary dynamics. To characterize these differences, we use the following classical parametrization of the genotypic fitness values.

$$w_{aa} = 1 \quad \text{normalization of the (relative) wildtype fitness} \quad (1.5a)$$

$$w_{AA} = 1 + s \quad s: \text{selection coefficient for the homozygote mutant} \quad (1.5b)$$

$$w_{Aa} = 1 + hs \quad h: \text{dominance coefficient for heterozygote fitness} \quad (1.5c)$$

Depending on the value of the dominance coefficient, we distinguish the following biological scenarios for the mutant allele A

$$h \begin{cases} > 1 & \text{overdominant} \\ = 1 & \text{(fully) dominant} \\ \in (\frac{1}{2}, 1) & \text{partially dominant} \\ = \frac{1}{2} & \text{codominant (or no dominance)} \\ \in (0, \frac{1}{2}) & \text{partially recessive} \\ = 0 & \text{(fully) recessive} \\ < 0 & \text{underdominant} \end{cases}$$

For all cases, the marginal allele fitnesses and mean fitness in HW equilibrium follow as

$$w_a = 1 + p \cdot hs \quad (1.6a)$$

$$w_A = 1 + q \cdot hs + p \cdot s \quad (1.6b)$$

$$\bar{w} = 1 + 2pq \cdot hs + p^2 \cdot s \quad (1.6c)$$

and the allele frequency change per generation of the mutant allele is

$$\Delta p = p' - p = \frac{w_A - \bar{w}}{\bar{w}} p = pq \frac{s(h + (1 - 2h)p)}{\bar{w}}.$$

In contrast to the haploid case, there is usually no explicit solution for the allele frequency $p(t)$ as a function of time. However, it is straightforward to derive the equilibrium frequencies of the dynamical system. We have $\Delta p = 0$ for

$$\begin{aligned} p = 0 \quad , \quad p = 1 \quad [\Leftrightarrow q = 0] & \quad (\text{monomorphic equilibria}) \\ h + (1 - 2h)p = 0 \quad \Rightarrow \quad p = \hat{p} = \frac{h}{2h - 1} & \quad (\text{polymorphic equilibrium}) \end{aligned}$$

The equilibrium at \hat{p} is in the interior of the frequency space, $0 < \hat{p} < 1$, if and only if either $h > 1$ (A is overdominant) or $h < 0$ (A is underdominant). We can distinguish three parameter ranges, based on the dominance coefficient, that lead to qualitatively different dynamical behavior.

1. In the whole parameter range $0 \leq h \leq 1$, ranging from complete recessiveness to complete dominance of the mutant allele A , we have

$$h + (1 - 2h)p > 0 \quad \text{for} \quad 0 < p < 1$$

and thus $\Delta p > 0$ for a beneficial mutant ($s > 0$), resp. $\Delta p < 0$ for a deleterious mutant ($s < 0$). The dynamical system therefore converges monotonically either to the equilibrium at $p = 1$ or to $p = 0$ for the beneficial or deleterious case, respectively.

2. If an equilibrium \hat{p} at an intermediate frequency exists, we can write

$$\Delta p = \frac{pqs(2h - 1)}{\bar{w}} (\hat{p} - p).$$

With $s > -1$, we also have

$$\bar{w} - pqs(2h - 1) = 1 + 2pqhs + p^2s - pqs(2h - 1) = 1 + ps > 0.$$

We therefore obtain monotone convergence of $p(t)$ toward the polymorphic equilibrium \hat{p} for the overdominant case ($h > 1$) if $s > 0$ and for the underdominant case ($h < 0$) if $s < 0$. In both cases, the heterozygote is the fittest genotype (*heterozygote advantage*). Note that an underdominant allele A corresponds to an overdominant allele a . The term *overdominance* is often used as synonymous to *heterozygote advantage*, implicitly using the allele with the higher fitness as reference.

3. Analogously, we find monotonic divergence from \hat{p} toward either $p = 0$ or $p = 1$ for the underdominant beneficial case ($h < 0$ and $s > 0$) and for the overdominant deleterious case ($h > 1$ and $s < 0$).

We see that heterozygote advantage (“overdominance”) is necessary and sufficient for the maintenance of genetic variation under selection at a single diploid locus. With $\bar{w} = 1 + 2p(1-p)hs + p^2s$ we have

$$\frac{\partial \bar{w}}{\partial p} = 2s(h + p(1 - 2h))$$

and thus

$$\Delta p = \frac{1}{2} pq \frac{1}{\bar{w}} \frac{\partial \bar{w}}{\partial p} = \frac{pq}{2} \frac{\partial \ln \bar{w}}{\partial p}.$$

We can therefore understand the evolutionary dynamics also as a process in the direction of increasing mean fitness \bar{w} . This is an example of *Fisher’s fundamental theorem* (see below). Mathematically, this means that \bar{w} is a so-called Lyapunov function of the dynamics.

Multiple alleles

It is easy to extend the 2-alleles case for a single diploid locus to the general case of k alleles, $\{A_1, \dots, A_k\}$ with frequencies $\{p_1, \dots, p_k\}$. Let $w_{ij} = w_{ji}$ be the fitness value of genotype $A_i A_j$, with frequency P_{ij} in the population. After random mating, the population is in HW equilibrium, thus $P_{ii} = p_i^2$ and $P_{ij} = 2p_i p_j$ for $i \neq j$. The marginal allelic fitnesses and the mean fitness are

$$w_i = \sum_j w_{ij} p_j \quad , \quad \bar{w} = \sum_i w_i p_i = \sum_{i,j} w_{ij} p_i p_j$$

and the change in allele frequencies is

$$p'_i = \frac{w_i}{\bar{w}} p_i \quad \text{resp.} \quad \Delta p_i = p'_i - p_i = \frac{w_i - \bar{w}}{\bar{w}} p_i. \quad (1.7)$$

Using

$$w_i = \frac{1}{2} \frac{\partial \bar{w}}{\partial p_i} \quad \text{and} \quad \bar{w} = \frac{1}{2} \sum_i p_i \frac{\partial \bar{w}}{\partial p_i}$$

we can also write

$$\Delta p_i = \frac{p_i}{2\bar{w}} \left(\frac{\partial \bar{w}}{\partial p_i} - \sum_j p_j \frac{\partial \bar{w}}{\partial p_j} \right) \quad (1.8)$$

Defining

$$\vec{\nabla}(\ln \bar{w}) = \left(\frac{\partial \ln \bar{w}}{\partial p_1}, \dots, \frac{\partial \ln \bar{w}}{\partial p_k} \right)^{(t)}$$

$(\dots)^{(t)}$ denoting transposition, and

$$\mathbf{G} = \begin{pmatrix} p_1(1-p_1) & -p_1 p_2 & -p_1 p_3 & \cdots \\ -p_2 p_1 & p_2(1-p_2) & p_2 p_3 & \cdots \\ \vdots & & \ddots & \end{pmatrix}$$

we can write the evolution equation in matrix form,

$$\Delta \mathbf{p} = \frac{1}{2} \mathbf{G} \cdot \vec{\nabla}(\ln \bar{w}). \quad (1.9)$$

Here, the *selection gradient* $\vec{\nabla}(\ln \bar{w})$ is a vector that points into the direction of steepest ascent in mean fitness \bar{w} . \mathbf{G} is the covariance matrix of allele frequencies ($\mathbf{G}_{ij} = \text{cov}[r_i, r_j]$, where $r_i = 1$ if a randomly drawn allele is A_i and zero otherwise). The diagonal elements $p_i(1-p_i)$ are the variances of Bernoulli distributions with parameter p_i , they are largest for $p_i = 1/2$. We see that selection does not necessarily drag a population into the direction of steepest fitness increase (direction of $\vec{\nabla}(\ln \bar{w})$), but always needs to “work on” genetic variation that is present in the population. Evolution proceeds in a direction where the fitness gain *times the genetic variation* is largest.

- In the case of *multiplicative fitness*, $w_{ij} = v_i v_j$, the mean fitness factorizes as $\bar{w} = (\sum_j v_j p_j)^2 =: \bar{v}^2$ and the marginal fitness is $w_i = v_i \sum_j v_j p_j = v_i \bar{v}$. The change in allele frequencies therefore becomes

$$\Delta p_i = \frac{v_i - \bar{v}}{\bar{v}}$$

and reproduces the dynamics of the haploid case. The haploid dynamics is therefore a special case of the diploid dynamics. Also, multiplicative fitness is the only case where selection does not lead to deviations from HW equilibrium.

- The equilibrium structure of the diploid dynamics can be complex. There are clearly at least k equilibria (all monomorphic states). In general, we have either $p_i = 0$, or $w_j = \bar{w}$ for all j with $p_j \neq 0$, at any equilibrium. For each choice of a (potentially empty) subset $S \subset \{1, \dots, k\}$, with $p_i = 0$ for $i \in S$ and $p_j > 0$ for $j \notin S$ (with j_1 the smallest index with $p_j > 0$), we can express the equilibrium condition as a linear equation system

$$\begin{aligned} p_i &= 0, & i \in S \\ w_j &= w_{j_1}, & j \notin S, j > j_1 \\ \sum_{i=1}^k p_i &= 1. \end{aligned} \quad (1.10)$$

There are $2^k - 1$ such equation systems for different choices of the subsets S . Each system has either zero, one, or infinitely many solutions. We conclude that in non-degenerate cases with a finite number of equilibria there are at most $2^k - 1$ equilibrium points. In particular, there is at most a single fully polymorphic equilibrium with $p_i > 0$ for all i .

- An easy example of a system with $2^k - 1$ coexisting equilibria is given by the fitness values $w_{ii} = 1$ for all i and $w_{ij} = 0$ for $i \neq j$. Frequently one is interested in the number of *stable* equilibria that can coexist. The maximum number of coexisting stable equilibria for a single diploid locus with k alleles is unknown.

- One can show that dominance of the fitter allele for all pairs of alleles is a necessary condition for a *stable fully polymorphic equilibrium*,

$$w_{ij} > \frac{w_{ii} + w_{jj}}{2}, \quad \forall i \neq j$$

[see Nagylaki 1992, p. 62]. However, pairwise overdominance, $w_{ij} > \max[w_{ii}, w_{jj}]$, is *not* necessary, while the stronger condition of *global overdominance*, $w_{ij} > \max_k w_{kk}$, is in general not sufficient. Computer simulations show that overdominance alone is not very efficient in maintaining many alleles segregating at a single locus.

- Since mean fitness is non-decreasing (see below) and thus a Lyapunov function, we can exclude cycling behavior for the dynamics.

Theorem: Mean fitness does not decrease [following Nagylaki 1992, p. 57/58]
Mean fitness is a non-decreasing function under selection on a single diploid locus, $\bar{w}' \geq \bar{w}$.
For a proof, we use *Jensen's inequality*

$$\sum_i p_i x_i^\alpha \leq \left(\sum_i p_i x_i \right)^\alpha, \quad \alpha \leq 1; \quad p_i \text{ probabilities}$$

to obtain a lower bound for the mean fitness \bar{w}' of the offspring generation,

$$\begin{aligned} \bar{w}' &= \sum_{ij} p'_i p'_j w_{ij} = \frac{1}{\bar{w}^2} \sum_{ij} p_i w_i p_j w_j w_{ij} && / w_i = \sum_k p_k w_{ik} \\ &= \frac{1}{\bar{w}^2} \sum_{i,j,k} p_i p_j p_k w_{ij} w_{ik} \frac{w_j + w_k}{2} = \frac{1}{\bar{w}^2} \sum_{i,j,k} p_i p_j p_k w_{ij} w_{ik} \frac{w_j + w_k}{2} && / (a + b) \geq 2\sqrt{ab} \\ &\geq \frac{1}{\bar{w}^2} \sum_{i,j,k} p_i p_j p_k w_{ij} w_{ik} (w_j w_k)^{1/2} = \frac{1}{\bar{w}^2} \sum_i p_i \left(\sum_j p_j w_{ij} w_j^{1/2} \right)^2 && / \text{(Jensen)} \\ &\geq \frac{1}{\bar{w}^2} \left(\sum_i p_i \sum_j p_j w_{ij} w_j^{1/2} \right)^2 = \frac{1}{\bar{w}^2} \left(\sum_j p_j w_j^{3/2} \right)^2 && / \text{(Jensen)} \\ &\geq \frac{1}{\bar{w}^2} \left(\left(\sum_j p_j w_j \right)^{3/2} \right)^2 = \bar{w} \end{aligned} \tag{1.11}$$

Continuous time model for selection

Mathematically, our model so far for the evolutionary dynamics has been a discrete dynamical system. A model in discrete time is realistic for some biological species (e.g. annual plants), it has some technical advantages (in particular, it allows for a separation of reproduction and selection) and it is easy to simulate on a computer. However, we have also seen that the number of explicit mathematical results that we can obtain is limited. It is

often more convenient (and/or more realistic biologically) to model evolution in continuous time. As we will see, we naturally obtain such a model if we study the discrete time model in a limit of weak selection. To this end, consider again a single locus with k alleles, $\{A_1, \dots, A_k\}$ with genotypic and marginal fitness values defined as

$$w_{ij} := 1 + \varepsilon m_{ij}; \quad w_i = 1 + \varepsilon m_i; \quad m_i = \sum_j m_{ij} p_j$$

and corresponding mean fitness

$$\bar{w} = 1 + \varepsilon \bar{m}; \quad \bar{m} = \sum_{i,j} m_{ij} p_i p_j$$

The dynamical equation reads

$$\Delta p_i = p'_i - p_i = \frac{\varepsilon (m_i - \bar{m})}{1 + \varepsilon \bar{m}} p_i.$$

Assume now that fitness differences per generation are small (weak selection), generation time is short (we thus have many generations per unit time interval). This can be done by scaling both fitness differences and generation time by ε . In the limit of $\varepsilon \rightarrow 0$, we then obtain

$$\dot{p}_i = \frac{dp_i(t)}{dt} = \lim_{\varepsilon \rightarrow 0} \frac{p_i(t + \varepsilon) - p_i(t)}{\varepsilon} = \lim_{\varepsilon \rightarrow 0} \frac{p'_i - p_i}{\varepsilon}$$

and thus

$$\dot{p}_i(t) = (m_i - \bar{m}) p_i. \tag{1.12}$$

This is the evolution equation in continuous time. Note that m_i and \bar{m} depend on all allele frequencies and \bar{m} is quadratic in the p_j . We thus have a system of coupled non-linear ordinary differential equations.

- The m_{ij} and m_i are also called *Malthusian fitness* parameters (or *log fitness*). They have the interpretation of growth rates per generation,

$$m_i = \lim_{\varepsilon \rightarrow 0} \frac{\log w_i}{\varepsilon}.$$

- The continuous-time evolution equation can alternatively be derived from a growth model with overlapping generations, where birth and death events occur continuously with given rates [e.g. Rice 2004, p. 15-17]. We note that the ODE (1.12) is only approximate, since a diploid population under selection in continuous time will always deviate from HW equilibrium (unless Malthusian fitness is additive, $m_{ij} = m_i + m_j$). Deviations only vanish in the limit of weak selection. A comprehensive derivation should also account for age structure in a population, with birth and death rates depending on age [see Nagylaki 1992 for a detailed model]. In this case, the dynamics can be much more complicated, but can reproduce (1.12) after the population has reached a *stable age distribution* [see the *Mathematical ecology* lecture for more on age-structured populations].

Sir Ronald A. Fisher, 1890–1962, is well-known for both his work in statistics and genetics. He is one of the founding fathers of population genetics (together with JBS Haldane and S Wright) that combined Darwinian selection and Mendelian inheritance in the so-called *Modern Synthesis* and led to the breakthrough of Darwinism in the early 20th century. Fisher's 1930 article on *The Genetical Theory of Natural Selection* defined large parts of the field. In statistics, Fisher's key achievement was his invention of the analysis of variance, or ANOVA. This statistical procedure allows to connect the observed deviations in experimental data to different controlled and uncontrolled underlying factors. It constituted a notable advance over the prevailing procedure of varying only one factor at a time in an experiment. Fisher summed up his statistical work in his book *Statistical Methods and Scientific Inference* (1956). Fisher became Galton Professor of Eugenics at University College, London in 1933. From 1943 to 1957 he was Balfour Professor of Genetics at Cambridge. He was knighted in 1952 and spent the last years of his life conducting research in Australia (adapted from Encyclopedia Britannica and Wikipedia).

- The continuous-time single-locus selection dynamics has the same equilibria as the discrete-time model and does therefore not lead to a simplification for this particular problem. However, as we will see below and in the next section, model derivations and extensions to include further evolutionary forces are often easier in continuous time.
- It is straightforward to show that mean Malthusian fitness is non-decreasing under (1.12),

$$\begin{aligned}
 \dot{\bar{m}} &= \sum_{ij} m_{ij}(\dot{p}_i p_j + p_i \dot{p}_j) = 2 \sum_{ij} m_{ij} p_i p_j (m_i - \bar{m}) \\
 &= 2 \sum_i p_i m_i (m_i - \bar{m}) = 2 \sum_i p_i (m_i - \bar{m})(m_i - \bar{m}) \\
 &= 2V_g
 \end{aligned} \tag{1.13}$$

where $V_g > 0$ is the *genetic variance in fitness*. We thus see that the increase in mean fitness is not just non-negative, but is always given by (twice) the current variance in fitness in the population. This is the assertion of *Fisher's fundamental theorem of natural selection* that goes back to R.A. Fisher (1930) and has been discussed in many population genetic textbooks. However, this theorem is only exact for a single locus in continuous time and only holds approximately for discrete time and in more general evolutionary situations.

1.3 Mutation-selection models

The ultimate source of all genetic variation in a population is mutation. So far, we have assumed that genetic variation is just given as an initial condition and have not modeled

its creation explicitly. Since selection is usually a much stronger force than mutation and leads to allele frequency changes over shorter time scales, this is often a reasonable approximation. However, for a more complete description of evolution over longer time scales, we need to include mutation into the model.

Only mutation

Usually, mutation occurs during reproduction (or: the production of gametes) due to errors in DNA copying. Each generation, there is a probability that an offspring individual does not inherit the allelic state of (one of) its parent(s), but rather a mutated allele. For a single locus and two alleles, A and a , assume that there is a fixed probability μ that an ancestor carrying the ancestral allele a produces an offspring with A allele. Vice-versa, there is a probability ν that A mutates back to a during reproduction. If the frequency of A alleles is p , the single-generation dynamics reads

$$\Delta p = p' - p = \mu(1 - p) - \nu p \quad (1.14)$$

with equilibrium ($\Delta p = 0$)

$$p = \hat{p} = \frac{\mu}{\mu + \nu}.$$

For an arbitrary number of alleles A_1, \dots, A_k and mutation probability from allele A_i to allele A_j denoted as μ_{ij} ($= \mu_{i \rightarrow j}$), we can define a *mutation matrix* \mathbf{U} as follows

$$U_{ij} = \mu_{ij}, \quad i \neq j; \quad U_{ii} = 1 - \sum_{j \neq i} \mu_{ij}. \quad (1.15)$$

With $\mathbf{p} = (p_1, \dots, p_k)$ the probability vector of allele frequencies, we can then write the evolution equation in matrix form as

$$\mathbf{p}' = \mathbf{p} \cdot \mathbf{U} \quad \text{and} \quad \mathbf{p}^{(n)} = \mathbf{p} \cdot \mathbf{U}^n \quad \text{for } n \text{ generations.} \quad (1.16)$$

We note the following

- The mutation matrix \mathbf{U} is a stochastic matrix that transforms probability vectors into probability vectors. All entries are non-negative and all rows of the matrix sum to 1.
- Assume that \mathbf{U} is *irreducible* and *aperiodic*. This is always the case, in particular, if all diagonal entries are positive (all alleles can be inherited without being mutated) and if we can get from each allele state to any other allele through mutation (or a series of mutations). Then we can use the *Perron-Frobenius theorem* to conclude that \mathbf{U} has a unique largest eigenvalue $\lambda_{\max} = 1$ with corresponding left eigenvector \mathbf{p}_{\max} that holds the equilibrium frequencies of the alleles A_1 to A_k under mutation. [See e.g. the lecture *Mathematical Ecology* for a proof of the Perron-Frobenius theorem.]
- Note that the mutation dynamics is the same for haploids or diploids.

Mutation and selection in discrete time

In discrete time, we can simply include mutation as a separate step into the life cycle. We define the allele frequency change during one generation, starting with newborn zygotes, as $p_i \rightarrow p_i^{(s)} \rightarrow p'_i$ with

$$p_i^{(s)} = \frac{w_i}{\bar{w}} p_i, \quad (1.17a)$$

$$p'_i = \left(1 - \sum_j \mu_{ij}\right) p_i^{(s)} + \sum_j \mu_{ji} p_j^{(s)}. \quad (1.17b)$$

The scheme applies to both haploids and (random mating) diploids, with w_i as marginal fitness for diploids. The first step accounts for viability selection, the second step for mutation during reproduction. It is easy to check that mutation in HW equilibrium changes the allele frequencies, but maintains HW proportions.

In the haploid case, we can still write down the explicit solution of the evolutionary process. Defining the *mutation-selection matrix* $\mathbf{C} = \mathbf{W} \cdot \mathbf{U}$, where \mathbf{U} is the mutation matrix (1.15) and $\mathbf{W} = \text{diag}[w_1, w_2, \dots]$ is the diagonal matrix holding the fitness values, we obtain

$$\mathbf{p}' = \frac{\mathbf{p} \cdot \mathbf{C}}{\bar{w}}, \quad (1.18a)$$

$$\mathbf{p}(t) = \frac{\mathbf{p}(0) \cdot \mathbf{C}^t}{\sum_i [\mathbf{p}(0) \cdot \mathbf{C}^t]_i}. \quad (1.18b)$$

The denominator in both equations just serves for the normalization of the frequency vector. If the matrix \mathbf{C} is primitive (aperiodic and irreducible), there is a unique globally stable and fully polymorphic equilibrium of the dynamics.

Perturbation analysis

For the diploid mutation-selection equation, there is no explicit solution and multiple equilibria can exist (just like for the case without mutation). For two alleles A and a , genotypic fitnesses as in Eq. (1.5), and forward and backward mutation rates μ and ν , respectively, the frequency change of the mutant allele A is

$$p' = f(p) = (1 - \nu) \frac{w_A}{\bar{w}} p + \mu \left(1 - \frac{w_A}{\bar{w}} p\right) \quad (1.19)$$

with

$$w_A = 1 + (1 - p) \cdot hs + p \cdot s \quad (1.20a)$$

$$\bar{w} = 1 + 2p(1 - p) \cdot hs + p^2 \cdot s \quad (1.20b)$$

as in Eq. (1.6). The equilibrium points $\hat{p} = f(\hat{p})$ are zeros of a third-order polynomial. Since the absorption points $\hat{p} = 0$ and $\hat{p} = 1$ are no longer equilibria, the exact solution is

no longer a simple expression. However, we can make use of the fact that mutation rates are usually very small ($\sim 10^{-8}$ per base or $\sim 10^{-5}$ per gene and generation). Because we know the solution in the absence of mutation, we can obtain an approximate solution for the mutation-selection dynamics by means of perturbation analysis. Since this is a technique that can be used more generally, we will present the steps in some detail, with the above problem as application.

Step 1 Identify the small parameters of the problem and write them as a product of a constant times a small perturbation parameter ε ,

$$\mu = \tilde{\mu} \cdot \varepsilon; \quad \nu = \tilde{\nu} \cdot \varepsilon.$$

This way, the dynamical equation (1.19) becomes a function of ε , $p' = f(\varepsilon, p)$.

Step 2 Write the (unknown) equilibrium solution as a formal power series in ε ,

$$\hat{p}(\varepsilon) := \hat{p}_0 + \varepsilon \hat{p}_1 + \varepsilon^2 \hat{p}_2 + \dots$$

and define

$$\begin{aligned} F(\varepsilon) &:= f(\varepsilon, \hat{p}(\varepsilon)) - \hat{p}(\varepsilon) \\ &= (1 - \tilde{\nu}\varepsilon - \tilde{\mu}\varepsilon) \frac{1 + hs(1 - \hat{p}(\varepsilon)) + s\hat{p}(\varepsilon)}{1 + 2hs\hat{p}(\varepsilon)(1 - \hat{p}(\varepsilon)) + s(\hat{p}(\varepsilon))^2} \hat{p}(\varepsilon) + \tilde{\mu}\varepsilon - \hat{p}(\varepsilon). \end{aligned}$$

We can then write the equilibrium condition as $F(\varepsilon) = 0$.

Step 3 Expand $F(\varepsilon)$ into a Taylor series in ε around 0

$$F(\varepsilon) = F(0) + F^{(1)}(0) \cdot \varepsilon + \frac{1}{2}F^{(2)}(0) \cdot \varepsilon^2 + \frac{1}{6}F^{(3)}(0) \cdot \varepsilon^3 + \dots$$

where $F^{(n)}(0) = \partial^n F(\varepsilon) / \partial \varepsilon^n |_{\varepsilon=0}$ denotes the n th derivative of $F(\varepsilon)$ at $\varepsilon = 0$. Assuming that the Taylor series converges, $F(\varepsilon) = 0$ implies $F(0) = 0$ and $F^{(n)} = 0$ for all derivatives.

Step 4 Solve the equations to the order desired.

- (i) $F(0) = 0$ The 0th order leads back to the selection dynamics without mutation.

$$\frac{1 + hs(1 - \hat{p}_0) + s\hat{p}_0}{1 + 2hs\hat{p}_0(1 - \hat{p}_0) + s\hat{p}_0^2} \hat{p}_0 - \hat{p}_0 = 0$$

We can pick any solution of this equation to derive correction terms. Here, we assume that the A mutant is deleterious, $s < 0$, in which case $\hat{p}_0 = 0$ is the stable equilibrium of the selection dynamics in the absence of overdominance.

$$(ii) \quad F^{(1)}(0) = 0$$

$$F^{(1)}(0) = \hat{p}_0 \cdot \frac{\partial}{\partial \varepsilon} \left[(1 - \tilde{\nu}\varepsilon - \tilde{\mu}\varepsilon) \begin{matrix} \cdots \\ \vdots \\ \cdots \end{matrix} \right] + \hat{p}_1 \frac{1 + hs(1 - \hat{p}_0) + s\hat{p}_0}{1 + 2hs\hat{p}_0(1 - \hat{p}_0) + s\hat{p}_0^2} - \hat{p}_1 + \tilde{\mu} = 0$$

Since $\hat{p}_0 = 0$, this results in $\hat{p}_1(1 + hs) - \hat{p}_1 + \tilde{\mu} = 0$ and thus

$$\hat{p}_1 = -\frac{\tilde{\mu}}{hs}. \quad (1.21)$$

$$(iii) \quad F^{(2)}(0) = 0$$

$$\begin{aligned} F^{(2)}(0) &= 2\hat{p}_2(1 + hs) + 2\hat{p}_1 \left[(-\tilde{\nu} - \tilde{\mu} - 2hs\hat{p}_1)(1 + hs) + s\hat{p}_1(1 - h) \right] - 2\hat{p}_2 \\ &= 2hs\hat{p}_2 - \frac{2\tilde{\mu}}{hs} \left[(\tilde{\mu} - \tilde{\nu})(1 + hs) + \tilde{\mu} - \tilde{\mu}/h \right] \end{aligned}$$

using $\hat{p}_0 = 0$ and \hat{p}_1 from (1.21). Thus

$$\hat{p}_2 = \left(\frac{\tilde{\mu}}{hs} \right)^2 \left[1 - \frac{1}{h} + \left(1 - \frac{\tilde{\nu}}{\tilde{\mu}} \right) (1 + hs) \right]. \quad (1.22)$$

Step 5 Collect all terms in $\hat{p}(\varepsilon)$, using the original biological parameters $\tilde{\mu}\varepsilon = \mu$ and $\tilde{\nu}\varepsilon = \nu$,

$$\hat{p} = \frac{\mu}{|hs|} + \left(\frac{\mu}{|hs|} \right)^2 \left[1 - \frac{1}{h} + \left(1 - \frac{\nu}{\mu} \right) (1 - |hs|) \right] + \mathcal{O}[\varepsilon^3]. \quad (1.23)$$

We see that frequency of a deleterious mutant in mutation-selection balance is

$$\hat{p} \approx \frac{\mu}{|hs|} \quad (1.24)$$

as long as selection is much stronger than mutation, $|hs| \gg \mu$. Back mutations do not affect this leading-order result.

In our derivation above, we have derived an approximation for the equilibrium frequency in mutation-selection balance, using perturbation theory around the stable equilibrium of the pure selection dynamics. To complete our analysis, we still need to assess the stability of the perturbed equilibrium. For a general discrete dynamical system $p' = f(p)$, an equilibrium point \hat{p} is asymptotically stable if for sufficiently small δ ,

$$|\delta'| = |f(\hat{p} + \delta) - f(\hat{p})| < |\delta|$$

If f is continuously differentiable, we have

$$\delta' = \lambda_{\hat{p}} \cdot \delta + \mathcal{O}(\delta^2); \quad \lambda_{\hat{p}} = \left. \frac{\partial}{\partial p} f(p) \right|_{\hat{p}}$$

and thus a stable equilibrium at \hat{p} if $|\lambda_{\hat{p}}| < 1$. For $|\lambda_{\hat{p}}| > 0$ the equilibrium is unstable, while for $|\lambda_{\hat{p}}| = 1$ stability depends on higher-order derivatives. At an perturbed equilibrium, we derive

$$\begin{aligned}\lambda_{\hat{p}}(\varepsilon) &:= \frac{\partial}{\partial p} f(\varepsilon, p) \Big|_{\hat{p}(\varepsilon) = \hat{p}_0 + \varepsilon \hat{p}_1 + \dots} \\ &= \lambda_{\hat{p}}(0) + \frac{\partial}{\partial \varepsilon} \lambda_{\hat{p}}(\varepsilon) \Big|_{\varepsilon=0} \cdot \varepsilon + \mathcal{O}[\varepsilon^2]\end{aligned}$$

If the unperturbed equilibrium is stable with $|\lambda_{\hat{p}}(0)| = |\lambda_{\hat{p}_0}| < 1$, this implies stability of the perturbed equilibrium for sufficiently small ε . Similarly, $|\lambda_{\hat{p}}| > 1$ implies that also the perturbed equilibrium is unstable. For the mutation-selection dynamics discussed above, we have $\lambda_{\hat{p}} = \lambda_0 = 1 + hs < 1$ for a deleterious mutant. In general, for $hs \neq 0$, the stability of the perturbed equilibrium is the same as the unperturbed one.

Mutation load

The effect of a deleterious mutation on an individual is measured by the corresponding reduction in fitness, given by the selection coefficient s (or by hs in a diploid heterozygote). Similarly, we can assess the effect of a deleterious mutation on the population level by the reduction in mean fitness in mutation-selection balance. The standard measure is the *mutation load*

$$L_m = \frac{w_{\text{opt}} - \bar{w}}{w_{\text{opt}}}, \quad (1.25)$$

where w_{opt} is the fitness of an “optimal” genotype that is free from deleterious mutations. If we normalize the optimal fitness $w_{\text{opt}} = 1$ (as in the mutation model) studied above, we simply have $L_m = 1 - \bar{w}$. With (1.20b) we obtain at the equilibrium $\hat{p} = -\mu/(hs) + \mathcal{O}[\mu^2]$,

$$L_m = -2hs\hat{p} - (s - 2hs)\hat{p}^2 = 2\mu + \mathcal{O}[\mu^2], \quad (1.26)$$

as long as $\mu \ll |hs|$. For arbitrarily many deleterious alleles A_i with mutation rates μ_{i0} from a fittest wildtype a , we obtain more generally

$$L_m = 2 \sum_{i \geq 1} \mu_{i0} + \mathcal{O}[\mu^2].$$

We see that the mutation load depends (to leading order) only on the mutation rates, but not on the fitness effects of the deleterious mutations. The reason is that a milder mutation with small $|hs|$ will segregate at a higher frequency $\hat{p} = \mu/|hs|$ in the population. To leading order, the effects of mutation frequency and mutation size on the mean fitness just cancel. This is also called *Haldane’s rule* or the *Haldane-Muller principle*. This has relevant consequences for programs of public health that aim for an increase of population-level parameters like the mean fitness. Indeed, according to the Haldane-Muller principle, the mean fitness in a population is neither altered by eugenics (birth control for diseased people, effectively increasing the deleterious fitness effect of a mutation) nor by a partial

JBS (John Burdon Sanderson) Haldane, 1892–1964, was a British geneticist, biometrician, physiologist, and popularizer of science who opened new paths of research in population genetics and evolution. Together with R.A. Fisher and Sewall Wright, but in separate mathematical arguments, he related Darwinian evolutionary theory and Gregor Mendel’s laws of heredity. Haldane also contributed to the theory of enzyme action and to studies in human physiology. He possessed a combination of analytic powers, literary abilities, a wide range of knowledge, and a force of personality that produced numerous discoveries in several scientific fields and proved stimulating to an entire generation of research workers.

Haldane announced himself a Marxist in the 1930s but later became disillusioned with the official party line and with the rise of the controversial Soviet biologist Trofim D. Lysenko. In 1957 Haldane moved to India, where he took citizenship and headed the government Genetics and Biometry Laboratory in Orissa (adapted from Encyclopedia Britannica).

Herrmann Joseph Muller 1890–1967, Nobel laureate in Medicine (1946) for his discovery of the mutagenic effect of X-rays was very concerned about the reduction of mean fitness in humans by radiation, also due to nuclear fallout caused by nuclear testing. Together with fellow scientists, he was a vocal critic of nuclear weapons testing (from Wikipedia).

cure of a genetic disease (reduction of $|hs|$). For population-level fitness, mildly deleterious mutations are as harmful as strongly deleterious ones. Only the reduction of mutation rates has a lasting effect on mean fitness.

Mutation and selection in continuous time

There are various ways to write down a mutation-selection equation in continuous time. The most widely used formalism is simply to assume that mutation and selection are independent processes that occur in parallel. This leads to the differential equation

$$\dot{p}_i = (m_i - \bar{m})p_i + \sum_j (\mu_{ji}p_j - \mu_{ij}p_i) \quad (1.27)$$

extending Eq. (1.12). The m_i are Malthusian fitness values (marginal fitnesses for diploids) and the μ_{ij} have the interpretation of mutation rates per time unit. Like for discrete time, the dynamics for haploids is fully solvable also in continuous time. For $m_i = \text{const}$ and $\bar{m} = \sum_i m_i p_i$, we can write

$$\dot{\mathbf{p}} = \mathbf{p} \cdot \mathbf{A} - \mathbf{p} \bar{m} \quad (1.28)$$

with matrix \mathbf{A} with entries $a_{ij} = m_i \delta_{ij} + \mu_{ij} - \sum_l \mu_{il} \delta_{ij}$. Like in the discrete case, the mean fitness \bar{m} is a common factor for all allele frequencies. It enforces normalization of the frequency vector \mathbf{p} during the dynamics, but does not affect the relative size of allele

frequencies p_i/p_j . We thus have a normalized linear dynamics for \mathbf{p} with solution

$$\mathbf{p}(t) = \frac{\exp[\mathbf{p}(0) \cdot \mathbf{A} t]}{\sum_i [\exp[\mathbf{p}(0) \cdot \mathbf{A} t]]_i}. \quad (1.29)$$

For a diploid locus with two alleles a and A , mutation rates μ from a to A and ν from A to a , and Malthusian fitness values

$$m_{aa} = 0; \quad m_{Aa} = hs; \quad m_{AA} = s \quad (1.30)$$

we have $m_A = sp_A + hs(1 - p_A)$ and $\bar{m} = sp_A^2 + 2hsp_A(1 - p_A)$ and Eq. (1.27) results in

$$\dot{p}_A = s(p_A + h(1 - 2p_A))p_A(1 - p_A) + \mu(1 - p_A) - \nu p_A. \quad (1.31)$$

This is a third-order equation unless $h = 1/2$ (case of no dominance), where the diploid dynamics reduces to an effective haploid one ($m_A - \bar{m} = (s/2)(1 - p_A)$), as in the haploid model with $m_A = s/2$ and $\bar{m} = (s/2)p_A$.