Genetic background (simplified)

DNA

Deoxyribonucleic acid; the primary genetic material of a cell; a polymer consisting of four types of nucleotides: adenine (A), guanine (G), thymine (T), and cytosine (C); typically contains two polynucleotide chains in the form of double helix (with A-T and G-C pairings); DNA are the largest biologically active molecules known; three nucleotides code for an amino acid of which there are 20. A protein consists of a few hundred amino acids.

Gene

- Classically, a unit of inheritance transmitted from generation to generation by a gamete (sperm or egg), which controls a particular characteristic of an individual.
- In modern genetics, the basic unit of inheritance comprising a specific sequence of nucleotides on a DNA chain that has a specific function and occupy a specific position (**locus**) on a chromosome; alternative forms of a gene are known as **alleles**.

Table 1: Gene number

Prokaryotes	1,000-8,000
Eukaryotes (except vertebrates)	7,000-15,000
Vertebrates	25,000-100,000

(Prokaryotes are organisms in which the genetic material is not enclosed in a cell nucleus. Bacteria are prokaryotes. Eukaryotes are organisms consisting of cells in which the genetic material in contained within a distinct nucleus. All organisms except bacteria are eukaryotes. Vertebrates are animals that have backbones. Vertebrates include the fishes, amphibians, reptiles, birds and mammals.)

Chromosome is a single thread-like molecule of DNA surrounded by various proteins.

Haploid organisms have a single set of chromosomes (bacteria, algae, mosses, fungi).

Diploid organisms have a double set of chromosomes (higher plants and animals). Humans have 22 matched pairs of chromosomes plus one pair of sex chromosomes.

Gamete is a reproductive cell (sperm or egg) that fuses with another gamete to form a **zygote**. Gametes are haploid. Zygotes develop to whole organisms.

1 One locus systems

1.1 Asexual haploid populations

1.1.1 Basic equations

We consider a population of asexual haploid individuals. We assume that there is no gene exchange between different organisms. Individuals reproduce by division (examples: bacteria, algae, fungi), and each individual has a single parental organism. The population has discrete and non-overlapping generations (that is adults are replaced by their offspring at the end of each generation). Population size is very large (and, thus, stochastic effects can be neglected).

We start with a *simplified* deterministic model assuming that individuals are different with respect to a single locus with k alleles. In other words, there are k different genetic types (=genotypes) of individuals. Few words about notation. We will use different **bold** letters to represent different genes with subscripts to denote different alleles. Thus, in the model under consideration there are k alleles $\mathbf{A}_1, \mathbf{A}_2, \dots, \mathbf{A}_k$.

Let $n_i(t)$ be the number of alleles $\mathbf{A}_i$ at the beginning of the generation t, and $N(t) = \sum_i n_i(t)$ be the (overall) population size. Both $n_i(t)$ and $N(t)$ are assumed to be sufficiently large. The life cycle of the population is illustrated in Figure 1.

Figure 1 will be here

We assume that individuals of different types differ with respect to *viability* v_i (defined as the probability that an $\mathbf{A}_i$ offspring survives to reproductive age) and *fertility* f_i (defined as the average number of offspring of an $\mathbf{A}_i$ adult). The number of alleles $\mathbf{A}_i$ in the next generation can be found easily:

$$n_i(t+1) = v_i\ f_i\ n_i(t)\ \equiv w_i\ n_i(t), \tag{1}$$

where $w_i \equiv v_i f_i$ is the *fitness* of $\mathbf{A}_i$. Here, fitness gives the average number of surviving offspring. Note that if either $v_i = 0$ (that is allele $\mathbf{A}_i$ is lethal) or $f_i = 0$ (that is $\mathbf{A}_i$ is sterile), fitness $w_i = 0$.

Instead of absolute numbers n_i we will mainly use frequencies. The frequency of allele $\mathbf{A}_i$ is

$$p_i(t) = n_i(t)/N(t). \tag{2}$$

Note that $\sum_i p_i = 1$.

Notation: we will use prime to denote the values of different variables in the next generation. For example: p_i', n_i', N'.

It is straightforward to write down the recurrent equations expressing the number of alleles $\mathbf{A}_i$ and the population size N in the next generation as a function of their present values and parameters:

$$n_i' = w_i n_i, \tag{3a}$$

$$N' = \sum_i n_i' = \sum_i w_i n_i = \sum w_i \frac{n_i}{N} N = (\sum w_i p_i) N = \overline{w} N, \tag{3b}$$

where

$$\overline{w} = \sum_i w_i p_i, \tag{4}$$

is the *mean fitness* of the population. By dividing equation (3a) by (3b) one finds the recurrent equation for allele frequencies:

$$p_i' = n_i'/N' = \frac{w_i}{\overline{w}} \frac{n_i}{N} = \frac{w_i}{\overline{w}} p_i. \tag{5}$$

The dynamics of the system under consideration can be completely described in terms of the overall population size and allele frequencies:

$$N' = \overline{w}\ N, \tag{6a}$$

$$p'_i = \frac{w_i}{\overline{w}}\ p_i. \tag{6b}$$

The change in the population size per one generation can be written as

$$\Delta N = N' - N = (\overline{w} - 1)N.$$

Let us write the average fitness of the population as $\overline{w} = 1 + \overline{r}$. Then the above equation can be rewritten as

$$\Delta N = \overline{r}N. \tag{7}$$

Therefore, $\overline{r} \equiv \overline{w} - 1$ gives the *average growth rate of the population* (also called the *Malthusian fitness*).

In general, fitness can depend on a number of factors (e.g. time, population size, population structure etc): $w_i = w_i(t, N, p)$, where p denotes the whole set of allele frequencies, $p = \{p_1, \ldots, p_k\}$. Let us consider some special cases.

- *No selection (i.e., no genetic differences with respect to fitness).* Note that there may be other genetic differences not considered here. If $w_i = w(N, t, p)$ for all i, then $\overline{w} = w(N, t, p)$ and equation (6) can be rewritten as

  $$\begin{aligned} N' =& w(N, t)\ N, \\ p'_i =& p_i. \end{aligned}$$

  The second equation tells us that allele frequencies do not change (there is no evolution). The first equation does not depend on the genetic structure of the population. It represents a standard population ecology model for the changes in the size of an isolated population. For example, if $w = const$, one has a model of an exponential growth $N' = wN$, whereas if $w = a + bN$ where a and b are some constants, one has a model of a logistic growth $N' = (a + bN)N$.

- *No density dependence.* If fitness w does not depend on N, that is if $w_i = w(t, p)$, then the dynamics of allele frequencies are completely independent of N. Thus, one can analyze equation (6b) *independently* of equation (6b). Note that, in general, the dynamics of the population size will still depend on the genetic structure of the population: $N' = w(t, p)N$. In general, with no density dependence the population either explodes ($N \to \infty$ which is unrealistic) or goes extinct ($N \to 0$).

- *Population size, N, is regulated independently of the population structure, p.* Specifically, we assume that fitness w can be factorized into two terms: $w_i = w_b(N)w_{g,i}(t, p)$ one of which depends on the population size and the other depends on the genotype. Population regulation independent of the genetic structure may happen if, for example, each generation produces many offspring but there is only a limited amount of resource, or if selection and population regulation act at different stages of the life cycle (as in many butterflies where the population size is usually regulated at the larval stage whereas selection acts on adults). Under the above assumption about fitnesses the ratio

  $$\frac{w_i}{\overline{w}} = \frac{w_b(N)w_{g,i}(t, p)}{\sum_j w_b(N)w_{g,j}(t, p)} = \frac{w_{g,i}(t, p)}{\sum_j w_{g,j}(t, p)}$$

  does not depend on N. Thus, one can analyze equation (6b) *independently* of equation (6b).

Below in analyzing the dynamic equations for allele frequencies we will always imply that the population size is regulated independently of the genetic structure of the population in a way similar to the one just discussed.

Sometimes instead of using equations of type (6b), it is more convenient to consider changes between two subsequent generations:

$$\Delta p_i \equiv p_i' - p_i = \frac{w_i - \overline{w}}{\overline{w}}\, p_i. \tag{8}$$

Both equation (6b) and equation (8) tell us that the frequency of an allele increases or decreases ($\Delta p_i > 0$ or $\Delta p_i < 0$) depending on whether its fitness is larger or smaller than the average fitness ($w_i > \overline{w}$ or $w_i < \overline{w}$). Note also that multiplying all fitnesses by a constant does not change the ratio $w_i/\overline{w}$. Thus, one can normalize fitnesses.

1.1.2 Major points:

- population size regulation independent of the genetic structure is usually implied in population genetic models,

1.1.3 Constant fitnesses

Here, we assume that fitnesses are constant. Let $\mathbf{A_1}$ be the fittest allele in the population. That is $w_1 > w_i$ for all $i = 2, \ldots, k$. Then using equation (6b)

$$\frac{p_i'}{p_1'} = \left(\frac{w_i}{\overline{w}}\, p_i\right) / \left(\frac{w_1}{\overline{w}}\, p_1\right) = \frac{w_i}{w_1}\,\frac{p_i}{p_1} < \frac{p_i}{p_1}.$$

Thus, p_i/p_1 decreases in time for all $i = 2, \ldots, k$. As time increases ($t \to \infty$), the frequencies of all alleles but the fittest approach zero ($p_i \to 0$), and the fittest allele becomes fixed ($p_1 \to 1$). Genetic variability will not be maintained in the population. One can say that *only the fittest survives.*

How long does it take for the fittest allele to take over? Let us consider two alleles: $\mathbf{A}_i$ and $\mathbf{A}_j$. Then

$$p_i'/p_j' = (w_i/w_j)(p_i/p_j)$$

Let $r_t = p_i/p_j$ be the ratio of allele frequencies at the t-th generation. Then the above equation can be rewritten as

$$r_{t+1} = \frac{w_i}{w_j} r_t = \frac{w_i}{w_j}\,\frac{w_i}{w_j} r_{t-1} = \cdots = (\frac{w_i}{w_j})^t r_0.$$

For example, if initially the alleles are at equal frequencies ($r_0 = 1$) and the fitness of allele $\mathbf{A}_i$ exceeds that of allele $\mathbf{A}_j$ by 5% ($w_i/w_j = 1.05$), then in the 50-th generation the ratio of the frequencies will be 11.47, and will increase to 131.5 by generation 100.

Note that the following *linear* (in time t) relation is true:

$$\ln(r_{t+1}) = \ln(r_0) + t\ln(\frac{w_i}{w_j}).$$

This relationship can be (and actually has been) tested in experiments using linear regression (pp.215-216 in the Hartl-Clark book).

1.1.4 Major points:

In an asexual haploid population with constant fitnesses:

- genetic variation is not maintained,

- only the fittest allele survives,
- the mean fitness of the population increases monotonically at a rate proportional to the variance in fitness,
- the time scale for the fittest allele to take over is order $1/s$, where s is the difference in fitness between the fittest and the second fittest alleles.

ADD: graphs of allele frequencies changing in time (*Maple*)

Homework Problem: The change in the mean fitness and the time scale.

1. Show that the change in the mean fitness per generation, $\Delta\overline{w} = \overline{w}' - \overline{w}$, can be represented as

$$\Delta\overline{w} = \frac{V_g}{\overline{w}}, \tag{9a}$$

where the genetic variance in fitness

$$V_g = \sum_i (w_i - \overline{w})^2 \; p_i. \tag{9b}$$

What does eq.(9a) tell us about the dynamics?

2. Show that the time for the fittest allele (with fitness w_1) to take over has order $1/(w_1 - w_2)$, where w_2 is the fitness of the second fittest allele. Hint: normalize fitnesses so that $w_2 = 1, w_1 = 1 + s$.

1.2 Diploid systems

We consider a (deterministic) model of a biological population where individuals are different with respect to a single locus with two alleles which we will denote **A** and **a**. Because in diploid organisms each individual has two genes at each locus (coming from maternal and paternal genotypes), there are three different genotypes: two *homozygotes* **AA** and **aa** and a heterozygote **Aa**. (We assume that heterozygotes **Aa** and **aA** are equivalent). Let x, y and z be the frequencies of genotypes **AA, Aa** and **aa** in the population ($x + y + z = 1$). The corresponding frequencies of alleles **A** and **a** are

$$\begin{aligned} p &= x + y/2, \\ q &= z + y/2 \end{aligned}$$

($p + q = 1$).

1.2.1 Random mating

We assume that reproduction is sexual, that individuals mate *randomly* with respect to the gene under consideration, and that generations are discrete and non-overlapping. We will consider two breeding schemes: *(i)* random union of gametes and *(ii)* random mating of individuals.

1.2.2 Random union of gametes

This method of modeling is applicable to organisms that release their gametes (sperm and eggs) into water, and to wind pollinated plants.

The probability that a sperm or egg carries **A** is p and the probability that a sperm or egg carries **a** is q. With random union of gametes the frequencies of genotypes **AA, Aa** and **aa** among offspring will be

$$\begin{aligned} x' &= p^2, \\ y' &= pq + qp = 2pq, \\ z' &= q^2, \end{aligned}$$

respectively. The frequencies of allele **A** and **a** among offsprings will be

$$\begin{aligned} p' &= x' + y'/2 = p^2 + pq = p, \\ q' &= z' + y'/2 = q^2 + pq = q. \end{aligned}$$

Thus, allele frequencies do not change whereas genotype frequencies are in *Hardy-Weinberg proportions* in one generation:

$$\mathbf{AA} : \mathbf{Aa} : \mathbf{aa} = p^2 : 2pq : q^2.$$

Note that the population state can be described by a single variable, say p.

1.2.3 Random mating of individuals

Here we assume that individuals form mating pairs. If mating pairs are formed randomly then the proportion of mating pairs of type **AA** × **AA** will be x^2, that of type **AA** × **aa** will be xz and so on. The table below shows the frequencies of all matings, and the frequencies of offspring produced from each mating.

Table 2: Mating types and offspring

Mating types		Frequency	Offspring frequency		
Female	Male	of mating	**AA**	**Aa**	**aa**
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

To find the frequency of a genotype among the offspring one sums up the products of the frequency of mating with the corresponding offspring frequency:

$$\begin{aligned} x' &= x^2 \times 1 + 2xy \times 1/2 + y^2 \times 1/4 = (x + y/2)^2 = p^2, \\ y' &= 2xy \times 1/2 + 2xz \times 1/2 + y^2 \times 1/2 + 2yz \times 1/2 = 2(x + y/2)(z + y/2) = 2pq, \\ z' &= ... = q^2. \end{aligned}$$

Thus, the genotype frequencies are in Hardy-Weinberg proportions ($p^2 : 2pq : q^2$) after a single generation of random mating. It is easy to see that allele frequencies will not change.

Note that if an allele, say **a**, is rare, i.e., $q \ll 1$, then

$$y = 2pq = 2q(1 - q) \approx 2q.$$

That is, the frequency of heterozygotes is twice the frequency of the rare allele. This property can be used to estimate the frequency of rare alleles. Also, if the population is in Hardy-Weinberg proportions, then the following equality must be true: $y^2 = 4xz$. This property can be used to check for Hardy-Weinberg proportions.

1.2.4 More alleles

Let there be k different alleles: $A_1, A_2, \ldots, A_k$. Now there are $k(k+1)/2$ possible genotypes. Let $P_{ij} = freq(A_i A_j)$ be the genotype frequencies and $p_i = \sum_j P_{ij}$ be the allele frequencies. One can show that with random mating, allele frequencies do not change

$$p_i' = p_i,$$

and that Hardy-Weinberg proportions

$$P_{ij}' = 2p_i p_j$$

are attained in a single generation.

Note that if generations are overlapping or there is selfing, then Hardy-Weinberg proportions are attained gradually.

1.3 Viability selection

We consider a one-locus two-allele population with alleles **A** and **a**. There are three possible genotypes **AA, Aa** and **aa**. Let p and q and x, y and z be the corresponding allele and genotype frequencies. Immediately after reproduction, the genotype frequencies among offspring are in Hardy-Weinberg proportions: $x = p^2, y = 2pq, z = q^2$. We assume that genotypes are different with respect to *viability* defined as the probabilities of survival to the age of reproduction. Let w_{AA}, w_{Aa} and w_{aa} be the corresponding viabilities. Because viability selection is the only selection type incorporated in the model, we will also call these values *fitnesses*. The genotype frequencies after (viability) selection are

$$\begin{aligned} x' &= cw_{AA}x, \\ y' &= cw_{Aa}y, \\ z' &= cw_{aa}z, \end{aligned}$$

where c is a normalizing coefficient necessary to satisfy the condition $x' + y' + z' = 1$. This coefficient is $1/\overline{w}$ where

$$\overline{w} = w_{AA}x + w_{Aa}y + w_{aa}z = w_{AA}p^2 + w_{Aa}2pq + w_{aa}q^2,$$

is the mean fitness of the population.

The allele frequency after selection is

$$p' = x' + y'/2 = \frac{w_{AA}x + w_{Aa}y/2}{\overline{w}} = \frac{w_{AA}p^2 + w_{Aa}pq}{\overline{w}} = \frac{(w_{AA}p + w_{Aa}q)p}{\overline{w}} = \frac{w_A}{\overline{w}}\, p,$$

where $w_A = w_{AA}p + w_{Aa}q$ is the *induced* fitnesses of alleles **A**. We can also define the *induced* fitnesses of alleles **a**: $w_a = w_{Aa}p + w_{aa}q$. Note that the mean fitness of the population can be represented as $\overline{w} = w_A p + w_a q$.

Because reproduction does not change the allele frequencies, the allele frequencies in the offspring will be p' as well. Thus, we have shown that under viability selection the dynamics of allele frequency are described by a recurrence equation

$$p' = \frac{w_A}{\overline{w}}\, p. \tag{10}$$

We can also consider the change in allele frequency between two subsequent generations, $\Delta p = p' - p$. One can show that the following equalities are true

$$\begin{aligned} \Delta p &= \frac{w_A - \overline{w}}{\overline{w}} p && \text{(11a)} \\ &= \frac{pq(w_A - w_a)}{\overline{w}} && \text{(11b)} \\ &= pq\frac{w_{Aa} - w_{aa} + (w_{AA} - 2w_{Aa} + w_{aa})p}{\overline{w}} \equiv pq\ \frac{g(p)}{\overline{w}} && \text{(11c)} \\ &= \frac{pq}{2}\frac{d\ln\overline{w}}{dp} && \text{(11d)} \end{aligned}$$

where $g(p) \equiv w_{Aa} - w_{aa} + (w_{AA} - 2w_{Aa} + w_{aa})p$ is a *linear* function of p. Note that equation (82d) describes a gradient-type dynamics. This equation tells us that allele frequency changes in such a way that the mean fitness always increases.

To obtain more detailed information about the allele frequency dynamics we will consider several cases. We will be using equation (82c).

1. $w_{aa} \leq w_{Aa} \leq w_{AA}$ (**A** is advantageous). Then

$$g(0) > 0, g(1) > 0 \Rightarrow g(p) > 0 \text{ for all } p\ \Rightarrow \Delta p > 0\ \Rightarrow p \to 1,$$

that is allele **A** gets fixed.

2. $w_{aa} \geq w_{Aa} \geq w_{AA}$ (**a** is advantageous). Then

$$g(0) < 0, g(1) < 0 \Rightarrow g(p) < 0 \text{ for all } p \ \Rightarrow \Delta p < 0 \ \Rightarrow p \rightarrow 0,$$

that is allele **a** gets fixed.

3. $w_{aa} \geq w_{Aa} \leq w_{AA}$ (underdominance). Let

$$\hat{p} = \frac{w_{aa} - w_{Aa}}{w_{AA} - 2w_{Aa} + w_{aa}}$$

$$\Delta p = \frac{pq}{\overline{w}}(w_{AA} - 2w_{Aa} + w_{aa})(p - \hat{p}).$$

Then, if $p > \hat{p}$, then $\Delta p > 0$ and $p \rightarrow 1$. If $p < \hat{p}$, then $\Delta p < 0$ and $p \rightarrow 0$. Thus, the system evolves to a monomorphic state. Which allele is fixed depends on the initial conditions. Note that the state with $p = \hat{p}$ is an unstable equilibrium.

3. $w_{aa} \leq w_{Aa} \geq w_{AA}$ (overdominance). It is easy to see that

$$p \rightarrow \hat{p}$$

for all initial conditions. Thus, with overdominance genetic variability is maintained. Here, overdominance is actually both sufficient and necessary condition for the maintenance of genetic variation.

1.3.1 Major points

In randomly mating 1-locus 2-allele diploid populations under constant viability selection

- mean fitnesses does not decrease;
- the population always evolves to an equilibrium;
- overdominance is both necessary and sufficient for the maintenance of genetic variation
- with underdominance, both monomorphic equilibria are stable simultaneously.

1.4 Technical section: Differential approximation

Usually it is much easier to formulate a model using discrete time (and non-overlapping generations). But it is much easier to analyze a model in continuous time. Here we consider how one can justify using a differential approximation (and differential equations) for models described by difference equations.

We start with a *difference* equation

$$\Delta p_i = \frac{w_i - \overline{w}}{\overline{w}}\, p_i$$

describing the change in an allele frequency between two generations as a result of selection specified by fitnesses w_i. Let

$$w_i = 1 + \epsilon s_i,$$

where ϵ is a small positive parameter ($<< 1$) and s_i are some coefficients. Note that the difference in fitness between any two alleles $w_i - w_j = \epsilon(s_i - s_j)$ and is order ϵ (i.e. very small). This is a **weak selection approximation** which is broadly used in modeling evolutionary processes. It is justified by a lot of experimental data showing that the strength of selection acting on individual alleles is generally small. [In general, we say that there is selection if individuals have different fitnesses.] Under the above approximation

$$\begin{aligned}\overline{w} &= \sum w_i p_i = \sum (p_i + \epsilon s_i p_i) = 1 + \epsilon \sum s_i p_i = 1 + \epsilon \overline{s}\\ w_i - \overline{w} &= \epsilon(s_i - \overline{s}).\end{aligned}$$

Thus, our basic equation can be rewritten as

$$\Delta p_i = \frac{\epsilon(s_i - \overline{s})}{1 + \epsilon \overline{s}}\, p_i \approx \epsilon(s_i - \overline{s}) p_i.$$

Finally, if we approximate a difference by a differential: $\frac{\Delta p_i}{1} \approx \frac{dp_i}{dt}$, and change time to $\tau = \epsilon t$, we end up with a *differential* equation

$$\frac{dp_i}{d\tau} = (s_i - \overline{s}) p_i.$$

One could get a similar equation by constructing a model for a population with overlapping generations.

1.4.1 Major points:

- a differential approximation of difference equations can be justified by invoking a weak selection assumption.

1.5 Mutation-selection balance

Mutations are random changes in the genetic material of a cell. Most mutations are harmful, but some are advantageous. Mutations occur naturally at low rates ($10^{-5} - 10^{-6}$ per gene per generation). Mutations are the ultimate source of genetic variation.

We will consider a populations of organisms different with respect to a single locus with two alleles, **A** and **a**. We assume that fitnesses are $w_A = 1$ (allele **A** is normal) and $w_a = 1 - s$ (allele **a** is deleterious, $s > 0$). Let p and q be the frequencies of the alleles ($p + q = 1$).

We already know that *after selection*:

$$p' = \frac{w_A}{\overline{w}}\ p,\ q' = \frac{w_q}{\overline{w}}\ q,$$

and that the change in the frequency of allele **A** is

$$\Delta_s p = \frac{pq(w_A - w_a)}{\overline{w}} = \frac{spq}{\overline{w}}\ (\geq 0).$$

We assume that alleles can mutate with a small probability μ ($<< 1$) which is the same for forward and backward mutations:

$$\mathbf{A} \xleftrightarrow{\mu} \mathbf{a}.$$

The allele frequency *after mutation* is

$$p'' = (1 - \mu)p' + \mu q' = p' + \mu(q' - p').$$

Thus the change per generation is

$$\Delta p \equiv p'' - p = p' - p + \mu(q' - p') = \frac{spq}{\overline{w}} + \mu\frac{w_a q - w_A p}{\overline{w}} = \frac{spq + \mu(-sq + q - p)}{\overline{w}}. \tag{12}$$

At equilibrium (that is at a balance of mutation and selection) $\Delta p = 0$ and

$$spq - \mu sq + \mu(q - p) = 0$$

which can be solved exactly. (This is a quadratic equation in p.) Instead of the exact solution, however, one can use a simple approximation. Because μ is small (say, $\approx 10^{-6}$), we expect q to be small as well, $q - p = 2q - 1 \approx -1$, $pq = (1 - q)q \approx q$. Thus, we expect $sq \approx \mu$ and

$$q^* \approx \frac{\mu}{s}, \tag{13}$$

which is the frequency of the deleterious allele **a** maintained in the population by mutation in spite of selection. The frequency of the deleterious allele will be rather small though. For example, with $s = .01$ and $\mu = 10^{-6}$, $q^* = 10^{-5}$.

Using a weak selection approximation (that is assuming that s is small so that $\overline{w} \approx 1$), equation (12) can be approximated by a (second oreder ordinary) differential equation

$$\dot{p} = -spq + \mu(q - p),$$

which can be solved exactly.

1.5.1 The Mutation load

The change of average fitness associated with maintaining the variability in a population was called the *genetic load* by Muller (1950). To Muller the load was a burden, measured in terms of the reduced fitness, but felt in terms of death, sterility etc. In most evolutionary considerations, however, it is used as a measure of the amount of natural selection associated with a certain amount of genetic variation. The genetic load is usually defined as

$$L = \frac{w_{max} - \overline{w}}{w_{max}},$$

where w_{max} is the maximum possible fitness.

Using our results above, at the mutation-selection balance equilibrium

$$w_{max} = 1, \ \overline{w} = (1 - q^*) \times 1 + q^* \times (1 - s) = 1 - \mu$$

so that the mutation load (that is the genetic load resulting from mutations maintaining deleterious alleles) is

$$L = \mu.$$

Surprisingly, this load does not depend on s. Thus, increasing the rate of even slightly deleterious mutations (with very small s) can be very harmful!

1.5.2 Major points

- mutation introduces and maintains genetic variation;
- the mutation load due to the deleterious mutations does not depend of the strength of selection against them.

1.6 Technical section: Stability analysis of systems of ordinary differential equations (ODE)

Exact solutions of even simple models are often unavailable. In such situations one has to use different *approximate* methods of which the analysis of stability of equilibria is very useful.

Let us consider a system of two ODE:

$$\dot{x} = f(x, y), \tag{14a}$$

$$\dot{y} = g(x, y). \tag{14b}$$

Definition. A point (x_0, y_0) is an equilibrium of (14) if $f(x_0, y_0) = g(x_0, y_0) = 0$. At equilibrium both $\dot{x} = \dot{y} = 0$ (no changes).

Existence of equilibria. To find equilibria, one has to solve a system of algebraic equations $f(x, y) = 0, g(x, y) = 0$.

1.6.1 Stability of equilibria

Linear systems. Before approaching the *nonlinear* system (14) let us first consider a system of two *linear* ODE:

$$\dot{x} = ax + by, \tag{15a}$$

$$\dot{y} = cx + dy. \tag{15b}$$

The general solution to (15) depends on the *eigenvalues* λ_1, λ_2 of stability matrix (Jacobian)

$$S = \begin{pmatrix} a & b \\ c & d \end{pmatrix}.$$

These eigenvalues satisfy to a *characteristic equation*

$$\lambda^2 - \lambda\, Tr(S) + Det(S) = 0, \tag{16}$$

where the *trace*, $Tr(S)$, and the *determinant*, $Det(S)$, of matrix S are

$$Tr(S) = a + d,\ Det(S) = ad - bc.$$

The solutions of the characteristic equation (16) are

$$\lambda = \frac{Tr(S)}{2} \pm \sqrt{(\frac{Tr(S)}{2})^2 - Det(S)}.$$

Note that $Tr(S) = \lambda_1 + \lambda_2,\ Det(S) = \lambda_1 \lambda_2$. If $Det(S) \neq 0$, the point $(0, 0)$ is the only equilibrium of (15).

There are three different cases to consider

- (i) λ_1 and λ_2 are real and different. A general solution of (15) is

  $$x(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t},$$
  $$y(t) = C_3 e^{\lambda_1 t} + C_4 e^{\lambda_2 t},$$

  where C_1, C_2, C_3, C_4 are coefficients that depend on initial conditions.

- (ii) λ_1 and λ_2 are real and equal ($\lambda_1 = \lambda_2 = \lambda$) A general solution of (15) is

  $$x(t) = C_1 e^{\lambda t} + C_2 t e^{\lambda t},$$
  $$y(t) = C_3 e^{\lambda t} + C_4 t e^{\lambda t}.$$

- (iii) λ_1 and λ_2 are complex ($\lambda = \alpha \mp i\beta$ where $i = \sqrt{-1}$). A general solution of (15) is

$$x(t) = C_1 e^{\alpha t}\cos(\beta t) + C_2 e^{\alpha t}\sin(\beta t),$$
$$y(t) = C_3 e^{\alpha t}\cos(\beta t) + C_4 e^{\alpha t}\sin(\beta t).$$

The intuitive *concept of stability*: the equilibrium is stable if the system returns to the equilibrium when slightly perturbed.

Case (i). Let $\lambda_1, \lambda_2 < 0$. Then both $x(t) \to 0, y(t) \to 0$ as $t \to \infty$. Thus, $(0,0)$ is stable. Let $\lambda_1 > 0$ and/or $\lambda_2 > 0$. Then in general $|x(t)| \to \infty$ and/or $|y(t)| \to \infty$. Thus, $(0,0)$ is unstable.
Case (ii). Let $\lambda < 0$. Then both $x(t) \to 0, y(t) \to 0$ as $t \to \infty$. Thus, $(0,0)$ is stable. Let $\lambda > 0$. Then in general $|x(t)| \to \infty$ and $|y(t)| \to \infty$. Thus, $(0,0)$ is unstable.
Case (iii). Let $\alpha < 0$. Then both $x(t) \to 0, y(t) \to 0$ as $t \to \infty$. Thus, $(0,0)$ is stable. Let $\alpha > 0$. Then in general $|x(t)| \to \infty$ and $|y(t)| \to \infty$. Thus, $(0,0)$ is unstable.

Summarizing: The equilibrium $(0,0)$ of (15) is stable if both $Re(\lambda_1) < 0$ and $Re(\lambda_2) < 0$ and is unstable otherwise ($Re(\lambda)$ is the real part of λ).

Note that both eigenvalues of S have negative real parts if

$$Tr(S) < 0 \text{ and } Det(S) > 0. \tag{17}$$

If either of these inequalities is violated, $(0,0)$ is unstable.

Nonlinear systems. Now let us return to the general system of two nonlinear ODE:

$$\dot{x} = f(x,y), \tag{18a}$$
$$\dot{y} = g(x,y). \tag{18b}$$

Let us consider an equilibrium (x_0, y_0). One can expand functions f and g in a Taylor series in a neighborhood of this equilibrium:

$$f(x,y) \approx f(x_0,y_0) + \frac{\partial f}{\partial x} + \frac{\partial f}{\partial y} + \text{ smaller terms},$$
$$g(x,y) \approx g(x_0,y_0) + \frac{\partial g}{\partial x} + \frac{\partial g}{\partial y} + \text{ smaller terms},$$

where all derivatives are evaluated at $x = x_0, y = y_0$.

Let $u = x - x_0$ and $v = y - y_0$ be the deviations of x and y from x_0 and y_0, respectively. Making the variable change and neglecting second and higher order terms results in the nonlinear system of ODE (18) being approximated by a linear system of ODE

$$\dot{u} = \frac{\partial f}{\partial x}u + \frac{\partial f}{\partial y}v, \tag{19a}$$
$$\dot{v} = \frac{\partial g}{\partial x}u + \frac{\partial g}{\partial y}v \tag{19b}$$

where all derivatives are evaluated at $x = x_0, y = y_0$. The corresponding stability matrix (Jacobian) is

$$S = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}.$$

where all derivatives are evaluated at $x = x_0, y = y_0$. Now we can use this matrix to deduce the behavior of the nonlinear system in a neighborhood of $x = x_0, y = y_0$.

General procedure:

- find an equilibrium
- compute the stability matrix (Jacobian) S at this equilibrium
- make conclusions about the eigenvalues of S
- make conclusions about conditions for stability/instability of the equilibrium

Table 3: Classification of equilibria

eigenvalues	equilibrium
$\lambda_1 > 0, \lambda_2 < 0$ (or $\lambda_1 < 0, \lambda_2 > 0$)	saddle
$\lambda_1 < 0, \lambda_2 < 0$	stable node
$\lambda_1 > 0, \lambda_2 > 0$	unstable node
$\lambda = \alpha \mp \beta i, Re(\lambda) < 0$	stable focus
$\lambda = \alpha \mp \beta i, Re(\lambda) > 0$	unstable focus

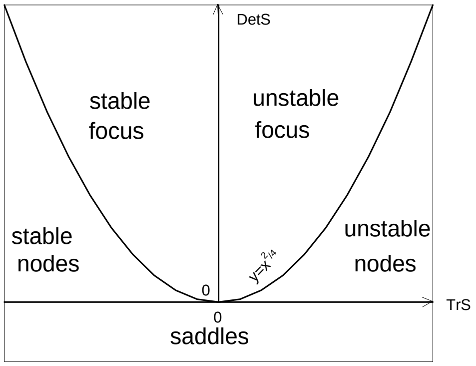

Figure 1: Conditions for stability given in terms of $Tr(S)$ and $Det(S)$.

1.6.2 Example

Let us consider a system of two ordinary differential equations

$$\dot{x} = x(a - bx) - cxy,$$
$$\dot{y} = dxy - (e + fy)y,$$

where all coefficients are positive.

One can interpret x as the density of a prey population which grows logistically in the absence of predator (if $y = 0$, then $\dot{x} = x(a - bx)$), and y as the density of predator which experiences density-dependent mortality (with rate $-(e + fy)y$). Terms $-cxy$ and dxy stand for the rate at which predation decreases the prey population and increases the predator population, respectively.

The system can have up to three equilibria:
1. $x = 0, y = 0$. At this equilibrium, which exists always, both populations are extinct.
2. $x = a/b, y = 0$. At this equilibrium, which exists always, there is no predator whereas prey is at the carrying capacity.
3. $x = x* \equiv (af + ce)/(bf + cd), y = y^* \equiv (ad - be)/(bf + cd)$. At this equilibrium, both populations are present. The equilibrium exists (that is, biologically meaningful) if $ad > be$.

Conditions for stability are as follows. The first equilibrium is never stable. (This is a saddle point with eigenvalues a and $-e$). The second equilibrium is stable if $ad < be$ and is unstable otherwise. (The eigenvalues are $-a$ and $ad - be)/b$ so that the equilibrium is a stable node if $ad < be$ and is a saddle point if $ad > be$.) The third equilibrium is stable if $ad > be$) that is whenever it exists. (The sign of the determinant of the stability matrix coincides with that of the difference $ad - be$, and if $ad > be$ then the trace is negative.)

Conditions for existence and stability of equilibria of this system can be summarized in a table:

Equilibrium (x, y)	Conditions for existence	Conditions for stability
$(0, 0)$	always	never
$(a/b, 0)$	always	$ad < be$
(x^*, y^*)	$ad > be$	$ad > be$

Thus, the general qualitative behavior is as follows: if $ad < be$, the predator dies out; if $ad > be$ both species coexist. (Note that conditions for stability do not depend on c and f. Other parameters affect conditions for stability in a specific way.)

1.7 Technical section: Stability of equilibria of difference equations

Let us consider a *linear* difference equation

$$x_{t+1} = ax_t. \tag{20}$$

The general solution of (83) is $x_t = a^t x_0$ where x_0 is the initial value of x. Thus, asymptotically (i.e., as $t \to \infty$) $|x_t| \to 0$ if $|a| < 1$, and $|x_t| \to \infty$ if $|a| > 1$. The only equilibrium point of (83) is $x^* = 0$. If $|a| < 1$, this equilibrium is stable (after a perturbation x will return back to $x^* = 0$). If $|a| > 1$, this equilibrium is stable (after a perturbation, x will not return back to $x^* = 0$).

Next we consider a single *non-linear* difference equation:

$$x_{t+1} = f(x_t).$$

Let x^* be an equilibrium of this equation (meaning that $x^* = f(x^*)$). To determine local stability properties of x^* one approximates f in a small neighborhood of x^* by a linear function:

$$x_{t+1} \approx f(x^*) + \frac{df(x)}{dx} \, (x_t - x^*)$$

The resulting equation can be rewritten as

$$x_{t+1} - x^* = \frac{df(x)}{dx} \, (x_t - x^*)$$

or, by introducing $y_t = x_t - x^*$ (which is the deviation of x_t from the equilibrium x^*) as

$$y_{t+1} = \frac{df(x)}{dx} \, y_t.$$

The last equation has the same form as equation (83). Thus, x^* is stable to small perturbations, if $|df(x)/dx| < 1$ at x^* and is unstable otherwise.

In a similar way one can consider a system of difference equations. For example, let us consider a system of two difference equations

$$\begin{aligned} x_{t+1} &= f(x_t, y_t), \\ y_{t+1} &= g(x_t, y_t). \end{aligned}$$

Assume that this system has an equilibrium (x^*, y^*):

$$x^* = f(x^*, y^*), y^* = g(x^*, y^*).$$

Consider the stability matrix (the Jacobian)

$$S = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}$$

evaluated at the equilibrium (x^*, y^*). One can show that this equilibrium is locally stable if the absolute values of all eigenvalues λ_i of the stability matrix S are smaller than 1: $|\lambda_i| < 1$. If at least for one eigenvalue $|\lambda_i| > 1$, the equilibrium is unstable.

1.8 Selection in a single locus (cont.)

1.8.1 Multiple alleles

We consider a diploid populations with k alleles $A_1, A_2, \ldots, A_k$ segregating at a locus of interest. Genotypes of individuals will be denoted as A_iA_j. Let $p_1, p_2, \ldots, p_k$ be the allele frequencies ($\sum p_i = 1$) and P_{ij} be the genotype frequencies which are in Hardy-Weinberg proportions in one generation: $P_{ij} = 2p_ip_j(i \neq j), P_{ii} = p_i^2$. Let w_{ij} be fitnesses (viabilities) ($w_{ij} = w_{ji}$). We also define the induced fitness of allele A_i as

$$w_i = \sum_j w_{ij}p_j, \tag{21}$$

and the mean fitness of the population:

$$\overline{w} = \sum w_ip_i = \sum_{ij} w_{ij}p_ip_j. \tag{22}$$

After selection, genotype frequencies are

$$P'_{ij} = \frac{w_{ij}}{\overline{w}}P_{ij}.$$

Allele frequencies among surviving adults are

$$p'_i = \sum_j P'_{ij} = \frac{\sum_j w_{ij}P_{ij}}{\overline{w}} = \frac{\sum_j w_{ij}p_ip_j}{\overline{w}} = \frac{w_ip_i}{\overline{w}}. \tag{23}$$

Because reproduction does not change allele frequencies, p'_i is also the allele frequency in the next generation. The change in allele frequency between two generations is

$$\Delta p_i = \frac{w_i - \overline{w}}{\overline{w}}p_i. \tag{24}$$

From eq. (22), $\frac{\partial \overline{w}}{\partial p_i} = 2\sum p_jw_{ij} = 2w_i$ so that $w_i = \frac{1}{2}\frac{\partial \overline{w}}{\partial p_i}$. From this and the first part of eq. (22), the mean fitness can be written as $\overline{w} = \frac{1}{2}\sum_i p_i\frac{\partial \overline{w}}{\partial p_i}$. This allows us to rewrite eq. (24) as

$$\Delta p_i = \frac{p_i}{2\overline{w}}\left(\frac{\partial \overline{w}}{\partial p_i} - \sum_j p_j\frac{\partial \overline{w}}{\partial p_j}\right) \tag{25}$$

Let $p = (p_1, \ldots, p_k)'$ be the vector of allele frequencies, and $\nabla \ln \overline{w} = (\frac{\partial \ln \overline{w}}{\partial p_1}, \ldots, \frac{\partial \ln \overline{w}}{\partial p_k})'$ be the gradient of $\ln \overline{w}$. Then eq. (25) can be rewritten as

$$\Delta p = \frac{1}{2}\ G\ \nabla \ln \overline{w}, \tag{26}$$

where the diagonal elements of matrix G are $p_i(1-p_i)$ and the non-diagonal elements of matrix G are $-p_ip_j$. Matrix G characterizes the degree and structure of genetic variation in the population. To better understand its meaning let us introduce a set of k *indicator variables*, l_i equal to 1 if a randomly choosen allele if of type $\mathbf{A}_i$ and to zero, otherwise. Note that $l_i^2 = l_i$. The expected value of l_i is p_i, the variance of l_i is $p_i(1-p_i)$ and the covariance of l_i and l_j is $-p_ip_j$. Therefore, matrix G is the variance-covariance matrix of vector $l = (l_1, \ldots, l_k)'$.

The following summarizes some results known for the dynamical systems (23) and (24).

- There can be only one isolated polymorphic equilibrium with all $p_i^* > 0$. At this equilibrium $w_i = \overline{w}$ for all $i = 1, 2, \ldots, k$. One can rewrite these conditions as $w_i = w_1$ for all $i = 2, 3, \ldots, k$. Thus, there are $k - 1$ linear algebraic equations for $k - 1$ independent variables $p_2^*, \ldots, p_k^*$. These equations can be solved using Cramer's rule. (Note that p_1^* can be found from the equality $p_1^* + p_2^* + \cdots + p_k^* = 1$). For special values of w_{ij} there can be no admissible polymorphic solutions (with $0 < p_i^* < 1$), a single solution, or an infinite number of solutions.
- The overall number of possible equilibria of (23) and (24) is $2^k - 1$.
- A unique admissible polymorphic solution will be stable if and only if the matrix $W = \{w_{ij}\}$ has exactly one positive eigenvalue, and at least one negative eigenvalue (Kingman, 1961).
- If matrix W has j positive eigenvalues, at most $k - j + 1$ alleles will exist with positive frequencies at the equilibrium (Kingman, 1961).
- Three *necessary* (but not sufficient!) conditions for stability of the polymorphic equilibrium (Lewontin et al., 1978; Nagylaki, 1992):
    1. for each i there exists some j such that $w_{ii} < w_{ij}$,
    2. for all i, j, $w_{ij} > (w_{ii} + w_{jj})/2$,
    3. "triangle inequality": for all i, j there exists some k such that $w_{ij} < w_{ik} + w_{jk}$.
- Let D_i be the determinant of the $i \times i$ submatrix in the upper-left corner of W and $D_1 = w_{11} > 0$. Let $D_i \neq 0$ for all i. The completely polymorphic equilibrium is asymptotically stable if $(-1)^i D_i < 0$ for all i.
- If the completely polymorphic equilibrium is stable, no other equilibria are stable.
- In the two-allele case, overdominance is both necessary and sufficient for the maintenance of both alleles. In the k-allele case, pairwise overdominance ($w_{ij} > w_{ii}, w_{jj}$) is not necessary, and the total overdominance ($w_{ij} > w_{ll}$) is not sufficient for the maintenance of all k alleles (examples from Lewontin et al. 1978).
- Lewontin et al. (1978) performed large-scale numerical simulations using random fitness assignement and random initial conditions and measuring the proportion of runs resulting in stable polymorphic equilibria. They used 3 types of fitness assignement: totally random, random subject to pairwise heterosis (with $w_{ij} > w_{ii}, w_{jj}$ for all i, j) and random subject to total heterosis (with $w_{ij} > w_{kk}$ for all a, j, k). The following table summarizes their results:

Table. Proportion of runs resulting in stable polymorphic equilibria with k alleles present (100,000 runs in the case of totally random fitness assignement, 10,000 runs in case with pairwise and total heterosis).

# alleles	totally random	pairwise heterosis	total heterosis
2	0.33466	1.0000	1.0000
3	0.04237	0.5224	0.7120
4	0.00240	0.1259	0.3433
5	0.00006	0.0116	0.1041
6	-	0.0003	0.0137
7	-	-	0.0011
8	-	-	-

The overall conclusion of this analysis is that heterosis alone is not a mechanism for maintaining many alleles segregating at a locus.

The above results give an impression that details of the fitness matrix $\{W_{ij}\}$ are very important and that no generalizations are possible. However, some very general results with far-reaching interpretations do exist.

- The average fitness does not decrease
$$\overline{w}_{t+1} \geq \overline{w}_t.$$
$\Delta\overline{w} \equiv \overline{w}_{t+1} - \overline{w}_t = 0$ only at equilibrium. All equilibria are local maxima of $\overline{w}$. (Proof from Nagylaki, 1992.)

- Fisher's fundamental theorem of natural selection (Fisher 1930)
$$\frac{d\overline{w}}{dt} = 2V_g,$$
where $V_g = \sum_i (w_i - \overline{w})^2 p_i$ is the additive genetic variance in fitness.

  Sketch of the proof using a differential framework. We start with a system of differential equations
$$\dot{p}_i = (w_i - \overline{w})p_i, w_i = \sum w_{ij}p_j, \overline{w} = \sum_{ij} w_{ij}p_ip_j.$$
Then
$$\begin{aligned}\frac{d\overline{w}}{dt} &= \sum_{ij} w_{ij}(\dot{p}_ip_j + p_i\dot{p}_j)\\ &= \sum_i(\sum_j w_{ij}p_j)\dot{p}_i + \sum_j(\sum_i w_{ij}p_i)\dot{p}_j\\ &= \sum_i w_i(w_i - \overline{w})p_i + \sum_j w_j(w_j - \overline{w})p_j\\ &= 2\sum_i(w_i - \overline{w} + \overline{w})(w_i - \overline{w})p_i = \sum_i (w_i - \overline{w})^2 p_i\end{aligned}$$

- Svirezhev's optimality principle: natural selection operates in such a way that the path followed as a population changes from one state to another is the one that minimizes the total genetic variance over the path (Svirezhev 1972).

  Svirezhev shows that the integral of the quantity
$$\sum_i \frac{\dot{p}_i^2}{p_i} + \sum_i p_i(w_i - \overline{w})^2$$
over the path from state 1 to state 2 → min. This quantity is equivalent to the genetic variance in fitness V_g.

  Newton's laws can be derived from the principle of least action. Equations of gene-frequency and fitness change can be found from Svirezhev's optimality principle.

1.9 Proof that the mean fitness does not decrease

(Kingman 1961 given in Nagylaki, 1992, p.57-58)

We will need Jensen's inequality: if x takes values x_i with probabilities p_i and $\mu \geq 1$, then

$$\sum_i p_i x_i^{\mu} \geq (\sum_i p_i x_i)^{\mu}. \tag{27}$$

Proof:

$$\begin{aligned}
\overline{w}' &= \sum_{ij} p'_i p'_j w_{ij} \\
&= \overline{w}^{-2} \sum_{ij} p_i w_i p_j w_j w_{ij} && \text{(28a)} \\
&= \overline{w}^{-2} \sum_{ijk} p_i p_j p_k w_{ij} w_{ik} (\frac{1}{2})(w_j + w_j) && \text{(28b)} \\
&= \overline{w}^{-2} \sum_{ijk} p_i p_j p_k w_{ij} w_{ik} (\frac{1}{2})(w_j + w_k) \\
&\geq \overline{w}^{-2} \sum_{ijk} p_i p_j p_k w_{ij} w_{ik} (w_j w_k)^{1/2} && \text{(28c)} \\
&= \overline{w}^{-2} \sum_i p_i \left[\sum_j p_j w_{ij} (w_j)^{1/2} \right]^2 \\
&\geq \overline{w}^{-2} \left[\sum_i p_i \sum_j p_j w_{ij} (w_j)^{1/2} \right]^2 && \text{(28d)} \\
&= \overline{w}^{-2} \left(\sum_j p_j w_j^{3/2} \right)^2 && \text{(28e)} \\
&\geq \overline{w}^{-2} \left[\left(\sum_j p_j w_j \right)^{3/2} \right]^2 && \text{(28f)} \\
&= \overline{w}
\end{aligned}$$

The numbered equations in the above series come, respectively, from $p'_i = w_i p_i / \overline{w}$, $w_i = \sum_k p_k w_{ik}$, the elementary fact that $a + b \geq 2(ab)^{1/2}$, Jensen's inequality with $\mu = 2$, $w_j = \sum_i p_i w_{ij}$, and Jensen's inequality with $\mu = 3/2$.

1.10 Fertility selection

There are many different fitness components (viability, fertility, the ability to find a mate, the ability to complete fertilization etc). So far, we studied only one of many diffrent fitness components - viability. Today, we will look at another important fitness component - fertility.

Let us consider a one-locus two-allele diploid population where individuals are different with respect to *fertility* rather than viability. We define fertility as the average number of offspring. In the most general case, fertility is a property of the mating pair. Therefore one needs to specify a 3×3 fertility matrix

female genotype	male genotype		
	AA	**Aa**	**aa**
AA	f_{11}	f_{12}	f_{13}
Aa	f_{21}	f_{22}	f_{23}
aa	f_{31}	f_{23}	f_{33}

.

Let x, y, z be the frequencies of genotypes **AA, Aa** and **aa** in the population. To derive the dynamic equations for x, y, z one has to consider all possible mating times and resulting offspring.

Table 1. Mating types and offspring.

Mating Types		Frequency of mating	Fertility of mating	Offspring		
Female	Male			**AA**	**Aa**	**aa**
AA	**AA**	x^2	f_{11}	1	0	0
	Aa	xy	f_{12}	1/2	1/2	0
	aa	xz	f_{13}	0	1	0
Aa	**AA**	xy	f_{21}	1/2	1/2	0
	Aa	y^2	f_{22}	1/4	1/2	1/4
	aa	yz	f_{23}	0	1/2	1/2
aa	**AA**	xz	f_{31}	0	1	0
	Aa	yz	f_{32}	0	1/2	1/2
	aa	z^2	f_{33}	0	0	1

Homework: derive general dynamic equations for x, y and z and find conditions for stability of the fixation equilibria: $x = 1, y = z = 0$ and $x = y = 0, z = 1$

In general, with fertility selection the population is not in Hardy-Weinberg proportions (thus, one needs to analyze genotype frequency dynamics rather than allele frequency dynamics), and the mean fitness (fertility) $\overline{f}$ can decrease.

Three general fertility schemes have been studied in detail.

- Additive fertilities

$$f_{ij} = f_i + m_j,$$

that is the fertility of a pair is a sum of the fertilities of a male and a female. In this case, the dynamics are identical to that in a one-locus two-allele viability selection case with parameters $f_1 + m_1, f_2 + m_2$ and $f_3 + m_3$ playing the role of viabilities w_{AA}, w_{Aa} and w_{aa}. In particular, the population is in Hardy-Weinberg proportions in one generation, and the necessary and sufficient condition for the maintenance of genetic variation is overdominance ($f_2 + m_2 > f_1 + m_1, f_3 + m_3$).

- Multiplicative fertilities

$$f_{ij} = f_i \; m_j,$$

that is the fertility of a pair is a product of the fertilities of a male and a female. In this case the Hardy-Weinberg proportions are attained in one generation. If there is no sex differences ($f_i = m_i$), the model is equivalent to that of viability selection. However, if $f_i \neq m_i$, the dynamics are much more complicated. There can be three polymorphic equilibria of which two can be stable simultaneously. The monomorphic equilibria $x = 1$ and $z = 1$ are stable if $m_2/m_1 + f_2/f_1 \leq 2$ and $m_2/m_3 + f_2/f_3 \leq 2$, respectively.

Note that the case of multiplicative fertility selection is equivalent to the case of two-sex viability selection with fitnesses

	AA	**Aa**	**aa**
females	f_1	f_2	f_3
males	m_1	m_2	m_3

- Symmetric fertilities

$$\begin{pmatrix} \alpha & \beta & \gamma \\ \beta & \delta & \beta \\ \gamma & \beta & \alpha \end{pmatrix} \tag{29}$$

In this case, the productivity of a mating depends on the degree of heterozygosity of mating pairs. The dynamic equations are

$$\phi x' = \alpha x^2 + \beta xy + 1/4 \; \delta y^2, \tag{30a}$$

$$\phi y' = \beta xy + \beta yz + 2\gamma xz + 1/2 \; \delta y^2, \tag{30b}$$

$$\phi z' = \alpha z^2 + \beta zy + 1/4 \; \delta y^2, \tag{30c}$$

where ϕ is the mean fertility. This model allows for up to three symmetric polymorphic equilibria (with $x^* = z^*$) and two asymmetric polymorphic equilibria (with $x^* \neq z^*$)!

Let us consider an extreme case of self-incompatibility when $\alpha = \beta = 0$. The dynamic equations become

$$\phi x' = 1/4 \; \delta y^2, \tag{31a}$$

$$\phi y' = 2\gamma xz + 1/2 \; \delta y^2, \tag{31b}$$

$$\phi z' = 1/4 \; \delta y^2. \tag{31c}$$

Thus, $x' = z'$ after a single generation. Note that this implies that no fixation is possible. Let $u = 2x/y$ and $\epsilon = \gamma/\delta$. Then the dynamic equation for u is

$$u' = F(u) \equiv \frac{1}{1 + \epsilon u^2}.$$

The consideration of the graph of $F(u)$ shows that there is a single equilibrium (describing a polymorphic population) at which the first derivative of F is negative. If $\epsilon = 4$, this equilibrium is at $u = 1/2$; the corresponding first derivative of F is equal to -1 (see the Figure). If $\epsilon < 4$, the graph of $F(u)$ crosses the line $y = u$ above the point $(1/2, 1/2)$. If $\epsilon > 4$, the graph of $F(u)$ crosses the line $y = u$ below the point $(1/2, 1/2)$. In the former case, the first derivative $F'(u) > -1$ at the equilibrium meaning the equilibrium is stable. In the latter case, $F'(u) < -1$ at the equilibrium meaning the equilibrium is unstable.

One can show that in this case, there exists a *globally stable cycle* with period two! To do this, one has to solve an algebraic equation $u = F(F(u))$. The relevant roots are $u_{\mp} = (1 \mp \sqrt{1 - 4/e})/2$ corresponding to cyclic solutions $u_-, u_+, u_-, u_+, \ldots$ and $u_+, u_-, u_+, u_-, \ldots$.

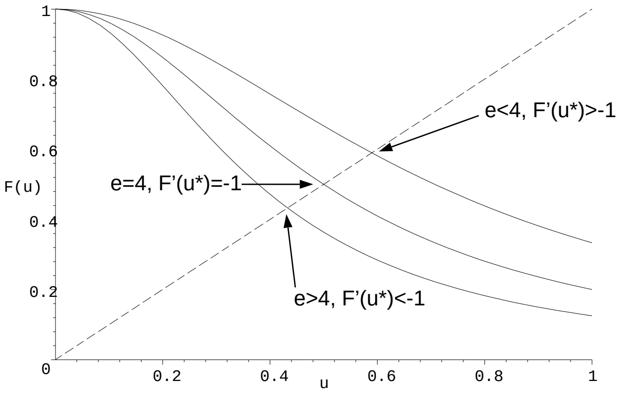

Figure 2: Function $F(u)$ for 3 different values of ϵ. The equilibria are at the intersection of $y = F(u)$ and $y = u$ (dashed line).

Note that one can interpret coefficients f_{ij} in the general fertility matrix as the probabilities of mating between genotypes i and j or as the viabilities of an offspring of mating between genotypes i and j. Thus, the framework (and results) developed for fertility selection can be directly applied to the cases of *sexual selection* and *assortative mating* as well as to the cases of *maternal* and *parental* selection.

Major points.

- In general, under fertility selection genotype frequencies are not in Hardy-Weinberg proportions, the mean fitness can decrease, there can be several simultaneously stable polymorphic equilibria, and cycling is possible.
- The additive fertility model and the multiplicative fertility model with no sex differences are mathematically equivalent to the model of constant viability selection.

1.11 Spatially heterogeneous selection

Most biological populations are spatially subdivided. Two very important consequences of spatial subdivision are non-random mating (mating could be viewed as random only for a limited spatial neighborhood), and spatial variation in selection regimes (coming from both abiotic and biotic factors). With spatial structure, both modeling and data analyses become much more complicated and various new effects emerge.

1.11.1 Levene (1953) model

We consider a one-locus two-allele population inhabiting n patches that differ in selection regimes. The genotype fitnesses (viabilities) in patch i are w^i_{AA}, w^i_{Aa} and w^i_{aa}. We assume that selection takes place locally (that is within a patch) and is followed by dispersal via a common migrant pool. Each path i contributes a constant proportion of individuals in the migrant pool, c_i ($\sum c_i = 1$). Let p be the frequency of allele **A** in the pool of migrants. At the beginning of each generations allele frequencies in all patches are equal to p. In each patch selection will change the allele frequency to some degree. The change in allele frequency in the i-th patch due to selection is

$$\Delta_i p = pq\frac{p(w^i_{AA} - w^i_{Aa}) + q(w^i_{Aa} - w^i_{aa})}{p^2 w^i_{AA} + 2pq w^i_{Aa} + q^2 w^i_{aa}}.$$

These "local" changes will result in a "global" change in the allele frequency in the migrant pool:

$$\Delta p = \sum_{i=1}^{n} c_i \Delta_i p.$$

We will assume that fitnesses are additive:

$$w^i_{AA} = 1 + s_i,\ w^i_{Aa} = 1,\ w^i_{aa} = 1 - s_i,$$

where the coefficients s_i vary between patches. With additive fitnesses, the general equation for p takes form

$$\Delta p = pq\sum_{i=1}^{n} \frac{c_i s_i}{1 + s_i(p - q)}. \tag{32}$$

We already know that with constant environment, additive viability selection does not maintain genetic variation. Our goal here is to show that with variable environment the maintenance of genetic variation is possible. We will do this by finding conditions under which both fixation states ($p = 0$ and $p = 1$) are unstable.

If $p \approx 0$, equation (32) tells us that p increases ($\Delta p > 0$) if

$$\sum c_i \frac{s_i}{1 - s_i} \approx \sum c_i (s_i + s_i^2) > 0,$$

which is the same as

$$-\sum c_i s_i < \sum c_i s_i^2.$$

In a similar way, if $q \approx 0$, p decreases ($\Delta p < 0$) if

$$\sum c_i s_i < \sum c_i s_i^2.$$

Thus, both alleles are *protected* (and no fixation is possible) if

$$|\sum c_i s_i| < \sum c_i s_i^2.$$

But, $\sum c_i|s_i| = |E\{s_i\}|$ is the average strength of selection and if all s_i are small, $\sum c_i s_i^2 = E\{s_i^2\} = (E\{s_i\})^2 + var\{s_i\} \approx var\{s_i\}$ is approximately the variance in selection intensities. Thus, if the variance in fitness is great enough, that is if

$$|E\{s_i\}| < var\{s_i\}, \tag{33}$$

polymorphism will occur. Note that for the inequality (33) to be true it is necessary to have both positive and negative s_i. We conclude that the more variable the environment, the more plausible polymorphism is.

1.12 Technical section: interaction of weak forces

Let the effect of one evolutionary force (say, selection) on a particular dynamic variable (say, allele frequency) be described by a equation $p_s = f(p, s)$, where s is a parameter characterizing the strength of the force. Let the effect of another evolutionary force (say, migration) on the dynamic variable be described by a equation $p_m = g(p, m)$, where m is a parameter characterizing the strength of the force. In the absense of a selective force, allele frequency does not change so that $p = f(p, 0)$ and $p = g(p, 0)$. Assuming that both forces are weak (i.e., $s, m << 1$),

$$p_s = f(p,s) \approx f(p,0) + s\frac{\partial f(p,s)}{\partial s}|_{s=0} = p + s\frac{\partial f(p,s)}{\partial s}|_{s=0} \equiv p + sF(p) \equiv p + \Delta_s p,$$
$$p_m = g(p,m) \approx g(p,0) + m\frac{\partial g(p,m)}{\partial m}|_{m=0} \approx p + m\frac{\partial g(p,m)}{\partial m}|_{m=0} \equiv p + mG(p) \equiv p + \Delta_m p,$$

where we have neglected second order terms in s and m. If the order of selective forces is selection-migration, then in the next generation

$$p' - p = g(p_s, m) - p = p_s + mG(p + \Delta_s p) - p = \Delta_s p + mG(p + sF(p)) \approx \Delta_s p + m\left(G(p) + s\frac{\partial G(p + sF(p))}{\partial s}|_{s=0}\right)$$

The last term is order ms and thus is much smaller than the first two terms (which are order s and m, respectively). Therefore,

$$\Delta p \equiv p' - p \approx \Delta_s p + \Delta_m p.$$

The same result will follow if the order of events is migration-selection.

General conclusions: if selective forces are weak, their effects are additive and their order is irrelevant.

1.13 Spatially uniform disruptive selection

1.13.1 Migration-selection balance: two patches

We consider a one-locus two-allele model with viability selection against hybrids (underdominance): $w_{AA} = 1, w_{Aa} = 1 - s, w_{aa} = 1$ where $1 > s > 0$. Local dynamics within a single isolated population) are described by a difference equation

$$\Delta p = \frac{pq(w_A - w_a)}{\overline{w}} = \frac{pq(p - q)}{\overline{w}},$$

which can be approximated (using a weak selection approximation $s << 1$) by a differential equation

$$\dot{p} = spq(p - q).$$

In a single population genetic variation is quickly lost with $p \to 0$ or 1 depending on initial conditions.

Assume that there are two sub-populations with individuals migrating between them with (migration) rate m. Let p_1 and p_2 be the frequencies of allele **A** in the first and second sub-population, respectively. After migration,

$$p_1' = (1 - m)p_1 + mp_2,$$
$$p_2' = (1 - m)p_2 + mp_1.$$

Thus, the changes in p_1 and p_2 due to migration are $\Delta_m p_1 = m(p_2 - p_1)$ and $\Delta_m p_2 = m(p_1 - p_2)$. With no other factors, migration will homogenize the system and allele frequencies with be the same ($p_1 = p_2$) asymptotically.

Using the differential approximation to describe the joint action of selection and migration on the allele frequencies, one gets a system of two ODE:

$$\dot{p}_1 = sp_1q_1(p_1 - q_1) + m(p_2 - p_1),$$
$$\dot{p}_2 = sp_2q_2(p_2 - q_2) + m(p_1 - p_2).$$

If there is no migration ($m = 0$, the populations are isolated), the dynamics are clear. If migration rate m is very large relative to selection, biological intuition tells us that migration will homogenize the population which will behave as a single randomly mating population. But what happens at intermediate migration rates? In particular, let initially different alleles be fixed in different populations (that is $p_1(0) = 1, p_2(0) = 0$ or $p_1(0) = 0, p_2(0) = 1$). What happens after individuals start migrating?

There are different equilibria: two monomorphic (with $p_1 = p_2 = 0$ or $p_1 = p_2 = 1$), a symmetric polymorphic (with $p_1 = p_2 = 1/2$), two asymmetric polymorphic (with $p1 = q2$)

$$p_1^* = 1/2 \mp \sqrt{1/4 - \epsilon}, p_2^* = 1/2 \pm \sqrt{1/4 - \epsilon},$$

where $\epsilon = m/s$, and four additional polymorphic equilibria. The latter reduce to $p_i = 1/2$ and $p_j = 0$ or 1 as $m \to 0$ and can be approximated for small ϵ. They are never stable. The monomorphic equilibria and the symmetric polymorphic equilibrium exist always. The asymmetric polymorphic equilibria exist (are feasible) if

$$\epsilon < 1/4.$$

Note that at these equilibria $p_i q_i = m/s$. Linear stability analysis shows that the monomorphic equilibria are always stable, whereas the symmetric polymorphic equilibrium is never stable. The asymmetric polymorphic equilibria are stable if

$$\epsilon < 1/6.$$

Thus, for small migration rates, specifically if $m < m_{cr} = s/6$, genetic variation can be maintained! Numerical examples of the critical migration rate m_{cr} for different coefficients of selection s:

$$s = .1 \Rightarrow m_{cr} = 1.7\%,$$
$$s = .5 \Rightarrow m_{cr} = 8.3\%,$$
$$s = .9 \Rightarrow m_{cr} = 15\%.$$

One can also consider a multipatch generalization of the two-patch model - a so-cold one-dimensional stepping-stone model. Assuming as before that selection acts against heterozygotes the dynamics of allele frequency p_i in patch i are described by

$$\dot{p}_i = sp_iq_i(p_i - q_i) + \frac{m}{2}(p_{i+1} + p_{i-1} - 2p_i).$$

where m is the probability to leave a patch, and it is assumed that individuals migrate only to a neighboring deme (with probability $m/2$ in each direction).

1.13.2 Migration-selection balance: continuous habitat

The one-dimensional stepping-stone model can be approximated by a reaction-diffusion equation. The idea is

- to write $p_i(t)$ as $p(x,t)$ where x specifies the spatial location,
- to write $p_{i+1}(t)$ and $p_{i-1}(t)$ as $p(x+\delta,t)$ and $p(x-\delta,t)$ where δ is a "distance" between the patches, and
- to approximate $p(x+\delta,t) + p(x-\delta,t) - 2p(x,t)$ by a Taylor series in δ assuming δ is small.

This results in a diffusion term

$$D\frac{\partial^2 p(x,t)}{\partial x^2},$$

where $D = m\delta^2/2$. Note that $m\delta^2$ is the mean square of the distance between the location where an individual was born and the location where he "experienced" selection ($(1-m) \times 0 + m/2 \times (\delta)^2 + m/2 \times (-\delta)^2 = m\delta^2$).

The case of underdominant selection is described by a partial differential equation (Bazykin 1969):

$$\frac{\partial p}{\partial t} = spq(p-q) + D\frac{\partial^2 p}{\partial x^2}. \tag{34}$$

We are looking for an equilibrium solution $p = p(x)$ ($\frac{\partial p}{\partial t} = 0$) such that $p(+\infty) = 1, p(-\infty) = 0$. This solution describing a "cline" in allele frequency corresponds to the polymorphic solution of the two-patch model studied above. Because of the symmetry of the model, one can expect the cline to be symmetric about its *center* $x_0 :\ p(x - x_0) = q(x_0 - x)$ where center x_0 is defined as a spatial location at which $p = 1/2$.

Cline width, w, can be defined as

$$w = 1/(\frac{dp}{dx}) \text{ at } x = x_0.$$

In Bazykin's model

$$w = 4\sqrt{D/s}. \tag{35}$$

Stronger selection (large s) and weaker migration (small D) result in narrow clines. [A second order ODE $y'' = f(y)$ can be rewritten as $d(y')^2/dx = 2f(y)y'$. Thus, $(y')^2 = 2\int f(y)dy + const$. For our model this results in $(p'(x))^2 =$

$(s/D)p^2(1-p)^2 + const$, where the constant must be zero because for $p = 0$ and $p = 1$ (that is at $x = -\infty$ and $x = +\infty$), $p'(x)$ must be zero.] Cline form is given by equation

$$p(x) = \frac{e^{\sqrt{\frac{s}{D}}(x-x_0)}}{1+e^{\sqrt{\frac{s}{D}}(x-x_0)}} = \frac{1}{2}\left[\tanh\left(\sqrt{\frac{s}{D}}(x-x_0)\right)+1\right]. \tag{36}$$

[This solution is found by solving a first order ODE $p'(x) = \sqrt{s/D}\; p(1-p)$ subject to the appropriate boundary conditions.] The cline is *neutrally stable* regarding to the location of the cline center x_0. Note that on a logit scale (that is using $\ln[p/(1-p)]$ instead of p) Bazykin's cline is described by a straight line.

The equations derived above can be used in analyzing *hybrid zones.* [Hybrid zone is a geographic region where genetically distinct populations meet and interbreed to some extent, resulting in some individuals of mixed ancestry. Many hybrid zones are thought to be formed following a secondary contact of different populations, and to be maintained by a balance between selection against hybrids and recombinant phenotypes and dispersal. Analysis of hybrid zones provides insights into the nature of species, the strength and mode of natural selection, the genetic architecture of species differences, and the dynamics of the speciation process. Many hybrid zones exhibit a gradual change ("cline") in a character or in allele frequency along a geographic transect. Theoretical studies of hybrid zones concentrate on the form of clines and the ability of genes to penetrate hybrid zones.]

1.13.3 Fisher equation

The local dynamics of an advantageous allele in a haploid population can be described by a simple ODE

$$\dot{p} = sp(1-p),$$

where parameter s characterizes the selective advantage of the allele. Adding space results in a reaction-diffusion equation for $p(x,t)$

$$\frac{\partial p}{\partial t} = sp(1-p) + D\frac{\partial^2 p}{\partial x^2}. \tag{37}$$

This is a classic equation introduced by Fisher (1937) and studied by Kolmogorov, Petrovsky and Piskounov (1937). If initial condition $p_0(x) = p(x,0)$ has compact support (if $p_0 = 1$ for $x \leq x_1$, $p = 0$ for $x \geq x_2$ where $x_1 < x_2$), and p_0 is continuous for $x_1 < x < x_2$), the solution of the Fisher equation asymptotically approaches a traveling wave describing invasion of the advantageous allele with speed $2\sqrt{sD}$. [A traveling wave solution can be written as $p(x,t) = P(z)$ with $z = x - ct$, where c is the wave speed.

J. D. Murray's book ("Mathematical Biology", Springer) should be consulted for more details.

1.14 Temporal heterogeneity: Haldane and Jayakar (1963) model

We consider a one-locus two-allele model with fitnesses varying from generation to generation. We assume that allele **A** is dominant:

$$w_{AA} = w_{Aa} = 1, \; w_{aa} = w_t.$$

In constant environment (that is with $w_t = const$), genetic variability is not maintained. [Note that the equality $w_{AA} = w_{Aa} = 1$ does not mean these fitnesses are constant in time (they are just normalized). Our goal is to show that maintenance of genetic variation is possible if the fitnesses (environment) vary in time.

The dynamics of allele frequencies are described by standard equations

$$p_{t+1} = \frac{1}{\overline{w}_t} p_t,$$
$$q_{t+1} = \frac{q_t w_t + p_t}{\overline{w}_t} q_t.$$

Introducing $u = p/q$, the change in u between two subsequent generations is

$$\Delta u_t \equiv u_{t+1} - u_t = 1 - w_t - \frac{w_t(1-w_t)}{u_t + w_t}.$$

If **a** is rare ($q_t << 1$), $u_t >> 1$ and $\Delta u_t \approx 1 - w_t$. The overall change in u over T generations is

$$u_T - u_0 = \sum_{t=1}^{T} \Delta u_t = T - \sum_{t=1}^{T} w_t.$$

Thus, q will increase if

$$\lim_{T\to\infty} \frac{1}{T} \sum_{t=1}^{T} w_t > 1.$$

Thus, if genotype **aa** is more fit "on average" than genotypes **AA** and **Aa**, it cannot be eliminated.

If **A** is rare ($p_t << 1$), then $u_t \approx 0$ and

$$\frac{u_{t+1}}{u_t} \approx \frac{1}{w_t}.$$

Over T generations

$$\frac{u_T}{u_0} = \frac{u_T}{u_{T-1}} \dots \frac{u_t}{u_{t-1}} \dots \frac{u_1}{u_0} \approx \frac{1}{w_1 w_2 \dots w_T}.$$

Thus, u and p will increase if

$$(w_1 w_2 \dots w_T)^{1/T} < 1.$$

Summarizing, allele **A** is not eliminated if the geometric mean fitness of **aa** is smaller than 1 whereas allele **a** is not eliminated if the arithmetic mean fitness of **aa** is larger than 1.

Note that if for some generations t, $w_t \approx 0$, then $\sum w_t/T$ is not affected significantly, but Πw_t will decrease dramatically. Thus, one can say that polymorphism is promoted if the recessive type is most fit, on the average, but is subject to occasional catastrophes.

We can also consider a selection scheme with fitnesses

$$w_{AA} = v_t, \; w_{Aa} = 1 \, w_{aa} = w_t.$$

Using $u = p/q$ as before one finds that

$$u_{t+1} = \frac{u_t v_t + 1}{w_t + u_t}\, u_t.$$

If allele **a** is rare ($q << 1, p \approx 1, u >> 1$), then

$$u_{t+1}/u_t \approx v_t,$$

and **a** cannot be lost if the geometric mean fitness of **AA** is smaller than 1:

$$(v_1 v_2 \dots v_T)^{1/T} < 1.$$

In a similar way, allele **A** cannot be lost if the geometric mean fitness of **aa** is smaller than 1:

$$(w_1 w_2 \dots w_T)^{1/T} < 1.$$

Note that both arithmetic mean fitnesses can be larger than one. Thus, polymorphism is maintained if the geometric mean fitnesses of homozygotes are smaller than that of heterozygotes. This is possible even if the mean arithmetic fitnesses of homozygotes exceed that of heterozygotes (underdominance on the average). For example, this can happen if rare environmental catastrophes (against homozygotes) are severe enough.