Mathematical Methods in Biology

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Contents

1 Introduction: The shape of functions

As an introduction, we study two simple biological models: the Hardy-Weinberg equilibrium of population genetics and the functional response of predators. These examples introduce some basic concepts about functions, and illustrate biological consequences of nonlinearity, i.e., the fact that most functions are curved.

1.1 Hardy-Weinberg equilibrium

1.1.1 Frequencies of genotypes and of alleles

Consider a population of diploid individuals, where two alleles (variants) of a gene are segregating. An individual may thus be homozygote for the first allele (A_1A_1), homozygote for the second allele (A_2A_2) or heterozygote (A_1A_2). Assume that each individual can be genotyped (this is straightforward e.g. for allozymes separated via electrophoresis or in case of codominant alleles like the MN blood group system). Then one can directly measure the number of A_1A_1 homozygotes (N_{11}), the number of A_2A_2 homozygotes (N_{22}) and the number of A_1A_2 heterozygotes (N_{12}) in a sample of $N = N_{11} + N_{12} + N_{22}$ individuals.

Let D, H and R denote respectively the *frequencies* of genotypes A_1A_1, A_1A_2 and A_2A_2, i.e., the number of individuals having a given genotype per the total number:

$$D = N_{11}/N, \quad H = N_{12}/N, \quad R = N_{22}/N \tag{1}$$

(The classic notation D, H, R comes from the words "dominant homozygote", "heterozygote" and "recessive homozygote", but is used also when there is no dominance.) Obviously, we have

$$D + H + R = (N_{11} + N_{12} + N_{22})/N = N/N = 1 \tag{2}$$

i.e., the frequencies add up to 1 (or 100%) as always.

Focus now on the population of all *alleles*. Because each diploid individual has two alleles, there are $2N$ alleles in N individuals. What fraction of these alleles is A_1, i.e., what is the *frequency* of A_1? Let us first count the *number* of A_1 alleles. Each A_1A_1 homozygote individual harbors two A_1 allele, which makes a total of $2N_{11}$ alleles in homozygotes; and each A_1A_2 heterozygote harbors one A_1 allele, which makes a total of N_{12} alleles in heterozygotes. A_2A_2 homozygotes have no A_1 allele at all. The total number of A_1 alleles is thus $2N_{11} + N_{12}$. Dividing the number of A_1 alleles with the total number of all alleles ($2N$) yields the frequency of A_1 alleles in the population:

$$p = \frac{2N_{11} + N_{12}}{2N} = \frac{N_{11}}{N} + \frac{1}{2}\frac{N_{12}}{N} = D + H/2 \tag{3}$$

Because the frequencies of alleles must also add up to 1, the frequency of A_2 is $q = 1 - p$.

Exercise: Show that $q = R + H/2$ and this is indeed equivalent to $q = 1 - p$.

1.1.2 Random mating

Given a population of parents with genotypic frequencies D, H and R as above, we now calculate the frequencies of genotypes among their offspring. We assume that the offspring are formed via *random mating*. This means that (i) each parent has the same chance to reproduce; (ii) each of the two alleles of the parent has equal chance to get into the offspring (fair meiosis); and (iii) the choice of the father does not depend on who the mother is.

What is the fraction of offspring who inherits allele A_1 from both parents? First choose a mother randomly from the population. With probability D, the mother has genotype A_1A_1 and therefore all her eggs carry A_1; with probability H, the mother is heterozygote (A_1A_2) and only half her eggs are A_1; and there is no other way of obtaining an A_1 egg. Summing up these two possibilities, the fraction $D + H/2$ of the eggs have allele A_1. Notice that this is exactly the frequency of A_1 alleles in the parents, $p = D + H/2$. Choosing a random allele of a random individual is of course the same as choosing a random allele from the entire population of alleles; and because a fraction p of all alleles is A_1, it happens with frequency p that the randomly chosen allele is A_1.

So far we have that a fraction p of the offspring started with an A_1 egg. By the same logic, we can say that a fraction p *of these eggs* received an A_1 sperm. A fraction p of fraction p is $p \times p = p^2$. Hence p^2 of all offspring inherits allele A_1 from both parents. We can thus say that the frequency of A_1A_1 homozygotes among the offspring is given by

$$D' = p^2 \tag{4}$$

where D' denotes the frequency of A_1A_1 homozygotes in the next generation (i.e., among the offspring) and p is the frequency of allele A_1 in the initial generation (among the parents).

This is a very important point, so I illustrate this also with numerical examples. Suppose that half the eggs, and also half the sperm, carry allele A_1, whereas the rest carries A_2. In this case, half the offspring started with an A_1 egg; and a half *of these* receive an A_1 sperm. Hence the fraction of offspring with genotype A_1A_1 is half of half, i.e., one quarter. This works the same way also if the frequencies of alleles are different from one half. If one third of eggs is A_1 and one third of these A_1 eggs receive A_1 sperm, then the frequency of A_1A_1 homozygote offspring is one third of one third or $(1/3) \times (1/3) = 1/9$. Or in general, the frequency of A_1A_1 offspring is $p \times p = p^2$.

Exercise: Use the same logic to show that the frequency of A_2A_2 homozygote offspring is given by $R' = q^2$.

Next, we ask what is the fraction of heterozygote offspring. This is a little more complicated, because heterozygote offspring can form in two different ways: either the egg is A_1 and the sperm is A_2, or the egg is A_2 and the sperm is A_1. The first possibility happens with frequency $p \times q$, because a fraction p of the eggs is A_1 and a fraction q of these eggs receive A_2 sperm. The second possibility happens with frequency $q \times p$, which is (the fraction of A_2 eggs) $\times$ (the fraction of A_1 sperm). Summing up the two possibilites, the frequency of heterozygote offspring is given by

$$H' = pq + qp = 2pq \tag{5}$$

The frequencies of all genotypes must add up to one also in the offspring generation. Indeed, we have

$$D' + H' + R' = p^2 + 2pq + q^2 = (p+q)^2 = 1^2 = 1 \tag{6}$$

There are two noteworthy facts regarding frequencies of genotypes and alleles under random mating:

(1) Whatever the initial frequencies of genotypes (i.e., for *arbitrary* D, H, R), the offspring genotypic frequencies are given by the fractions

$$D' = p^2, \quad H' = 2pq, \quad R' = q^2 \tag{7}$$

where $p = D + H/2$ is the frequency of allele A_1 in the initial population and $q = 1 - p$ is the frequency of A_2. The fractions p^2, $2pq$ and q^2 are called *Hardy-Weinberg frequencies* (or Hardy-Weinberg equilibrium). One round of random mating is sufficient to establish the Hardy-Weinberg frequencies of genotypes.

(2) The allele frequency does not change from generation to generation. Indeed, in the offspring generation the frequency of allele A_1 is given by

$$p' = D' + H'/2 = p^2 + (2pq)/2 = p(p+q) = p \tag{8}$$

which is the same as the frequency of allele A_1 in the initial population. Random mating gives equal chance to every allele to get into the next generation, and hence does not alter the frequency of alleles.

1.1.3 Is a population in Hardy-Weinberg equilibrium?

Suppose we measure the genotypic frequencies in a population as in equation (1). Is this population in Hardy-Weinberg equilibrium (which is the null expectation), or is there a discrepancy from the Hardy-Weinberg frequencies (for example, due to nonrandom mating or natural selection)?

Given the genotypic frequencies D, H, R, we can directly calculate the allele frequencies $p = D + H/2$ and $q = R + H/2$ as in equation (3). *If* the population is in Hardy-Weinberg equilibrium, *then* we have

$$D = p^2, \quad H = 2pq, \quad R = q^2 \tag{9}$$

i.e., the equations

$$D = (D + H/2)^2, \quad H = 2(D + H/2)(R + H/2), \quad R = (R + H/2)^2 \tag{10}$$

hold for the measured values of D, H, R. (With finite samples, there may be some discrepancy due to sampling error, but the discrepancy from the above equations should not be statistically significant; this can be checked using a χ^2-test.)

An interesting example for *violating* the Hardy-Weinberg frequencies comes from observations in herbaria. The specimens of a herbarium often deviate from the Hardy-Weinberg frequencies such that there are fewer heterozygotes than expected (this is sometimes called the *Wahlund effect*). The most likely reason for deviating from the Hardy-Weinberg frequencies is that the speciments were collected from different localities, and the local populations differ in their allele frequencies. We explore the effects of spatial variation in the next section.

1.1.4 Spatial structure

In order to study the effect of spatially variable allele frequency on the frequency of heterozygotes, it is useful to plot the function $H(p) = 2p(1 - p)$ (note that we substitute $q = 1 - p$ into $H = 2pq$ in order to have H explicitly as a function of p). The function $H(p) = 2p(1 - p)$ is an "upside down" parabola, which has value zero (i.e., crosses the horizontal axis) at $p = 0$ and at $p = 1$ (figure 1). This function is *concave*, because where it is increasing (in the interval $0 \leq p < \frac{1}{2}$), it is increasing less and less; and where it is decreasing (in the interval $\frac{1}{2} < p \leq 1$), it is decreasing steeper and steeper.

As an example, suppose that half the individuals of a large sample come from a population where the local allele frequency is p_1, whereas the remaining half comes from a population with allele frequency p_2. Each local population is in Hardy-Weinberg equilibrium. Therefore, half the sample contains heterozygotes with frequency $H(p_1)$ and the other half of the sample contains heterozygotes with frequency $H(p_2)$ (black dots in figure 1). The frequency of heterozygotes in the entire sample is the average of these two, i.e.,

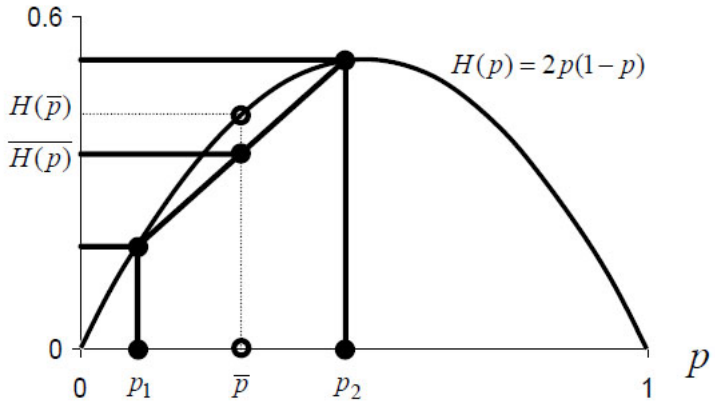


Figure 1: Spatial variation in allele frequency causes a shortage of heterozygotes due to Jensen's inequality

$\overline{H(p)} = (H(p_1) + H(p_2))/2$. Note that we *first* evaluated $H(p)$ at different points and *then* took the average of these values.

To check whether the sample is in Hardy-Weinberg equilibrium, we need to calculate the allele frequency of the sample. Because half the individuals have allele frequency p_1 and the other half has allele frequency p_2, the allele frequency of the entire sample is $\overline{p} = (p_1 + p_2)/2$. Based on this value, the Hardy-Weinberg frequency of heterozygotes would be $H(\overline{p})$ (empty circle in figure 1). Note that in this calculation, we *first* took the average of several p values and *then* evaluated $H(\overline{p})$ at the average allele frequency $\overline{p}$.

As figure 1 illustrates, the average frequency of heterozygotes, $\overline{H(p)}$, is less than the Hardy-Weinberg frequency at the average allele frequency, $H(\overline{p})$. This is because the function is concave ("bends down"). $\overline{H(p)}$ is the frequency of heterozygotes measured in the sample (e.g. in the herbarium); $H(\overline{p})$ is the Hardy-Weinberg expectation. Hence the concave shape of $H(p)$ explains why the measured value of heterozygote frequency is less than expected from the Hardy-Weinberg frequency, i.e., why populations with a spatial structure exhibit a shortage of heterozygotes.

An extreme example is if one local population harbors almost exclusively A_1 alleles such that almost every individual is A_1A_1 homozygote, whereas the other local population harbors almost exclusively A_2 alleles such that almost every individual is A_2A_2 homozygote. Collecting an equal number of individuals from both sites yields a sample where ca half the individuals are A_1A_1 and half the individuals are A_2A_2; the allele frequency of the sample is about $1/2$, but there are virtually no heterozygotes!

1.1.5 Jensen's inequality

The effect seen in figure 1 is known as *Jensen's inequality*. This inequality states that with any concave function (as H in figure 1), the average of function values (such as $\overline{H(p)}$) is less than the function evaluated at the average ($H(\overline{p})$. With convex functions, the result

is opposite: the average of function values exceeds the function evaluated at the average of its variable. Using the general notation f for a function that depends on variable x, Jensen's inequality thus states that

- $\overline{f(x)} < f(\overline{x})$ if f is concave
- $\overline{f(x)} > f(\overline{x})$ if f is convex

(assuming that x indeed varies; if there is no variation in x, then of course averaging makes no difference, and both $\overline{f(x)}$ and $f(\overline{x})$ simply equal to $f(x)$). It is a very common mistake to mix up $\overline{f(x)}$ and $f(\overline{x})$. They are *not* the same, except if f is linear (neither concave nor convex), which is an exceptional case:

- $\overline{f(x)} = f(\overline{x})$ if f is linear

  Exercise: Show graphically that $\overline{f(x)} > f(\overline{x})$ holds when f is convex. You might use the convex function $D(p) = p^2$ and show, by analogy to figure 1, that spatial structure leads to an excess of homozygotes.

Jensen's inequality shows up in many diverse biological phenomena. The above example shows how variation in allele frequency leads to a shortage of heterozygotes; in the next section, we study how variable prey density affects the food intake of predators.

1.2 Functional response of predators

The functional response of a predator, $\phi(x)$, gives the number of prey individuals eaten by one predator per unit of time as a function of prey density, x. Obviously, if prey is not present at all ($x = 0$) then the predator cannot eat any ($\phi(0) = 0$). One expects intuitively that the more prey are present, the more the predator eats, so that $\phi(x)$ is an increasing function of x. However, the predator cannot eat an arbitrarily high number of prey in a given time even if it is "bathing" in prey (i.e., ϕ is *bounded*) because it takes some time to handle (catch, kill, consume and digest) each prey individual. Denote the time necessary to handle one prey by T. If there is so much prey that the predator wastes no time for searching but it is is constantly handling prey, then in 1 unit of time it can eat $1/T$ prey individuals. Hence $\phi(x)$ must go to $1/T$ as prey density x goes to infinity.

To calculate $\phi(x)$, we assume that the predator is either searching for prey or handling prey; and the number of prey the predator finds is proportional to the time used for searching and also to prey density. Hence the number of prey found in 1 unit of time, $\phi(x)$, is given by $\phi(x) = \beta \cdot [\text{search time}] \cdot x$, where β is the *constant of proportionality* that characterizes how easy it is to find prey, called the capture rate. If the predator finds $\phi(x)$ prey, then it is handling for time $\phi(x) \cdot T$. The search time is all time from the unit time interval not used for handling; hence we have $[\text{search time}] = 1 - \phi(x)T$, and

$$\phi(x) = \beta[1 - \phi(x)T]x \tag{11}$$

Solving this equation for the unknown $\phi(x)$ yields

$$\phi(x) = \frac{\beta x}{1 + \beta T x} \tag{12}$$

This function is known as the *Holling type II* functional response of predators. It is a hyperbola, a concave increasing function of prey density x (see figure 2). It satisfies our intuitive expectations: $\phi(0)$ is indeed 0, and when x is very large (such that $1+\beta T x \approx \beta T x$ in the denominator), then its value is approximately $1/T$.

> **Exercise:** Show that the formula in (12) is indeed the solution of equation (11).

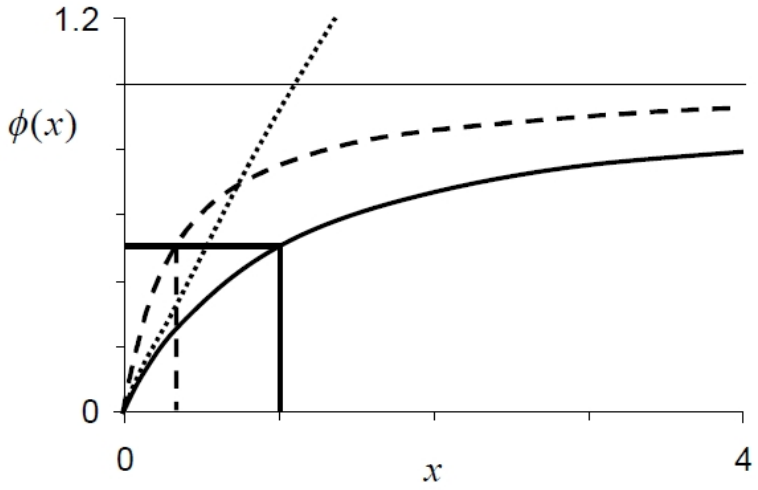


Figure 2: The Holling type II functional response of predators, $\phi(x) = \frac{\beta x}{1+\beta T x}$. Solid curve: $\beta = 1$, $T = 1$; dashed curve: $\beta = 3$, $T = 1$. Both the solid and dashed curves eventually saturate to $1/T = 1$ (horizontal line), but with different speed and half-saturation values (vertical lines placed such that $\phi(x) = \frac{1}{2T} = \frac{1}{2}$). Dotted curve: $\beta = 1$, $T = 0.1$; because of short handling time, this curve is approximately linear over the range shown (outside this range, it will slowly saturate to $1/T = 10$).

To characterize how fast the function saturates to its asymptotic value $1/T$, it is customary to calculate the *half-saturation* value: the value of x at which $\phi(x)$ is half of $1/T$. Denote the half-saturation value by $x_{1/2}$. Then, by definition, we have

$$\phi(x_{1/2}) = \frac{1}{2T}$$

and also

$$\phi(x_{1/2}) = \frac{\beta x_{1/2}}{1 + \beta T x_{1/2}}$$

so that

$$\frac{\beta x_{1/2}}{1 + \beta T x_{1/2}} = \frac{1}{2T} \tag{13}$$

Solving equation (13) yields

$$x_{1/2} = \frac{1}{\beta T} \tag{14}$$

Exercise: Verify this solution.

If the capture rate β is high, then the functional response has a low half-saturation value, i.e., it saturates quickly to its asymptotic value (compare the solid and dashed curves in figure 2). This corresponds to the situation where predators catch prey easily, so that they spend their time mostly by handling at already moderate densities of prey. If β is small, then the half-saturation value is high such that the function saturates only slowly, and the number of prey eaten approaches its asymptotic value only at high prey densities.

If the handling time T is short, then the half-saturation value is large and also the asymptote $1/T$ is high (cf. figure 2). This means that the functional response is approximately linear over the range of "usual" prey densities. With the ideal case of no handling time ($T = 0$) the function never saturates and we obtain the linear or Holling type I functional response $\phi(x) = \beta x$.

Exercise: Reproduce figure 2 using Excel or any similar software. Experiment with other values of parameters (β, T) and interpret why the shape of the function changes as it does when the parameter values are varied.

In nature, the density of prey is usually not constant but fluctuates over time. Because $\phi(x)$ is a concave function of x, Jensen's inequality states that

$$\overline{\phi(x)} < \phi(\overline{x}) \tag{15}$$

whenever x is not constant. Here $\overline{\phi(x)}$ is the average number of prey eaten by the predator, and $\phi(\overline{x})$ is the number of prey the predator would eat if prey density were constant at its mean, $\overline{x}$. This means that the fluctuation in prey density is harmful for predators: they could eat more prey if prey density were constant with the same average but without the fluctuation. Periods of high prey density do not compensate for periods of low prey

density. This is because the functional response is concave ("bending down") such that at times of higher prey density, the predator cannot consume proportionally more prey; in turn, this is because the predator wastes time with handling in periods of high prey density.

As we shall see later, predators of long handling time do not only suffer from fluctuating prey density because of their strongly nonlinear functional response, but also *make* prey density fluctuate. In such a population, a predator of short handling time enjoys an advantage because it is less sensitive to prey fluctuations. As the short-handling predator spreads, the fluctuations diminish, which favours the long-handling predator. Two predators can coexist on a single prey in a non-equilibrium ecosystem, countering the classic competitive exclusion principle valid for equilibrium populations ("at most as many consumers [predators] as resources [prey]"). This non-equilibrium coexistence is ultimately due to Jensen's inequality.

1.3 Box 1: Other examples for Jensen's inequality

Examples for Jensen's inequality abound in mathematical biology, because nonlinear functions are very common. We briefly mention two more examples here:

(1) *Photosynthetic assimilation in plants.* The assimilation rate (amount of assimilated carbon per leaf area per time) is a saturating function of irradiance. This is because at low levels of irradiance, the available light is limiting photosynthesis; but at high levels of irradiance, other processes (such as carbon dioxide uptake) are limiting, so that assimilation cannot increase indefinitely with increasing irradiance. Because the assimilation rate is a concave function of irradiance, fluctuating levels of irradiance yield less assimilated carbon than what would be obtained if irradiance were kept constant at its average level. Fluctuating irradiance is typical for example in forest understories: light penetrates between the trees depending on the Sun's exact angle, so that a given patch of understory leaves is in sunlight only for minutes at a time. Measuring the average irradiance (e.g. the amount of light through an entire day) and calculating the expected assimilation that corresponds to the average light absorbed seriously overestimates the true amount of assimilated carbon (see Ruel and Ayres 1999 in *Trends in Ecology and Evolution* for data).

(2) *Von Bertalanffy's growth equation.* The size of an aminal with indeterminate growth (such as fish) is often modelled with the equation

$$L(t) = L_\infty - (L_\infty - L_0)e^{-\alpha t}$$

where $L(t)$ is body length at age t, L_0 and L_∞ are respectively the size at birth and the limiting size at very old age, and α characterizes how fast the animal grows towards its limiting size. $L(t)$ is a concave function of age t. Hence in a stock of variable age, it would be incorrect to calculate the average age $\bar{t}$ and infer the average length from the above function as $L(\bar{t})$; this would overestimate the true average length, $\overline{L(t)}$.

Exercise: Draw figures to visualize the above examples and use these figures to explain what Jensen's inequality implies when light respectively age varies.

2 First foray into dynamics: Exponential decay

With models describing dynamics, we investigate how a certain quantity, such as the concentration of a biomolecule or the size of a population, changes as a function of time. As a first example for dynamic phenomena, we study the process of *exponential decay*. This is the simplest but very common dynamical process, which applies to the decay of any entities with no memory or aging. Examples include the decay of radioactive atoms and the decay of biomolecules (RNA, proteins, medicines, etc.): Their internal structure does not change with time since formation, and hence they decay independently of their age. Sometimes exponential decay is used as an approximation for mathematical simplicity, for example in models of population dynamics where all individuals are assumed to be identical independent of age, or in models of epidemics where it is often assumed that infected individuals recover or die independently of how long they have been infected.

2.1 Constructing the model

Let $x(t)$ denote the number of atoms/molecules/individuals "alive" at time t. Equivalently, x may denote the concentration of molecules (number per fixed volume) or the density of individuals (number per fixed area), but for the ease of speaking, here we shall treat x as a number. To calculate how $x(t)$ changes with time, compare x now $[x(t)]$ with x a short time interval, Δt, later $[x(t + \Delta t)]$:

$$x(t + \Delta t) = x(t) - [\#\text{ decayed in } \Delta t]$$

If the time interval Δt is *short*, then the probability of decaying is proportional to Δt and can be written as $\alpha \Delta t$. α is the *rate* of decay. "Rate" is a heavily abused word in biology, but its real meaning is this: *a rate multiplied with a short time interval gives the probability that an event* (such as decay) *happens in that short time interval*. Hence $\alpha \Delta t$ is the fraction of $x(t)$ which is going to decay in Δt, i.e.,

$$[\#\text{ decayed in } \Delta t] = \alpha \Delta t \cdot x(t)$$

and so we have

$$x(t + \Delta t) = x(t) - \alpha \Delta t \cdot x(t) \tag{16}$$

When we assume that α is a given number (a constant), we assume that the probability of decay does not change with time, hence there is no aging.

By subtracting $x(t)$ from both sides and dividing with Δt, equation (16) is rewritten as

$$\frac{x(t + \Delta t) - x(t)}{\Delta t} = -\alpha x(t) \tag{17}$$

The numerator of the left hand side $(x(t+\Delta t)-x(t))$ is the change in x during Δt, which

we may write simply as Δx:

$$\frac{\Delta x}{\Delta t} = -\alpha x(t) \tag{18}$$

Finally, we make Δt *infinitesimally small*: We make Δt extremely close to zero (but not exactly zero; we want to divide with it!) or, in other words, we take the *limit* as Δt goes to zero. Obviously, this will make also Δx infinitesimally small: the shorter time we wait, the less change occurs. We write "dx" and "dt" for the infinitesimal changes and thus obtain

$$\frac{dx}{dt} = -\alpha x(t) \tag{19}$$

The expression $\frac{dx}{dt}$ is the *derivative* of $x(t)$ with respect to time, which measures how fast $x(t)$ changes in time (amount of change per amount of time). Equation (19) is a *differential equation*. In the next chapter, we shall study derivatives in detail and will be able to solve this differential equation (see section 3.6). For now, we just write down the solution:

$$x(t) = x(0)e^{-\alpha t} \tag{20}$$

where $x(0)$ is the initial number of atoms/molecules/individuals, i.e., the number of those "alive" at time 0. The factor $e^{-\alpha t}$ is the fraction "alive" also at time t. In this expression, e is a number: it is called the base of the natural logarithm and its value is $e = 2.71828...$. The factor $e^{-\alpha t}$ can also be written as $\exp(-\alpha t)$, the two mean exactly the same.

2.2 Box 2: Why e=2.71828...?

Here we go a little deeper into equation (20), this material can be skipped on first reading. We investigate whether equation (20) is indeed the solution of the differential equation (19), or, equivalently, of equation (16). To check whether equation (20) is the solution, we substitute $x(t) = x(0)e^{-\alpha t}$ into the original equation (16):

$$\begin{aligned} x(t+\Delta t) &= x(t) - \alpha\Delta t \cdot x(t) \\ x(0)e^{-\alpha(t+\Delta t)} &= x(0)e^{-\alpha t} - \alpha\Delta t \cdot x(0)e^{-\alpha t} \qquad (*) \end{aligned}$$

We can cancel $x(0)$ on both sides. Moreover, we can write $e^{-\alpha(t+\Delta t)}$ as $e^{-\alpha t}e^{-\alpha\Delta t}$, which yields

$$e^{-\alpha t}e^{-\alpha\Delta t} = e^{-\alpha t} - \alpha\Delta t \cdot e^{-\alpha t}$$

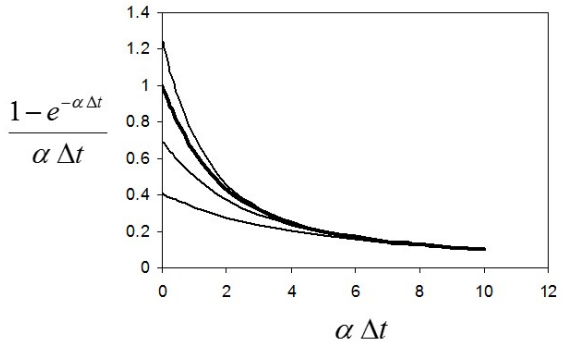
Now we can cancel also $e^{-\alpha t}$, and we obtain

$$e^{-\alpha\Delta t} = 1 - \alpha\Delta t$$

that can be rearranged into $1 - e^{-\alpha\Delta t} = \alpha\Delta t$ or

$$\frac{1 - e^{-\alpha\Delta t}}{\alpha\Delta t} = 1$$

This last equation is equivalent to the equation marked with $(*)$; hence if $x(t) = x(0)e^{-\alpha t}$ is indeed the solution, then this last equation must be true. The expression on the left hand side, $\frac{1-e^{-\alpha\Delta t}}{\alpha\Delta t}$, depends on two numbers: the product $\alpha\Delta t$ and the number e. Let us plot $\alpha\Delta t$ as a function of $\alpha\Delta t$, using different numbers in place of e. In the figure below, I took 1.5 for e and got the lowermost curve; took 2 and got the second curve from below; and took 3.5 for the uppermost curve (all thin lines).



Exercise: Use e.g. Excel to draw this figure yourself.

Because we must consider very short time intervals for Δt, we are interested in the left edge of the figure, where $\alpha\Delta t$ is close to zero. The curves clearly take different values at the left edge. What we want, for $\frac{1-e^{-\alpha\Delta t}}{\alpha\Delta t} = 1$ to be true, is that our curve hits the vertical axis at 1. Substituting 1.5 for e is thus not good, because the lowermost curve hits the axis below 1; substituting 2 for e is better but still not good; and with substituting 3.5, we overshoot the target because the uppermost curve hits the axis above 1. The proper value of e is therefore somewhere between 2 and 3.5. By refining the above procedure (i.e., by trial and error on ever finer scales, a procedure called successive approximation), one can obtain the proper value of e as precisely as wanted. The result is $e = 2.71828....$ Substituting this value for e, we obtain the thick curve of the figure, which takes the correct value 1 on the vertical axis. The function $x(t) = x(0)e^{-\alpha t}$ is therefore indeed the solution of the decay process described in equation (16), provided we use the numerical value $e = 2.71828....$

The exponential decay process applies to many natural phenomena and is important also in pure mathematics. $e = 2.71828...$ is an extremely important number precisely because when using this number, $x(t) = x(0)e^{-\alpha t}$ tells us how exponential decay progresses with time.

2.3 Half-life

Figure 3 shows how $x(t) = x(0)e^{-\alpha t}$ depends on time t. An important property of this curve is successive halving: in a certain time interval $x(t)$ drops to half of the initial value $x(0)$; then *in the same* time interval it drops to half of the remaining half, i.e., to the quarter of $x(0)$; and so on. This is easily verified by noting that $x(2t) = x(0)e^{-2\alpha t} = x(0)[e^{-\alpha t}]^2$, so that if $x(t) = \frac{1}{2}x(0)$ with $[e^{-\alpha t}] = \frac{1}{2}$, then $x(2t) = \frac{1}{4}x(0)$. Heuristically, this property is a direct consequence of having no aging or memory. The atoms/molecules/individuals that remain "alive" after the first halving do not remember

of how long they have been alive; they have a "fresh start" at every moment and their future is independent of their past. They will do exactly the same what has already happened: their number will halve again in the same time as before. This time interval is called the *half-life* and denoted by $t_{1/2}$.

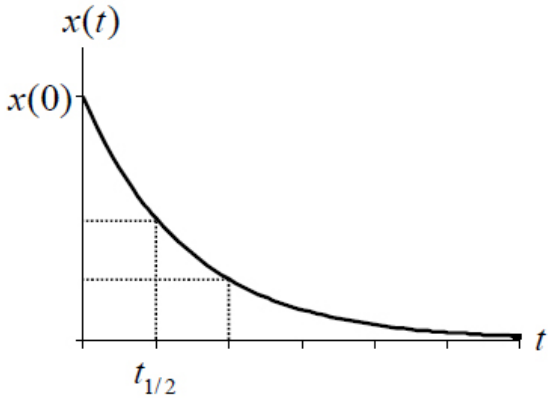


Figure 3: Exponential decay

To calculate the half-life $t_{1/2}$, we simply solve the equation $[e^{-\alpha t}] = \frac{1}{2}$ to obtain

$$t_{1/2} = \frac{\ln 2}{\alpha} \tag{21}$$

In practice, it is often the half-life of a process what is easy to find in the literature (such as the half-life of a radioactive substance) and we need to calculate the rate of decay:

$$\alpha = \frac{\ln 2}{t_{1/2}} \tag{22}$$

Exercise: Verify the above formulas.

Note that the decay rate α is measured in units of 1/time (for example, 1/year or 1/sec). This is obvious in equation (22), where α is given as the number $\ln 2 = 0.6931...$ divided with the half-life time. But it is also obvious already in equation (20), where the product αt is in the exponent. Exponents must be dimensionless (=unit-less); it would make no sense to say "two to the power millimetre". If αt is to be dimensionless, then the unit of t must cancel againts the unit of α, i.e., the unit of α must be 1 over the unit of time.

A higher decay rate α means a shorter half-life (see equation (21). With higher α, the successive halving process plays out faster: the exponential decay process is the same, only accelerated. This again can be seen also directly from equation (20). The value of $x(t) = x(0)e^{-\alpha t}$ depends on the product αt. When α is higher, the same value of

this product is attained at a smaller value of t; hence $x(t)$ takes the same value at an earlier time. We say that the decay rate α *scales time*. Changing α does not change the properties of the process, only makes it play out faster or slower. In this sense, there is only one exponential decay process; fast-decaying proteins and long-lived radioisotopes do not differ but in the time scale.

2.4 Example for exponential decay: Carbon dating

A straightforward application of the exponential decay process is the dating of archeological samples by the ^{14}C-method. ^{14}C is a radioactive isotope of carbon with half-life $t_{1/2} = 5730$ years. The atmospheric concentration of ^{14}C is remarkably constant at one ^{14}C-atom per 10^{12} carbon atoms. Plants incorporate ^{14}C at the atmospheric concentration, such that when the plant lived, the concentration of ^{14}C in its tissues was $x(0) = 1/10^{12} = 10^{-12}$. When the plant dies, the ^{14}C atoms are no longer renewed by metabolism but only decay through time. Measuring the amount of ^{14}C left by the present time t gives the value of $x(t)$. The decay rate α can be calculated from the half-life $t_{1/2}$ as in (22). Thus in the equation $x(t) = x(0)e^{-\alpha t}$, the only unknown is t, the age of the sample. Solving the equation for t yields the age of the sample in terms of quantities that are either known from the literature $(x(0), \alpha)$ or measured in the experiment $(x(t))$:

$$t = \frac{1}{\alpha} \ln\left(\frac{x(0)}{x(t)}\right) \tag{23}$$

Exercise: Verify the above solution.

2.5 Expected lifetime

Next to the half-life, there is another characteristic time associated with an exponential decay process, the expected lifetime of an individual (or atom etc.). The expected lifetime gives the average time for which an individual lives. The expected lifetime is thus calculated as the following thought experiment: Take a population of N individuals (N needs to be large to avoid sampling errors), wait until each individual dies, and mark each individual with its age at death. The average of these numbers is the expected lifetime, T.

The expected lifetime is the reciprocal of the decay rate, i.e., $T = 1/\alpha$. To see this heuristically, note that by the definition of the average age at death, T is the sum of lifetimes of all N individuals divided by N; hence NT is the total lifetime of all individuals. With decay rate α, we expect $NT\alpha$ deaths to occur in NT time. But the number of deaths is N because everybody has died; hence $NT\alpha = N$ and we have $T = 1/\alpha$.

Note that the expected lifetime, $1/\alpha$, is longer than the half-life, $(\ln 2)/\alpha \approx 0.6931/\alpha$. In statistical terms, the half-life corresponds to the median of lifetime.

2.6 Alternative modes of decay

In many systems there are several ways of decay such that several exponential decay processes occur in parallel and "compete" with each other. For example, the potassium isotope ^{40}K can decay in three disctinct way: (i) a beta-decay (emitting an electron from the nucleus) produces ^{40}Ca; (ii) a positron-emission produces ^{40}Ar; and (iii) the same isotope ^{40}Ar can also be produced without emitting a positron but by capturing an electron from the atom's own innermost orbital. An enzyme-substrate complex can decay either into the enzyme and the product (if the chemical reaction the enzyme catalyzes did take place) or into the enzyme and the substrate (if it did not). An infected person may cease to be infected via recovery, death due to the disease, or natural death (here we shall assume that recovery and death occur at constant rates and are therefore exponential decay processes, which is of course only an approximation).

With several modes of decay, we may ask how fast the number of atoms (or molecules or individuals) decreases; and what is the probability that an atom (or molecule or individual) decays in a certain way rather than in other possible ways. For example, how fast does a population of infected people cease to exist? And what is the probability that an infected person recovers rather than dies?

Denote the rates of recovery, disease-induced death, and natural death by v, α, and μ, respectively. An infected person will recover in the next short time interval Δt with probability $v\Delta t$; he will die because of the disease with probability $\alpha\Delta t$; and he will die a natural death with probability $\mu\Delta t$. The probability that *something* happens so that the person ceases to be infected is $(v+\alpha+\mu)\Delta t$. Hence the rate of decay in any of the three ways is $v+\alpha+\mu$, the sum of the rates of the individual decay processes. The number of infected decreases according to the exponential function $x(t) = x(0)e^{(v+\alpha+\mu)t}$, and the expected lifetime of an infection equals $\frac{1}{v+\alpha+\mu}$.

To calculate the probability that a person recovers rather than dies, consider the next short time interval Δt, in which he recovers with probability $v\Delta t$ and ceases to be infected in some way with probability $(v+\alpha+\mu)\Delta t$. Hence *if* the person ceases to be infected in Δt, then the probability that this happens via recovery is $\frac{v\Delta t}{(v+\alpha+\mu)\Delta t} = \frac{v}{v+\alpha+\mu}$. If the person remains infected, then the same will happen in the next Δt interval: if he is not infected at its end, then he has recovered with probability $\frac{v}{v+\alpha+\mu}$. The person eventually either recovers or dies, i.e., after sufficiently many such short Δt intervals, he is not infected any longer. Because in each Δt the probability of recovery (if anything happens) is the same, also the eventual probability of recovery is $\frac{v}{v+\alpha+\mu}$, the ratio of the rate of the desired decay process (recovery) and the total decay rate (sum of individual decay rates). In other words, the probability that decay occurs in a specific way is the rate of the desired decay process (v) times the expected lifetime ($\frac{1}{v+\alpha+\mu}$) in which this decay should occur.

2.7 Example for multiple modes of decay: K-Ar dating

The potassium-argon dating method is widely used in geology and paleontology, especially for dating older rocks. ^{40}K decays at rate $\alpha_{Ca} = 4.92 \cdot 10^{-10}$/year into ^{40}Ca and at rate $\alpha_{Ar} = 6.21 \cdot 10^{-11}$/year into ^{40}Ar (the latter is the sum of rates of positron decay and electron capture, both producing Ar, see above).

> **Exercise:** Show that the half-life of ^{40}K is approximately $1.25 \cdot 10^9$ years; this long half-life makes the K-Ar method so useful in geology.

The date obtained by the K-Ar method is the time when the rock was last molten. Argon escapes from molten rock, so that all argon we find in the sample has been accumulated by the decay of ^{40}K since the rock solidified. We can measure the amount of ^{40}K present in the sample today ($x(t)$) and the amount of argon present today ($y(t)$); measuring calcium is useless because ^{40}Ca is a common isotope that was present, in unknown abundance, already when the rock formed.

From exponential decay, we know that the amount of remaining ^{40}K is given by

$$x(t) = x(0)e^{-\alpha t} \tag{24}$$

where $\alpha = \alpha_{Ca} + \alpha_{Ar}$ is known, but the initial amount of ^{40}K ($x(0)$) is not. Argon accumulates from the decay of ^{40}K such that the number of argon atoms ($y(t)$) is the number of ^{40}K atoms that already decayed ($x(0) - x(t)$) times the probability p that the atom decayed into Ar rather than into Ca. We thus have

$$y(t) = p[x(0) - x(t)] \tag{25}$$

and we can calculate p from the decay rates as $p = \frac{\alpha_{Ar}}{\alpha_{Ca}+\alpha_{Ar}} = 0.11$. Hence we have two equations with two unknown quantities, $x(0)$ and the age of the sample, t.

To solve these equations, let us divide $y(t)$ with $x(t)$,

$$\frac{y(t)}{x(t)} = p\Big[\frac{x(0)}{x(t)} - 1\Big] = p[e^{\alpha t} - 1] \tag{26}$$

from which we can express the age of the sample

$$t = \frac{1}{\alpha} \ln\Big(\frac{1}{p}\frac{y(t)}{x(t)} + 1\Big) \tag{27}$$

such that on the right hand side, all quantities are known (α, p) or measurable ($x(t), y(t)$).

> **Exercise:** Verify the above solution.

3 Differentiation

Differentiation, or taking the derivative, is a basic tool in analysing how functions behave. In this course, we study differentiation via two applications of of utmost importance, optimization models and dynamic models.

3.1 Optimization models

In optimization models, we want to find the best value of a variable which is in our control. Finding the best choice is of course a very common problem when we control a biochemical system, for example, set up a chemostat to produce as much antibiotics as possible. Finding the best variant is also a focal question when studying adaptation by natural selection; here natural selection is the mechanism that selects the best. We start with describing one simple example, which we shall use as the running example in this chapter; other applications will be treated afterwards and among the homework problems and projects.

Suppose that a female has to decide how many eggs to lay, or a plant has to decide how many seeds to produce. Having more offspring is of course better, or, more precisely, having more offspring yields higher fitness and is spread by natural selection *everything else being equal*. But everything else is not equal. A parent has a given amount of resources to produce the offspring, and the more offspring are produced, the less resource can be invested in each of them. The parent thus faces the *size-number trade-off*: if it starts with more offspring, each of them will be smaller and/or weaker, and therefore each of them will have a lower probability to survive till adulthood. What matters for the parent's fitness is the number of offspring who do survive and reproduce. Producing too few offspring is obviously suboptimal; but also producing too many offspring is suboptimal, because most of them will not survive.

Suppose that the probability that an offspring survives till adulthood, s, is an exponentially decreasing function of offspring number:

$$s(x) = s_{max}e^{-kx} \tag{28}$$

The formula given in (28) is just one possible example, and we shall later study the same problem with other trade-off functions as well. In the example of (28), s_{max} is the probability of survival for a very well-fed offspring, i.e., when the number of offspring is close to zero such that the parent can invest a lot in each of them: if x is close to zero, $s(x)$ is close to $s(0) = s_{max}e^0 = s_{max}$. The parameter k shows how fast offspring survival decreases with the number of offspring.

> **Exercise:** Plot $s(x)$ with different values for s_{max} and k and explain the differences.

To find the optimal value of offspring number x, the parent has to maximize the number of *surviving* offspring, which is given by

$$f(x) = x \cdot s(x) = s_{max} x e^{-kx} \tag{29}$$

$f(x)$, the function to be maximized, is sometimes referred to as the *goal function* (although this term is mainly used in other fields and less in mathematical biology). The function in (29) is shown in figure 4. The task is to find the value of x where the value of $f(x)$ is the highest; this is marked as x_{opt} in the figure. To this end, we need to study how $f(x)$ behaves as a function of x.

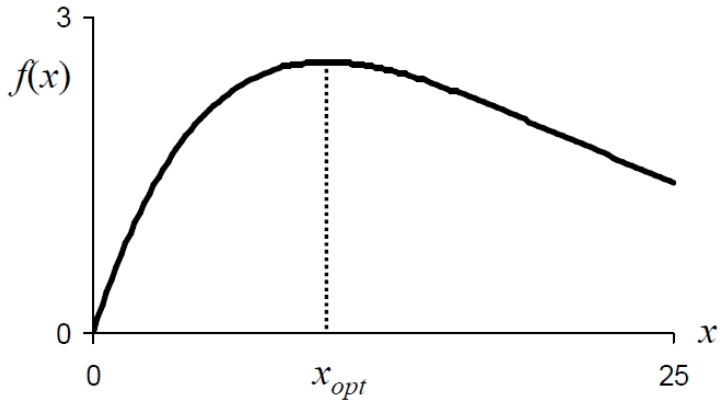


Figure 4: Optimal fecundity. $f(x)$ is as given in (29) with parameters $s_{max} = 0.7$ and $k = 0.1$.

3.2 Dynamic models

Very often, we are interested in how things change in time; hence how the concentration of a substance or the density of a population behaves as a function of time. When constructing a model, we account for processes that change the concentration or density, and hence in the first place we obtain equations describing the change rather than the concentration or density itself. As the next step, we need to find the concentration or density as a function of time such that the function indeed obeys the change we specified in the model. The exponential decay process in equations (19) and (20) illustrates this. The object on the left hand side of equation (19) is called a *derivative*, and we write down an equation for the derivative from first principles. An equation containing a derivative is called a *differential equation* (or ordinary differential equation, ODE). The solution to the differential equation in (19) is given by the function in (20), i.e., $x(t)$ in (20) behaves as a function of time as prescribed by (19).

When solving a differential equation such as (19), we face a somewhat different task than in optimization models. In optimization models, we construct the goal function first and then investigate how it changes with changing its variable. In dynamic models, however, we have first an equation for the change and then need to find the function itself. Nevertheless, in both cases we are concerned with changes of function values as a consequence of changing their variables, and differentiation gives the technique to describe such changes mathematically.

3.3 The derivative

If we want to know how $f(x)$ changes if we change x, the obvious thing is to compare the value of f at x with the value of f at a somewhat different point $x+\Delta x$; i.e., compare $f(x)$ and $f(x+\Delta x)$ as shown in figure 5a. If the difference $\Delta f = f(x+\Delta x) - f(x)$ is positive, then the function increases; if the difference is negative, then the function decreases over Δx.

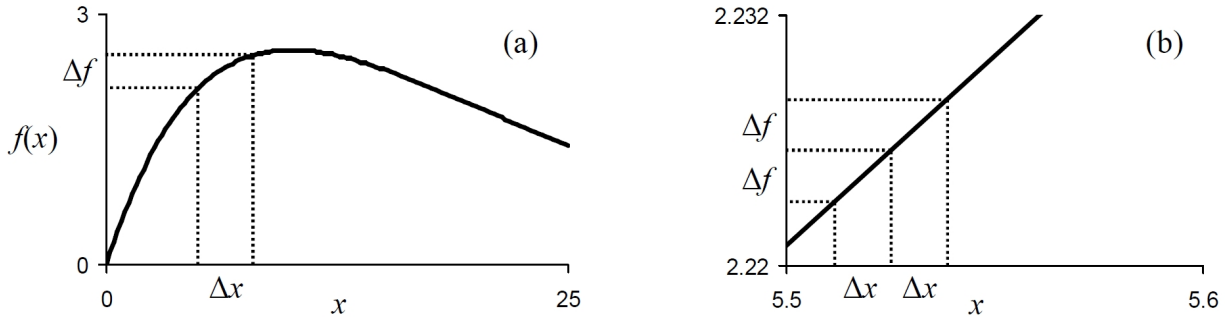


Figure 5: Differentiation. (a) Δf is how much the function value changes if we increase x by Δx. (b) An enlarged part of the figure in (a); note the different scale. Over a small range of x, the function is approximately linear, so that each small increment Δx makes the function to increase by (approximately) the same amount, Δf.

If we want an accurate picture of how $f(x)$ behaves as a function of x, we need to consider *small* intervals for Δx. Indeed, if Δx is too large, then f might be both increasing and decreasing within Δx; and these changes are not seen when we compare only the endpoints of the interval, x and $x + \Delta x$. We should therefore choose a small Δx and determine how much the function changed over a short interval; then we can increase x again and again by small increments Δx, and "piece" the overall shape of the function from many small steps.

Over a short range of x, any smooth function[1] is approximately linear (see figure 5b). This means that if we increase x by two Δx steps rather than by one, then the function

[1]In this course we consider only smooth functions, i.e., we assume that all derivatives exist and are continuous. Almost all functions a theoretical biologist is likely to encounter are smooth.

changes (approximately) by twice Δf; and in general, the change in f is proportional to the change in x, as long as the change in x is small. The difference quotient $\Delta f/\Delta x$ characterizes the speed of change and remains approximately the same over short ranges of x. Geometrically, $\Delta f/\Delta x$ is the slope of the line that approximates the function over a short range of x (figure 5b).

How small should Δx be? What is described above becomes more and more accurate as we make Δx shorter. Hence we take the *limit* of Δx going to zero ($\Delta x \to 0$): In a thought experiment, we repeat the above with ever smaller Δx, and recalculate the quotient $\Delta f/\Delta x$ for ever smaller Δx. What we obtain in this way is the derivative of f, denoted by df/dx. The change of "Δ" into "d" emphasizes that we have taken the limit $\Delta x \to 0$, or, in other words, that the change dx is now *infinitesimally small* (note that we never make Δx equal to zero, because then we cannot form the quotient $\Delta f/\Delta x$). The mathematical notation for this is

$$\frac{df}{dx} = \lim_{\Delta x \to 0} \frac{\Delta f}{\Delta x} \tag{30}$$

which reads like this: the derivative of f with respect to x, df/dx, is defined as the limit of the quotient $\Delta f/\Delta x$ as Δx goes to zero.

It is important to keep in mind that $\Delta f/\Delta x$, and therefore also the derivative df/dx, depend on the value of x where we calculated the difference $\Delta f = f(x+\Delta x) - f(x)$. If we place the Δx interval at a different location on the x-axis in figure 5a, we get a different value for Δf; for example, it we place it to the right of the maximum of the function, then Δf will be negative. The derivative itself is a function of x.

The derivative of f evaluated at a point x is often written as $f'(x)$; the notations f' and df/dx mean the same. There are also other notations used in the literature. For example a dot as in $\dot{f}$ also means the derivative of f, and is used especially often if f is a function of time.

As f' is a function of x, f' itself can be differentiated with respect to x. The function thus obtained, f'', is called the *second derivative* of f. One can of course continue and differentiate f'' to obtain the third derivative $f''' \equiv f^{(3)}$, then differentiate $f^{(3)}$ to obtain $f^{(4)}$, etc., but these higher derivatives are rarely used in mathematical biology.

The next two sections (3.4 and 3.5) treat the technical side of differentiation: how to calculate f' for any given f. Section 3.7 discusses how to use the derivatives to explore the shape of functions: for example, how to find minima or maxima of a given function. These parts can be read in arbitrary order; if you wish, study first what the derivatives are good for and return afterwards to how to obtain them.

3.4 Derivatives of simple functions

We illustrate the principles of how derivatives are calculated with three simple examples: the derivatives of the constant function $f(x) = c$; of the linear function $f(x) = a + bx$; and of the quadratic function $f(x) = x^2$. Afterwards, we list the derivatives of other commonly used functions.

Constant functions. If the function always returns the same number c, i.e., $f(x) = c$ for all x, then no matter how we change x, the change in $f(x)$ will be zero. Hence $\Delta f = 0$ at any x. From the definition of the derivative in (30), we have that the derivative of the constant function $f(x) = c$ is $f'(x) = 0$.

Linear functions. Consider now a general linear function written as $f(x) = a + bx$. To calculate the derivative, we form the difference $\Delta f = f(x + \Delta x) - f(x)$; substituting $f(x) = a + bx$ gives $\Delta f = (a + bx + b\Delta x) - (a + bx) = b\Delta x$. The quotient $\Delta f/\Delta x$ is therefore always b; this is true for every Δx, so that it is also true in in (30) when we take the limit as Δx goes to zero. Hence the derivative of the linear function $f(x) = a + bx$ is the constant function $f'(x) = b$. The derivative does not depend on x because the linear function has the same slope everywhere. The constant function is a special linear function with $b = 0$, and we obtained that its derivative is zero accordingly.

The quadratic function $f(x) = x^2$. The previous two examples were in fact "too simple", because the derivatives turned out to be constants independent of x. Taking the derivative of $f(x) = x^2$ illustrates how the procedure works in general. As before, we need to calculate the difference $\Delta f = f(x + \Delta x) - f(x)$; substituting $f(x) = x^2$ yields $\Delta f = (x + \Delta x)^2 - x^2$. We need to simplify this by writing out the square $(x + \Delta x)^2$:

$$\Delta f = (x + \Delta x)^2 - x^2 = x^2 + 2x\Delta x + \Delta x^2 - x^2 = 2x\Delta x + \Delta x^2$$

Next, we divide with Δx to obtain the quotient $\Delta f/\Delta x$:

$$\frac{\Delta f}{\Delta x} = 2x + \Delta x$$

Finally, we take the limit as Δx goes to zero: this means that the second term in $2x + \Delta x$ becomes infinitesimally small and thus negligible. The derivative of the function $f(x) = x^2$ is therefore $f'(x) = 2x$.

Table 1 lists the derivatives of simple functions most often encountered in mathematical biology. Note that the derivative of $f(x) = x^2$ we derived above is a special case for the derivative of the power function $f(x) = x^n$ with $n = 2$. The exponential function $f(x) = e^x$ is a very special function because its derivative is the same as itself. This property holds only with $e = 2.71828...$, and in fact this is the reason why $e = 2.71828...$

is such an important number.

	Function	*Derivative*
Constant:	$f(x) = c$	$f'(x) = 0$
Linear:	$f(x) = a + bx$	$f'(x) = b$
Power:	$f(x) = x^n$	$f'(x) = nx^{n-1}$
Exponential:	$f(x) = e^x$	$f'(x) = e^x$
Logarithm:	$f(x) = \ln x$	$f'(x) = 1/x$

Table 1: Derivatives of simple functions

3.5 Rules of differentiation

Derivatives of more complicated functions can be broken down to those of simple functions using the rules of differentiation listed in Table 2.

	Function	*Derivative*
Sum:	$f(x) = g(x) + h(x)$	$f'(x) = g'(x) + h'(x)$
Product:	$f(x) = g(x)h(x)$	$f'(x) = g'(x)h(x) + g(x)h'(x)$
	$f(x) = cg(x)$	$f'(x) = cg'(x)$
Quotient:	$f(x) = \frac{h(x)}{g(x)}$	$f'(x) = \frac{h'(x)g(x) - h(x)g'(x)}{g(x)^2}$
Reciprocal:	$f(x) = \frac{1}{g(x)}$	$f'(x) = -\frac{g'(x)}{g(x)^2}$
Chain rule:	$f(x) = h(g(x))$	$f'(x) = h'(g(x))g'(x)$
Exponential:	$f(x) = e^{g(x)}$	$f'(x) = e^{g(x)}g'(x)$
Logarithm:	$f(x) = \ln(g(x))$	$f'(x) = \frac{g'(x)}{g(x)}$

Table 2: Rules of differentiation

The first rule says that sums can be differentiated term by term. For example, the function $f(x) = x^2 + 3x + 1$ can be seen as the sum of two functions, $g(x) = x^2$ and

$h(x) = 3x + 1$. The derivatives of these functions are $g'(x) = 2x$ and $h'(x) = 3$; hence the derivative of their sum, the original function, is $f'(x) = 2x + 3$.

Differentiating products, as given by the second rule, is a little more complicated. Take the example of $f(x) = 4xe^x$. This is the product of $g(x) = 4x$ and $h(x) = e^x$, and the derivatives of the factors are $g'(x) = 4$ and $h'(x) = e^x$. The derivative of the product is therefore $f'(x) = g'(x)h(x) + g(x)h'(x) = 4e^x + 4xe^x = 4e^x(1 + x)$. Note the symmetry in the rule: in both terms of the derivative, one factor is differentiated and the other is not.

A special case of the product rule is when one of the factors is a constant ($f(x) = cg(x)$). Because the derivative of the constant is zero, we are left with the term where the constant is not differentiated but the other factor, $g(x)$ is; hence the derivative is $f'(x) = cg'(x)$.

> **Exercise:** Show how the derivative of the reciprocal is obtained as a special case of the quotient's rule.

One of the most important rules is the *chain rule*, which deals with functions of functions. For example, let's differentiate the function $f(x) = \ln(a + bx)$. This is the logarithm function of the linear function $a + bx$. In other words, the logarithm is the "outer function", and this outer function is to be evaluated at the "inner function" $a+bx$. The chain rule says that the derivative of $f(x)$ is the derivative of the outer function ln at the inner function $a + bx$, multiplied with the derivative of the inner function $a + bx$. The derivative of the logarithm $\ln x$ is $1/x$ (see Table 1), but the derivative needs to be evaluated at $a + bx$, i.e., we get $1/(a + bx)$. This is to be multiplied with the derivative of the inner function $a + bx$, which is b. The derivative of $f(x) = \ln(a + bx)$ is therefore $f'(x) = b/(a + bx)$.

> **Exercise:** Obtain the last two rules listed in Table 2 as special cases of the chain rule. (These last two rules are in fact not separate rules and are listed only for convenience, as they are used often.)

3.6 Example: Exponential decay

As a simple application of derivatives, we return to the exponential decay equation,

$$x'(t) = -\alpha x(t) \tag{31}$$

as given in equation (19) (recall that dx/dt and $x'(t)$ are the same thing). To "solve" this equation means to find $x(t)$ as a function of time such that if we differentiate $x(t)$, we get what is on the right hand side. We can now show that the solution of this differential equation is

$$x(t) = x(0)e^{-\alpha t} \tag{32}$$

as said in section 2. To do this, we evaluate the two sides of equation (31) using the proposed solution (32) and check that they are the same.

On the left hand side, we have the derivative of x with respect to time, t. Notice that here $x(t)$ plays the role of $f(x)$ in Tables 1 and 2, i.e., t is here what x is in the tables (a rather common confusion of notation!). Taking the derivative of $x(t) = x(0)e^{-\alpha t}$ with respect to the variable t, we obtain $x'(t) = x(0)e^{-\alpha t}(-\alpha)$ in the following way. First, the constant factor $x(0)$ remains in the derivative (see the third row of Table 2). Then we use the chain rule to differentiate the exponential function $e^{-\alpha t}$: the derivative of the exponential function is the exponential function $e^{-\alpha t}$ itself (see Table 1), times the derivative of its exponent $-\alpha t$, which is $-\alpha$. This assembles into the result $x'(t) = x(0)e^{-\alpha t}(-\alpha)$, or, written more neatly,

$$x'(t) = -\alpha x(0)e^{-\alpha t} \qquad \text{(left hand side)}$$

On the right hand side of equation (31), we have $-\alpha x(t)$. Here we simply substitute $x(t) = x(0)e^{-\alpha t}$ to obtain

$$-\alpha x(t) = -\alpha x(0)e^{-\alpha t} \qquad \text{(right hand side)}$$

The results on the left hand side and on the right hand side are the same. This means that the proposed solution $x(t) = x(0)e^{-\alpha t}$ is indeed the solution of the differential equation in (31).

Notice that in this section, we did not actually solve the differential equation in (31), but we have checked that the proposed function $x(t) = x(0)e^{-\alpha t}$ is indeed a solution. How can one come up with such a proposed solution? In the case of the exponential decay equation, we are looking for a function $x(t)$ such that its derivative (the left hand side of equation (31)) is almost the same as the function itself ($x(t)$ on the right hand side of equation (31)), the difference being only a constant factor ($-\alpha$). Since the derivative of the exponential function is the exponential function itself, the exponential function is a natural candidate for the solution. In these lecture notes, we do not pursue solving differential equations from scratch, because most biologically interesting models have no analytical solutions. However, differential equations can be solved numerically (see section 4.3), and even better, much of the biologically relevant information can be extracted without actually finding an explicit solution (section 4.5).

3.7 Geometric interpretation of derivatives

Recall the definition of the derivative from equation (30):

$$\frac{df}{dx} = \lim_{\Delta x \to 0} \frac{\Delta f}{\Delta x}$$

where Δf is how much the function has increased while x increased by Δx, and $\lim_{\Delta x \to 0}$ means that we consider infinitesimally small increments in Δx. From this definition, it is immediately obvious that if the function is strictly increasing, then $\frac{\Delta f}{\Delta x}$ is positive and

therefore the derivative is positive; and the opposite holds when the function is strictly decreasing. (The word "strictly" is inserted to exlude the case of a constant function, which is increasing or decreasing at zero speed.) Hence we have that

- if $f(x)$ is a strictly increasing function of x, then $f'(x) > 0$; and
- if $f(x)$ is a strictly decreasing function of x, then $f'(x) < 0$.

For example, the function f in figure 6 is increasing left to its maximum so that $f'(x) > 0$ when x is left to the thick vertical line; and f is decreasing right to its maximum so that $f'(x) < 0$ when x is right to the thick vertical line (compare the top two panels is figure 6).

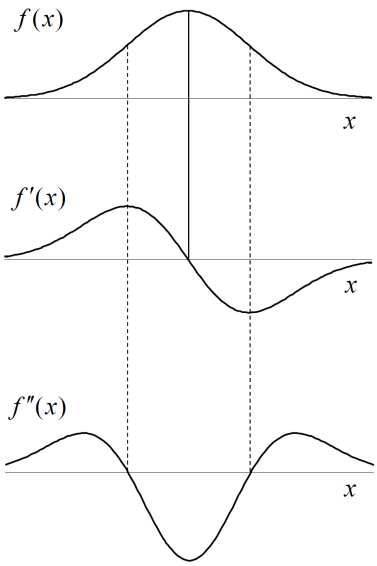


Figure 6: The Gaussian function $f(x) = \exp(-x^2/2)$ shown with its derivative f' and second derivative f''.

When a function has a maximum, it turns from increasing (positive derivative) to decreasing (negative derivative), so that at the point of maximum, the derivative is zero (see figure 6). If we know that the function has a maximum, then we can use the equation $f'(x) = 0$ to calculate the value of x where the maximum occurs (examples will be described below). The same is true, however, for minima: When a function has a minimum, it turns from decreasing (negative derivative) to increasing (positive derivative), so that also at a point of minimum the derivative is zero. The equation $f'(x) = 0$ therefore can yield the position of either a maximum or a minimum (for example in an optimization problem, either the best or the worst solution!).

To tell apart maxima and minima, we need to observe how the derivative changes with x (use figure 6 to follow this reasoning). If $f(x)$ has a maximum, then it is first

increasing and then decreasing, so that its derivative $f'(x)$ is first positive and then negative; therefore the derivative $f'(x)$ is a decreasing function of x. This means that the derivative of the derivative, $f''(x)$ is negative at a maximum. At a minimum, the opposite happens: $f(x)$ is first decreasing and then increasing, so that its derivative $f'(x)$ is first negative and then positive; therefore the derivative $f'(x)$ is an increasing function of x, i.e., $f''(x)$ is positive at a mimimum.

> **Exercise:** Figure 6 illustrates only the case of a maximum. Draw an analogous figure to explain how the derivatives behave in case the function has a minimum.

In summary,

- $f'(x) = 0$ with $f''(x) < 0$ implies that f has a maximum at x;
- $f'(x) = 0$ with $f''(x) > 0$ implies that f has a minimum at x.

Note that in the unlikely (and unlucky) case if both $f'(x)$ and $f''(x)$ are zero at some point x, we cannot tell if this point is a maximum, a minimum, or neither (one needs to know the values of higher derivatives for this special case).

The second derivative informs us about how the first derivative changes. A negative second derivative says that the first derivative is decreasing; hence the function is either increasing less and less steeply or decreasing more and more steeply. This means that the function is *concave*. In the opposite case of a positive second derivative, the function is increasing more and more steeply or decreasing less and less steeply; the function is thus *convex*. Note that at its maximum, the function must be concave, and hence the second derivative is negative. Similarly, at its minimum, the function must be convex, and hence the second derivative is positive, as seen above. The function shown in figure 6 is concave inbetween the dashed vertical lines and convex outside. The points where convex turns into concave or *vice versa* (dashed lines in figure 6) are called *points of inflection*.

> **Exercise:** Draw a function that has zero first and second derivatives at the same point (for example at $x = 0$, i.e., $f'(0) = 0$ and $f''(0) = 0$) and has neither a maximum nor a minimum at this point. Such a point is called a horizontal point of inflection.

3.8 Example: Optimal fecundity 1

As a first example for optimization models, let us solve the problem of optimal fecundity posed in section 3.1. This is a direct application of the method of finding the maximum of a function.

The best strategy for the female described in section 3.1 is to choose the number of her offspring x such that the number of offspring who survive till adulthood, $f(x) = s_{max}xe^{-kx}$, is maximal (cf. equation 29). To find the maximum of this function, we take its derivative:

$$f'(x) = s_{max}[e^{-kx} + xe^{-kx}(-k)] = s_{max}e^{-kx}[1 - kx] \tag{33}$$

and find the point(s) where the derivative equals zero:

$$s_{max}e^{-kx}[1 - kx] = 0 \tag{34}$$

The only solution of this equation is $x = 1/k$ and this is the candidate optimal fecundity. Whether it is indeed the best choice of offspring number (a maximum, yielding the most surviving offspring) or the worst choice (a minimum, yielding the least surviving offspring) depends on the second derivative evaluated at $x = 1/k$. To obtain the second derivative, take the first derivative

$$f'(x) = s_{max}e^{-kx}[1 - kx] \tag{35}$$

and differentiate again:

$$f''(x) = s_{max}[e^{-kx}(-k)(1 - kx) + e^{-kx}(-k)] \tag{36}$$

We need the value of the second derivative $f''(x)$ at the point $x = 1/k$, where $(1-kx) = 0$ (the first term in the brackets vanishes) and therefore

$$f''(1/k) = s_{max}[e^{-k(1/k)}(-k)] < 0 \tag{37}$$

Because the second derivative is negative, the point $x = 1/k$ is indeed a maximum, i.e., $x = 1/k$ is the optimal number of offspring.

A weakness of this example is that we assumed a particular form for juvenile survival as a function of offspring number ($s_{max}e^{-kx}$ as given in equation 28). It is clear that survival should not be an increasing function of fecundity, but this particular decreasing function was an arbitrary choice. The next example will illustrate how an optimization model can yield useful results even if its functions are not specified.

3.9 Example: Optimal fecundity 2

In a different model of optimal fecundity, assume that the amount of resources invested in every one offspring is fixed. If a female produces more offspring, she uses up more

resources of her own, and this decreases her own chance of survival. Let $p(x)$ denote the probability of survival for a female with x offspring. Each of the offspring survive with probability s, which is constant because each offspring receives the same amount of resources independently of x.

Assume clonal reproduction so that the offspring are identical to their mother; and assume that the offspring mature in one year, such that surviving offspring are indistinguishable from their mother. The best fecundity x then maximizes the expected number of identical descendants,

$$f(x) = xs + p(x) \tag{38}$$

We do not specify how $p(x)$ depends on x. Therefore we cannot determine the value of the optimal fecundity; but we can nevertheless draw important qualitative conclusions about the optimal reproductive strategy.

At the optimal value of x, the first derivative must be zero:

$$f'(x) = s + p'(x) = 0 \tag{39}$$

and the second derivative must be negative

$$f''(x) = p''(x) < 0 \tag{40}$$

Hence we obtain an optimal fecundity only if $p(x)$ is a concave function of x. But what happens if p is convex?

Figure 7 helps to interpret this result. The thick curves show concave (panel (a)) and convex (panel (b)) examples for $p(x)$ as a function of x. The points of these curves represent the possible reproductive strategies of the female. As the female invests more and more into her offspring, her survival is less and less, up to the point where she invests everything into the offspring such that she dies after reproduction; this defines the maximum possible fecundity, x_{max}.

In the same figure, we draw lines along which the *value* of $f(x)$ remains the same ("iso-f lines"). To find all points on the (x, p) plane where the value of $f(x)$ is equal to a given number c, rearrange the equation $f(x) = sx + p = c$ into $p = c - sx$, which corresponds to a straight line with slope $-s$. Such lines are drawn in figure 7. The higher is the value of c, the higher the line $p = c - sx$ lays in the figure. If c is too high (dotted lines), then the line does not have any common point with the curve of possible strategies; this high value of $f(x)$ cannot be achieved by any choice of x. If we lower the value of c (i.e., shift the line downwards), at some point the line touches the curve; the first point of

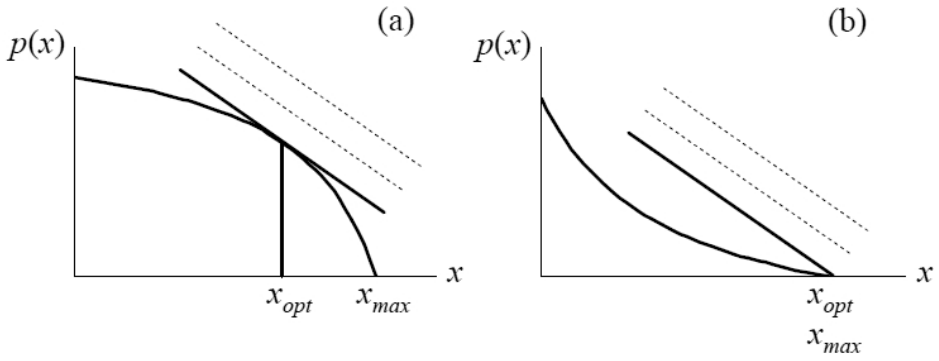


Figure 7: Iteroparity (a) versus semelparity (b) at the optimal fecundity. See text for explanation.

tangent corresponds to the optimal fecundity x_{opt}, which belongs to the line with highest possible c and therefore produces the highest possible value of $f(x)$.

In panel (a), this happens at an intermediate value of x. Females making the best choice x_{opt} have a positive probability of survival ($p(x_{opt}) > 0$), i.e., they may reproduce several times in their life: the optimal reproductive strategy is *iteroparous*. In contrast, in panel (b), the highest value of $f(x)$ belongs to the maximum fecundity ($x_{opt} = x_{max}$), where the probability of survival is zero: the female can reproduce only once, so that the optimal strategy is *semelparous*.

If $p(x)$ is a convex function of fecundity x, then the optimal number of offspring is always the maximum number of offspring (or zero; but such a population would not be viable). This optimum we did not find with the standard method of differentiation because it is at an endpoint of the interval of permissible values of x. At boundary optima like this, the derivative of $f(x)$ need not be zero; indeed the value of $f(x)$ would increase if we could increase x beyond x_{max}, only this is impossible because it would imply a negative probability of survival. Hence when searching for the maxima (or minima) of a function on a bounded set of possible values of x, one always has to check separately whether the boundary points represent maxima (or minima).

> **Exercise:** Using figure 7b, show graphically that there is a minimum of $f(x)$ (a worst choice of offspring number) at some intermediate value of x. Finding the point where $f'(x) = 0$ but not checking the second derivative would yield this minimum rather than the intended optimum!

If $p(x)$ is a concave function of fecundity x, then iteroparity can be optimal as shown in figure 7a. This optimum can be found as the point where $f'(x) = 0$; as we derived above, the second derivative is negative when p is concave, so that the solution of $f'(x) = 0$ gives the optimal number of offspring. The upshot of the analysis is that iteroparity is possible *only* with concave p.

Exercise: Show that the reverse of the above statement is not true: the optimal reproductive strategy is not always iteroparous when $p(x)$ is a concave function of x.

3.10 Example: Optimal foraging

Many animals exploit resources of patchy distribution. These face the question of how long to forage in a patch of resource, and when to abandon the (partially) exploited patch in order to search for an unexploited one. For example, how long should a bee stay on one flower and when to fly to the next?

The optimal foraging time will depend on the balance between how much resource can be gained from the current patch and how much could be obtained elsewhere. Let $g(t)$ denote the amount of resource, measured in terms of energy, extracted from a patch in t time. Obviously, $g(0) = 0$ (no resource is obtained in zero time), $g(t)$ is an increasing function of time (longer search means more particles of resource found), and $g(t)$ saturates to the total resource content of the patch as t goes to infinity (no more can be extracted than what is in the patch). It is therefore reasonable to assume that $g(t)$ is a convace increasing function. Its precise shape is however often not known, so at this point, we do not make any specific assumptions about it.

When the animal moves on to the next patch, the travel takes time T and implies an energy loss z. Hence considering the entire unit of foraging in one patch and finding the next patch, the net energy gain is $g(t) - z$ energy in $t + T$ time, i.e., the average energy intake per unit of time is

$$E(t) = \frac{g(t) - z}{t + T} \tag{41}$$

where we assume that the patches are identical (each has the same amount of resources that can be extracted according to the same function g) and also the travel costs are always the same.

The optimal foraging strategy maximizes the energy intake per unit of time, $E(t)$. To find the optimum, we require that the derivative of $E(t)$ is zero, i.e.,

$$E'(t) = \frac{g'(t)(t + T) - (g(t) - z)}{(t + T)^2} = 0 \tag{42}$$

which can be rearranged into

$$g'(t) = \frac{g(t) - z}{t + T} \tag{43}$$

In the right hand side of this equation, we recover $E(t)$ itself (cf. equation (41)), so that we have

$$g'(t) = E(t) \tag{44}$$

Because $g(t)$ is the total amount of resource extracted from a patch in time t, its derivative, $g'(t) = dg/dt$, is the instantaneous rate of energy intake: how much more energy dg can be obtained currently (at time t) from the patch per dt time. If g is a concave function as assumed above, then $g'(t)$ is a decreasing function of time, such that $g'(t)$ is large positive when the animal starts foraging in a fresh patch and becomes smaller and smaller as the patch is emptied and it becomes harder to find more resource in it. Equation (44) says that the animal should abandon foraging in the current patch when its instantaneous rate of energy intake is to drop below the average energy intake per unit time. In other words, stay in the patch only as long as it is better than the average; use all foraging time for energy gain higher than the average energy gain. The average energy gain will be diminished by the unavoidable costs of travel, but do not diminish it further by foraging in patches less productive than the average. Because the moment of optimal departure is when the average intake exactly balances the instantaneous intake, this result is known as the *marginal value theorem*.

From equation (44), we can assess how the optimal foraging time changes across different environments. If it takes a longer time to find a new patch (T is longer), then $E(t) = \frac{g(t)-z}{t+T}$ is smaller, which means that the animal should quit at a lower value of $g'(t)$; because g is concave, this translates into a longer foraging time. Similarly, if the energy cost of finding a new patch (z) is higher, then $E(t)$ is smaller and the optimal foraging time is longer. Hence the harder it is to find a new patch, the more one should exploit the current one.

The marginal value theorem in equation (44) is sufficient to predict qualitative properties of the optimal foraging strategy. If we want more results, we need to make more assumptions in the model: For a quantitative prediction of the actual foraging time, we need to specify how $g(t)$ depends on time.

> **Exercise:** Suppose that $g(t)$ is a hyperbolically saturating function of time given by $g(t) = \frac{at}{1+bt}$ and assume (for simplicity) $z = 0$. Show that the optimal foraging time is then $t = \sqrt{T/b}$. This optimum indeed increases with T as argued above, but increases less than proportionally: a *fourfold* increase in T will double the optimal foraging time.

3.11 Example: Evolutionarily stable dispersal strategy

This final example differs from our previous optimization models in a very important aspect: Here the reward achieved by an individual depends not only on its own choice of action, but also on what the other members of the population do. The particular model we investigate below is due to Hamilton and May (1973); but many other important models of evolutionary ecology share the property that the fitness of an individual depends not only on the focal individual but also on what the rest of the population does.

Consider an annual plant that needs to decide how many of its seeds should disperse and how many should stay at the place where the mother plant lived. The plants live in small sites, which can support only one full-grown plant; of the seeds that germinate in such a site, one randomly selected seed will develop into an adult plant and all others die. Dispersal is a risky process: Of the dispersed seeds, many land outside suitable sites (e.g. on rock, in water, etc.) and perish.

Assume that each plant produces a large number F of seeds, and let s denote the probability that a dispersed seed survives dispersal and lands in one of the N suitable sites (we assume that N is also large). The population consists of plants that disperse a fraction d of their seeds; in other words, d is the *resident strategy* used by all members of the population. Imagine that in this resident population, there appears a new mutant strategy, which disperses a fraction d_{mut} of its seeds. Our first question is, what should d_{mut} be to have the highest number of surviving seeds?

Obviously, the number of surviving seeds is the number of sites that will be occupied by the adult offspring of the mutant plant. We can calculate this as follows. First, the plant has $(1-d_{mut})F$ seeds that do not disperse but stay in the site where the mother lived. In addition to these, there are some seeds of other plants that have dispersed and landed in the mutant's site. In total, the population has N plants, NF seeds, NFd dispersed seeds and $NFds$ dispersed seeds that arrive safely at a site; but because there are N sites, only $NFds/N = Fds$ of the dispersed seeds arrive at the specific site of the mutant. Together with the mutant's own nondispersed seeds, the site has $(1-d_{mut})F + sdF$ seeds before the seedlings start to compete. The probability that one of the mutant's seeds is the one who wins the site is the fraction of mutant seeds among all competing seeds:

$$\frac{(1-d_{mut})F}{(1-d_{mut})F + sdF} = \frac{1-d_{mut}}{1-d_{mut}+sd} \tag{45}$$

where in the second part F has been cancelled.

Second, the mutant plant can win also other sites by its dispersed seeds. Every seed that the mutant disperses and which survives dispersal arrives at a site previously occupied by a resident plant. This site thus has $(1-d)F$ seeds that have not dispersed, and sdF resident seeds that arrive by dispersal (as above). The single mutant seeds wins this site

with probability

$$\frac{1}{(1-d)F + sdF + 1} \approx \frac{1}{(1-d)F + sdF} \tag{46}$$

where the approximation holds because F is large, such that adding one mutant in the denominator does not matter. Because the mutant has $sd_{mut}F$ successfully dispersed seeds (analogously to the resident, but with d_{mut} instead of d), the number of sites won by the dispersed seeds is

$$\frac{sd_{mut}F}{(1-d)F + sdF} = \frac{sd_{mut}}{(1-d) + sd} \tag{47}$$

where again F has been cancelled in the second part. Taken (45) and (47) together, the number of sites won by the seeds of one mutant parent is

$$W(d_{mut}, d) = \frac{1 - d_{mut}}{1 - d_{mut} + sd} + \frac{sd_{mut}}{(1-d) + sd} \tag{48}$$

This expression depends on the mutant dispersal strategy d_{mut}, but also on the resident dispersal strategy d; i.e., the reward to the action taken by the mutant depends on what the other members of the population do. This is emphasised in the notation when we write W, the number of surviving offspring, explicitly as a function of both d_{mut} and d.

Suppose that the resident strategy d is known. To find out which choice of the mutant strategy d_{mut} yields the highest number of surviving offspring in this given resident population, we must take the derivative of $W(d_{mut}, d)$ with respect to d_{mut}, treating d simply as a constant. This is denoted with the sign of the partial derivative, "∂", in the following way:

$$\frac{\partial W(d_{mut}, d)}{\partial d_{mut}} \tag{49}$$

which is read out as "the partial derivative of W with respect to d_{mut}" and means simply that we differentiate as if d_{mut} were the only variable and treat d as constant (see also Box 3). Taking the derivative of (48) in this way, we obtain

$$\begin{aligned} \frac{\partial W(d_{mut}, d)}{\partial d_{mut}} &= \frac{-(1 - d_{mut} + sd) + (1 - d_{mut})}{(1 - d_{mut} + sd)^2} + \frac{s}{(1-d) + sd} = \\ &= \frac{-sd}{(1 - d_{mut} + sd)^2} + \frac{s}{1 - d + sd} \end{aligned} \tag{50}$$

At the best choice of d_{mut}, the above derivative equals zero, i.e.,

$$\frac{-sd}{(1 - d_{mut} + sd)^2} + \frac{s}{1 - d + sd} = 0 \tag{51}$$

As usual, we can solve this last equation for d_{mut}. The resulting value of d_{mut} is however not an optimal strategy, because it is best only against a particular resident population with dispersal strategy d; for this reason, it is called *the best reply to d*.

Exercise: Calculate the second derivative to see whether the solution of equation (51) is indeed a maximum, i.e., the best reply and not the worst reply!

Suppose first that the best reply to d is a strategy different from d itself, as shown in Figure 8a. In this case, the best reply strategy is better than d in the sense that it has more surviving offspring than the resident, so that the number of mutants using the best reply strategy will increase; we say that the mutant *invades* the resident. Invasion is always possible unless the best reply to d is d itself[2]. This special situation is shown in Figure 8b; here all mutants different from d have fewer surviving offspring than the resident strategy, and hence cannot invade. When d is the best reply to itself so that it cannot be invaded, then it is called an *Evolutionarily Stable Strategy* or ESS in short (d_{ESS} in Figure 8b). After a long evolutionary time, we expect that all possible invasion events have taken place, and the strategy found in a population is the evolutionarily stable strategy.

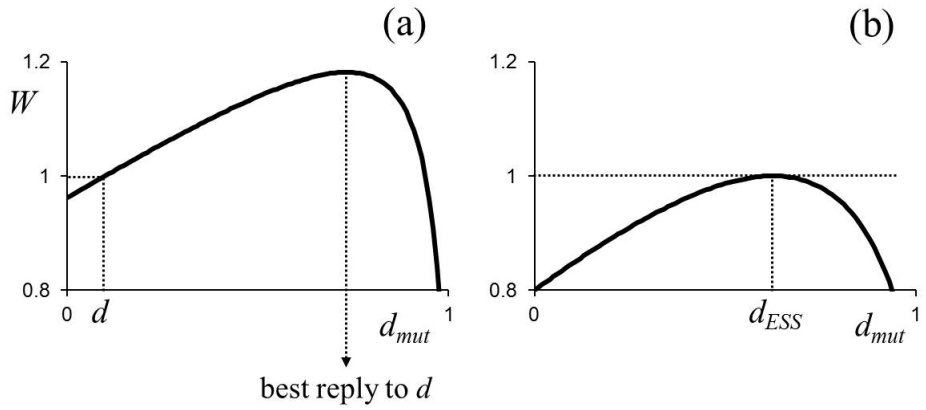


Figure 8: (a) Fitness of the possible mutant strategies d_{mut} in the resident population of $d = 0.1$ assuming $s = 0.4$. The mutant with the highest fitness is the best reply to d. Notice that d itself has fitness = 1; this is because the resident population fills every site in each year, such that on average, each parent plant has 1 surviving offspring. (b) When the resident strategy is the ESS, then the best reply to d is d itself. All other mutant strategies have fitness less than 1.

To find the evolutionarily stable strategy d_{ESS}, we simply demand that the best reply-equation written as equation (51) above holds when d_{mut} is d itself:

$$\frac{-sd}{(1-d+sd)^2} + \frac{s}{1-d+sd} = 0 \tag{52}$$

[2]In this model, W always has a single maximum as a function of d_{mut}. In general, it is possible in principle that W has two peaks of equal hight, such that a strategy different from d is exactly as good as d itself and is thus an alternative best reply; but this is a very unlikely (in technical terms, structurally unstable) situation that will change by the slightest change of model parameters.

Dividing both sides with s and multiplying with $(1-d+sd)^2$ we arrive at

$$-d+1-d+sd=0 \tag{53}$$

which is easily solved for the ESS value of d,

$$d_{ESS}=\frac{1}{2-s} \tag{54}$$

Exercise: Reconstruct Figure 8 using equations (48) and (54).

This result has a surprise. Suppose that s is nearly zero (which is, actually, a realistic assumption; in reality, most of the dispersed seeds land outside any suitable site and therefore do not survive). In this case, $2-s$ in the denominator of (54) is nearly 2, and the evolutionarily stable dispersal strategy is $d_{ESS}\approx\frac{1}{2}$; this means that the plant should disperse half of its seeds even when dispersed seeds almost surely die!

The reason behind this result lays in what happens to the non-dispersed seeds. They all remain in their natal site, and compete against seeds that arrive from elsewhere but also against each other. If s is very small, then hardly any seeds arrive from elsewhere (almost all dispersed seeds perish); the non-dispersed seeds thus compete almost only against each other. Since there are many seeds (F is large, so that also $(1-d)F$ is large) of which only one can survive, also each non-dispersed seed will almost surely die. It is not in the plant's interest that its offspring kill each other, hence dispersal is advantageous even when it has a high mortality cost. Dispersal is favoured by natural selection because of *kin competition* (competition among siblings) in the natal site.

Exercise: Extend the above model for perennial plants. Assume that each adult plant survives with probability p till next year and dies with probability $1-p$ before the seeds germinate ($p=0$ corresponds to an annual plant). If an adult plant is alive in a site, then all seeds that germinate in the site die; i the site has been emptied by the death of the adult plant, then one of the seeds develops into an adult plant. Derive $W(d_{mut},d)$ for a perennial plant and investigate whether p affects the evolutionarily stable strategy d_{ESS}.

3.12 Box 3: Partial derivative

Functions may depend on several variables. To take some examples, the function $f(x,y)=x+2y$ simply adds x to twice y; or $f(x,y)=xy$ computes the area of a rectangle with sides x and y. When differentiating multivariate functions, we need to be explicit the derivative is taken with respect to which variable (and for this reason, the notation "$f'(x,y)$" will not do). The *partial derivative* sign

$\frac{\partial f}{\partial x}$ denotes that the derivative is taken with respect to x, whereas the value of y is fixed and therefore y is considered to be a constant. The partial derivative of $f(x, y) = x+2y$ with respect to x is $\frac{\partial f}{\partial x} = 1$, because the derivative of the first term, x, is 1 and the second term is a constant. Of course one can also take the partial derivative with respect to y, which means we treat x as a constant; for $f(x, y) = x + 2y$, this yields $\frac{\partial f}{\partial y} = 2$. When the function is not linear, the derivative depends on the values of x and y (just as $f'(x)$ depends on x). For example, the partial derivative of the function $f(x, y) = e^{x+2y}$ with respect to x is $\frac{\partial f}{\partial x} = e^{x+2y}$ (depends on both x and y) and its derivative with respect to y is $\frac{\partial f}{\partial y} = 2e^{x+2y}$.

4 Dynamical systems

Dynamical systems describe how variables change in time: For example, how concentrations of biomolecules or densities of populations change. Dynamical systems can be set in continuous time (such as a model of a chemical reaction) or in discrete time (such as a population with seasonal bursts of reproduction). In this chapter, we deal only with systems in continuous time. These systems are modelled with ordinary differential equations (ODEs).

Exponential decay is dynamical system we have already studied in detail (see section 2). It is given by the differential equation

$$\frac{dx}{dt} = -\alpha x(t) \tag{55}$$

where α is the rate of decay, i.e., in a short time interval dt a particle decays (or an individual dies) with probability αdt. Exponential decay is a simple process because the decay of each particle (or the death of each individual) is considered to be independent of the rest of the system. We start studying dynamical systems with constructing models where different molecules or individuals interact with each other.

4.1 Mass action

A simple interaction occurs in chemical reactions such as in

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C$$

Denote the concentrations of A, B and C with a, b, and c, respectively. (Using smallcase letters to denote the concentrations of the corresponding chemicals is a very common practice in modelling chemical reactions.) In the derivation below we shall refer to a, b

and c also as the number of molecules, but these are indeed equivalent: the concentration is the number of molecules per a fixed volume where the reaction takes place.

The backward reaction is a simple exponential decay of C into A and B, which occurs at rate k_2, i.e., one molecule of C decays with probability $k_2 dt$ in time dt. The forward reaction needs the interaction of A and B. Here $k_1 dt$ is the probability that a given, individual molecule of A reacts with a given, individual molecule of B in dt time. Multiplying with the number of B molecules, b, gives the probability $k_1 b\, dt$ that a given, individual molecule of A reacts with any B molecule present. Multiplying this with the number of A molecules, $k_1 ab\, dt$ is the number of reactions that take place in time dt. These reactions increase the number of C molecules, whereas exponential decay decreases the number of C: $dc = k_1 ab\, dt - k_2 c\, dt$. The concentration of C thus changes according to the differential equation

$$\frac{dc}{dt} = k_1 ab - k_2 c \tag{56}$$

The number of interactions between two kinds of particles is thus proportional to the concentrations of both (the first term on the right hand side of (56) contains the product of concentrations a and b). This is called the *mass action law*. The dynamics of chemical reactions are combinations of the mass action law (when interaction happens in "bimolecular reactions") and exponential decay (isolated "monomolecular reaction"). We do not have to go through the above reasoning again in each particular model; instead, using the same logic implicitly, we can write mass action terms for each interaction and exponential decay terms for each isolated reaction (see the next section for illustration). As with exponential decay, mass action is not restricted to chemical reactions but occurs in many other "well-mixed" systems with random movement and lack of spatial structure. For example, predators may encounter prey or females may encounter males according to the mass action law.

The rates k_1 and k_2 are defined in a different way, and this reflects in their units. The exponential decay rate k_2 has the unit 1/time, such that the unit of the term $-k_2 c$ is concentration per time, corresponding to the unit of the left hand side dc/dt. The unit of the mass action rate k_1 is however 1/concentration/time. In the term $k_1 ab$, the unit of k_1 has to remove one concentration unit from ab next to contributing the unit 1/time to arrive at the required unit concentration/time for the product $k_1 ab$.

The differential equation (56) has the variables a and b on its right hand side, which change in time, and for which we do not have yet information from the model. Such equations are said to be *not autonomous* because they assume some extra information. We should thus write equations also for the change of a and b.

One molecule of A and one molecule of B are used up in the reaction that produces C, hence the number of A and the number of B decrease by $k_1 ab\, dt$ in time dt. During

the same time, the both number of A and the number of B increase by the number of C molecules that decay, $k_2 c\, dt$. Hence we arrive at the equations

$$\frac{da}{dt} = -k_1 ab + k_2 c \tag{57a}$$

$$\frac{db}{dt} = -k_1 ab + k_2 c \tag{57b}$$

Note that the terms of equations (57a,b) directly correspond to the terms of (56). This implies that the *sum* of a and c and analogously the sum of b and c do not change: $\frac{d(a+c)}{dt} = \frac{da}{dt} + \frac{dc}{dt} = -k_1 ab + k_2 c + k_1 ab - k_2 c = 0$ and analogously $\frac{d(b+c)}{dt} = 0$. $a(t) + c(t)$ and $b(t) + c(t)$ are thus constants in time: we have found *conservation laws* in the model. A molecule A may be present in its free form or may be present as part of molecule C, but the sum of free A and A in C remains the same as was present initially (and the same for B).

We can use the conservation laws to express the concentrations $a(t)$ and $b(t)$ at any time t with simple algebraic equations rather than using the differential equations (57a,b). Denote the total amount of A and B present initially by $a_0 = a(0) + c(0)$ and $b_0 = b(0) + c(0)$, respectively (a_0 and b_0 are numbers that include also those molecules that are initially "hidden" in C). Because $a(t) + c(t)$ is the same at any time t, it must be the same as at time 0, i.e., $a(t) + c(t) = a_0$ and $b(t) + c(t) = b_0$. From these, we can calculate the concentrations of A and B at any time from the concentration of C as $a(t) = a_0 - c(t)$ and $b(t) = b_0 - c(t)$.

Using the conservation laws, we can rewrite equation (56) as

$$\frac{dc}{dt} = k_1 (a_0 - c)(b_0 - c) - k_2 c \tag{58}$$

to arrive at a single autonomous differential equation that, together with the conservation laws, describes the full dynamics of the reaction.

4.2 Example: Modelling membrane transport

This section illustrates the construction of differential equations for arbitrarily complicated mass action models. The transport of molecules such as sugar (glucose) through the cell membrane is one of many processes that involves a number of chemical reactions. For the membrane transport of sugar, the sugar molecule is first bound to a carrier protein, a trans-membrane protein that can turn "outside" and "inside". The reaction is of course reversible, so we have

$$C_e + S_e \underset{k_-}{\overset{k_+}{\rightleftharpoons}} X_e$$

where C_e denotes the carrier protein with "external" configuration, S is sugar (or other substrate) outside the cell, and X_e is the complex of the protein and sugar, in the configuration where the sugar is still on the outside. To transport the sugar molecule through the membrane, the complex flips between its "external" and "internal" configurations:

$$X_e \underset{k}{\overset{k}{\rightleftharpoons}} X_i$$

Inside the cell, the complex releases the sugar molecule in a reversible way:

$$X_i \underset{k_+}{\overset{k_-}{\rightleftharpoons}} C_i + S_i$$

where C_i is the carrier protein in its "internal" configuration and S_i is a sugar molecule inside the cell. Finally, the carrier protein can flip between its two configurations also without binding sugar:

$$C_e \underset{\tilde{k}}{\overset{\tilde{k}}{\rightleftharpoons}} C_i$$

Notice that to simplify the model, we assumed that (i) how well the carrier protein binds or unbinds sugar does not depend on its configuration (the rates k_+ and k_- are the same in "exterior" and "interior" reactions); and (ii) the change of configuration goes at the same rate in both directions (k for the complex and $\tilde{k}$ for the free carrier protein).

Each of the above reactions follows either the mass action law or exponential decay. Hence the dynamics are given by the following differential equations:

$$\frac{dc_e}{dt} = -k_+ s_e c_e + k_- x_e - \tilde{k} c_e + \tilde{k} c_i \tag{59a}$$
$$\frac{ds_e}{dt} = -k_+ s_e c_e + k_- x_e \tag{59b}$$
$$\frac{dx_e}{dt} = k_+ s_e c_e - k_- x_e - k x_e + k x_i \tag{59c}$$
$$\frac{dx_i}{dt} = k_+ s_i c_i - k_- x_i - k x_i + k x_e \tag{59d}$$
$$\frac{ds_i}{dt} = -k_+ s_i c_i + k_- x_i \tag{59e}$$
$$\frac{dc_i}{dt} = -k_+ s_i c_i + k_- x_i - \tilde{k} c_i + \tilde{k} c_e \tag{59f}$$

Exercise: Verify the above equations.

Exercise: Show that the membrane transport model obeys two conservation laws: $c_e + c_i + x_e + x_i$ and $s_e + s_i + x_e + x_i$ are constants. Interpret these verbally.

Exercise: Show that in equilibrium the concentrations inside and outside the cell are the same (the transport process equalises the concentration of sugar on the two sides of the membrane). This is because we assumed that the reaction rates do not depend on the configuration of the carrier protein; if the rates differ for "external" and "internal" proteins, then the transport can work as a pump. To find the equilibrium, set all changes equal to zero in equations (59) (see section 4.5).

4.3 Numerical solution of differential equations

Solving a differential equation such as (55) or (58) means to give their variables explicitly as functions of time, i.e., to be able to tell the concentrations or the number of individuals at any time t. The solution of the exponential decay process was given in equation (20). In many cases, however, solving a differential equation analytically is either difficult or simply impossible. We can however solve them numerically.

The simplest algorithm to obtain a numerical solution is the Euler method. As an example, we take the differential equation (58), and approximate the infinitesimal quantities dc and dt with small but finite changes Δc and Δt:

$$\frac{\Delta c}{\Delta t} = k_1(a_0 - c)(b_0 - c) - k_2 c$$

Start with the known initial concentration $c(0)$ and calculate how c changes in one short time step Δt:

$$\Delta c = [k_1(a_0 - c(0))(b_0 - c(0)) - k_2 c(0)]\Delta t$$

and then update c with its change to obtain c measured after time Δt has elapsed:

$$c(\Delta t) = c(0) + \Delta c = c(0) + [k_1(a_0 - c(0))(b_0 - c(0)) - k_2 c(0)]\Delta t$$

Now we can use $c(\Delta t)$ as the starting value to recalculate the change of c over the next short time step,

$$\Delta c = [k_1(a_0 - c(\Delta t))(b_0 - c(\Delta t)) - k_2 c(\Delta t)]\Delta t$$

and update again with the new value of Δc

$$c(2\Delta t) = c(\Delta t) + \Delta c = c(\Delta t) + [k_1(a_0 - c(\Delta t))(b_0 - c(\Delta t)) - k_2 c(\Delta t)]\Delta t$$

to arrive at the concentration measured $2\Delta t$ time after the start. Repeating the steps of recalculating Δc and updating c gives the concentration values at times $t = 3\Delta t, 4\Delta t$, and so on. We can continue this algorithm as far as we like, i.e., we can obtain the concentration for as long time as we want.

The Euler algorithm is easily implemented in any simple programming language, but even in an Excel worksheet. To execute this algorithm in Excel, set up a column for time (this starts with 0 and increases by Δt increments) and a column for c, which starts with the initial concentration $c(0)$. In next row of column c, put in the sum of the previous value of c and the change $\Delta c = [k_1(a_0 - c)(b_0 - c) - k_2 c]\Delta t$ calculated with the previous value of c. As a result, you get two columns with matching times and concentrations.

The Euler algorithm works well as long as Δt is small enough. It depends on the concrete model and its parameter values how small is "small enough"; if however the algorithm produces strange outcomes, the first thing is to do it again with smaller Δt. There are also much more sophisticated and efficient algorithms to solve ODEs numerically, and these are implemented in software like MatLab or Mathematica.

4.4 Logistic growth of bacteria

Let ρdt be the probability that in dt time, a bacterium undergoes cell division and hence increases the number of bacteria by 1. With N bacteria in the population, $N\rho dt$ of them divides in dt and hence the size of the population increases by $dN = N\rho dt$ in dt time. The number of bacteria therefore obeys the differential equation

$$\frac{dN}{dt} = \rho N(t) \tag{60}$$

If the growth rate ρ were constant, then we would have a differential equation of the same type as equation (19), with two changes: the variable is now N rather than x (this is a trivial change of notation), and $\rho = -\alpha$. Therefore the solution of (60) would be the solution of (19), given in equation (20), with the same two changes; it would thus read $N(t) = N(0)e^{\rho t}$. This result is however impossible. $N(t) = N(0)e^{\rho t}$ (with $\rho > 0$) means exponential growth of population size; the bacteria would continue growing indefinitely, and would attain impossibly large population sizes in actually rather short time.

> **Exercise:** Under ideal conditions, bacteria can grow at rate $\rho = 0.045$/min. Calculate how long it would take to have $2 \cdot 10^{35}$ descendants of a single initial bacterium if the ideal conditions could be maintained. $2 \cdot 10^{35}$ bacteria weigh about as much as the Earth.

In reality, the growth rate ρ is not constant but depends on the amount of the limiting resource. Consider a so-called *batch culture* of bacteria, which is initiated with a given

amount of the resource and then kept closed during bacterial growth. Suppose the limiting resource is a mineral, for example phosphorous or iron, which is built into the cells but is not destroyed by metabolism. The growth rate is proportional to the amount of resource available for the bacteria, so that $\rho(t) = aC(t)$ where $C(t)$ denotes the concentration of free resource in the culture, so that equation (60) becomes

$$\frac{dN}{dt} = aC(t)N(t)$$

To solve this equation, we need information about $C(t)$. We could write a second differential equation for how C changes in time; this is however not necessary, because the system exhibits a conservation law. The resource (e.g. an atom of phosphorous) may be present freely available in the solution of the culture or may be part of a bacterial cell, but it is not destroyed, cannot get out of the closed batch culture, and is not provided anew from the outside. Hence the total amount of resource in the system, which is the sum of free resource and resource incorporated in bacteria, must remain constant. If each cell contains k particles of the resource, then the total amount of resource is $C_T = C(t) + kN(t)$, and this is the same at any time t; consequently the same as at time zero, i.e., $C_T = C(0) + kN(0)$ is the total amount of resource initially present.

We can now express $C(t)$ from the conservation law as $C(t) = C_T - kN(t)$. Substituting this into the differential equation we obtain the population growth equation

$$\frac{dN}{dt} = a[C_T - kN(t)]N(t)$$

This dynamics is known as logistic population growth. Our equation is however not yet in the standard form found in the literature. To reduce the equation to its best known form, we factor C_T out of the brackets

$$\frac{dN}{dt} = aC_T\left[1 - \frac{kN(t)}{C_T}\right]N(t)$$

and put k into the denominator of the denominator

$$\frac{dN}{dt} = aC_T\left[1 - \frac{N(t)}{C_T/k}\right]N(t)$$

aC_T is the product of two constants, which we can denote by $r = aC_T$; similarly, C_T/k is a number that we shall denote by $K = C_T/k$. With this new notation, we obtain the familiar form of the logistic equation,

$$\frac{dN}{dt} = rN(t)\left[1 - \frac{N(t)}{K}\right] \tag{61}$$

r and K are called the intrinsic rate of increase and the carrying capacity of the environment.

The intrinsic rate of increase is the rate of increase when $N(t)$ is negligibly small compared to K; then $N(t)/K$ is almost zero and we have

$$\frac{dN}{dt} = rN(t)\left[1 - \frac{N(t)}{K}\right] \approx rN(t)$$

i.e., nearly exponential growth at rate r. The intrinsic rate of increase $r = aC_T$ is proportional to the total amount of resource C_T and gives the speed of growth when virtually all resource is freely available.

The "carrying capacity of the environment" is a historic but somewhat misleading name. If $N(t) = K$, then $1 - N(t)/K = 0$ and the right had side of the logistic equation (61) is zero; hence K is the size of the population where the bacteria stop growing. Indeed, if $N(t) = K$, then the amount of free resource is $C(t) = C_T - kK = C_T - k(C_T/k) = 0$. The environment has enough resource to make K cells of bacteria, and in this sense it is the "carrying capacity of the environment"; the value of K however depends on how many resource particles a single cell needs (k), which is a property of the bacteria and not of their environment. A more efficient strain of bacteria, the cells of which need less resources (lower k), has a higher carrying capacity in the same external environment.

> **Exercise:** Solve the differential equation of logistic growth numerically, and plot $N(t)$ as a function of time. Use the following parameter values first (and later experiment with others): $r = 2.5, K = 1, N(0) = 0.01, \Delta t = 0.1$.

> **Exercise:** Extend the model to incorporate the death of bacteria at a constant rate μ, assuming that upon death, the resource formerly part of the cell becomes instantly available as free resource. Show that the model still leads to the logistic equation but with $r = aC_T - \mu$ and $K = (aC_T - \mu)/(ak)$; note that the death rate influences both the intrinsic rate of increase and the carrying capacity.

There are several other models of population growth that also lead to the logistic equation (61). The logistic equation is also often accepted as a baseline model of population growth on a phenomenological basis, i.e., without derivation but noting that it is a simple model that behaves in a biologically reasonable way. The mechanistic underpinning described in this section has one peculiar feature: in this model, it is not possible for N to exceed K, because with $N > K$ there would be less resource in total than the amount of resource incorporated in bacteria. $N > K$ is however possible if mortality is taken into account (see the exercise), and also in other mechanistic models leading to the logistic equation. In the next section, we investigate the properties of equation (61) allowing $N(t)$ to be any non-negative number.

4.5 Equilibria and their stability

The logistic equation (61) is an example for a single autonomous ordinary differential equation

$$\frac{dN}{dt} = f(N) \tag{62}$$

where, in case of the logistic equation, $f(N) = rN[1-N/K]$. The variable could of course be denoted by x rather than N, which is more usual in mathematics, but here we keep N because we use the logistic model as running example. We write "$f(N)$" rather than the explicit expression $rN[1 - N/K]$ on the right hand side of (62) because the methods described in this section are applicable generally; later we shall look at other models with different functions on the right hand side, but analyse them exactly in the way outlined here.

Equations of the form (62) can be solved numerically[3] to obtain the value of $N(t)$ at any time t. The logistic equation is simple enough such that it could also be solved analytically, but finding analytic solutions for more complicated equations can be very hard or even impossible. We can however learn a lot from the model even without obtaining an explicit solution for $N(t)$.

The first important question to ask is whether the model has an equilibrium (or several equilibria). The equilibrium is a value of N that stays constant in time, i.e., at equilibrium the time derivative $\frac{dN}{dt}$ is zero (there is no change in N). From equation (62), $\frac{dN}{dt} = 0$ whenever $f(N) = 0$, i.e., we have to find the zeros of function f in order to locate the equilibria of the model.

In case of the logistic equation, f is given by $f(N) = rN[1 - N/K]$. To find the equilibria of the logistic model, we solve the equation

$$rN\left[1 - \frac{N}{K}\right] = 0$$

There are two solutions to this: either $N = 0$ or the expression in the brackets is 0, which occurs when $N = K$. The logistic model has thus two equilibria: (i) the so-called *trivial* equilibrium $\hat{N}_1 = 0$ and (ii) the nontrivial equilibrium $\hat{N}_2 = K$. The "hat" is often used to denote the equilibrium value of a variable (although in these lecture notes we suppress the hats when it is clear from the context that we mean an equilibrium value). At the trivial equilibrium, the population is absent; this state being an equilibrium corresponds to the trivial fact that bacteria cannot appear without other bacteria producing them. The trivial equilibrium exists in all population models of closed systems (where inflow or immigration is excluded). The more interesting ("nontrivial") equilibrium is where the

[3]The function f needs to satisfy some mild conditions for the solution to exist and to be unique, but these conditions are met in biological models.

population equilibrates at a positive size.

An equilibrium is a state such that no more change occurs and the system stays there if the system is already there. We must however ask whether our system can ever arrive at a given equilibrium if the initial state is anything else than the equilibrium itself. It is of course very unlikely to start exactly with the equilibrium state, and small random perturbations (not explicitly included in the model) occur in virtually all natural systems that remove the system from its equilibrium.

An equilibrium is said to be *locally stable*[4] if the system returns to the equilibrium after a small perturbation (i.e., from an initial state sufficiently close to the equilibrium itself). *Global stability* means convergence to the equilibrium from any (biologically meaningful) initial state.

To establish the stability of equilibria, plot $f(N)$ (the entire right hand side of the differential equation) as a function of N. Figure 9 shows this plot for the logistic model, $f(N) = rN[1 - N/K]$. All points where the graph of f intersects the horizontal axis are such that $f(N) = 0$, i.e., these are the equilibrium points. In intervals of N where $f(N)$ is positive the differential equation (62) says that N is increasing, i.e., the system is moving to the right on the horizontal axis (see the arrows in figure 9). Conversely, in intervals where $f(N)$ is negative N is decreasing, i.e., the system is moving to the left. The stability of equilibria is easily seen from inspection of these movements. In the logistic model (figure 9), the trivial equilibrium at $N = 0$ is unstable because if N is perturbed to a value slightly higher than 0, N will increase and will therefore leave the trivial equilibrium point. In contrast, the nontrivial equilibrium $N = K$ is stable. If N is perturbed to a point below K, $f(N)$ is positive such that N increases towards $N = K$; and conversely, if N is perturbed to a point above K, then $f(N)$ is negative and N decreases towards $N = K$. In fact, the population arrives at $N = K$ from every positive initial size (K is globally stable).

We can also formulate the condition for stability analytically. For an equilibrium $\hat{N}$ to be locally stable, $f(N)$ must be positive for N somewhat smaller than $\hat{N}$; and $f(N)$ must be negative for N somewhat higher than $\hat{N}$. $f(N)$ therefore has to be a decreasing function near the equilibrium point (cf. figure 9). We can thus say that $\hat{N}$ is a stable equilibrium if $f(\hat{N}) = 0$ (it is an equilibrium) as well as $f'(\hat{N}) < 0$ (stable).

> **Exercise:** Show that if $f(\hat{N}) = 0$ and $f'(\hat{N}) > 0$, then $\hat{N}$ is an unstable equilibrium (hint: draw a graph for this case).

[4]The term "stability" means slightly different concepts in mathematics and in theoretical biology. Here we follow the latter usage. What we call "stable" a mathematician would call "asymptotically stable". There exist equilibria that are "stable in the sense of mathematics" but are not asymptotically stable; in the theoretical biology literature as well as in these lecture notes, these equilibria are not described as "stable".

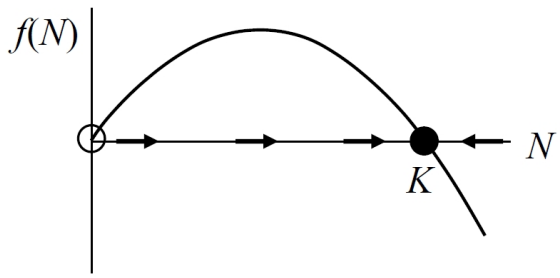


Figure 9: Stability of equilibria in the logistic model. There is an unstable equilibrium at $N = 0$ (open circle) and a stable equilibrium at $N = K$ (filled circle). The arrows show the direction of change in N: N is increasing where $f(N) > 0$ and N is decreasing where $f(N) < 0$.

Exercise: Show that if f is a continuous function (can be drawn without lifting the pencil from the paper), then stable and unstable equilibria alternate (hint: draw a function with many equilibria).

In summary, we can con conclude that in a model given by $\frac{dx}{dt} = f(x)$,

- the equilibria are the solutions of the equation $f(\hat{x}) = 0$
- an equilibrium $\hat{x}$ is stable if $f'(\hat{x}) < 0$ and unstable if $f'(\hat{x}) > 0$.

In this abstract notation, read "$f(x)$" simply as "what is on the right hand side of the differential equation". In the (unlikely) case $f'(\hat{x}) = 0$, the stability of the equilibrium depends on higher order derivatives ($f''(\hat{x})$ etc.) and cannot be decided with the above method.

4.6 Equilibria of reversible processes

In this section, we investigate the equilibria and their stability in two examples of reversible processes. The simplest reversible process is when A transforms into B and B transforms back into A:

$$A \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} B$$

A and B can, for example, represent two conformational states of a molecule; or they can represent behavioural states of an individual, for example hiding from a predator *vs* foraging. Let x denote the concentration of A. Since the total number of A and B molecules (or individuals) is constant (we have a conservation law), the concentration of B is the total concentration minus x; if we denote the total concentration of $A + B$ with the constant K, we can write the concentration of B as $K - x$.

The concentration of A is decreasing as A decays into B, and the concentration of A increrases as B decays into A. These two exponential decay processes yield the differential equation

$$\frac{dx}{dt} = -\alpha x + \beta(K - x)$$

which we can rearrange into

$$\frac{dx}{dt} = \beta K - (\alpha + \beta)x \tag{63}$$

To find the equilibrium of this model, we must find x such that the right hand side of the differential equation is zero:

$$\beta K - (\alpha + \beta)x = 0$$

which easily solves to

$$\hat{x} = \frac{\beta K}{\alpha + \beta} \tag{64}$$

To see whether the equilibrium is stable, we take the derivative of the right hand side of the differential equation (63). Denote the right hand side with $f(x)$; i.e., $f(x) = \beta K - (\alpha + \beta)x$ and therefore the derivative is $f'(x) = -(\alpha + \beta) < 0$. Since the derivative is negative (for all possible values of x, and hence also for the equilibrium value $\hat{x}$), the only equilibrium we have found in (64) is always stable.

Suppose that A and B are behavioural states such that A represent individuals hiding from a predator and B are foraging individuals. Foraging individuals go into hiding when they sense the presence of a predator; hence the reaction rate β is proportional to the density of predators. Figure 10 shows how the equilibrium $\hat{x}$ depends on β, i.e., how the number of hiding individuals increases with the density of predators. Here the total number of individuals is set to $K = 1$, such that $\hat{x}$ can be seen as the fraction of individuals hiding. If there are no predators and hence $\beta = 0$, all individuals are foraging and none are hiding; but as β increases because the density of predators increases, more and more individuals are hiding and $\hat{x}$ tends to 1, its limiting value when β goes to infinity (cf. equation (64): when β is large, $\hat{x} = \frac{\beta K}{\alpha+\beta} \approx \frac{\beta K}{\beta} = K = 1$.)

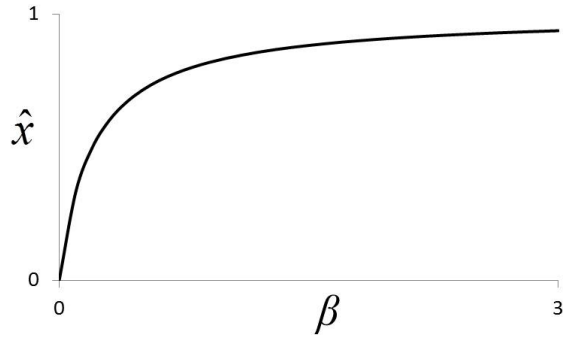


Figure 10: The equilibrium given in (64) as a function of the backwards reaction rate β, for $K = 1$ and $\alpha = 0.2$.

As a second example for reversible processes, we revisit the chemical reaction in section 4.1,

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C$$

As we have derived above, this process can be described with a single differential equation given in equation (58), which was

$$\frac{dc}{dt} = k_1(a_0 - c)(b_0 - c) - k_2 c \tag{65}$$

One can find the equilibrium concentration $\hat{c}$ by solving the equation

$$k_1(a_0 - c)(b_0 - c) - k_2 c = 0 \tag{66}$$

for c. This is a quadratic equation, so that it is readily solvable, but the solution is not very "neat". Can we say something useful about this model without solving for the equilibrium first?

If we had solved the equilibrium equation in (66), we would proceed to find out whether the equilibrium is stable. Let us do this step now. We take the right hand side of the differential equation in (65) and differentiate with respect to c; i.e., we take $f(c) = k_1(a_0 - c)(b_0 - c) - k_2 c$ and obtain

$$f'(c) = -k_1(b_0 - c) - k_1(a_0 - c) - k_2$$

Exercise: Check that the derivative $f'(c)$ is correct.

In this model, b_0 is the total amount of B present either free or as part of C; and hence $b_0 - c$ is the concentration of free B molecules, which cannot be negative. Hence the first term in the derivative, $-k_1(b_0 - c)$ is negative or at most zero. The same holds for the second term, $-k_1(a_0 - c)$. The last term, $-k_2$, is obviously negative. Taken together, the derivative $f'(c)$ is always negative independently of the value of c; and this means that whatever equilibria we may find for c, it must be stable.

In the last exercise of section 4.5, we have seen that stable and unstable equilibria alternate. However, we have just concluded that we do not have any unstable equilibria in the present model; this immediately implies that there cannot be more than one equilibrium. We have thus learned a very useful fact: the model has at most one equilibrium and it is stable.

We can now complete the analysis by showing that there is an equilibrium; i.e., that we can take away the words "at most" from "at most one equilibrium". If we put $c = 0$ into the right hand side of equation (58), we get $k_1 a_0 b_0$, which is positive; the concentration of C is increasing when C is absent. But c cannot increase without bound, because there is only a limited amount of A and B present. Indeed, suppose that the total amont of A is less than the total amount of B such that $a_0 < b_0$ (of course the same argument would hold for the opposite case as well), and that all of A is already incorporated into molecules of C such that the concentration of free A is zero, $a_0 - c = 0$. In this case, the right hand side of (58) equals $-k_2 c$, which is negative. Because the right hand side of (58) is positive at $c = 0$ and negative at $c = a_0$, it must be zero for some c inbetween; and this point is an equilibrium. We thus conclude that the model (i) has an equilibrium; and (ii) only one equilibrium; and (iii) this equilibrium is stable.

4.7 The harvested logistic model

Suppose that a population grows according to the logistic model but it is also harvested by humans or exploited by a predator. We can modify the logistic model given in equation (61) above,

$$\frac{dN}{dt} = rN\left[1 - \frac{N}{K}\right]$$

to include an extra term that describes death due to harvesting. If h is the harvesting rate such that each individual is harvested with probability $h\Delta t$ in a short time interval Δt, then a total number $hN\Delta t$ individuals are removed by harvesting and we obtain the differential equation

$$\frac{dN}{dt} = rN\left[1 - \frac{N}{K}\right] - hN \tag{67}$$

for the dynamics of the harvested population.

> **Exercise:** Show that the harvested logistic model has two equilibria, the trivial equilibrium $\hat{N}_1 = 0$ and a nontrivial equilibrium at $\hat{N}_2 = \frac{r-h}{r}K$.

> **Exercise:** Show that if $h < r$, then the trivial equilibrium is unstable and the nontrivial equilibrium is positive and stable; and if $h > r$, then the trivial equilibrium is stable and the nontrivial equilibrium is negative (also unstable, but we are not concerned with a biologically impossible equilibrium).

The conclusions of the above two exercises are summarized in Figure 11, which shows the equilibria as functions of the harvesting rate h. The trivial equilibrium $\hat{N}_1 = 0$ coincides with the horizontal axis; it is unstable (marked with a dashed line) as long as h is less than r and it is stable (solid line) when h exceeds r. The nontrivial equilibrium $\hat{N}_2 = \frac{r-h}{r}K$ is a linear function of h; $\hat{N}_2 = K$ when $h = 0$ and $\hat{N}_2$ hits zero when $h = r$. When positive, the nontrivial equilibrium is stable. The dynamics of population density are indicated with arrows; the population density always moves towards the (only) stable equilibrium.

What happens to a population if we harvest it at an increasing rate? As long as the harvesting rate h remains below the intrinsic growth rate r, the population will equilibrate at its stable equilibrium $\hat{N}_2$. Naturally, the equilibrium population size $\hat{N}_2$decreases as h increases, so that there is a quantitative change with h, but qualitatively the outcome remains the same, the population reaches its nontrivial equilibrium. If, however, the harvesting rate exceeds the intrinsic growth rate, then the population goes to the stable trivial equilibrium, i.e., it goes extinct due to overexploitation.

It is evident in Figure 11 that the dynamics has two different domains, one in the range $h < r$ and one in $h > r$. At the point $h = r$, there is a *qualitative* change as h increases:

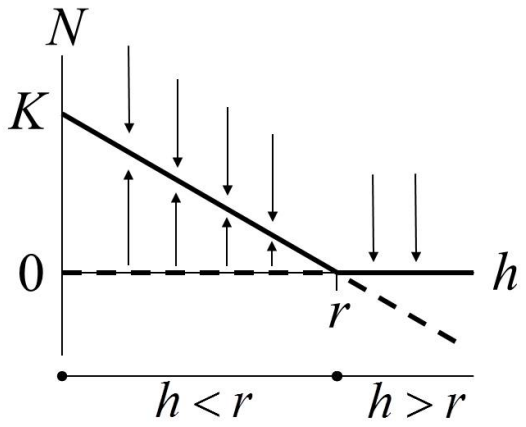


Figure 11: The equilibria of the harvested logistic model. Solid line: stable equilibrium; dashed line: unstable equillibrium. The arrows indicate the dynamics of population size N for various harvesting rates h.

the nontrivial equilibrium loses its stability and the trivial equilibrium becomes stable as the two equilibria cross each other. A qualitative change in the dynamics is called a *bifurcation*, and the value of the model parameter where the bifurcation occurs (here $h = r$) the *bifurcation point*. The type of bifurcation where two equilibria cross and exchange stability, as shown here, is called a *transcritical bifurcation*. In the harvested logistic model, overexploitation leads to extinction through a transcritical bifurcation of equilibria.

> **Exercise:** At the positive equilibrium $\hat{N}_2$, one can harvest $h\hat{N}_2$ individuals per unit time. If h is close to zero, then the number of harvested individuals is of course small; but if h is close to r, then then $\hat{N}_2$ is close to zero such that $h\hat{N}_2$ is again small. This suggests that there is an optimal harvesting rate that maximizes $h\hat{N}_2$, the number of individuals harvested per unit time. Find the optimal harvesting rate and show that if one harvests at the optimal rate, then the population equilibrates at $\hat{N}_2 = K/2$. Compare this result with the numerical solution of the logistic model obtained in an exercise of section 4.4: can you explain why it is best for harvesting to keep the population at size $K/2$?

4.8 Prey dynamics when harvested by a predator with Holling type II functional response

In the previous section, we assumed that harvesting occurs at a constant rate h; this means that for each individual, the risk of being harvested is constant, so that the total number of harvested individuals per unit of time, hN, is simply proportional to population density. In section 1.2, however, we argued that even if prey abounds, a predator cannot

handle (capture, consume and digest) an arbitrary number of prey in one unit of time. If the predator gets saturated, then the harvesting rate is not constant, but is given by the Holling type II functional response that we derived in equation (12): the expression

$$\phi(N) = \frac{\beta N}{1 + \beta T N}$$

gives the number of prey harvested by one predator per unit of time when prey density is N, where β is the capture rate of searching predators and T is the handling time needed to capture, consume and digest an individual prey. If P predators are present, then P times the above expression is the total number of harvested prey. Substituting this harvesting term in place of hN in equation (67), we arrive at the model

$$\frac{dN}{dt} = rN\Big(1 - \frac{N}{K}\Big) - \frac{\beta N}{1 + \beta T N} P \tag{68}$$

To analyze the dynamics of this model, we should first find its equilibria. To solve for $\frac{dN}{dt} = 0$ in equation (68), it is necessary to rewrite the two terms on the right hand side such that they have a common denominator. We thus rearrange equation (68) into

$$\frac{dN}{dt} = \frac{N}{1 + \beta T N}\left[r\Big(1 - \frac{N}{K}\Big)\Big(1 + \beta T N\Big) - \beta P\right] \tag{69}$$

This model can have three equilibria: the trivial equilibrium $\hat{N} = 0$ and the two solutions of the quadratic equation

$$\left[r\Big(1 - \frac{N}{K}\Big)\Big(1 + \beta T N\Big) - \beta P\right] = 0 \tag{70}$$

It is easy to solve the above quadratic equation, but the result is a relatively complicated formula. To gain better insight, we proceed with a graphical analysis.

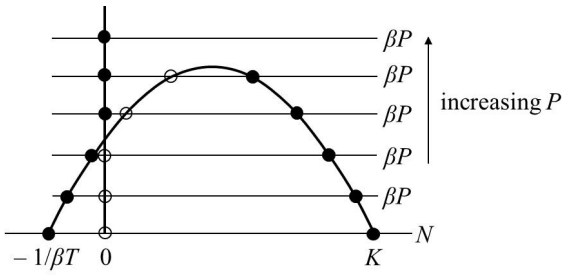


Figure 12: The equilibria of a population harvested by a predator with Holling type II functional response. Filled circles mark stable equilibria; open circles are unstable equilibria. The equilibria left of the vertical axis are negative and therefore are biologically irrelevant. See the text for further explanation.

Figure 12 shows how equation (69) can be used to visualize the equilibria. In this figure, the trivial equilibrium $\hat{N} = 0$ corresponds to the vertical axis. The parabola drawn with a bold line is the graph of $r(1 - N/K)(1 + \beta TN)$, the first term in the brackets; note that its roots are at $N = -1/\beta T$ where the factor $(1 + \beta TN)$ is zero and at $N = K$ where $(1 - N/K)$ is zero. The nontrivial equilibria of equation (69) are where the bracket is zero, i.e., where the parabola equals the constant βP. In Figure 12, several possible values of βP are marked with the horizontal lines.

If the predator is absent ($P = 0$ such that $\beta P = 0$), then the logistic population has one positive equilibrium at $N = K$, which is stable (this is marked on the horizontal axis at K). At a low predator density P (lowest horizontal line), the model still has only one positive equilibrium, although it is at a density $\hat{N}$ somewhat below K. To see that this equilibrium is stable, notice that left of this equilibrium, the parabola runs above the horizontal line. This means that $r(1 - N/K)(1 + \beta TN)$ exceeds βP, such that $\frac{dN}{dt}$ in equation (69) is positive, i.e., N increases when it starts below the equilibrium.

Higher predator density P corresponds to higher horizontal lines in Figure 12. Between the second and the third line (counting from below), a qualitative change occurs: the trivial equilibrium becomes stable, and a new positive equilibrium appears that is unstable. This is a transcritical bifurcation, similar to the one described in the harvested logistic model in section 4.7. As P increases further, the unstable and stable positive equilibria get closer to each other, until finally (between the uppermost two horizontal lines) they collide and disappear. This type of bifurcation is called a *fold bifurcation*. For very high predator densities, the stable trivial equilibrium is the only equilibrium, and the population goes extinct.

Figure 13 summarizes how the equilibria change with changing predator density P: at low values of P, there is one positive equilibrium which is stable and the trivial equilibrium is unstable; for higher P (i.e., $P > P_T$) the trivial equilibrium is stable and there is a new unstable positive equilibrium; and for the highest values of P (i.e., $P > P_F$) only the trivial equilibrium remains. There is no new information in this figure, but it is a more convenient summary of our conclusions from Figure 12. A figure like Figure 13 is commonly referred to as a *bifurcation diagram*. Here the horizontal axis is for a *bifurcation parameter*, i.e., a parameter of the model we vary and investigate the effect of (here the bifurcation parameter is P), and this axis is divided into intervals where the dynamics is qualitatively different (the division points are the transcritical bifurcation point P_T and the fold bifurcation point P_F). For easy reference, arrows mark the dynamics of N (on the vertical axis) for various values of P (this is often omitted).

Exercise: Find P_T, the value of predator density where the transcritical bifurcation occurs. Hint: check the stability of the trivial equilibrium.

Exercise: Find P_F, the value of predator density where the fold bifurcation occurs. Hint: find the maximum of the parabola in Figure 12.

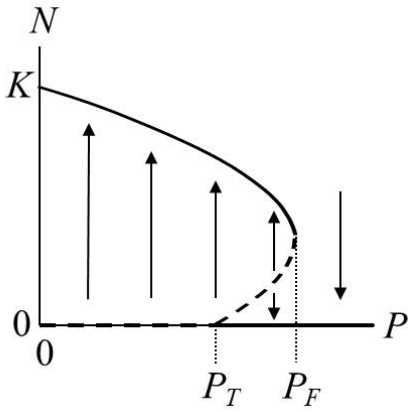


Figure 13: The bifurcation diagram of the model in equation (69). Solid lines are stable equilibria, dashed lines are unstable equilibria. P_T marks the transcritical bifurcation point and P_F marks the fold bifurcation point. The arrows indicate the dynamics of population size N for various fixed values of predator density P.

Overexploitation (too high predator density) leads to extinction in this model, but in a different way than in the harvested logistic model of the previous section. If we increase the harvesting rate h in Figure 11, the population gradually declines towards zero equilibrium density; in practice, the dangerously low population densities give an advance warning of extinction. In contrast, extinction occurs abruptly in Figure 13. When P is just slightly below the fold bifurcation point P_F, the population still has a positive equilibrium with fairly high population density; but after a small increase in P, the population suddenly crashes to extinction. A *catastrophic bifurcation* such as the fold bifurcation in this model, which leads to extinction without advance warning from low densities, raises serious concerns for conservation biology.

The two models also differ in what happens if we try to re-introduce an already extinct population. Suppose that in the harvested logistic model of the previous section, h became too high and the population went extinct (see Figure 11). It is sufficient to decrease h just below the point where extinction happened ($h = r$); a new population can then be established by introducing just a few individuals, because N will increase from a low density to the positive equilibrium whenever $h < r$. This is different in the current model. If P is decreased just below P_F (where extinction happened in the first place), the trivial equilibrium is still stable; this means that the population cannot be re-established from a low initial density. One has to introduce either a large population (which is quite difficult in practice), or has to move P not just below P_F but below P_T (much lower!) for a successful reintroduction. This fact is called a *histeresis effect*: one change (extinction) happens at $P = P_F$, but its opposite (reintroduction) happens at a different point $P = P_T$, such that inbetween both states (positive population density and extinction) are stable.

4.9 Time scale separation: The Michaelis-Menten model of enzyme kinetics

The Michaelis-Menten model of enzyme kinetics describes the simplest enzymatic reaction,

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X \overset{k_2}{\rightarrow} E + P$$

where E denotes the enzyme, S is its substrate, X is the enzyme-substrate complex, and P is the product. The enzyme-substrate complex can decay either into the enzyme and the original substrate, without arriving at the product (backward reaction) or into the enzyme and the product (forward reaction). Both decays are simple exponential decay processes involving only one molecule, the complex. The capture of the substrate by the enzyme occurs according to the mass action law.

Denote the concentrations of E, S, X and P by e, s, x and p, respectively. (Using smallcase letters for the concentrations of chemicals denoted by the corresponding capitals is a common practice, but note that here the letter e is a variable and is not the base of the natural logarithm!) We could write four differential equations to model the changes of these four variables. It is however not necessary to have all four ODEs in the model, because the reaction obeys two conservation laws:

(i) The total number of enzyme molecules, counting both free enzyme molecules (E) and enzymes part of the complex (X) does not change. Therefore at any time t, the sum $e(t) + x(t)$ is a constant number, which we shall denote by e_0. If we know $x(t)$, we can always calculate the free enzyme concentration $e(t)$ at any time t from $e(t) = e_0 - x(t)$, and hence we shall not need a differential equation for $e(t)$.

(ii) Similarly, the total number of substrate *plus* product molecules is not changing; the enzyme catalyses the transformation of S into P such that foe each molecule of S used up, there is a molecule of P produced. Hence $s(t) + p(t) = s_0$ is constant. Because we can calculate $p(t)$ as $p(t) = s_0 - s(t)$, we shall not need a differential equation for $p(t)$.

The differential equations describing the change of the two remaining variables, $s(t)$ and $x(t)$, are

$$\frac{ds}{dt} = -k_1 es + k_{-1} x \tag{71a}$$

$$\frac{dx}{dt} = k_1 es - (k_{-1} + k_2) x \tag{71b}$$

The right hand sides of these equations still contain the variable $e(t)$. We substitute $e(t) = e_0 - x(t)$ to make the equations autonomous, i.e., to have only those variables on

the right hand sides for which we have the derivatives on the left hand sides:

$$\frac{ds}{dt} = -k_1(e_0 - x)s + k_{-1}x \tag{72a}$$

$$\frac{dx}{dt} = k_1(e_0 - x)s - (k_{-1} + k_2)x \tag{72b}$$

In this form (and given the initial concentrations $s(0)$ and $x(0)$), the equations contain all necessary information so that they could be solved numerically as described above.

For the analysis of this model, we assume that the enzyme concentration is *much* lower than the concentration of the substrate. This assumption is entirely realistic. The enzyme is a large protein molecule, of which relatively few can be present in a cell or in a test tube. In contrast, the substrate is typically a small molecule, of which there is much more in the same reaction volume. Our key assumption is therefore that $e_0 \ll s(t)$ (for all time t considered), and this naturally implies $x(t) \ll s(t)$.

To see the consequences of this assumption (and to avoid working with numbers of widely different magnitude), it will be useful to write all small numbers ($e_0, x(t)$) as a small constant ϵ times a "normal" number (which may vary with time): write e_0 as $e_0 = \epsilon e_0^*$ and $x(t) = \epsilon x^*(t)$, where the "starred" quantities are "normal" and comparable to $s(t)$. For example, if e_0 is $5 \cdot 10^{-9}$ and $x(t)$ varies around $2 \cdot 10^{-9}$, then we might fix $\epsilon = 10^{-9}$ such that $e_0^* = 5$ and $x^*(t)$ varies around 2.

Substituting this notation into the equations (72a,b) and noting that $\frac{dx}{dt} = \frac{d\epsilon x^*}{dt} = \epsilon \frac{dx^*}{dt}$ since ϵ is a constant, we obtain

$$\frac{ds}{dt} = -k_1\epsilon(e_0^* - x^*)s + k_{-1}\epsilon x^*$$

$$\epsilon\frac{dx^*}{dt} = k_1\epsilon(e_0^* - x^*)s - (k_{-1} + k_2)\epsilon x^*$$

In the first equation, there is a factor ϵ in each term of the right hand side, so that we can factor it out. In the second equation, there is an ϵ in every term *on both sides*, so that ϵ cancels out from the equation:

$$\frac{ds}{dt} = \epsilon\big[-k_1(e_0^* - x^*)s + k_{-1}x^*\big] \tag{73a}$$

$$\frac{dx^*}{dt} = k_1(e_0^* - x^*)s - (k_{-1} + k_2)x^* \tag{73b}$$

The fact that ϵ remains on the right hand side of equation (73a) but disappears from equation (73b) means that the process described by (73a) is much slower than the process described by (73b). Indeed, in the same time interval dt, x^* changes by a "normal" number times dt, but s changes only by ϵ times a similar quantity! There are many orders

of magnitude difference between the change in x^* and the change in s. In other words, the two processes play out on different time scales, ds/dt being slow and dx^*/dt being fast.

To analyse a system with such time scale separation, first focus on the fast process given by (73b). During the time necessary for x^* to equilibrate, s is changing so slowly that it can be treated as constant. We can thus determine the equilibrium of x^* at a given (temporarily unchanging) value of s: This is called the *quasi-equilibrium* of the fast variable x^*, because on the fast time scale it is like an equilibrium, but eventually x^* will slowly change as it tracks the slowly changing value of s.

At the quasi-equilibrium, the right hand side of equation (73b) is zero, so that we have

$$k_1(e_0^* - x^*)s = (k_{-1} + k_2)x^*$$

which we can solve for the quasi-equilibrium value of x^* as follows:

$$\begin{aligned} k_1 e_0^* s &= k_1 x^* s + (k_{-1} + k_2)x^* = x^*(k_1 s + k_{-1} + k_2) \\ x^* &= \frac{k_1 e_0^* s}{k_1 s + k_{-1} + k_2} \end{aligned}$$

Next, we turn to the slow dynamics given by equation (73a). On the time scale necessary for s to change by any appreciable amount, x^* has long reached its quasi-equilibrium, so that x^* is always at $x^* = \frac{k_1 e_0^* s}{k_1 s + k_{-1} + k_2}$ evaluated at the current value of s. We can therefore substitute the quasi-equilibrium of x^* into equation (73a). As a preliminary step, we collect all terms containing x^*:

$$\frac{ds}{dt} = \epsilon\big[- k_1(e_0^* - x^*)s + k_{-1}x^*\big] = \epsilon\big[- k_1 e_0^* s + (k_1 s + k_{-1})x^*\big]$$

so that we need to substitute the (mildly) complicated expression $x^* = \frac{k_1 e_0^* s}{k_1 s + k_{-1} + k_2}$ at only one place:

$$\frac{ds}{dt} = \epsilon\big[- k_1 e_0^* s + (k_1 s + k_{-1})\frac{k_1 e_0^* s}{k_1 s + k_{-1} + k_2}\big]$$

From this point on, there is no further use in carrying ϵ, so we revert to the original constant $e_0 = \epsilon e_0^*$ and also simplify the equation:

$$\begin{aligned} \frac{ds}{dt} &= -k_1 e_0 s + (k_1 s + k_{-1})\frac{k_1 e_0 s}{k_1 s + k_{-1} + k_2} = \\ &= k_1 e_0 s\Big[- 1 + \frac{k_1 s + k_{-1}}{k_1 s + k_{-1} + k_2}\Big] = \\ &= k_1 e_0 s\frac{k_1 s + k_{-1} - (k_1 s + k_{-1} + k_2)}{k_1 s + k_{-1} + k_2} = \\ &= k_1 e_0 s\frac{-k_2}{k_1 s + k_{-1} + k_2} = \\ &= -\frac{k_1 k_2 e_0 s}{k_1 s + k_{-1} + k_2} \end{aligned} \tag{74}$$

The resulting single differential equation describes how fast the substrate concentration decreases as the ezyme converts the substrate into the product.

In most textbooks, the Michaelis-Menten equation is written in the form

$$\frac{ds}{dt} = -\frac{\lambda s}{s + K_M} \tag{75}$$

This is the same as equation (74) with $\lambda = k_2 e_0$ and K_M (the so-called Michaelis constant) given by $K_M = \frac{k_{-1}+k_2}{k_1}$.

Exercise: Show that the last statement is true.

Exercise: Show that λ is the asymptotic speed of transforming the substrate into the product. Explain why this speed would be attained only when substrate concentration is infinite, and why it is proportional to the total amount of the enzyme, e_0.

Exercise: Show that the Michaelis constant K_M is the half-saturation value of the speed of processing the substrate, i.e., that the enzyme is working at half of its maximum speed when the concentration of the substrate equals K_M.

4.10 A genetic switch

As a last example, we consider a fairly complex model that illustrates the principles behind genetic switches. To differentiate into various tissues during ontogenesis, cells needs to switch certain sets of genes on or off. The switch must be inducable (so that with different initial conditions, cells with the same genome can arrive at different final states) and must also be stable against random perturbations of the concentrations of the regulating molecules.

Whether a certain set of genes is active or not depends on the presence of transcription factors, proteins that bind to regulating DNA-sequences upstream from the structural genes and determine whether the genes are being transcribed or not. The simplest switch consists of two sets of genes. Each set of genes includes the gene of a transcription factor (U and V, respectively) and each set of genes is preceded by a separate regulating DNA-sequence (R_U and R_V, respectively). Both regulating sequences can bind one transcription factor at a time. If the regulating sequence R_U binds transcription factor U, then the genes regulated by R_U are active; these genes include the gene for U. Hence U must be present for its own production. The alternative transcription factor, V, can also bind to R_U (when it is free of U) but binding V does not activate R_U. R_U is inactive so that U is not being produced if either V is bound to R_U or R_U is free. In other words, binding U is necessary to activate the genes under R_U including the gene for U, and V can prevent activation simply by taking the place of U (this is called *competitive inhibition*

by V). The regulating sequence R_V works analogously: it can bind either U or V but it is activated only when V is bound to it; and it controls, among other genes, the gene producing V.

The chemical reactions of binding and dissociation of transcription factors to and from regulating sequence R_U are thus

$$R_U + U \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_U U$$

$$R_U + V \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_U V$$

and, analogously, the same reactions involving regulating sequence R_V are

$$R_V + U \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R_V U$$

$$R_V + V \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_V V$$

Notice that, for simplicity, we have made the assumption that R_V binds its own activating factor V at the same rate k_1 at which R_U binds U; and so forth, each pair of analogous reactions has the same rate for the two regulating sequences. This need not be so chemically, but nevertheless this simplified model will serve as a useful illustration of the processes underlying a genetic switch.

Let x denote the probability that (or fraction of time while) R_U binds U and is therefore active; and let y denote the probability R_U that binds V. With probability $1 - x - y$, the regulating sequence is free and is available for binding either U or V. Denoting the concentrations of U and V respectively by u and v, the first set of the above reactions translates into the differential equations

$$\frac{dx}{dt} = k_1(1 - x - y)u - k_{-1}x \tag{76a}$$

$$\frac{dy}{dt} = k_2(1 - x - y)v - k_{-2}y \tag{76b}$$

whereas the second set of reactions is described by

$$\frac{dp}{dt} = k_2(1 - p - q)u - k_{-2}p \tag{77a}$$

$$\frac{dq}{dt} = k_1(1 - p - q)v - k_{-1}q \tag{77b}$$

where p and q are the probabilities of R_V having U and V bound, respectively.

Now we turn to the production and decay of the transcription factors U and V. U is being produced at a constant rate a when R_U has U bound, which occurs in fraction x of time; hence the speed of production is ax. U decays at a constant rate μ. Next to production and decay, the concentration of U changes also because it is binding to or dissociating from the regulating sequences as shown by the reactions above. u is thus changing according to

$$\frac{du}{dt} = ax - \mu u - k_1(1-x-y)u + k_{-1}x - k_2(1-p-q)u + k_{-2}p \tag{78a}$$

and, analogously, v is changing according to

$$\frac{dv}{dt} = aq - \mu v - k_2(1-x-y)v + k_{-2}y - k_1(1-p-q)v + k_{-1}q \tag{78b}$$

Note that once again, we simplified the model by assuming that the production and decay rates a and μ are the same for both transcription factors. The six equations in (76a,b), (77a,b) and (78a,b) constitute the model.

Binding unbinding of the transcription factors are simple chemical reactions that play out much faster than protein synthesis and decay. Therefore the dynamics given by equations (76a,b) and equations (77a,b) occur on a fast time scale where the total amounts of U and V can be considered (almost) constants. We can thus investigate two time scales separately: first we determine the quasi-equilibrium of the fast binding-unbinding processes in (76a,b) and in (77a,b), and then we use the quasi-equilibria to investigate the slow processes of production and decay.

1. *Fast time scale.* To determine the quasi-equilibrium of equations (76a,b), we set the right hand sides to zero:

$$\begin{aligned} k_1(1-x-y)u - k_{-1}x &= 0 \\ k_2(1-x-y)v - k_{-2}y &= 0 \end{aligned}$$

which is equivakent to

$$\begin{aligned} k_1(1-x-y)u &= k_{-1}x \\ k_2(1-x-y)v &= k_{-2}y \end{aligned}$$

The easiest way to solve these equations for x and y is to multiply the first equation with k_2v and the second equation with k_1u such that the first terms of the two equations become the same:

$$\begin{aligned} k_1k_2(1-x-y)uv &= k_{-1}k_2vx \\ k_1k_2(1-x-y)uv &= k_1k_{-2}uy \end{aligned}$$

Because $k_{-1}k_2vx$ and $k_1k_{-2}uy$ are equal to the same quantity, they must be equal to each other. From $k_{-1}k_2vx = k_1k_{-2}uy$, we obtain $y = \frac{k_{-1}k_2vx}{k_1k_{-2}u}$. Finally, we substitute this into the first equation $k_1(1-x-y)u = k_{-1}x$ to obtain

$$\begin{aligned} k_1\left(1 - x - \frac{k_{-1}k_2vx}{k_1k_{-2}u}\right)u &= k_{-1}x \\ k_1u &= x\left[k_1u + \frac{k_{-1}k_2v}{k_{-2}} + k_{-1}\right] \\ x &= \frac{k_1u}{k_1u + \frac{k_{-1}k_2v}{k_{-2}} + k_{-1}} \end{aligned}$$

The result becomes more transparent if we divide both the numerator and the denominator by k_{-1}: then the constant in the denominator becomes 1, and everywhere else we see *ratios* of reaction constants:

$$x = \frac{(k_1/k_{-1})u}{(k_1/k_{-1})u + (k_2/k_{-2})v + 1}$$

For brevity, we shall write $\alpha = (k_1/k_{-1})$ and $\beta = (k_2/k_{-2})$. With this new notation, we have at the quasi-equilibrium

$$x = \frac{\alpha u}{\alpha u + \beta v + 1} \tag{79}$$

We do not detail the calculation of the quasi-equilibrium of equations (77a,b). Because the reactions are analogous and we assumed equal reaction rates for analogous processes, the quasi-equilibrium

$$q = \frac{\alpha v}{\beta u + \alpha v + 1} \tag{80}$$

can be obtained simply by exchanging the roles of transcription factors, i.e., writing the same as in (79) but changing every u into v and *vice versa*.

2. *Slow time scale.* We can now substitute the quasi-equilibria into the slow dynamics in equations (78a,b). First of all, notice that the third and fourth terms of equation (78a) are the same (only with opposite sign) as the right hand side of (76a); because the right hand side of (76a) is zero at quasi-equilibrium, these two terms cancel from (78a). Similarly, the last two terms of (78a) cancel because they are the zero at quasi-equilibrium by (77a). Hence (78a) simplifies to

$$\frac{du}{dt} = ax - \mu u = \frac{a\alpha u}{\alpha u + \beta v + 1} - \mu u$$

where in the last part we have substituted the quasi-equilibrium value of x from equation

(79). Analogously, equation (78b) simplifies to

$$\frac{dv}{dt} = aq - \mu v = \frac{a\alpha v}{\beta u + \alpha v + 1} - \mu v$$

where we used equations (76b) and (77b) to cancel the last four terms of (78b) and then substituted the quasi-equilibrium value of q from equation (80).

The last step of the analysis is to find the equilibria and their stability of the slow processes given by the two ODEs we have got,

$$\frac{du}{dt} = \frac{a\alpha u}{\alpha u + \beta v + 1} - \mu u \tag{81a}$$

$$\frac{dv}{dt} = \frac{a\alpha v}{\beta u + \alpha v + 1} - \mu v \tag{81b}$$

We shall use *phase plane analysis* to investigate the dynamics given by this pair of differential equations. The phase plane is a coordinate system with axes u and v, where we mark at each point whether u and v increase or decrease. It is easiest to construct this plot by first finding the points where u or v does not change, i.e., where $\frac{du}{dt} = 0$ or $\frac{dv}{dt} = 0$.

From equation (81a), $\frac{du}{dt} = 0$ if

$$\frac{a\alpha u}{\alpha u + \beta v + 1} = \mu u$$

This equation holds

1. if $u = 0$: this is a *trivial equilibrium*, which says that no transcription factor U can be produced if no U is present. (Recall that U activates its own gene such that the gene cannot be transcribed without U binding to the regulating sequence R_U.)

2. or else if

   $$\frac{a\alpha}{\alpha u + \beta v + 1} = \mu$$

   To plot this solution on the (u, v) phase plane, solve for v:

   $$\begin{aligned} a\alpha &= \mu(\alpha u + \beta v + 1) \\ a\alpha - \mu - \mu\alpha u &= \mu\beta v \\ v &= \frac{a\alpha - \mu - \mu\alpha u}{\mu\beta} \end{aligned} \tag{82}$$

   and plot the resulting v as a function of u (figure 14). As seen from (82), the graph is a straight line intercepting the v-axis at $\frac{a\alpha-\mu}{\mu\beta}$ (substitute $u = 0$ into (82)) and intercepting the u-axis at $\frac{a\alpha-\mu}{\mu\alpha}$ (solve (82) for the value of u where $v = 0$). This line contains points of the phase plane where $\frac{du}{dt} = 0$ and is called the *zero growth line* of the first variable, u.

Exercise: Construct the zero growth line of the second variable, v, using the condition $\frac{dv}{dt} = 0$ in equation (81b). In particular, show that (i) there is a trivial equilibrium at $v = 0$; and (ii) the zero growth line of v intercepts the u-axis at $\frac{a\alpha-\mu}{\mu\beta}$ and intercepts the v-axis at $\frac{a\alpha-\mu}{\mu\alpha}$ as shown in figure 14.

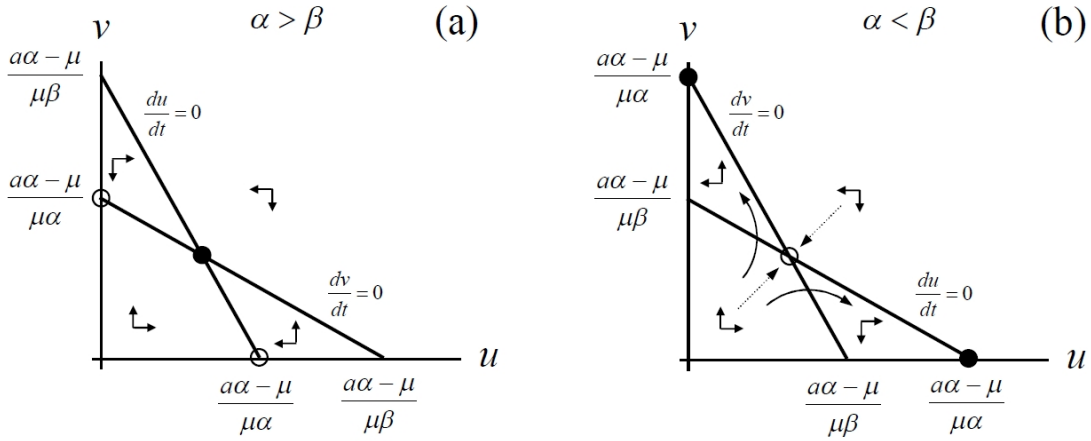


Figure 14: Phase plane analysis of equations (81). The straight lines are the zero growth lines; small arrows show the directions of change; filled circles mark stable equilibria; open circles are unstable equilibra (the origin is always an unstable equilibrium but being trivial, it is not marked). (a) $\alpha > \beta$, the interior equilibrium is stable. (b) $\alpha < \beta$, the interior equilibrium is a saddle and the two boundary equilibria are stable. Dotted arrow: the exceptional trajectory that leads into the saddle point. Typical trajectories are shown in continuous lines.

The zero growth lines show where $\frac{du}{dt} = 0$ and $\frac{dv}{dt} = 0$ holds on the phase plane: these are the lines across which the sign of respectively $\frac{du}{dt} = 0$ and $\frac{dv}{dt} = 0$ change from postive to negative or *vice versa*. To decide in which areas of figure 14 u and v are increasing or decreasing, consider first substituting small values of u and v into equations (81) such that

$$\begin{aligned} \frac{du}{dt} &= \frac{a\alpha u}{\alpha u + \beta v + 1} - \mu u \approx (a\alpha - \mu)u \\ \frac{dv}{dt} &= \frac{a\alpha v}{\beta u + \alpha v + 1} - \mu v \approx (a\alpha - \mu)v \end{aligned}$$

We shall henceforth assume that $a\alpha - \mu$ is positive such that both u and v increase exponentially when small (this assumption is also made in figure 14).

Exercise: Show that if $a\alpha-\mu$ is negative, then both u and v always decrease in time so that both transcription factors disappear from the system and neither set of genes will be transcribed.

Both $\frac{du}{dt}$ and $\frac{dv}{dt}$ are positive near the origin, and their signs can change only when crossing their respective zero growth lines. Therefore at all points below both zero growth lines both u and v are increasing (this is denoted by the small arrows of figure 14). As we cross the zero growth line of u, the sign of $\frac{du}{dt}$ becomes the opposite and correspondingly the horizontal arrow switches direction. Similarly, the vertical arrows switch direction when crossing the zero growth line of v. Hence from establishing the signs of the derivatives in just one area (which we took the area near the origin), it is easy to deduce how the directions of change vary across the graph.

Note that these arrows only give qualitative information about the direction of change, but do not fully determine the shape of the actual trajectory the system follows. For example, "going up and to the right" may mean going up very fast and going to the right only slowly; this results in an almost vertical trajectory which just slightly slants to the right. But the same configuration of arrows may also mean going to the right very fast and going up only slowly, which yields an almost horizontal trajectory. This means that the zero growth lines and arrows will not always give full information about the behaviour of the system. Yet they are a very useful mean of analysis, and in our example, we can deduce all important information just from figure 14.

The intersection of the zero growth lines represents a point where both $\frac{du}{dt}$ and $\frac{dv}{dt}$ are zero: This is an equilibrium point. Other equilibria are on the boundary (on the axis lines) and correspond to the trivial equilibria of $u = 0$ or $v = 0$. One such boundary equilibrium is at the intersection of the zero growth line of v with the vertical axis (where $u = 0$); another boundary equilibrium is at the intersection of the zero growth line of u with the horizontal axis (where $v = 0$); and the origin (where both $u = 0$ and $v = 0$) is also a ("very trivial") equilibrium point.

The stability of the equilibria depend on the relative position of the zero growth lines. Consider first the configuration shown in figure 14a, where $\alpha > \beta$ so that the intercepts $\frac{a\alpha-\mu}{\mu\alpha}$ are below the intercepts $\frac{a\alpha-\mu}{\mu\beta}$. From the orientation of the arrows, it follows that all trajectories starting with positive u and v must eventually arrive at the interior equilibrium at the intersection of the zero growth lines (to convince yourself, try to draw a trajectory that keeps as far away from the interior equilibrium as possible while obeying the directions of the arrows). Hence in this case, the interior equilibrium is stable.

Exercise: Show that with $\alpha > \beta$, all boundary equilibria are unstable.

A stable interior equilibrium means that the cell produces both transcription factors and therefore both sets of genes are active (part of the time, i.e., when binding their respective transcription factors). All cells arrive at the same equilibrium, irrespectively of their initial state determined e.g. by their exposure to growth factors during embryonic development. There is no differentiation between cells: With $\alpha > \beta$, this system does *not* work as a genetic switch.

The situation changes dramatically when $\alpha < \beta$ (figure 14b). In this case, the interior equilibrium is not stable but it is a so-called *saddle point*. If we perturb the system into the area with arrows "up-left" or into the area with arrows "down-right", the trajectory must leave the equilibrium point. In the other two areas, there is one exceptional direction (through the origin) along which the trajectory leads to the interior equilibrium; all other trajectories however turn either right or left, and arrive at one of the two stable boundary equilibria (see figure 14b). Because it is infinitely unlikely that a random perturbation would put the system on the exceptional trajectory ending at the saddle point, a natural system cannot be expected to remain near the saddle.

The two boundary equilibria where either only U is produced or only V is produced (filled circles in figure 14b) are alternative stable equilibria. The cell may settle at either of them, depending on its initial condition determined by processes during embryonic development. Once it has settled at an equilibrium, however, this state remains stable: It takes a very large perturbation to move the system over the saddle point such that it would be attracted by the alternative boundary equilibrium. This system thus corresponds to a genetic switch that is both inducable (via its initial conditions) and stable against reasonable perturbations. The two equilibria correspond to two different sets of genes being active, i.e., to two differentiated states of the cell.

The condition for having a genetic switch is thus $\alpha < \beta$, or, in terms of the original parameters,

$$\frac{k_1}{k_{-1}} < \frac{k_2}{k_{-2}}$$

(recall that $\alpha = k_1/k_{-1}$ and $\beta = k_2/k_{-2}$ by definition). This inequality is satisfied if k_2 is sufficiently large (or k_{-2} is sufficiently small), i.e., if the transcription factor that competitively *inhibits* the regulated genes binds easily to (and/or does not easily dissociate from) the regulating sequence. In such a case, there is a positive feedback: for example, an initially somewhat more abundant U efficiently prevents the production of V; consequently V is unable to prevent the production of U; the more U is produced, the more V is shut down.