Basic methods in Theoretical Biology

Part 2: Examples

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Dept. Theoretical Biology, Vrije Universiteit, Amsterdam

Issued by:

Dept. Theoretical Biology, Inst. Ecological Science,
Faculty of Earth and Life Science, Vrije Universiteit, Amsterdam
`http://www.bio.vu.nl/thb/`
deb@bio.vu.nl

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Chapter 1

Why bats loose their way above meadows

It is widely known that bats cry at high frequencies and listen to the echo for orientation. They observe the time lag between cry and echo, and the intensity and the frequency of the echo. While crying, they stop listening by separating the earbones using muscles. Evidence suggests that bats are able to detect the echo of a cry in the first period of silence after the cry only. This poses constraints on orientation and cry features. We will study this briefly for the greater horseshoe bat, which cries at 83 kH during a period of $S_1 = 0.07$ s and keeps its nose during a period of $S_2 = 0.07$ s. (Many species of bat change frequency during a cry, but horseshoe bats don't.)

The bat flies at height h above a plane with speed v. We choose x, y- coordinates in the plane such that the bat is (at height h) above the origin at time $t = 0$ and flies in the y-direction (see Fig.1.1). It is known that sounds travel through air of a pressure of 101 kPa at 20°C with a speed of $c = 344$ m/s. The time delay between cry and echo and the intensity only depend on the distance, d, between bat and the object causing the echo. Apart from the accuracy in the detection, these two signals contain basically the same information. Let us study the time delay, called T, which will appear to put a constraint of about 24 m on the horizon for the bat. The distance d_t to the object changes with time t, depending on the angle, α, between the direction of the object and the direction of the flight. Suppose that the bat does not change direction. Application of the cosine rule in triangle ABC in Fig.1.1 learns that

$$d_t = \sqrt{d_0^2 + t^2 v^2 - 2tvd_0 \cos \alpha_0} \tag{1.1}$$

Assume that the bat cries in point B and hears the echo in point C. So the time needed for the bat to travel from B to C equals the time needed for the sound to travel from B to A and back to C. The time delay is then given by the implicit equation

$$T = \frac{d_0 + d_T}{c} \tag{1.2}$$

So we find

$$T = \frac{2d_0(c - v\,\cos\alpha_0)}{c^2 - v^2} \tag{1.3}$$

This delay now has to obey $T < S_+ \equiv S_1 + S_2$, which poses a horizon for the bat. It is only able to detect an object if

$$d_0 < \frac{S_+(c^2 - v^2)}{2(c - v\,\cos\alpha)} \tag{1.4}$$

If the bat flies at height h above the plane, then the distance to a point (x, y) on the plane at time $t = 0$ is

$$d_0(x, y, h) = \sqrt{x^2 + y^2 + h^2} \tag{1.5}$$

The cosine of the angle between the direction of the point (x, y) and the direction of flight is given by

$$\cos\alpha(x, y, h) = \frac{y}{d_0(x, y, h)} \tag{1.6}$$

The x, y- coordinates of the points observable for the bat are found from (1.4)-(1.6) to obey

$$2c\sqrt{x^2 + y^2 + h^2} - 2vy < S_+(c^2 - v^2) \tag{1.7}$$

The boundary of this area obeys the equation

$$2c\sqrt{x^2 + y^2 + h^2} - 2vy = S_+(c^2 - v^2) \tag{1.8}$$

which is equivalent with the ellips equation

$$x^2 + (1 - v^2/c^2)(y - \frac{1}{2}vS_+)^2 = \frac{1}{4}S_+^2(c^2 - v^2) - h^2 \tag{1.9}$$

In view of the shape of the ears, it is not likely that bats are able to detect sounds from behind very well. So in fact the 'visible' patch is only half an ellips. From the right-hand side of (1.9) it immediately follows that a bat flying higher than

$$h = \frac{1}{2}S_+\sqrt{c^2 - v^2} \tag{1.10}$$

is unable to observe the plane at all. For practical purposes, v is negligibly small in comparison with c. In that case the border of the visible patch is a circle with radius $\sqrt{\frac{1}{4}S_+^2(c^2 - v^2) - h^2}$ and the greater horseshoe bat has to fly lower than some 24 m, in order to observe the plane.

Because of the cry-listen sequences, observations come in discrete images, rather than continuously changing ones. For effective orientation, it will be necessary that subsequent images have substantial overlap, in order to recognize the same object in these images. The front border is given by

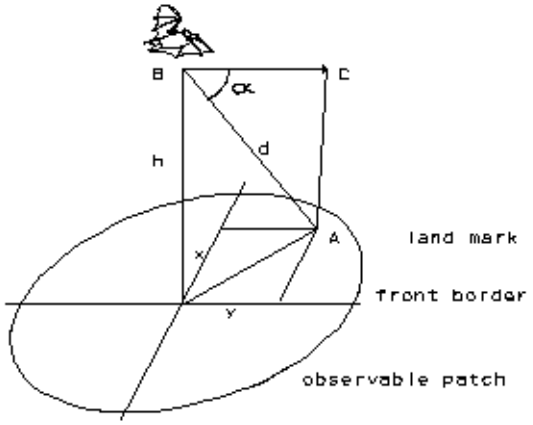

Figure 1.1: A bat, flying above a plane, can only observe objects within a rather small circular patch beneath it.

$$y = \frac{1}{2} v S_+ + \sqrt{\frac{1}{4} S_+^2 c^2 - \frac{h^2 c^2}{c^2 - v^2}} \tag{1.11}$$

Greater horseshoe bats seem to react to objects at $d = 8$ – 10 m. If the object is in the plane in the direction of flight, it is at $y' = \sqrt{d^2 - h^2}$. For $v \ll c$, (1.11) gives a front border of $y = \sqrt{c^2 S_+^2/4 - h^2}$. The distance $y - y'$ is covered in a time of $(y - y')/v$, in which some $(y - y')/(vS_+)$ snap shots are taken. At a height of 4 m and a speed of $v = 20\,\mathrm{km/h}$ $= 5.55\,\mathrm{m/s}$, this means that the bat is in principle able to observe the object during 2.8 s in some 20 images, neglecting reaction time.

The time delay depends on both the distance d to the object and the relative speed $v \cos\alpha$, see (1.3). (The relative speed is found by taking the derivative of (1.1) at time $t = 0$, or by decomposing the speed vector). So the bat needs additional information, which it obtains from the ratio between the frequencies of cry and echo, which depends, if $v \ll c$, on relative speed only, as shown below. This ratio differs from 1 by the Doppler effect which acts two times in fact: we are dealing with a moving source (the crying bat in point B, Fig.1.1.) and a moving observer (the listening bat in point C). Writing f_B, f_A, f_C for the frequency in B, A and C respectively, we find

$$f_A = \frac{c}{c - v\,\cos\alpha_0} f_B. \tag{1.12}$$

$$f_C = \frac{c + v\,\cos\alpha_T}{c} f_A. \tag{1.13}$$

So, the ratio of the frequencies is given by

$$\frac{f_C}{f_B} = \frac{c + v\,\cos\alpha_T}{c - v\,\cos\alpha_0}. \tag{1.14}$$

If $v \ll c$ this can be approximated by

$$\frac{f_C}{f_B} = 1 + \frac{2v}{c}\cos\alpha_0. \tag{1.15}$$

By using both the time delay T and the frequency ratio f_C/f_B, the bat is able to determine the distance of objects and the angle between their direction and the direction of flight. But this is not enough to determine the exact position of an object. A circle of points, perpendicular to the direction of flight, cannot be distinguished. Additional information is obtained making use of the phase shift of the echo between both ears. (The asymmetric ears of barn owls enhance their ability to detect such a phase difference. Notice that we, humans, can easily determine direction, but we have more problems with distance.) The sensitivity of the ears is usually maximal at cry-frequency, while the cry-frequency is optimized to detect direction and so phase shifts. The phase shift as a fraction, F, of the period of the sound, f/c, from a source which is at an angle β with the axis through the ears is given by

$$F = \frac{f\,l}{c}\cos\beta \tag{1.16}$$

where l is the distance between the ears. When the information of time delay, Doppler effect and phase shift has been combined, only two points cannot be distinguished, which lay symmetrically to the horizontal plane in which the bat flies. By turning its nose a bit, the bat is able to determine the exact position of the object.

The product fl appears to be more or less constant for different species. For us, with $f = 7\,\mathrm{kH}$ (normal conversation level) and $l = 0.12\,\mathrm{m}$, $fl = 0.84\,\mathrm{kHm}$. The greater horseshoe bat has $f = 84\,\mathrm{kH}$ and $l = 0.01\,\mathrm{m}$, giving $fl = 0.84\,\mathrm{kHm}$, while the lesser horseshoe bat has $f = 112\,\mathrm{kH}$ and $l = 0.0075\,\mathrm{m}$, giving $fl = 0.84\,\mathrm{kHm}$ again. If the greater horseshoe bat approaches its prey rapidly, causing an increase in echo frequency due to the Doppler effect, it lowers its voice to compensate.

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Level key

basic

Method keys

cosine, theorem!Pythagoras.

Area keys

behavioural sciences

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Chapter 2

The musselwatch

To monitor the concentration of a pollutant in waterways, it sometimes makes sense to determine the concentration in mussels, $Q(t)$, which have been exposed in such waterways, rather than to determine the concentration in the water, $c(t)$. The first argument is that of bio-availability. Not all of the chemically determined pollutant in the water is actually available to organisms, due to a variety of chemical forms in which the pollutant is present (e.g. ligands). Therefore tissue concentrations provide information which is more relevant to the problem of pollution. Another argument is that the concentration of pollutant might have some sharp peeks, which are easy to miss in infrequent determinations of concentrations in the water. Mussels, in some way, integrate the external concentration in time. Therefore it should still be possible to observe a trace of such peeks in tissue concentrations at infrequent sampling, if, at least, the mussels do not close their valves during such peeks. Let us study this argument in more detail.

Suppose that the tissue concentration follows a simple one-compartment process, i.e.

$$Q' = \frac{Kc(t) - Q}{\tau}, \qquad \text{given } Q(0) \tag{2.1}$$

where Q' stands for the change of Q in time. For other symbols, see Table 2.1. So, if we know $Q(t)$ in sufficient detail, and if it is sufficiently smooth, we can reconstruct $c(t)$ through

$$c(t) = \frac{Q(t) + \tau Q'(t)}{K} \tag{2.2}$$

For the present purpose, we need an explicit expression of $Q(t)$ in terms of $c(t)$, however, because we want to study the effects of rapidly changing water concentrations. The solution is found from (2.1) to be

$$Q(t) = Q(0)e^{-t/\tau} + \frac{K}{\tau}\int_0^t e^{-(t-s)/\tau} c(s)\, ds \tag{2.3}$$

If $c(t)$ is actually constant, (2.3) reduces to

$$Q(t) = Q(0)e^{-t/\tau} + cK\left(1 - e^{-t/\tau}\right) \tag{2.4}$$

Table 2.1: List for frequently used symbols

Symbols	Dimension	Meaning
t	time	time
τ	time	time constant of elimination
T	time	residence time of water in the lake
d	time	length of an interval, say a day
c	weight/vol	concentration in water
Q	weight/vol	concentration in tissue
K		bio-accumulation factor

Now we will approximate the continuous function $c(t)$ by a step function which changes only at discrete, equidistant time points t_i. That is, $c(t)$ is constant over a time interval $(t_i, t_i + d)$, at value c_i. The tissue concentration at the end of the interval is given by

$$Q_{i+1} = Q(t_i + d) = rQ_i + (1 - r)Kc_i \tag{2.5}$$

with $Q_i = Q(t_i)$ and $r = e^{-d/\tau}$. Now we assume that the values c_i represent trials taken independently from some probability density function. This is reasonable for the situation in a river, where well-mixed water surrounding the mussel is completely replaced in an interval of length d. The schedule (2.5) is known as a (first-order) stochastic difference equation or an autoregression process, because the new value for Q is a weighted sum of the old value and an independent random variable. Alternatively, it can be expressed in a so-called moving average scheme:

$$Q_{i+1} = r^{i+1}Q_0 + (1 - r)K \sum_{j=0}^{i} r^j c_{i-j} \tag{2.6}$$

The expected value for Q_{i+1} will be

$$\mathcal{E}Q_{i+1} = r^{i+1}Q_0 + (1 - r)K\,\mathcal{E}c_i \sum_{j=0}^{i} r^j \tag{2.7}$$

Ultimately, i.e. for large i, we have

$$\mathcal{E}Q_i = (1 - r)K\,\mathcal{E}c_i \sum_{j} r^j = K\,\mathcal{E}c_i \tag{2.8}$$

So, the ultimate mean tissue concentration is just the mean external concentration times the bio-accumulation factor K. This result corresponds with the deterministic situation if c is constant. Then $Q(\infty) = Kc$, as can be seen directly from (2.4).

The variance of the tissue concentrations is found from (2.6) to be

$$\mathrm{var}\, Q_{i+1} = (1 - r)^2 K^2 \mathrm{var}\, c_i \sum_{j=0}^{i} r^{2j} \tag{2.9}$$

Ultimately we have

$$\operatorname{var} Q_i = \operatorname{var} c_i K^2(1-r)/(1+r). \tag{2.10}$$

So, for the ratio of the coefficients of variation, CV, we have

$$\frac{\operatorname{CV} c_i}{\operatorname{CV} Q_i} = \sqrt{\frac{1+r}{1-r}} \tag{2.11}$$

This ratio is larger than 1, which means that $\operatorname{CV} Q_i < \operatorname{CV} c_i$. The quotient is increasing in r, so when r is large (i.e. τ is large compared with d), the behaviour of the tissue concentration will be much more smooth than the behaviour of the concentration in the water.

The subsequent tissue concentrations are correlated, as opposed to the concentrations in the water. This is expressed by the so-called autocovariance function $\operatorname{cov}(Q_{i+h}, Q_i)$, or the autocorrelation function $\operatorname{corr}(Q_{i+h}, Q_i)$ (both considered as functions in h), given by

$$\operatorname{cov}(Q_{i+h}, Q_i) = r^{|h|} \operatorname{var} Q_i \tag{2.12}$$

and

$$\operatorname{corr}(Q_{i+h}, Q_i) = \frac{\operatorname{cov}(Q_{i+h}, Q_i)}{\operatorname{var} Q_i} = r^{|h|} \tag{2.13}$$

Show this by writing Q_{i+h} in terms of Q_i using (2.5) several times. We can also study the interdependence of Q_{i+h} and c_i by looking at the (cross-)correlation function $\operatorname{corr}(Q_{i+h}, c_i)$ which in this case can easily be derived to be

$$\operatorname{corr}(Q_{i+h}, c_i) \equiv \frac{\operatorname{cov}(Q_{i+h}, c_i)}{\sqrt{\operatorname{var} Q_i \operatorname{var} c_i}} = \sqrt{1-r^2}\, r^{h-1} \quad \text{for } h > 0 \tag{2.14}$$

The crosscorrelation function in Fig.2.1 shows how the concentration in tissue lags behind concentration fluctuations in the water. The value $r = 0.8$ has been chosen in (2.13) and (2.14). This smoothing also results in a gradually decreasing autocorrelation function of Q.

Usually, the behaviour of water concentrations shows more 'memory'. Suppose, we have a lake of constant volume V, with an inflow and an outflow of water at rate v per unit of time. Writing T for V/v, which is known as the residence time, we have for the concentration c in the lake and f in the inflowing water, assuming a one-compartment process:

$$c' = (f(t) - c)/T \qquad \text{given } c(0) \tag{2.15}$$

The solution, in analogy with (2.3), is:

$$c(t) = c(0)e^{-t/T} + \frac{1}{T}\int_0^t e^{-(t-s)/T} f(s)\, ds \tag{2.16}$$

We will approximate $f(t)$ the same way we did $c(t)$. That is, f is constant over an interval (t_i, t_{i+d}) at value f_i. Then we have

$$c_{i+1} = sc_i + (1-s)f_i \qquad \text{with } s = e^{-d/T} \tag{2.17}$$

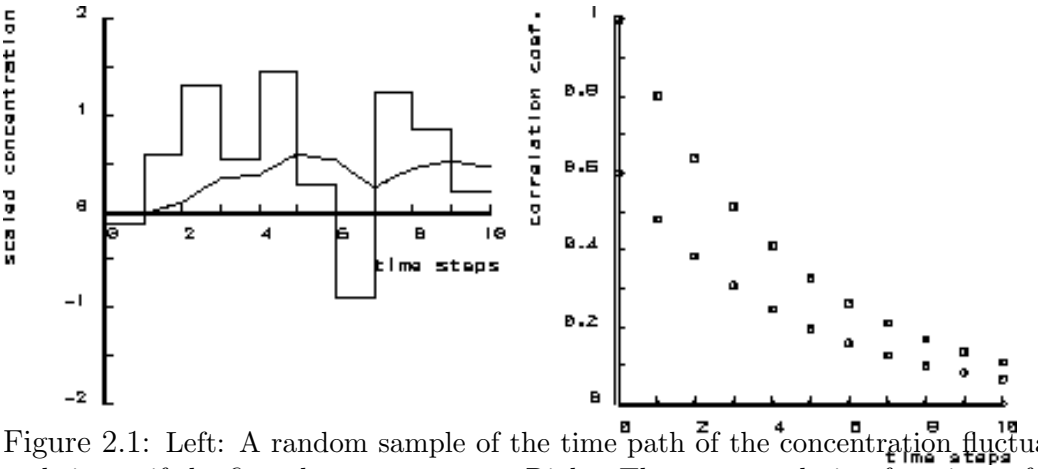

Figure 2.1: Left: A random sample of the time path of the concentration fluctuations in water and tissue, if the first show no memory. Right: The autocorrelation functions of concentrations in water, $\diamond$, and tissue, $\square$ and their cross correlation function, $\circ$.

This is again an auto-regression scheme if the f_i's are independent and identically distributed. Ultimately we have, analogously with (2.8) and (2.10), $\mathcal{E}c_i = \mathcal{E}f_i$ and $\text{var}\, c_i = \text{var}\, f_i(1-s)/(1+s)$. So the (ultimate) mean and variance of c_i do not depend on i. The main difference with the river situation is that subsequent values for c_i are now correlated. The autocovariance function (see (2.12)) is given by

$$\text{cov}\,(c_{i+h}, c_i) = s^{|h|}\text{var}\, c_i \tag{2.18}$$

We can express the variance of Q_i in terms of that for c_i using (2.6):

$$\begin{aligned}
\text{var}\, Q_{i+1} &= (1-r)^2K^2\text{var}\,(\sum_j r^j c_{i-j}) \\
&= (1-r)^2K^2\sum_{j,k}\text{cov}\,(r^j c_{i-j}, r^k c_{i-k}) \quad \text{for } j,k = 0,1,\ldots \\
&= (1-r)^2K^2\text{var}\, c_i \sum_{j,k} r^{j+k}s^{|j-k|} \\
&= (1-r)^2K^2\text{var}\, c_i \,\frac{1+rs}{(1-r^2)(1-rs)} \\
&= K^2\text{var}\, c_i \,\frac{1-r}{1+r}\,\frac{1+rs}{1-rs}
\end{aligned} \tag{2.19}$$

Now, we arrive at the following ratio for the coefficients of variation of the water and the tissue concentrations:

$$\frac{\text{CV}\, c_i}{\text{CV}\, Q_i} = \sqrt{\frac{1+r}{1-r}\,\frac{1-rs}{1+rs}} \tag{2.20}$$

which reduces, as expected, to the river situation (2.11) for $s = 0$. The ratio is larger than 1. It is an increasing function in r, but decreasing in s. So we can conclude that the tissue concentrations will show less variation than the external concentrations indeed, and that the reduction can be significant if the process governing the external concentrations has little memory and if the tissue concentrations are following the external concentrations slowly.

The time behaviour of the tissue concentration and its relation with the water concentration is further illustrated by the autocovariance and the cross-covariance functions. To obtain these functions, we first write (2.17) into the moving-average scheme

$$c_{i+1} = (1-s)\sum_{k=0}^{\infty} s^k f_{i-k} \tag{2.21}$$

which we substitute into (2.6), obtaining for large i

$$Q_{i+1} = K\frac{(1-s)(1-r)}{s-r}\sum_{k=0}^{\infty}(s^k - r^k)f_{i-k} \tag{2.22}$$

Straightforward expansion gives

$$\begin{aligned}
&\mathrm{cov}\,(Q_i, Q_{i-h}) = \\
&\quad = \frac{1-s}{1+s}\frac{1-r}{1+r}\frac{K^2 \mathrm{var} f_i}{1-rs}\frac{(1-r^2)s^{|h|+1} - (1-s^2)r^{|h|+1}}{s-r} \\
&\quad = \mathrm{var}\, Q_i \frac{(1-r^2)s^{|h|+1} - (1-s^2)r^{|h|+1}}{(1+rs)(s-r)}
\end{aligned} \tag{2.23}$$

and, for $h = 0, 1, 2, \ldots$, we have

$$\begin{aligned}
&\mathrm{cov}\,(Q_i, c_{i-h-1}) = \\
&\quad = \mathrm{var} f_i\, K(1-s)^2\frac{1-r}{s-r}\left(\frac{s^{h+1}}{1-s^2} - \frac{r^{h+1}}{1-rs}\right) \\
&\quad = \sqrt{\mathrm{var}\, Q_i\, \mathrm{var}\, c_i}\sqrt{\frac{1-r^2}{(s-r)^2}\frac{1-rs}{1+rs}}\left(s^{h+1} - \frac{1-s^2}{1-rs}r^{h+1}\right)
\end{aligned} \tag{2.24}$$

The auto- and cross-covariance functions contain information about the interdependence of the variables. We started to study the case of independent concentrations in the water, which results in an autocovariance function, which starts at $\mathrm{var}\, c_i$ for time lag $h = 0$, but drops to zero for $h = 1, 2, \ldots$. The cross-covariance function in Fig.2.1 shows how the concentration in tissue lags behind concentration fluctuations in the water. The values $s = 0$ and $r = 0.8$ has been chosen in (2.23), (2.24) and (2.18). This smoothing also results in a gradually decreasing autocovariance function. When the concentration in the water has some memory, like that modelled in (2.17), the autocovariance function of concentrations in the water drops gradually, as expected. See Fig.2.2, where s has been chosen 0.6. The cross-covariance function now shows first an increase. However, the way the tissue follows the concentrations in the water, was exactly the same as in Fig.2.1. It is therefore very difficult to interprete covariance functions without a model for the way the variables depend on each other.

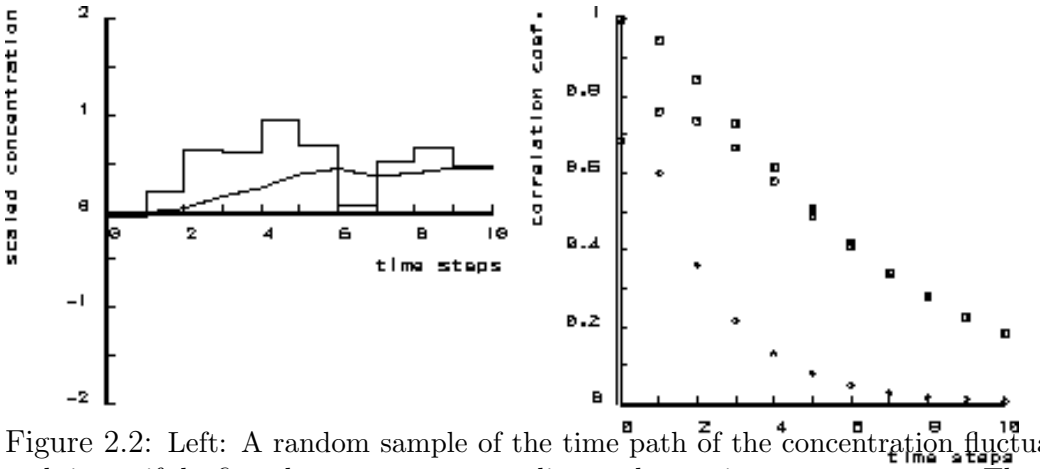

Figure 2.2: Left: A random sample of the time path of the concentration fluctuations in water and tissue, if the first shows memory according to the moving average process. The autocovariance functions of concentrations in water, $\diamond$, and tissue, $\square$ and their cross-covariance function, $\circ$.

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Level key

basic

Method keys

variable!random, state!transient, coefficient!variation, function!correlation, process!stochastic, variance series.

Area keys

ecotoxicology, physiology.

Info

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Chapter 3

Individuals as discrete units with a juvenile stage

In a constant environment, any population eventually grows exponentially. If $N(t)$ denotes the number of individuals at time t, we have $N(t) = N(0)\exp\{rt\}$, where r is called the population growth rate. It is found from the characteristic equation

$$1 = \int_0^\infty F(a)R(a)e^{-ra}\,da \tag{3.1}$$

where $F(a)$ denotes the survival probability at age a and $R(a)$ the reproduction rate at age a. Suppose that an individual survives up to a high age, so that $F(a) = 1$, and that it is able to have offspring at a constant rate R, after age J, so $R(a) = R(a > J)$. Then (3.1) reduces to

$$e^{-rJ} = r/R \tag{3.2}$$

This equation for r must be solved numerically. For $J = 0$, we have that $r = R$. For increasing J, r is falling extremely rapid (see Fig.3.1). This means that neonates giving birth to new neonates would dominate population growth. This unrealistic property is an intrinsic feature of all models allowing this behaviour, like all unstructured models for population dynamics (e.g. Lotka-Volterra equations).

The reproduction rate is so far a continuous function of age. Obviously, this is unrealistic, because individuals are discrete units. It would be more appropriate to gradually fill a buffer with energy assigned to reproduction and to convert it to a new individual as soon as enough energy is gathered. In that case, the reproduction rate becomes $R(a) = (a = J + i/R)/da$, for $i = 1, 2, \ldots$. For an adult, the mean reproduction rate is again R young per time. Now, (3.1) reduces for $F(a) = 1$ to

$$1 = \sum_{i=1}^{\infty} e^{-r(J+i/R)} = e^{-r/R-rJ}\left(1 - e^{-r/R}\right)^{-1} \tag{3.3}$$

In analogy with (3.2), we can rewrite (3.3) to

$$e^{-rJ} = e^{r/R} - 1 \tag{3.4}$$

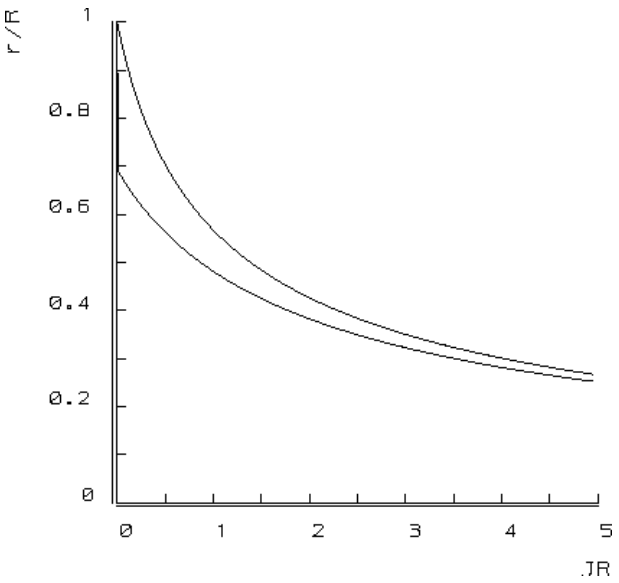

Figure 3.1: The population growth rate depends heavily on the length of the juvenile period, particularly when individuals are not modelled as discrete units (upper curve).

If we compare (3.2) with (3.4), we can observe the effect of individuals being discrete units rather than continuous flows of biomass. For $J = 0$, (3.4) gives $r = R \ln 2$, which is a fraction of some 0.7 of the value we got from (3.2). For increasing juvenile periods, the effect becomes less important (see Fig.3.1).

Level key

basic

Method keys

state!steady, definition!implicit, function!exponential.

Area keys

population dynamics.

Info

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Chapter 4

Stable age-distribution

Suppose that in a constant environment, the survival probability of a female individual with age a, is given by $F(a)$, and that its reproduction rate is $R(a)$. Let $n(a,t)\,da$ denote the number of females at time t having an age somewhere in the interval $\{a,\, a+da\}$. Then the total number of individuals, $N(t)$, is given by $N(t) = \int_0^\infty n(a,t)\,da$. How will the population develop if we specify the composition of a population at time $t = 0$, say by $n(a,0) = n_0(a)$? To evaluate the population, we need to know the birth rate at time t, $B(t)$. If the reproduction rate was a constant R, we could easily state $B(t) = N(t)R$. However, because reproduction rate is age dependent, we must calculate birth rates in every 'age class' and 'add them up', or in mathematical terms

$$B(t) = \int_0^\infty n(a,t)R(a)\,da \tag{4.1}$$

So if we know $n(a,t)$ we can calculate $B(t)$. On the other hand we can see that $n(a,t)$ is determined by $B(t-a)$ in the following way: individuals having age a at time t are the individuals which were born at time $t-a$ and have survived up to age a. Again in mathematical terms

$$n(a,t) = B(t-a)F(a) \tag{4.2}$$

Notice that the right-hand side of this expression contains in fact a probabilistic term, $F(a)$. On the population level it can be interpreted as 'the fraction surviving age a'.

Substitution of (4.2) in (4.1) gives the following integral equation for $B(t)$

$$B(t) = \int_0^\infty B(t-a)F(a)R(a)\,da \tag{4.3}$$

In this equation our assumed knowledge of the population at time $t = 0$ has not yet been used. This can be achieved by making a census in time in (4.3). If $a > t$ we can rewrite (4.2) as $B(t-a) = n_0(a-t)/F(a-t)$. Substitution in (4.3) results in

$$B(t) = \int_0^t B(t-a)F(a)R(a)\,da + \int_t^\infty \frac{n_0(a-t)}{F(a-t)}F(a)R(a)\,da \tag{4.4}$$

This equation is known as the renewal equation. It can be read as follows: births at time t originate from individuals born since $t = 0$ and from individuals already present in the population at $t = 0$. The latter term is usually called $G(t)$.

We assume there is some value ω such that $F(a) = 0$ and $R(a) = 0$ for $a > \omega$ (ω can be interpreted as the maximal age). Then $G(t) = 0$ for $t > \omega$. Now suppose that the solution of (4.4) is of the form $B(t) = C\,e^{rt}$, for some value for r, then (4.4) reduces (for $t > \omega$) to

$$Ce^{rt} = \int_0^\omega Ce^{r(t-a)}F(a)R(a)\,da$$

Dividing by $C\,e^{rt}$ we get the following equation for r

$$1 = \int_0^\omega e^{-ra}R(a)F(a)\,da \tag{4.5}$$

This equation is known as the characteristic equation. It is possible to show that, under some smoothness restrictions on the reproduction function $R(a)$, this equation has exactly one real root r_1. The other roots are complex and have a real part smaller than $|r_1|$. The general solution appears to be a linear combination $\sum_i C_i e^{r_i t}$. For large values of t the exponential $e^{r_1 t}$ will be dominant, so the the asymptotic solution will be $C_1\,e^{r_1 t}$. (The smoothness restrictions on $R(a)$ are violated if for instance reproduction is only possible at certain particular ages. The information about the composition of the initial population then never gets lost.)

From (4.2) it follows that $n(a,t) = C\,e^{-r_1 a}e^{r_1 t}F(a)$ and that $N(t) = C\,e^{r_1 t}\int_0^\omega e^{-r_1 a}F(a)\,da$. This implies that r_1 represents the (eventual) population growth rate and that not only the total number of individuals is eventually growing exponentially, but also the number in each age class. Now we define the so-called stable age distribution $f(a)$ as

$$f(a) \equiv \frac{n(a,t)}{N(t)} = \frac{e^{-r_1 a}F(a)}{\int_0^\omega e^{-r_1 s}F(s)\,ds} \tag{4.6}$$

It can be conceived as the probability density of the age of a randomly selected individual in a really large population, exponentially growing in a constant environment.

As an example, consider a micro-organism growing exponentially from volume W_b to volume $2W_b$ in interval ω, after which it divides into two parts of volume W_b again. Here $W(a) = W_b 2^{a/\omega}$ for $0 < a < \omega$. If there are no actual deaths, we can fictively put $F(a) = (a < \omega)$ and $R(a)\,da = 2(a = \omega)$. From (4.5) we obtain $r = (\ln 2)/\omega$. In principle, a population of such micro-organisms has no stable age distribution because of the mentioned phenomenon that the initial age distribution continues to exercise its influence. In practice however, there will be enough scatter among the division intervals of the daughter cells to destroy synchronicity. It seems safe therefore to neglect this problem and obtain from (4.6) the semi-stable age distribution

$$f(a)\,da = 2^{1-a/\omega}\frac{\ln 2}{\omega}\,da \tag{4.7}$$

Alternatively, we can recast this into the semi-stable size distribution by substituting $a = \omega\,\ln(W/W_b)/\ln 2$ and $da = \omega(W\,\ln 2)^{-1}\,dW$ into (4.7). We obtain $f(W)\,dW =$

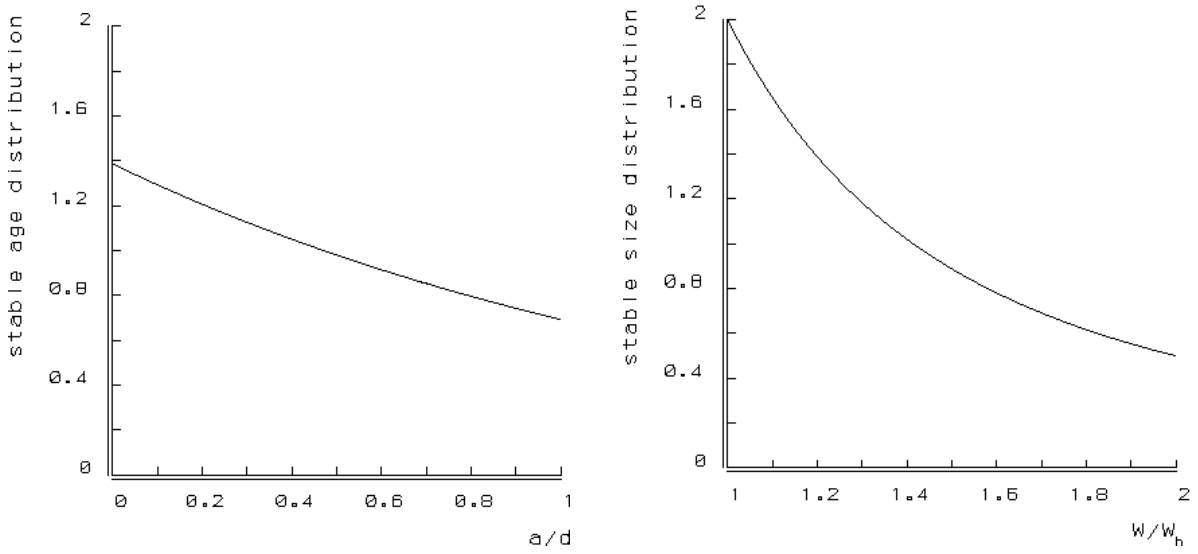

Figure 4.1: The stable age (left) and size (right) distribution of exponentially growing micro-organisms that divide in two parts.

$2W_bW^{-2}\,dW$. See Fig.4.1. Thus we see that the size distribution is independent from the population growth rate. In practice it will be dependent nonetheless, because at high population growth rates cells start a new DNA duplication cycle, before the former one is fully completed. This results in increasing cell sizes at high population growth rates.

The notion of stable age distributions is important in the theory of population dynamics. For practical purposes it is essential to realize that they eventually occur only in populations living in constant environments. This condition will not occur for a long period, outdoors. Apart from seasonal changes in the environment, an exponentially growing population will soon exhaust its resources, depending on the population growth rate.

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Level key

medium

Method keys

state!steady, distribution!frequency, definition!implicit, function!exponential, integral!convolution.

Area keys

population dynamics.

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Chapter 5

The Ames test

The Ames test is a bioassay for testing the mutagenic potential of chemicals on the basis of the frequency of backward mutations in histidine auxotrophic mutants of the pathogenic bacterium *Salmonella typhimurium* (i.e. these bacteria have been mutated such that they are no longer able to synthesize the amino acid histidine themselves, so they need it in the medium). At the start of the experiment, a certain amount of (primairy) histidine auxotrophs are inoculated on an agar plate containing a rich medium with, however, a little bit of histidine and the chemical to be tested. (Usually, there are several plates with different concentrations of chemical.) The incolated bacteria grow and divide, until the histidine is exhausted. So each produces a micro-colony, usually consisting of some 100 bacteria. If one or several bacteria have been permanently converted to the prototrophic state, however, its colony will continue to grow and will become visible with the naked eye. Its is then called a revertant colony. The growing state seems to be a condition for the expression of the backward mutation. So, no visible mutations occur after colony growth ceased due to histidine limitation. For mutagenic chemicals, the number of revertant colonies generally increases linearly with its concentration, at a rate that is taken to be proportional to its mutagenic potential. Let us study the quatitative aspect.

To derive an expression for the number of revertant colonies, we first need the fixation probability $p_f(a)$, which is the probability that a prototrophic cell of age a at time zero will grow into a revertant colony after the moment the histidine is exhausted. Generally, this fixation probability is less than 1 because prototrophic cells may become extinct due to conversion to multiple auxotrophy. This extinction probability is easily found from the probability generating function, G, of the number of prototrophic cells arising from a prototrophic cell after division, i.e. $G(s) = (p_d + q_d s)^2$, where $q_d \equiv 1 - p_d$ and p_d is the conversion probability from a prototrophic cell into a multiple auxotrophic one in a period d, i.e. the division interval. The extinction probability $q_f(d) \equiv 1 - p_f(d)$, of prototrophic cells starting with a prototrophic one of age d is given by $q_f(d) = G\left(q_f(d)\right)$. If the probability rate for conversion of a multiple auxotrophy to a primairy auxotrophy or prototrophy is neglibibly small, and if the conversion probability rates from primary auxotrophy and prototrophy to multiple auxotrophy is equal and constant at value β, say, we have $p_d = 1 - e^{-\beta d}$. This leads to $q_f(d) = \min(p_d^2/q_d^2, 1)$. For an arbitrary initial age a, we should account for the probability of conversion to multiple auxotrophy before the

moment of first division, so

$$\begin{aligned} q_f(a) &= p_{d-a} + q_{d-a} q_f(d) = \min(p_a + q_a p_d^2/q_d^2, 1) \text{ or} \\ p_f(a) &= 1 - q_f(a) = e^{\beta a}(2 - e^{\beta d})_+ \end{aligned} \tag{5.1}$$

where the + sign indicates the maximum of zero and the term within the brackets.

Suppose that we inoculate with I cells (usually some 10^8) and that the amount of histidine is just enough for the formation of H cells on the plate. Suppose further that the division interval d is constant. The number N of cells on the plate then grows exponentially in time, i.e. $N(t) = I\, 2^{t/d}$, as long as the histidine is not limiting. This occurs at time T, found from $N(T) = I + H$, giving $T = d(\ln 2)^{-1} \ln(1 + H/I)$. In writing an expression for the probability on a revertant colony, we have to realize that the inoculated cells as well as the cells present at T, have not been exposed to the chemical during their full life cycle. To deal with this fact, we partition T as $T \equiv kd + c$, where $k \in \{0, 1, 2, \cdots\}$ and $c \in (0, d)$. Suppose that each inoculated cell has a probability p_A of being primary auxotrophic and p_P of being prototrophic. If the probability rate of conversion from primary auxotrophy to prototrophy is small and constant at value α, say, the probability, $p_r(a)$, that an inoculated cell of age a will grow into a revertant colony is given by

$$\begin{aligned} p_r(a) = p_P p_f(a) &+ p_A \alpha \int_0^{d-a} e^{-t\beta} p_f(a + t)\, dt \\ &+ p_A \alpha \sum_{i=1}^{k-1} 2^i \int_{id-a}^{d+id-a} e^{-t\beta} p_f(t - id + a)\, dt \\ &+ p_A \alpha 2^k \int_{d+dk-a}^{dk+c} e^{-t\beta} p_f(t + a - kd)\, dt \end{aligned}$$

Suppose that we start with the stable age distribution for the inoculated cells, i.e. $f(a)\, da = 2^{1-a/d} d^{-1} \ln 2\, da$. The probability that a randomly chosen cell will then grow into a revertant colony is after some calculations found to be

$$\begin{aligned} p_r &= \int_0^d p_r(a) f(a)\, da \\ &= \frac{\ln 2 \left(2 - e^{\beta d}\right)^2}{(\ln 2 - \beta d)_+} \left(p_P + p_A \frac{\alpha d}{\ln 2 - \beta d} \left[\left(1 + \frac{H}{I}\right)^{1 - \beta d/\ln 2} - 1 \right] \right) \end{aligned} \tag{5.2}$$

which reduces for negligibly small β to

$$p_r = p_P + p_A \alpha d H/(I \ln 2) \tag{5.3}$$

The number of revertant colonies will be binomially distributed, but in view of the small number of revertant colonies with respect to the number of inoculated cells, it is safe to use the approximation with the Poisson distribution with parameter $I p_r$. If each molecule

of the chemical has an equal (and small) probability of causing a mutation, a will be proportional to the concentration. One can use likelihood based linear Poisson regression, to obtain the propartionality constant from the number of revertant colonies at several concentrations of test compound.

In conclusion, (5.3) confirms the empirical observation that the mean number of revertant colonies depends linearly on the concentration of chemical. However, it also reveals that a number of other factors contribute as well, like the age distribution and the amount of inoculated cells, the amount of histidine supplied and the division interval (and so the composition of the medium). In practice these problems are "solved" by standardization. Additional complications arise if the chemical also affects growth (so prolonging the period of exposure), particularly if the agar contains slightly mutagenic compounds (due to autoclavation, and referred to as "background" mutations).

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Level key

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Method keys

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Area keys

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Chapter 6

Extinction in constant environments

The larvacean *Oikopleura dioica* is one of the major feeders on the nannoplankton in North Sea. Contrary to its congeners, it is not hermaphroditic, but does sport the heroic way of reproduction by dying upon reproduction. So, the lifetime is in fact the juvenile period J, say. (Quite a few species exhibit this trait, like most cephalopods for instance.) As long as environmental conditions do not change, it seems safe to assume that the number of offspring of female i, X_i, can be conceived as a random trial from some probability distribution, $P\{X_i = x\}, x = 0, 1, \cdots$, say, which is identical for all i's. Here we also assume that the age at reproduction does not vary, so the individuals stay synchronized. The total number of individuals in the population in the t-th generation is then given by

$$N_t = \sum_{i=1}^{N_{t-1}} X_i$$

Such a process is called a branching process. The mean, the variance of the number of individuals in the population and the extinction probability in a patch of water can be evaluated by relatively simple means using the probability generating function $G_t(s) \equiv \sum_{i=0}^{\infty} P\{N_t = i\}s^i$, starting with 1 individual (so $P\{N_0 = 1\} = 1$, giving $G_0(s) = s$).

We first derive an expression for the probability generating function for number of individuals in the t-th generation.

$$\begin{aligned}
G_t(s) &= \sum_{i=0}^{\infty} P\{N_t = i\}s^i \\
&= \sum_{i=0}^{\infty}\sum_{j=0}^{\infty} P\{N_t = i|N_{t-1} = j\}P\{N_{t-1} = j\}s^i \\
&= \sum_{i=0}^{\infty}\sum_{j=0}^{\infty} P\{X_1 + X_2 + \cdots + X_j = i\}P\{N_{t-1} = j\}s^i \\
&= \sum_{j=0}^{\infty} P\{N_{t-1} = j\}\sum_{i=0}^{\infty} P\{X_1 + X_2 + \cdots + X_j = i\}s^i \\
&= \sum_{j=0}^{\infty} P\{N_{t-1} = j\}[G_1(s)]^j
\end{aligned}$$

$$= \quad G_{t-1}\left(G_1(s)\right) = G_1\left(G_{t-1}(s)\right) \tag{6.1}$$

The mean of the number of individuals in the t-th generation, m_t, is found from $m_t = \frac{d}{ds}G_t(1) \equiv G_t'(1)$. We find

$$m_t = G_t'(1) = G_1'(1)G_{t-1}'(1) = [G_1'(1)]^t = m_1^t \tag{6.2}$$

This expression shows that it is possible to connect the mean numbers $m_1^0, m_1^1, m_1^2, \ldots$ for time $0, J, 2J, \ldots$ with an exponential function

$$m(t) = \exp\{tJ^{-1}\ln m_1\}.$$

The population growth rate is thus $J^{-1}\ln m_1$. The mean approaches 0 for $m_1 < 1$, i.e. when a female, on average, no longer replaces herself.

The variance of the number of individuals in the t-th generation, σ_t^2, is found from $\sigma_t^2 = G_t''(1) + G_t'(1) - (G_t'(1))^2$. We find from (6.1) that

$$\begin{aligned} G_t''(1) &= G_1''(1)[G_{t-1}'(1)]^2 + G_1'(1)G_{t-1}''(1) \\ &= (\sigma_1^2 + m_1^2 m_1)m_1^{2t-2} + m_1 G_{t-1}''(1) \\ &= (\sigma_1^2 + m_1^2 - m_1)\left(m_1^{2t-2} + m_1^{2t-3} + \cdot + m_1^{t-1}\right) \end{aligned}$$

Substitution shows that

$$\sigma_t^2 = \sigma_1^2 m_1^{-1}(m_1-1)^{-1}m_1^t(m_1^t-1) \text{ for } m_1 > 1 \tag{6.3}$$

$$\sigma_t^2 = t\sigma_1^2 \text{ for } m_1 = 1 \tag{6.4}$$

The coefficient of variation, $\mathrm{CV}_t \equiv \sigma_t/m_t$, appears to become constant after some generations, when $m_1^t \gg 1$. From (6.2) and (6.3), we have

$$\mathrm{CV}_t = \sigma_1/\sqrt{m_1(m_1-1)} \tag{6.5}$$

This coefficient becomes 0 if $m_1 = 1$, however. The reason for this lies in extinction becoming certain in the long run as long as $P\{X_i = 0\} \neq 0$. Under the latter condition, the probability of extinction can be positive even for $m_1 > 1$. Let $q_t \equiv P\{N_t = 0\} = G_t(0)$ be the probability of extinction at or prior to the t-th generation. From (6.1), we must have that

$$Q_t = G_t(0) = G_1\left(G_{t-1}(0)\right) = G_1\left(Q_{t-1}\right)$$

So, eventually, we must have an extinction probability $0 < Q_\infty < 1$, such that

$$Q_\infty = G_1(Q_\infty) \tag{6.6}$$

If more positive roots of (6.6) exists, we must have the smallest one. See Fig.6.1. If $P\{X_i = 0 \vee X_i = 1\} < 1$, $G_1(s)$ must be a convex function in s as $G_1''(s) > 0$. We also

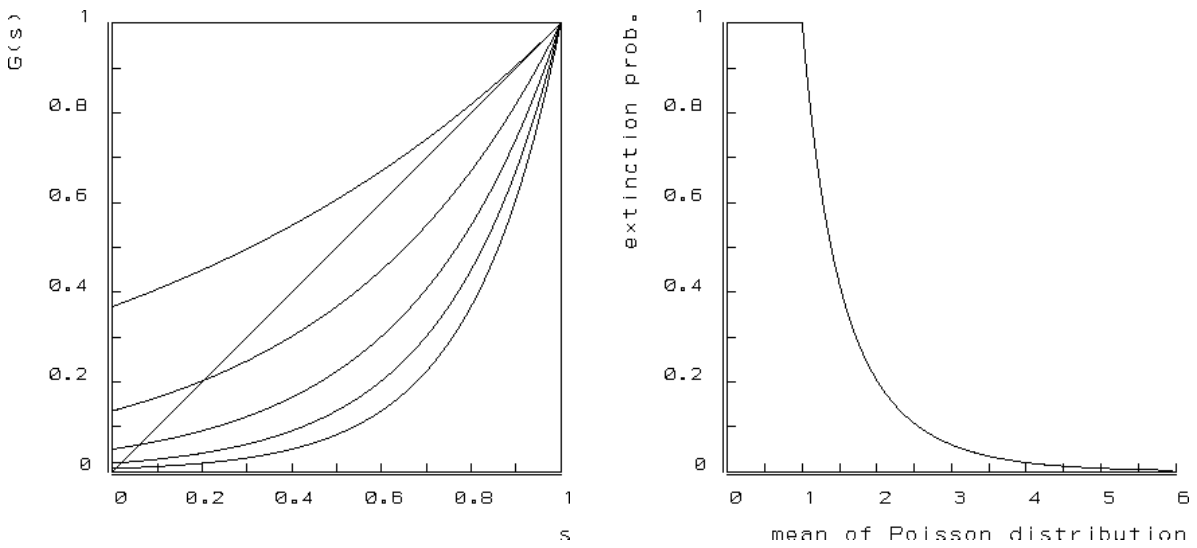

Figure 6.1: Left:The probability generating function of the Poisson distribution and its relation with the extinction probability. $m = 1, 2, 3, 4, 5$. Right: The extinction probability in populations with a Poisson distributed number of offspring.

have that $G_1(1) = 1$, so there exists at most one positive root of (6.6) less than 1 and it exists only if $G_1'(1) > 1$, i.e. when $m_1 > 1$. This implies the certain ultimate extinction for $m_1 = 1$.

As an example, we can take a Poisson distribution with parameter m, say, for the number of (female) offspring per female. The probability generating function is then given by $G(s) = \exp\{m(s-1)\}$. The ultimate extinction probability Q_∞, is according to (6.6) found from $Q_\infty = \exp\{m(Q_\infty - 1)\}$. Fig.6.1 gives the solution as a function of the mean number of offspring, m. We have to realize that the expected time of extinction, given that it occurs, will decrease for increasing m.

This exposition shows that it is possible to evaluate some biologically relevant facts for the behaviour of branching processes, without specifying the complete distribution for the number of offspring from a female. The formulation in terms of branching processes can be generalized in several respects, but from a biological point of view it is too rigid to be really useful. It is for instance possible to let the mother survive after giving birth, but then it seems not realistic that her next brood should coincide with that of her offspring. Introduction of an age-structure seriously complicates the formulation. Even more serious problems in the formulation arise, when food supply becomes limiting due high numbers of individuals.

Further reading

Example 3 for the same equation as the one for extinction probability in populations with Poisson distributed number of offspring, but with a totally different interpretation.

Example 5 for application in populations of dividing organisms

Bibliography

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Level key

medium

Method keys

variable!random, process!branching, series, coefficient!variation, variance, expectation, distribution!Poisson, function!exponential.

Area keys

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Info

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Chapter 7

Some quantities really stink

For people involved in applications, mathematicians are notorious for their passion for anomalies, like infinite variances. Much to the enjoyment of mathematicians and to the annoyance of applicants, they do occur in "real life", every now and then. Mandelbrot [Mandelbrot, 1974] explained the long-known odd behaviour of this number [Luria and Delbrück, 1943] by showing that for rather general assumptions for the growth and mutation process, the number of rare mutants in an old colony of bacteria follows a stable distribution, which has infinite (higher) moments depending on the so-called stability exponent.

The derivation makes use of a defining property of stable distributions: the sum of two independent identically distributed random variables X_1 and X_2 can be scaled such that it follows the same distribution for properly chosen values for the location parameter, L, and scale parameter, S. So, X_1, X_2, as well as $S(2)\,(X_1 + X_2 - L(2))$ all follow the same distribution. The normal distribution is a well known for this property, where $S(2) = 1/\sqrt{2}$; It is the only stable distribution having a finite variance. Generally, one has $S(2) = 1/\sqrt[a]{2}$, where a is known as the stability exponent, satisfying $0 < a < 2$. For $a < 2$, the X's have infinite variance and for $a < 1$, the X's also have an infinite mean.

Suppose that a we observe a bacterial colony, growing from one inoculated non-mutant cell. The mutation probability rate is assumed small, constant and equal for each cell. We choose the unit of time such that the division interval of the initial cell equals $t^* = \ln 2$ and the origin such that the first cell divides at $t = 0$. Suppose that the number of mutants, $M(t)$, at time t grows exponentially with population growth rate $r > 1$, such that $M(t)\exp\{-rt\}$ tends to limit $F(x)$ one can call the asymptotic distribution of $M(t)$. The number of mutants resulting from both daughter cells, $M_1(t)$ and $M_2(t)$ respectively, are independent, and $L_1 = M_1(t)\exp\{-rt\}$ and $L_2 = M_2(t)\exp\{-rt\}$ both tend to the distribution $F(x)$. Assuming that the probability that the inoculated cell becomes a mutant is negligibly small, the number of mutants in the whole colony is given by $M(t) = M_1(t) + M_2(t)$ in a period $t + t^*$ after inoculation. So the distribution of $M(t)\exp\{-r(t+t^*)\} = (L_1+L_2)\exp\{-rt^*\}$ also tends to $F(x)$. Therefore $F(x)$ is a stable distribution, with a stability exponent found from $\sqrt[a]{2} = \exp\{-rt^*\}$ to be $a = 1/r$.

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Level key

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Method keys

variable!random, variance, distribution!normal, function!exponential.

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Chapter 8

How to prepare media from salts

The composition of liquid growth media is frequently given in its ion composition in literature. The preparation of such media from salts diluted in aqua dest leads to the practical problem of how to combine available salts in a way best approximating the given composition. Let us call the sought grams of salt $\mathbf{S} \equiv (s_1, \cdots, s_k)^T$ and the known molars of ion $\mathbf{U} \equiv (u_1, \cdots, u_r)^T$. Elementary chemistry allows us to compose a matrix $\mathbf{M}$, such that a typical element m_{ij} stands for the molar contribution of 1 gram of salt j to ion i. If we want to prepare a litre of medium, the problem is thus to find a useful $\mathbf{S}$, given $\mathbf{M}$ and $\mathbf{U}$. We can only hope for a unique solution if $k \leq r$. Let us assume this to be the case.

Let us first try to minimize the sum of the absolute errors. So, we are looking for $\mathbf{S}$, such that

$$f \equiv \sum_{i=1}^{r} (u_i - \sum_{j=1}^{k} m_{ij} s_j)^2 \tag{8.1}$$

is minimal for all possible choices for $\mathbf{S}$. In matrix notation we have $\mathbf{S}|f \equiv (\mathbf{U} - \mathbf{MS})^T(\mathbf{U} - \mathbf{MS})$ is minimal. To find such a $\mathbf{S}$, we have to solve $\frac{d}{d\mathbf{S}} f = \mathbf{0}$. In elements we have

$$\frac{df}{ds_l} = -2 \sum_{i=1}^{r} \left(u_i - \sum_{j=1}^{k} m_{ij} s_j \right) m_{il} = 0 \text{ for } l = 1, \cdot, k. \tag{8.2}$$

In matrix notation this becomes

$$\frac{d}{d\mathbf{S}} f(\hat{\mathbf{S}}) = -2\mathbf{M}^T(\mathbf{U} - \mathbf{M}\hat{\mathbf{S}}) = \mathbf{0} \text{ or } \mathbf{M}^T\mathbf{U} = \mathbf{M}^T\mathbf{M}\hat{\mathbf{S}}.$$

In terms of the latter notation, the solution is easily written down, if it exists:

$$\hat{\mathbf{S}} = (\mathbf{M}^T\mathbf{M})^{-1}\mathbf{M}^T\mathbf{U}. \tag{8.3}$$

So, we have to multiply the column vector $\mathbf{U}$ to the left by the matrix $(\mathbf{M}^T\mathbf{M})^{-1}\mathbf{M}^T$. This matrix is known as the (left) generalized Moore inverse of the matrix $\mathbf{M}$. It is an inverse, because multiplication by its original results in the identity matrix, $(\mathbf{M}^T\mathbf{M})^{-1}\mathbf{M}^T\mathbf{M}$. It is generalized because originally, the inverse matrix is only defined for square matrices. It is a

particular generalized inverse, because more ways exist to define an inverse matrix, namely the right generalized inverse. The left and the right inverse are identical for a symmetrical (and thus square) matrix only, if they exist.

Usually, the ions differ widely in abundance. From a biological point of view, the way they play a role in supporting life can be widely different. Therefore it is questionable wether the loss function f makes sense on physical grounds. A lot more elegant is to minimize the sum of relative errors rather than the absolute ones. The loss function now takes the form

$$\begin{aligned} f &= \sum_{j=1}^{r} \left(\left(u_j - \sum_{i=1}^{k} m_{ji} s_i \right) / u_j \right)^2 \\ &= \sum_{j=1}^{r} \left(1 - \sum_{i=1}^{k} m_{ji} s_i / u_j \right)^2 \end{aligned} \tag{8.4}$$

In matrix notation we have

$$\hat{\mathbf{S}} | f = (\mathbf{1} - \mathbf{N}\hat{\mathbf{S}})^T (\mathbf{1} - \mathbf{N}\hat{\mathbf{S}}),$$

where $\mathbf{N} \equiv [\mathrm{diag}(\mathbf{U})]^{-1}\mathbf{M}$. In elements, we have to solve

$$\frac{df}{ds_l} = -2 \sum_{j=1}^{r} (1 - \sum_{i=1}^{k} n_{jl} s_i) n_{jl} = 0 \text{ for } l = 1, \cdot, k \tag{8.5}$$

The solution, if it exists, is of course

$$\hat{\mathbf{S}} = (\mathbf{N}^T \mathbf{N})^{-1} \mathbf{N}^T \mathbf{1}. \tag{8.6}$$

Although this choice for $\mathbf{S}$ will be satisfying in most practical cases, it is possible that one or more elements of $\hat{\mathbf{S}}$ are negative. Since it is far from easy to take a certain salt out of a solution, we might want to have non- negative solutions only. This has to be obtained by changing the salts to be use for the preparation of the medium.

As an example, consider the preparation of artificial seawater, as far as the main ions are concerned, from a set of salts. Table 8.1 gives the relevant data. An "exact" solution is not possible, because the given combination of ions is not electrically neutral. The values has been axtracted from "the handbook", ignoring the many rare ions. We can conclude that, when both magnesiumchloride and magnesiumsulfate are available, the sum of relative errors can be made quite small. The option with magnesiumsulfate only, has to be preferred above that with magnesiumchloride only. In practice we should bother about how to prevent gyps to precipitate, in this case.

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Table 8.1: The preparation of artificial seawater. The i,j-th element of the matrix **N** is obtained by dividing the i,j-th element of the main table given below, by the molar concentration of ion i of seawater (second column) and the molar weight of salt j (second row). The last three rows consist of the best choice for salts using one or both magnesium salts in g/l. The first component indicates the sum of relative errors.

		NaCl	KCl	$MgCl_2$ $.6H_2O$	$MgSO_4$ $.7H_2O$	$CaCl_2$ $.H_2O$	NaBr	$SrCl_2$
Mol.	weight	94	74	203	246	129	103	159
	mM							
Cl^-	536	1	1	2		2		2
Na^+	456	1				1		
Mg^{2+}	56		1	1				
SO_4^{2-}	28			1				
Ca^{2+}	10				1			
K^+	9.7	1						
Br^-	0.813					1		
Sr^{2+}	0.092						1	
5.03E-5		42.7	0.718	5.67	6.89	1.29	0.0837	0.0146
2.05E-1		44.8	0.719	0	8.27	1.29	0.0837	0.0146
1.01E 0		40.4	0.717	11.22	0	1.29	0.0837	0.0146

Level key

basic

Method keys

matrix!generalized inverse, matrix!diagonal, transposition, error!absolute, error!relative

Area keys

experimental biology.

Info

Filename: ex008; Date 1989/07/04; Author: Bas Kooijman

Chapter 9

Roots at war

Optimizing crops of cereals has been and will be of vital importance in cultural development. In principle it is possible to obtain some 160 seeds from one seed of classical cereals like barley or rye in a year. Such high yielding factors are not met in practice, however. At present, our highly priced modern technology is able to reach a value of some 10 till 20. In the 18-th century, it was 7 à 8. Extrapolating backwards, it is generally assumed that at the birth of european agriculture, it has been some 3 à 4. Great surprise when Reynolds (1979) obtained yield factors of 60 till 80, with a mean well above 30 during some 15 years, in the Butcher-Hill Ancient Farm Research Project. This project aims to mimic the old Babylonian technique as close as possible (including the use of old races, obtained from eastern Turkey). Looking for explanations of this remarkable result, it has been argued that the Babylonians planted the seeds in a honeycomb pattern, while later technologies use random patterns (obtained by throwing handfuls wide from the lab). In the honeycomb pattern, with an appropriate seed to seed distance, competition between plants would be significantly reduced as compared with random patterns. Let us study this explanation more closely, using the notion of Dirichlett cells.

The Dirichlett cell belonging to a particular plant is defined as the set of sites nearest to that plant with respect to the other plants, Fig.9.1. Dirichlett cells can be considered as the plane analogue of intervals between points on a time axis. In a honeycomb pattern with mean plant density m per unit of surface area, all Dirichlett cells are identically honeycomb shaped with a surface area of $1/m$. The 6 nearest plants to a typical plant all are at a distance $\sqrt{2\,/\,\sqrt{3}m}$. Initially, i.e. just after sowing, there are no roots. After some time they will start to grow and approximately occupy a circle with radius r. Suppose that the roots of all plants grow equally fast. As long as $r < 1/\sqrt{2\sqrt{3}m}$, the roots do not interfere. The fraction of unused land is then $1 - \pi r^2/m$. If the roots continue to grow, they will make contact with that of neighbouring plants. Suppose that they will cease growing at the places of contact, but continue to grow, where no neighbours are felt. We can define a dimensionless index for competition as one minus the ratio of the actual surface area the roots of a plant occupy and the potential one, when no neighbours where present. The potentially occupied surface area is taken to be πr^2. Initially, the competition index is 0. If the roots travel further than a distance $\sqrt{2\,/\,3^{3/2}m}$ from the plant, all land will be

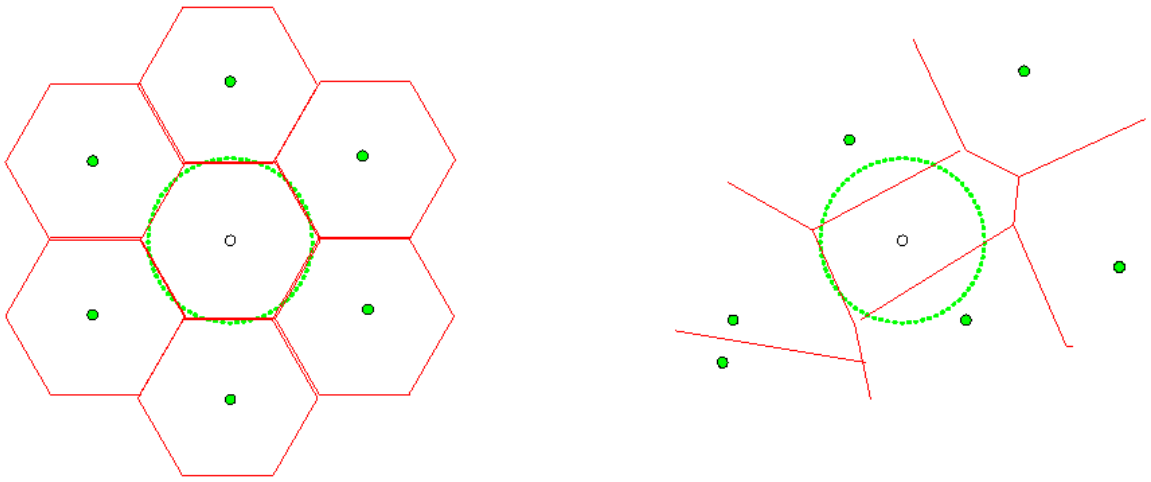

Figure 9.1: Dirichlett cells of a honeycomb and a random pattern.

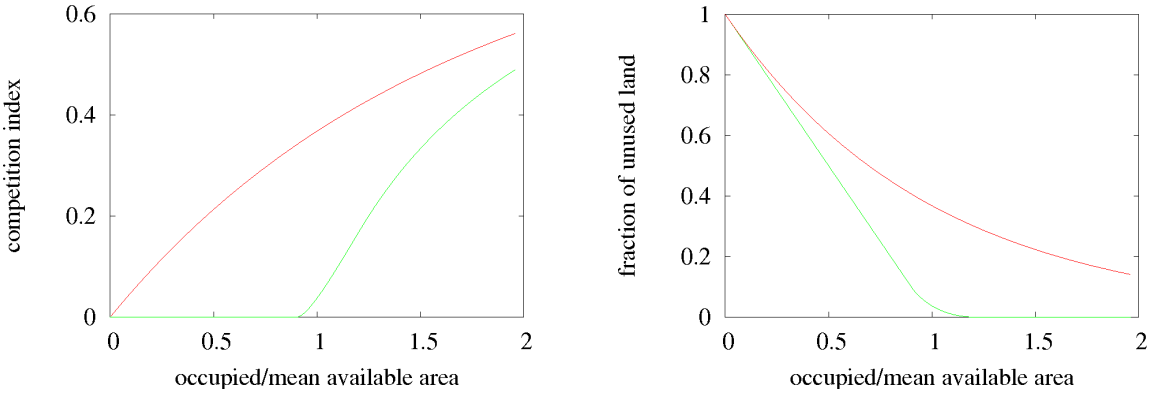

Figure 9.2: Competition indices and fraction of unused land for honeycomb (green) and random (red) patterns as function of the size of the roots relative to the sowing density.

occupied and the competition index is $1-(m\pi r^2)^{-1}$. If $1/\sqrt{2\sqrt{3}m} < r < \sqrt{2\,/\,3^{3/2}m}$, straightforeward geometry learns that the competition index is $\{\arctan c - c/(1+c^2)\}6/\pi$, with $c=\sqrt{r^2m2\sqrt{3}-1}$, Fig.9.2. The fraction of unused land becomes $1-c\sqrt{3}-r^2m(\pi-6\arctan c)$. Suppose that the seed density has been chosen such that the roots of a fully grown (lonely) plant occupy an area of just $1/m$, i.e. the surface area available for one plant. So, $r=1/\sqrt{\pi m}$. In a honeycomb pattern, the competition index then 0.037, with the same fraction of land still unoccupied.

Now let us consider random patterns. We idealize the sowing process, such that it is reasonable to assume that the number of seeds falling into a plot of unit size follows a Poisson distribution with parameter m. Now no two Dirichlett cells have the same shape and size. It is extremely difficult, indeed, to tell more of the surface area of Dirichlett cells in random patterns than their mean, which is obviously $1/m$, and their variance, which is a cumbersome expression (Matern, 1960). Their shape, which is determined by the position

of neighbouring plants also varies considerably. The number of neighbouring plants, i.e. plants having adjacent Dirichlett cells, can vary between 3 and a lot. So we must follow a totally different approach to find expressions for the competition index and the fraction of land not in use by the plants. The latter fraction is easily found, if we realize that it corresponds with the probability that no plants are present within a circle of radius r from a randomly selected site. Since such a circle has surface area πr^2, this probability is the zero-probability of a Poisson distribution with parameter $m\pi r^2$, i.e. $\exp\{-m\pi r^2\}$. To obtain the competition index, it is helpful to note that the ratio of the actually and the potentially occupied area of a plant corresponds with the probability P_r, say. P_r being the probability that a randomly selected site within a circle with radius r from a randomly selected plant is within its Dirichlett cell. This means that the distance between such a site and our plant, say s, is smaller than any distance to other neighbouring plants. Given a particular site, the latter probability equals $\exp\{-m\pi s^2\}$. We find P_r, by mixing the latter probability with the probability density, $f(s)$ say, of a random site at distance s from the plant. This probability density is easily derived from its distribution function. The probability that the distance between a random site within a circle of radius r and the centre, is less than s, is $\pi s^2(\pi r^2)^{-1}$. So $f(s)\,ds = \frac{d}{ds}\pi s^2(\pi r^2)^{-1} = 2sr^{-2}\,ds$. So, P_r is given by $P_r = \int_0^r \exp\{-m\pi s^2\}2sr^{-2}\,ds = (m\pi r^2)^{-1}(1 - \exp\{-m\pi r^2\})$. The competition index is thus $1 - P_r$, thus $1 - (m\pi r^2)^{-1}(1 - \exp\{-m\pi r^2\})$, Fig.9.2. If the seed density, m, has been chosen such that a full-grown plant just occupies an area equal to the mean surface area of the Dirichlett cells, so $\pi r^2 = 1/m$, the competition index is 0.368, while the same fraction of land is still unoccupied.

In conclusion we can state that in random patterns the competition index and the fraction of unused land is 10 times as high, compared with honeycomb patterns, if plants are sowed as dense as possible. It seems safe to assume that growth, and so yield, is increasingly retarded for increasing competition indices. Wether or not the difference between the yield factors can be fully explained by the difference in competition indices, is beyond the scope of the present analysis. Other factors of importance include nutrient supply. The Babylonians seem to allow a significant amount of weeds growing between the grain, which was sufficiently competitive to the weeds to defeat adverse effects on growth. After the season, the weeds were plight through the soil, supplying adequate nutrients as well as improving soil structure. The reason why the romans did not adapt the babylonian techniques is possibly due to their aim of maximizing yield per man-hour. (The Babylonians possibly used their hands in collecting grain for private use mostly.)

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Level key

basic

Method keys

variable!random, distribution!Poisson, tangent.

Area keys

bioproduction.

Info

Filename: ex009; Date: 1989/07/04; Author: Bas Kooijman

Chapter 10

Many ways to hyperbolic responses

The feeding rate, v, of an animal as a function of food density, X, expressed as number of particles per surface area or volume, is often well described by the hyperbolic function, $v = v_m X/(K + X)$, where K is known as the saturation constant or Michaelis constant, i.e. the density at which food intake is half of the maximum (Holling, 1969). It also well describes the feeding rate of ciliates on organic particles (phagocytosis), or the uptake of substrate by bacteria, or the enzyme mediated transformation of substrates. Although these processes differ considerably in detail, some common principle might be rate limiting. Let us try to study it.

Suppose that the handling time of a particle takes a certain time τ and that particles arriving during handling are ignored. ("Handling" is meant here in the wide sense. For feeding animals it might refer to the act of catching and eating as well as to decomposing the particles in the gut or transfer of products across the gut wall.) It is not essential that the handling time is fixed; It might be a random variable with mean τ, but is has to be independent of food density. Suppose further that the number of particles arriving in a unit of time is Poisson distributed with a parameter proportional to the particle density, λ, say $f\lambda$. Here f relates to a filtering rate or a speed of the animal relative to the prey particles, which is again independent of particle density. The time between subsequent arrivals is then exponentially distributed, with mean $1/f\lambda$. The time between the end of a handling period and the next arrival is again exponentially distributed with mean $1/f\lambda$. (To see this, one should make use of a defining property for an exponentially distributed variable Y, that both Y and $Y|Y > y$ are identically distributed). The number, N, of particles eaten in period T is thus given by $T = N(\tau + 1/f\lambda)$. The mean ingestion rate, $I = N/T$, is thus $I = 1/(\tau + 1/f\lambda) = \tau^{-1}\lambda/\{(\tau f)^{-1} + \lambda\}$, which is hyperbolic in the density λ. The saturation constant is inverse to the product of the handling time and the filtering (or searching) rate. The maximum ingestion rate is inverse to the handling time. (Here we measure the ingestion rate by the ratio of a fixed number of particles eaten and the mean time it takes the animal to do this. If we fix the feeding period, rather than the number of particles eaten, the mean ingestion rate might, in principle, deviate from the hyperbolic function. Moreover, we make sure that the particle density does not change)

So far, we considered one server, i.e. the individual, handling the particles. Now we consider a large but fixed number, M, of identical servers handling particles simulata-

neously, but without interference. Think of them as active sites (enzyme molecules) in a membrane, of particles as substrate molecules and of catching as adsorption. If θ stands for the fraction of busy servers, then is the change of this fraction due to new arrivals is given by $d\theta/dt = k_a\lambda M(1-\theta)$, where the rate constant k_a, the absorption rate, plays exactly the same role as the filtering or searching rate f. The change of the fraction of busy servers due to finishing the handling of particles is proportional to the number of busy servers, so it is given by $d\theta/dt = k_d M\theta$, where the rate constant k_d, the desorbtion rate, is just inverse to the mean handling time τ. In equilibrium, the fraction θ does not change, so $k_a\lambda M(1-\theta) = k_d M\theta$, or $\theta = K\lambda/(1+K\lambda)$, with $K = k_a/k_d$. The fraction of occupied sites as a function of the density of absorbtable particles (i.e. partial pressure in gasses), is called the adsorption isotherm in physical chemistry. If the sites operate independently, like here, and so give rise to a hyperbolic function, this isotherm is called the Langmuir isotherm. The absorption rate of particles, is easily found by substituting the Langmuir isotherm into the change in the busy fraction of servers:

$$k_a\lambda M(1-\theta) = k_a\lambda M\{1 - K\lambda/(1+K\lambda)\} = k_a\lambda M/(1+K\lambda) = k_d M\lambda/(K^{-1}+\lambda).$$

So the absorption rate depends hyperbolically on the particle density. The saturation constant has the interpretation of the ratio of the desorption and the absorption rate constants and the maximum absorbtion rate of particles equals the number of servers times the desorption rate. If the desorbed particals are transformed with respect to the absorbed ones, the process stands for an enzym mediated transformation of subtrate into product. The simple kinetics discussed here is known as the Michaelis-Menten kinetics. The condition of constant particle density can be somewhat relaxed. If the total number of particles, L, is really large with respect to the number of servers (a condition by Briggs and Haldane, 1925), or if the rate of product formation k_d is really small (a condition by Michaelis & Menten, 1913), or if KM is really small with respect to $(K+L)^2$, (a more general condition by Segel, 1984), the reaction still follows a Michealis-Menten kinetic.

Although the interpretation in terms of physical chemistry differs considerably from the feeding individuals, from a more abstract point of view, the mechanisms are closely related indeed. The essential element is the busy period and, if more servers are around, they operate identically and idependently. It is quite well possible that the hyperbolic response also arises from completely different mechanisms. Consider the next conjecture: If a substrate is to be transformed into a product, which itself serves as a substrate for the next step, etc, and if the response functions are all of the same type, one gets accumulation of intermediates, if the response functions or not of the hyperbolic type. (Note that linear response functions are a special case of the hyperbolic ones). This conjecture implies that, if accumulation of intermediates has be prevented, the fouraging behaviour has to be regulated in a way such that the response function is of the hyperbolic type. In this case, there is no need for simple busy server mechanisms to generate a hyperbolic response.

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Level key

basic

Method keys

variable!random, isocline, state!steady, distribution!Poisson, distribution!exponential, distribution!frequency.

Area keys

bioproduction, energetics.

Info

Filename: ex010; Date: 1989/07/04; Author: Bas Kooijman

Chapter 11

Stochastic self-ionization of water in cells

When a water molecule dissociates, one of its dipolar H-O bondsbreaks into a positively charged hydrogen ion, H^+, and a negatively charged hydroxyl ion, OH^-. The hydrogen ion, a proton,has a short lifetime as a free particle; its combines with a water molecule to form a hydronium ion, H_3O^+. This binding increases the valence angle of the water molecule from 105° to 120°, so making the added proton indistinguishable from the other two. The extra proton possibly jumps from one water molecule to another. The precise structure of liquid water is still not known with certainty, but for practical purposes it is still convenient to refer to the concentration of hydrogen ions in a solution, $[H^+]$, even though what is really meant is the concentration of hydronium ions. The dissociation of water and the sociation of H^+ and OH^- are, in the mean in an otherwise constant environment, equally fast processes and at 25°C, we have $[H^+][HO^-] = 10^{-14}\,M^2$. In a pure water, $[H^+] = [HO^-] = 10^{-7}\,M$, which is frequently given in its log-transformed form: $pH = -\log[H^+]$, where $[H^+]$ is expressed as mole per litre.

The pH it one of the most important properties of a biological fluid. It influences e.g. enzyme activities; a change in pH can trigger cell growth and division; the movements of protons across a membrane, down the electrochemical gradient, is coupled to the synthesis of ATP in chloroplasts, mitochondria and bacteria. The pH is found to be regulated within a narrow band around a pH of 7, rather independent of the pH in the environment. Yet, there might be a lower limit to the fluctuations due to the stochastic behaviour of the dissociation of water. Think, for the sake of argument, of a bacterium of volume $0.25\,mm^3 = 0.25\,10^{-15}\,dm^3$, consisting of pure water at 25°C. For a specific density of $1\,g/\,mm^3$, it weights $0.25\,10^{-12}\,g$. The number of water molecules is some $(0.25/18)\,6\,10^{23-12} = 8\,10^9$, while the number of protons is $10^{-7}\,6\,10^{23}\,0.25\,10^{-15} = 15$. The relatively small number of protons calls for a consideration of the stochastic fluctuation of the number of 'free' protons.

We assume that each water molecule dissociates independently from the others with a constant probability rate of k_1. The probability rate of the binding of a proton with a hydroxyl ion, is taken to be proportional to the product of their concentrations (and so with their numbers in a fixed volume) with a proportionality constant of k_2. The

number of protons, say n, is necessarily the same as the number of hydroxyl ions because of electroneutrality and mass balance. We can safely neglect the decrease of the number of water molecules, say C, due to dissociation. If $P_n(t)$ denotes the probability that the number of protons at time t equals n, we have for $n = 1, 2, \cdots$

$$\begin{aligned} P_n(t+\Delta t) &= k_2(n+1)^2\,\Delta t\,P_{n+1}(t) + k_1 C\,\Delta t\,P_{n-1}(t) + \\ &\quad + [1-(k_2 n^2 + k_1 C)\,\Delta t]P_n(t) + o(\Delta t) \end{aligned} \tag{11.1}$$

where $o(\Delta t)$ refers to the probability that more than one event (i.e. dissociation or binding) occurs during a time increment Δt. If we bring the term $P_n(t)$ to the left, divide by Δt and let Δt approach to zero, we arrive at

$$P_n'(t) = k_2(n+1)^2 P_{n+1}(t) + k_1 C P_{n-1}(t) - (k_2 n^2 + k_1 C)P_n(t) \tag{11.2}$$

where $P_n'(t)$ denotes the derivative of $P_n(t)$ with respect to the time. For $n = 0$ we have

$$P_0(t+\Delta t) = k_2\,\Delta t\,P_1(t) + [1 - k_1 C\,\Delta t]P_0(t) + o(\Delta t) \tag{11.3}$$

and so

$$P_0'(t) = k_2 P_1(t) - k_1 C\,\Delta t\,P_0(t) \tag{11.4}$$

which is a special case of (11.2) when we make the appointment that $P_{-1}(t) = 0$. So, (11.2) represents the stochastic model for the number of 'free' protons.

By comparison, the corresponding deterministic model would be

$$n'(t) = k_1 C - k_2 n^2(t) \tag{11.5}$$

Separation of variables and integration gives

$$\frac{n(t)-m}{n(t)+m} = \frac{n(0)-m}{n(0)+m}e^{-t/\tau}, \tag{11.6}$$

where m denotes the equilibrium number of 'free' protons in the deterministic model, which is given by $m = \sqrt{Ck_1/k_2}$, and τ the relaxation time, which is given by $\tau = 1/\sqrt{4Ck_1k_2}$. At 25°C, $k_1 = 2.4\,10^{-5}\mathrm{s}^{-1}$ and $k_2 = 10^3\,\mathrm{ion}^{-1}\mathrm{s}^{-1}$ (in ice, k_2 is faster!).This gives a relaxation time of some 36μs.

We now continue with a further analysis of the stochastic model. As long as we are interested in processes with relaxation times much longer than $36\,\mu$s, we can confine ourselves to the limiting probability distribution of n for large t, where we have that $P_n'(\infty) = 0$. When we divide by k_2, call $Ck_1/k_2 = m^2$, as before, and abbreviate $P_n(\infty)$ to P_n, (11.2) reduces in the limit to

$$(n+1)^2 P_{n+1} + m^2 P_{n-1} - (n^2 + m^2)P_n = 0 \tag{11.7}$$

Starting with $P_1 = m^2 P_0$, and using (11.7) in the form

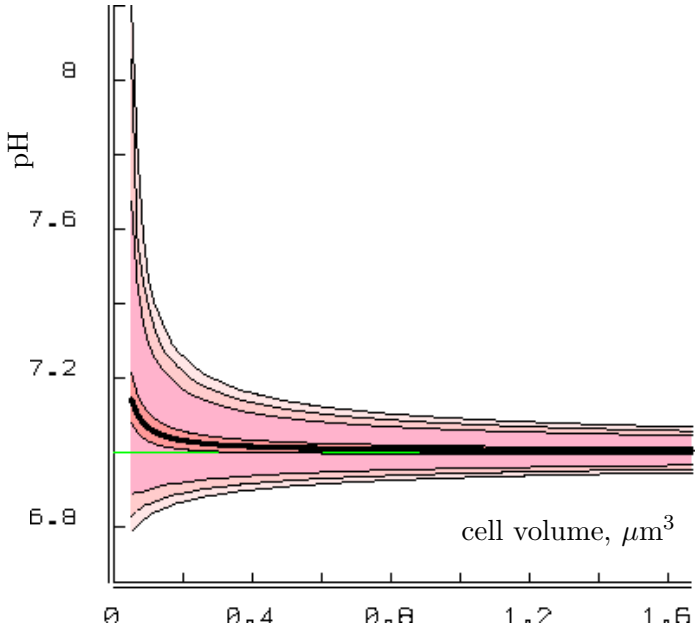

Figure 11.1: The 95%, 90%, 80% and 60% confidence intervals of pH in cells of pure water with pH 7 as a function of the cell size. They increase dramatically for decreasing cell sizes for cells (or cell compartments) less than 0.5 μm^3. The thick curve represents the mean pH, which goes up sharply for very small cell sizes.

$$P_{n+1} = \Big((n^2+m^2)P_n - m^2 P_{n-1}\Big)\,(n+1)^{-2},$$

we find by induction that $P_n = (m^n/n!)^2 P_0$. This relation determines the probabilities up to an arbitrary factor. Obviously, we must have that $\sum_{n=0}^{\infty} P_n = 1$. The series $I_0(x) = \sum_{i=0}^{\infty}(x/2)^{2i}(i!)^{-2}$ is well known as the modified Bessel function. So $\sum_{n=0}^{\infty}(m^n/n!)^2 = I_0(2m)$. We therefore arrive at

$$P_n = (m^n/n!)^2 I_0^{-1}(2m) \tag{11.8}$$

This probability distribution relates to the Poisson distribution by just squaring the Poisson probabilities and renormalizing to assure that the sum of the probabilities remains 1. The normalizing constant $I_0^{-1}(2m)$ in (11.8) compares with e^{-m} in the Poisson distribution.

Since $I_0'(x) = (2/x)\sum_{i=0}^{\infty} i(x/2)^{2i}(i!)^{-2}$, so $\sum_{n=0}^{\infty} n(m^n/n!)^2 = mI_0'(2m)$, the expected number of protons equals $\mu = mI_0'(2m)/I_0(2m)$. This is lower than the value m, which should be expected on the basis of the deterministic model. This is obvious when we obtain the variance by summing (11.7) for $n = -1, 0, 1, \cdots$ It is found to be $\sigma^2 = m^2 - \mu^2 = m^2\left(1 - (I_0'(2m)/I_0(2m))^2\right)$. Although it is less than the variance of a Poisson distribution with the same mean it is still considerable for small m, as is illustrated in Fig 11.1, which shows that the 95% confidence interval of the pH in a 0.25 mm^3 cell of neutral pH ranges from 6.85 to 7.15.

The lifetime of a randomly selected water molecule, a hydroxylion and a hydronium ion follow an exponential distribution with mean k_1^{-1}, i.e. some $4.16\,10^4$ s = 11.55 h, for water and k_2^{-1}, i.e. some 10^{-3} s, for both ions at 25°C. Diffusion causes these particles to displace in time, t, over a mean distance of $\sqrt{2Dt}$, where D denotes the diffusion coefficient. For

H_2O, OH^- and H^+, the latter is 2.26, 5.3 resp. $9.31\,10^{-5}\,cm^2s^{-1}$ at 25°C. The mean total lifetime displacement in an unbounded body of pure water is thus 1.37 cm, 3.26 μm and 4.32 μm, as a crow flies. This means that the limited size of a cell is likely to influence the transport, even apart from influences exercised by, e.g. the membrane.

We made some simplifying assumptions. The first one is that the cell consists of pure water, which is obviously not true. Its cytoplasma is well buffered. Although a full analysis would certainly be immensely complex, it is by no means certain that the stochastic fluctuations are more restricted in buffered mixtures. Buffers primarily balance net fluxes, but we did not discuss that situation. The assumption that water molecules dissociate independently from each other is hard to test at the moment. The significance of the weak bonds certainly depends on temperature. The intention of the example is to draw attention to the odd behaviour of the concept proton 'concentration' in small bodies. It might be relevant e.g. when we measure enzyme performance in well mixed extracts and try to evaluate its consequence for the living cell.

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Level key

medium

Method keys

variable!random, interval!confidence, series, order, state!steady, process!birth and death, distribution!frequency.

Area keys

molecular biology, cell biology.

Info

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Chapter 12

How many extinct species?

The number of described living species still increases dramatically in groups like bacteria, mites and insects. In groups like vertebrates or spermatophytes, the number of described living species shows signs of saturation. How about the number of extinct species? The conditions allowing fossilization to occur are rare. Most layers containing fossils are inaccessible. The number of discovered accessible layers gradually increases with research intensity. Here we will try to use preliminary knowledge about the number of living species for estimating the number of extinct ones.

Suppose that a species gives rise to a new one with a constant probability rate, say λ, and that it becomes extinct with another constant probability rate, say μ. The latter implies that the existence time of a species follows an exponential distribution, with a mean existence time of $1/\mu$. If $N(t)$ denotes the number of living species at time t, $M(t)$ the cumulative number of species and $p_{mn}(t)$ the simultaneous probability that the number of living species equals n and that the cumulative number of species equals m, then $p_{mn}(t+\Delta t)$ can be expressed as a function of $p_{mn}(t)$:

$$\begin{aligned} &p_{mn}(t+\Delta t) = \\ &\quad p_{mn}(t)\{1-(\lambda+\mu)n\,\Delta t\} + p_{m-1,n-1}(t)(n-1)\lambda\,\Delta t + \\ &\quad + p_{m,n+1}(t)(n+1)\mu\,\Delta t + o(\Delta t) \end{aligned} \tag{12.1}$$

When we transport the term $p_{mn}(t)$ from the left to the right, divide both sides by Δt and let $\Delta t \to 0$, we arrive at

$$p'_{mn}(t) = p_{m-1,n-1}(t)(n-1)\lambda + p_{m,n+1}(t)(n+1)\mu - p_{mn}(t)n(\lambda+\mu) \tag{12.2}$$

This simple model defines the probability evolution of both numbers of species, if we specify the initial condition, e.g. $p_{11}(0) = 1$. So we start with one single species for sure. The marginal probability evolution of N (, obtained by dropping the index m in (12.2),) is known as the linear birth and death process. We can extract useful information from (12.2), without actually solving the complete probability distribution as a function of time.

The expected number of living species, $\mathcal{E}N$, is found from (12.2) by multiplying both sides with N and summing over all m and n. It is for this purpose convenient to define

$p_{mn}(t)$ for negative values of m and n as well, but put them equal to zero. This allows us to sum over $m, n = -1, 0, 1, \cdots$ We then arrive at

$$\mathcal{E}'N = \lambda\,\mathcal{E}N(N+1) + \mu\,\mathcal{E}N(N-1) - (\lambda+\mu)\,\mathcal{E}N^2 = (\lambda-\mu)\,\mathcal{E}N \tag{12.3}$$

For $\mathcal{E}N(0) = 1$, we can solve $\mathcal{E}N(t)$:

$$\mathcal{E}N(t) = \exp\{(\lambda-\mu)t\} \tag{12.4}$$

In a similar way, we can multiply both sides of (12.2) by M, sum over all m and n, arriving at

$$\mathcal{E}'M = \lambda\,\mathcal{E}\,(M+1)N + \mu\,\mathcal{E}MN - (\lambda+\mu)\,\mathcal{E}MN = \lambda\,\mathcal{E}N \tag{12.5}$$

For $\mathcal{E}M(0) = 1$, we can solve $\mathcal{E}M(t)$:

$$\mathcal{E}M(t) = 1 + \int_0^t e^{(\lambda-\mu)s}\,ds = (\lambda\,\mathcal{E}\,N(t) - \mu)\,/(\lambda-\mu) \tag{12.6}$$

As an aside, we can evaluate the variance of N as follows. First we multiply both sides of (12.2) by N^2 and sum over all m and n, arriving at

$$\begin{aligned}\mathcal{E}'N^2 &= \lambda\,\mathcal{E}N(N+1)^2 + \mu\,\mathcal{E}N(N-1)^2 - (\lambda+\mu)\,\mathcal{E}N^3 \\ &= 2(\lambda-\mu)\,\mathcal{E}N^2 + (\lambda-\mu)\,\mathcal{E}N\end{aligned} \tag{12.7}$$

We then subtract the derivative of $\mathcal{E}^2N$, which is $2\,\mathcal{E}N\,\mathcal{E}'N$:

$$\mathrm{var}'\,N = \mathcal{E}'N^2 - (\mathcal{E}^2N)' = 2(\lambda-\mu)\,\mathrm{var}\;N + (\lambda+\mu)\,\mathcal{E}N \tag{12.8}$$

For var $N(0) = 0$ and noting, in general that $Y' = cY + f(t)$ has $Y(t) = Y(0)e^{tc} + \int_0^t e^{(t-s)c}f(s)\,ds$ as solution, we find

$$\mathrm{var}\;N(t) = (\mathcal{E}N(t) - 1)\,\mathcal{E}N(t)(\lambda+\mu)/(\lambda-\mu) \tag{12.9}$$

This means that the variation coefficient of N is given by

$$\mathrm{CV}\;N(t) \equiv \sqrt{\mathrm{var}\;N(t)}/\,\mathcal{E}N(t) \to \sqrt{(\lambda+\mu)/(\lambda-\mu)} \tag{12.10}$$

So, as for branching processes, the variation coefficient approaches a constant value. This is not mere coincidence, because the linear birth and death process can be conceived as a branching process by letting the generation time shrink to an infinitesimally small time increment Δt, while the offspring distribution for 0,1 or 2 young has been tied to this increment via the probabilities $\mu\,\Delta t$, $(1 - (\lambda+\mu)\,\Delta t)$ and $\lambda\,\Delta t$.

In a similar way, we obtain

$$\mathrm{cov}'\,MN = (\lambda-\mu)\,\mathrm{cov}\;MN + \lambda\,\mathcal{E}N + \lambda\,\mathrm{var}\;N \tag{12.11}$$

which gives for cov $MN(0) = 0$:

$$\text{cov } MN(t) = (\text{var } N(t) - 2\mu t\, \mathcal{E}N(t))\, \lambda/(\lambda - \mu) \tag{12.12}$$

and

$$\text{var}'\, M = 2\lambda \,\text{cov } MN + \lambda\, \mathcal{E}N \tag{12.13}$$

which gives for var $M(0) = 0$:

$$\text{var } M(t) = \frac{\lambda}{(\lambda-\mu)^2}\left[\lambda \,\text{var } N(t) + \mu\, \mathcal{E}N(t)(\frac{\lambda+\mu}{\lambda-\mu} - 4\lambda t) - \mu\frac{\lambda+\mu}{\lambda-\mu}\right] \tag{12.14}$$

from which follows that CV $M(t) \to$ CV $N(t)$ for large t, and that the correlation coefficient between M and N approaches 1 for large t.

The expected number of extinct species is given by $\mathcal{E}M(t) - \mathcal{E}N(t)$. Using (12.6), we find that $\mathcal{E}M(t) - \mathcal{E}N(t) = \mathcal{E}N(t)\mu/(\lambda-\mu)$. Since μ equals (mean species existence time)$^{-1}$ and $\lambda - \mu$ equals (ln expected no of living species)/(evolution time), we have that

$$\frac{\text{no of extinct spec.}}{\text{no of spec.}} = \frac{\text{evolution time}}{\text{mean spec.existence time . ln no of spec.}}$$

For vertebrates, which fossilize relatively well, due to their hard bones, the evolution time took some 600 Ma to arrive at some 42000 living species. The mean existence time of vertebrate species is estimated to be some 2-3 Ma, based on fossil records, which means that for each living species, we expect some $600/(2.5 \text{ ln } 42000) \simeq 23$ extinct ones. The values for λ and μ might differ between phyla. If we roughly estimate 30 million living eukaryotic species to exist, which took some 2000 Ma to evolve, and if we adopt the vertebrate mean species existence time, we expect some 46 extinct species for each living one.

This model is irrealistically simple. This is obvious from the fact that, for this model, the extinction probability of a richly diversified group is extremely small. Yet such groups, like trilobites, ammonites and dinosaurs, became extinct, nonetheless. At present, the possible occurrence of periodic mass extinctions is in hot debate. Such complicating phenomena would only increase the number of extinct species to be expected. The above calculations could therefore be considered as a lower bound on the number of extinct species.

During the last 300 year, 150 vertebrate species have been recorded to became extinct, mainly due to direct or indirect action of man. The expected extinction rate equals $\mu\, \mathcal{E}N$, which amounts to some 5.6 species in the last 300 year. The proper answer to the question posed in the title is therefore: too many!

Further reading on vertebrate evolution: [Carroll, 1988]; On 'natural' and man-induced extinctions: [Stanley, 1987, Lewin, 1986]. Example 6 for extinction and variation coefficients in branching processes.

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Level key

basic

Method keys

variable!random, variance, order, state!steady, coefficient!variation, process!birth and death, distribution!frequency.

Area keys

evolution.

Info

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Chapter 13

Sitting out a lag phase

In a constant environment, a population of bacteria is growing exponentially after some lag phase, both in number as in biomass, i.e. the change in biomass is proportional to the biomass itself. Almost all chemical reactions in the synthesis of biomass are enzyme mediated. Yet enzymes in isolation do not increase autocatalytically. This contradictions first calls for a closer analysis.

Suppose that we have two enzymes each of which increases its substance by the addition of something derived from the working of the other. Then we shall have

$$X_1' = \mu_1 X_2 \text{ and } X_2' = \mu_2 X_1 \tag{13.1}$$

Think e.g. of the interplay of nucleic acids and proteins, each of which playing a decisive role in the synthesis of the other. In order to obtain the solution of (13.1), we first write it as

$$\mathbf{X}' \equiv \begin{pmatrix} X_1' \\ X_2' \end{pmatrix} = \begin{pmatrix} 0 & \mu_1 \\ \mu_2 & 0 \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \equiv \mathbf{M}\mathbf{X} \tag{13.2}$$

If $\mathbf{B}$ is the matrix with eigenvectors of $\mathbf{M}$ in its columns, and $\mathbf{\Lambda}$ the diagonal matrix with eigenvalues, so $\mathbf{M}\mathbf{B} = \mathbf{B}\mathbf{\Lambda}$, the solution of (13.2) can be written like

$$\begin{aligned} \mathbf{X}(t) &= e^{\mathbf{M}t}\mathbf{X}(0) = \sum_{i=0}^{\infty} \frac{1}{i!}(\mathbf{M}t)^i \mathbf{X}(0) = \sum_{i=0}^{\infty} \frac{1}{i!}\mathbf{B}(\mathbf{\Lambda}t)^i \mathbf{B}^{-1}\mathbf{X}(0) \\ &= \mathbf{B}\left(\sum_{i=0}^{\infty} \frac{1}{i!}(\mathbf{\Lambda}t)^i\right)\mathbf{B}^{-1}\mathbf{X}(0) = \mathbf{B}\begin{pmatrix} e^{\lambda_1 t} & 0 \\ 0 & e^{\lambda_2 t} \end{pmatrix}\mathbf{B}^{-1}\mathbf{X}(0) \end{aligned}$$

The eigenvalues $\lambda_{1,2}$ of $\mathbf{M}$ are easily found to be $\pm\sqrt{\mu_1\mu_2}$, and

$$\mathbf{B} = \begin{pmatrix} \sqrt{\mu_1/\mu_+} & -\sqrt{\mu_1/\mu_+} \\ \sqrt{\mu_2/\mu_+} & \sqrt{\mu_2/\mu_+} \end{pmatrix}, \text{ so } \mathbf{B}^{-1} = \frac{1}{2}\begin{pmatrix} \sqrt{\mu_+/\mu_1} & \sqrt{\mu_+/\mu_2} \\ -\sqrt{\mu_+/\mu_1} & \sqrt{\mu_+/\mu_2} \end{pmatrix}$$

with $\mu_+ = \mu_1 + \mu_2$. Substitution finally results in

$$X_i(t) = P_i e^{\mu t} + Q_i e^{-\mu t}, \text{ for } i = 1, 2 \tag{13.3}$$

with $P_i + Q_i = X_i(0)$ and $\mu = \lambda_1 = \sqrt{\mu_1 \mu_2}$. This leads to

$$\begin{aligned} X_1(t) &= \frac{1}{2}\left(X_1(0) + \frac{\mu_1}{\mu} X_2(0)\right) e^{\mu t} + \frac{1}{2}\left(X_1(0) - \frac{\mu_1}{\mu}\right) e^{-\mu t} \\ X_2(t) &= \frac{1}{2}\left(X_1(0) + \frac{\mu}{\mu_1} X_1(0)\right) e^{\mu t} + \frac{1}{2}\left(X_2(0) - \frac{\mu}{\mu_1}\right) e^{-\mu t} \end{aligned} \tag{13.4}$$

Ultimately, the second term in (13.4) vanishes and the ratio X_1/X_2 becomes constant at value μ_1/μ and the population grows exponentially. So the cyclic autosynthetic reactions as modelled in (13.1) is consistent with exponential growth of biomass, indeed.

For the purpose of, e.g., relating the chemical composition of cells to that of the medium, one needs cells growing at steady state (here: growing exponentially). After inoculation, the culture usually shows a lag phase (i.e. a deviation from exponential growth, which becomes apparent by plotting the logarithm of the number of cells against time). So we have to wait a while before taking the sample material. Now, let us study the length of the lag phase, $t(\mu_1, \mu_2)$, after a (momentary) transition from an environment in which the population was growing exponentially at rate $\mu = \mu'$, into and environment in which the population eventually will grow exponentially at rate $\mu = \mu''$. If both μ_1 and μ_2 are proportional to μ, there will be no lag phase at all, i.e. $t(\mu', \mu'') = 0$. It seems realistic to assume that only one, say μ_1, is increasing with μ, while the other remains constant, so $\mu_2 = \mu^2/\mu_1$.

From a mathematical point of view, we have to wait infinitely long for exponential growth, since the second term in (13.4) vanishes only asymptotically. Being practical, let us accept exponentiality, if the relative error of the number of cells is less than a small fraction ξ, i.e. $|X_1(t) - X_1^*(t)|/X_1^*(t) = \xi$, where $X_1^*(t)$ represents the first term in (13.4), i.e.

$$X_1^*(t) = \frac{1}{2}\left(X_1(0) + (\mu_1/\mu) X_2(0)\right) e^{\mu t}$$

.
This leads to

$$\left|1 - \frac{\mu_1}{\mu}\frac{X_2(0)}{X_1(0)}\right| e^{-2\mu t} \left(1 + \frac{\mu_1}{\mu}\frac{x_2(0)}{X_1(0)}\right)^{-1} = \xi \tag{13.5}$$

The same can be done for X_2, of course, but this will lead again to relation (13.5). When we choose a certain value for ξ, we can solve the length of the lag phase t, given $X_1(0)/X_2(0) = \mu_1/\mu'$ and $\mu = \mu''$. The solution is

$$t(\mu', \mu'') = \frac{1}{2\mu''} \ln \frac{|1 - \mu'/\mu''|}{\xi(1 + \mu'/\mu'')} \tag{13.6}$$

The range of values for μ' and μ'' is restricted to $(0, \mu^*)$, because for negative values, the only steady state is that of being extinct, while values larger than the maximum growth rate μ^* are biologically impossible. A natural scaling for the length of the lag phase is therefore the dimensionless variable $t^* = \mu^* t$, expressed in terms of the dimensionless arguments $\lambda = \mu/\mu^*$. We arrive at

$$t^*(\lambda', \lambda'') = \frac{1}{2\lambda''} \ln \frac{|\lambda'' - \lambda'|}{\xi(\lambda'' + \lambda')} \tag{13.7}$$

A plot of (13.7) is given in Fig.13.1. If μ' and μ'' differ only a little bit, i.e. when $(1-\xi)/(1+\xi) < \mu''/\mu' < ((1+\xi)/(1-\xi))$, the apparent lag phase is zero, which is the result of our acceptance of a relative error of ξ. This is a bit artificial, which becomes obvious when we could slowly increase or decrease μ. We would have to wait a time zero for each incremental change, in other words, we would not have to wait at all for any change. The relative errors would built up this way, far beyond our setting of ξ, of course. Apart for this artifact, some rather counter-intuitive results are obvious from Fig.13.1. The length of the lag phase in an up shift, is not equal to that of a down shift, i.e. $t^*(\lambda', \lambda'') \neq t^*(\lambda'', \lambda')$. Further: Starting from a small initial growth rate, we have to wait longer to reach steady states for a bit higher new growth rate, than for a much higher one. Finally: We have to wait really long in case of a significant down shift. This illustrates that it is extremely difficult to standardize the cells to conditions of a small growth rate. This is important, because this is the usual condition outdoors, which we need to reach when we want, e.g, to exclude growth for the study of maintenance.

These results are possibly easier to remember, when we express the lag phase in the number of division intervals in the new situation, where $\mu = \mu''$. In steady state we have $N(t+d) = N(t)\exp\{\mu'' d\}$ for the number of bacteria at time $t+d$, which equals $2N(t)$, for time $d(\mu'') = \mu''^{-1} \ln 2$. If we divide the lag time in (13.6) by this division interval, we arrive at

$$\frac{t(\mu', \mu'')}{d(\mu'')} = \frac{1}{2\ln 2} \ln \frac{|\mu'' - \mu'|}{\xi(\mu'' + \mu')} \tag{13.8}$$

The role of μ' and μ'' in (13.8) is now symmetric, and the largest number of division intervals in the lag phase, i.e. when μ' or μ'' equals 0, is $-(\ln \xi)/(2 \ln 2)$. See Fig.13.1.

The model (13.1) can easily be extended to more than two types of enzyme, in which case the population growth rate, μ, equals the geometric mean of the rate of increase of the different enzyme types, μ_1, μ_2, $\mu_3, \cdots$. It remains rather easy, because of the linearity. Such a system can be conceived as a first approximation to the more usual hyperbolic rate functions, where the substrate concentrations are small with respect to the saturation constants (see example 10).

Although the presented modelling of population growth in terms of chemical reactions is considered standard in microbiology (, the classical results given in Hinshelwood (1952) are followed here), a warning seems appropriate for skipping levels of organisation (here: the cell), and a too loose reference to variables that can be measured directly or indirectly.

Further reading for a classical and still relevant work on enzyme performance in growing cells: [Hinshelwood, 1952].

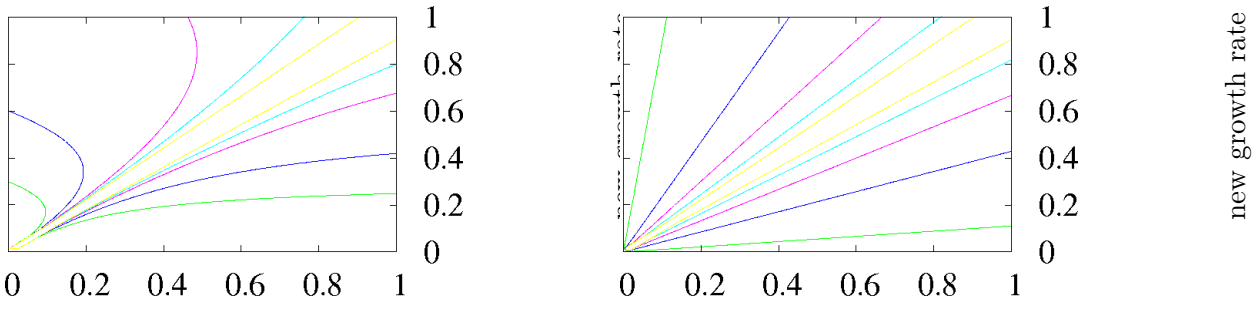

Figure 13.1: Left: Contours for the length of the lag phase following a transition from one exponential growth rate to another, accepting a relative error of 0.05. The growth rates are expressed as fractions of the maximal growth rate. The contours of values 5, 2.5, 1, 0.5 and 0 are shown for the time lag times the maximum growth rate times $-2/\ln\xi$. Right: the lag-phases expressed as numbers of division intervals while in the new growth rate. The contours of values 2, 1.5, 1, 0.5 and 0 are shown

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Level key

basic

Method keys

series, state!steady, matrix!diagonal, value!eigen, vector!eigen.

Area keys

cell biology, enzyme kinetics, population dynamics, reaction kinetics.

Info

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Chapter 14

How many cytochromes?

Cytochromes are membrane proteins that contain a heme prosthetic group similar to that in hemoglobin or myoglobin. Therefore they have a large number of resonance forms, which can be made visible through their elaborate light absorption spectra. Differences in heme structure result in differences in absorption spectra as well as reduction potential, or tendency to accept an electron. Because of their role in cell energetics, it is important to determine the number of different cytochromes in a living cell, and their respective absorption spectra. The usual approach is to extract them from the membranes, purify them through e.g. electrophoresis and determine their spectra in solution. This procedure might strongly change the cytochromes. Below, we will describe how partial modelling can be used to unravel the different spectra of each cytochrome, from a table of extinction coefficients of an unknown mixture of membrane bound cytochromes for different electric potentials and wave lengths.

The modelling makes use of the fact that the reduced form of cytochomes absorb light several orders of magnitude better than the oxidized form. The model is then the Nernst equation for the potential with respect to the standard hydrogen electrode, E, as a function of the ratio of the concentration of oxidized cytochrome, c_o, and the reduced one, c_r:

$$E = E_0 + \ln\{c_o/c_r\}RT/F \tag{14.1}$$

where E_0 denotes the midpoint potential of the redox couple at pH 7.0 (in mV), R the gas constant ($8.314\,\mathrm{J\,K^{-1}mol^{-1}}$), T the absolute temperature and F the Faraday constant ($96.494\ \mathrm{J\ mV^{-1}mol^{-1}}$). So, at 298 K, $RT/F = 25.68\,\mathrm{mV}$. Obviously, we have that $c_o + c_r = c_+$, which is constant, so $c_o = c_+ - c_r$. Rearrangement of (14.1) gives

$$c_r = c_+[1 + \exp\{(E - E_0)/25.68\}]^{-1} \tag{14.2}$$

The absorption at a certain wave length λ_i, at a potential E_j, is assumed to be just the sum of the separated absorptions of the different cytochromes, plus and independent error in measurement. The expected extinction coefficients is thus

$$x_{ij} \;=\; \sum_s a_{is}p_{js} \text{ with} \tag{14.3}$$

$$p_{js} = [1 + \exp\{(E_j - E_{0s})/25.68\}]^{-1} \tag{14.4}$$

The extinction coefficients to be measured are taken to be

$$x_{ij} + \xi_{ij} \tag{14.5}$$

where the measurement errors ξ_{ij}'s are assumed to be independently normally distributed with a common variance σ^2. We will assume that there exists l different cytochromes, where l is a number chosen through a procedure still to be described. If we collect the coefficients in matrices, through $\mathbf{X} \equiv \{x_{ij}\}_{rk}$, $\mathbf{A} \equiv \{a_{is}\}_{rl}$, $\mathbf{P} \equiv \{p_{js}\}_{kl}$ and $bf\Xi \equiv \{\xi_{ij}\}_{rk}$, the expected extinction coefficients can be compactly written as

$$\mathbf{X} = \mathbf{A}\mathbf{P}^T + \mathbf{\Xi} \tag{14.6}$$

Through the introduction of a free parameter for the extinction of each cytochrome at a specified wave length, we do not assume any functional form for the absorption spectra. We buy this flexibility with a significant amount of parameters. For a table of rk measurements (i.e. extinction coefficients $\mathbf{Y} \equiv \{y_{ij}\}_{rk}$) with r wavelengths and k potentials, we have $(r+1)l + 1$ parameters (i.e. rl parameters $\mathbf{A}$, l parameters for $\mathbf{E} \equiv \{E0_s\}_l$ and σ^2). We can only hope to estimate all these parameters if $k \gg l$ and if the range of potentials covers the range of sufficiently different midpoint potentials to some extend.

We estimate the parameter values from the measurements on the basis of the maximum likelihood criterion. So, have to maximize the ln likelihood

$$\ln L(\mathbf{A}, \mathbf{E}, \sigma^2) = \frac{-rk}{2} \ln\{\pi\sigma^2\} + \frac{1}{2\sigma^2} \sum_{ij} (x_{ij} - y_{ij})^2 \tag{14.7}$$

as function of the listed arguments. The values for the $\mathbf{A}$ and $\mathbf{E}$ for which this maximum of $\ln L$ is reached, called $\hat{\mathbf{A}}$, $\hat{\mathbf{E}}$ and $\hat{\sigma^2}$ are the sought parameter values. We obtain them by solving

$$\frac{d \ln L(\hat{\mathbf{A}}, \hat{\mathbf{E}}, \hat{\sigma}^2)}{d\, a_{is}} = -\frac{1}{\hat{\sigma}^2} \sum_j (y_{ij} - \hat{x}_{ij}) \hat{p}_{js} = 0 \tag{14.8}$$

$$\text{for } i = 1, \cdots, r; s = 1, \cdots, l$$

$$\frac{d \ln L(\hat{\mathbf{A}}, \hat{\mathbf{E}}, \hat{\sigma}^2)}{d\, E_{0t}} = \frac{-1}{25.68\, \hat{\sigma}^2} \sum_{ij} (y_{ij} - \hat{x}_{ij}) \hat{a}_{it} \hat{p}_{tj} (1 - \hat{p}_{tj}) = 0 \tag{14.9}$$

$$\text{for } t = 1, \cdots, l$$

$$\frac{d \ln L(\hat{\mathbf{A}}, \hat{\mathbf{E}}, \hat{\sigma}^2)}{d\, \sigma^2} = \frac{-rk}{\hat{\sigma}^2} + \frac{1}{2\hat{\sigma}^4} \sum_{ij} (y_{ij} - \hat{x}_{ij})^2 = 0 \tag{14.10}$$

The caps on x and p indicate that $\hat{\mathbf{A}}$, $\hat{\mathbf{E}}$ and $\hat{\sigma}^2$ must be substituted in the defining equations (14.3) and (14.4). Equations (14.8) and (14.9) are also obtained using the least squares criterion for estimating the parameters. Because of (14.5), this model can be classified as a non-linear regression one. The solution of (14.8) is

$$\hat{\mathbf{A}} = \mathbf{Y}\hat{\mathbf{P}}^T(\hat{\mathbf{P}}\hat{\mathbf{P}}^T)^{-1} \tag{14.11}$$

The solution of (14.10) is

$$\hat{\sigma}^2 = \frac{1}{rk}\sum_{ij}(y_{ij} - \hat{x}_{ij})^2 \tag{14.12}$$

The solution of (14.9) is less easy to obtain. The leading factor can be omitted, of course, but that is all we can do simplifying (14.9). We have to solve it numerically. We define

$$f_t(\mathbf{E}) = \sum_{ij}(y_{ij} - x_{ij})a_{it}p_{tj}(1 - p_{tj}) \tag{14.13}$$

where we substitute (14.11) for the values $\mathbf{A}$ (which also occur in $\mathbf{X}$). We then find a solution for $\mathbf{E}$, through the Newton Raphson procedure, for $\mathbf{F} \equiv \{f_t\}_l$

$$\mathbf{E}_{i+1} = \mathbf{E}_i - [\mathbf{F}'(\mathbf{E}_i)]^{-1}\mathbf{F}(\mathbf{E}_i),\ i = 0, 1, \cdots \tag{14.14}$$

where the sequence of vectors $\mathbf{E}_i$, $i = 0, 1, \cdots$ converge to the sought vector $\hat{\mathbf{E}}$ after an appropriate choice for $\mathbf{E}_0$. The expression for the derivative of $\mathbf{F}$ with respect to $\mathbf{E}$, denoted by $\mathbf{F}'$ in (14.14), is extremely massive. This is one obvious place where a numerical evaluation makes life bearable. So we take

$$f'_{st}(\mathbf{E}) \simeq \left(f_s(E_{01}, \cdots, E_{0,t-1}, E_{0t} + d, E_{0,t+1}, \cdots, E_{0l}) - f_s(E)\right)/d$$

for some small chosen value for d. Note that for each iteration in (14.14), we have to calculate $\mathbf{A}$ in (14.11) $1 + l$ times to obtain $\mathbf{F}$ and $\mathbf{F}'$. The size of required computer memory and time depends on r, k and l. Because we were able to get explicit expressions for most parameters, i.e. $1 + rl$, only l parameters have to be obtained numerically. In practice this means that, provided that l is not too large, the calculations do not give rise to serious problems. We now discuss the way to determine l.

When we choose $l = 1, 2, \cdots$ we introduce rapidly more parameters, which results in an increasingly better fit, irrespective of the real number of cytochromes. This is reflected in the value of the ln likelihood function in the point of the maximum likelihood estimates, which is given by

$$\ln L_l(\hat{\mathbf{A}}, \hat{\mathbf{E}}, \hat{\sigma}^2) = \left(1 - \ln \pi\hat{\sigma}^2\right) rk/2 \tag{14.15}$$

where the index l is attached to indicate that L depends on l. In order to decide on the value for l, we study the increase in fit through the likelihood ratio statistic

$$\begin{aligned} \lambda(l) &\equiv 2\ln L_l(\hat{\mathbf{A}}, \hat{\mathbf{E}}, \hat{\sigma}^2) - 2\ln L_{l-1}(\hat{\mathbf{A}}, \hat{\mathbf{E}}, \hat{\sigma}^2) \\ &= \left(\ln \hat{\sigma}_l^2 - \ln \hat{\sigma}_{l+1}^2\right) rk \end{aligned} \tag{14.16}$$

Here, again, the index l is attached to $\hat{\sigma^2}$ to indicate that it depends on l. Application of the likelihood ratio theory learns that the proper value for l is found, when, for the first

time for increasing l, $\lambda(l)$ is not unlikely to represent a random trial from a χ^2 density with parameter $r+1$. This is decided when $\lambda(l)$ is less than the upper α-quantile for the chi-square density with parameter $r+1$, at probability of an error of the first kind of α. The strict application of the likelihood ratio theory is a bit problematic in this case, because the number of parameters is increasing with the number of wave lengths. It does not increase with the number of potentials, however.

After having determined l, this way, we can test the model through the residuals $\mathbf{Y} - \mathbf{X}$, which should represent random (independent) trials form a normal density. If the model fails the test, we could try to improve it by e.g. assuming that the error of measurement is proportial to the mean. We then arrive at a bit more complicated likelihood function, but no new estimation problems arise.

Figures 14.2 and 14.1 illustrate the application of the presented theory for *Escherichia coli*-data from [Wielink, 1986]. This bacterium appears to posses 4 cytochromes.

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Level key

medium

Method keys

variable!random, matrix, estimate!maximum likelihood, distribution!normal, function!likelihood, error!type 1, iteration!Newton Raphson, model!regression.

Area keys

cell biology.

Info

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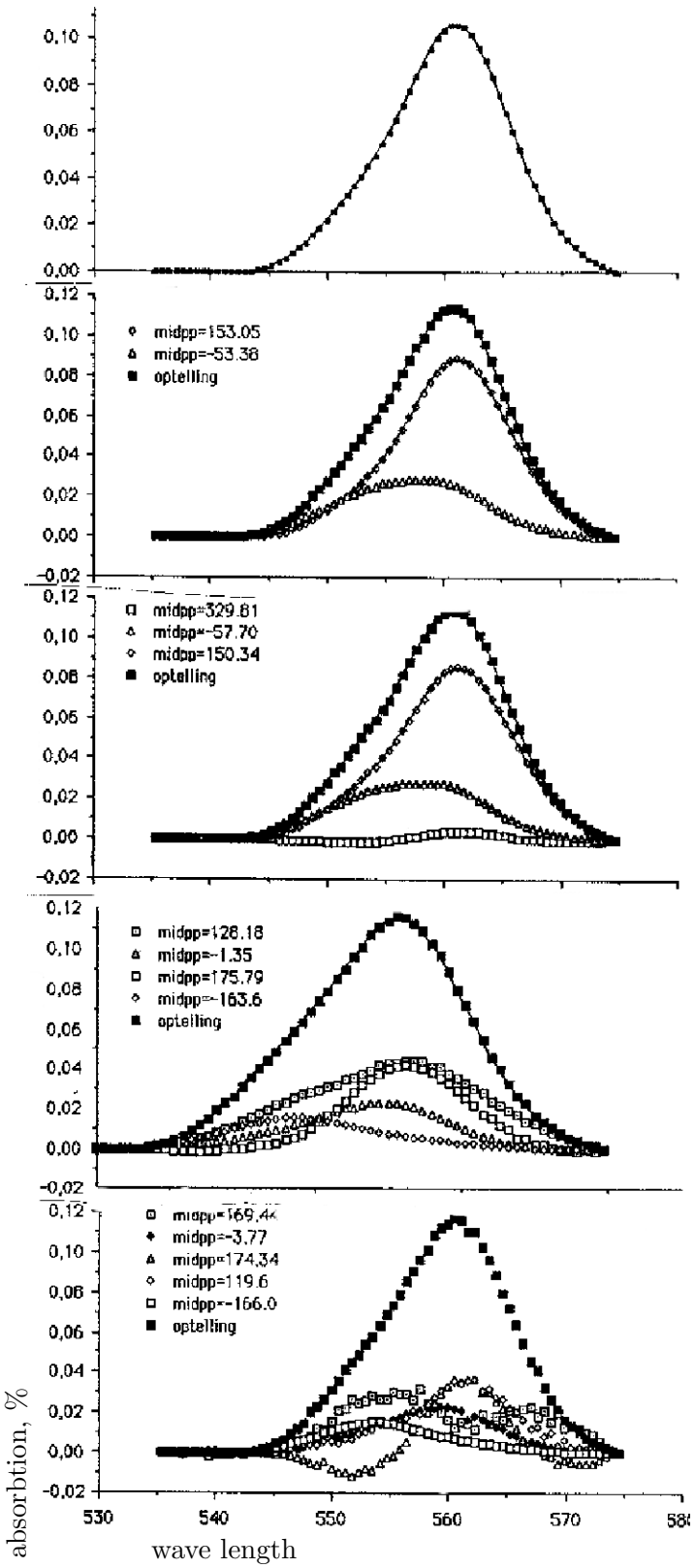

Figure 14.1: The estimated absorption spectra of the cytochromes of *E. coli*, assuming that it is a mixture of 1, 2, 3, 4 or 5 different cytochromes. The midpoint potentials are given.

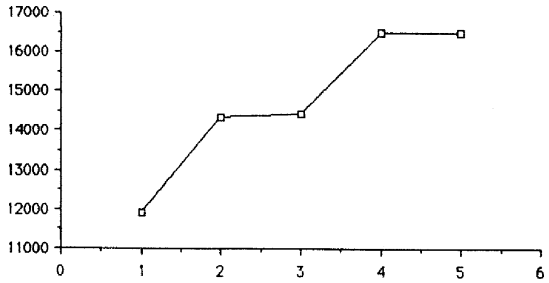

Figure 14.2: The plot of the supremum of the ln likelihood function, as a function of the number of different cytochromes. We should decide that there are 4 different cytochromes at $\alpha = 0.01$.

Chapter 15

A flock as shy as the shiest

Walking along the beach in winter, one is likely to meet a flock of sandpipers. When approaching, one bird usually grows nervous and the flock flies off. The minimum distance tends to increase with the size of the flock. Approach at close range seems only possible for solitairy individuals. Social effects, like reassurance for being only one of the many potential victims of the approaching 'predator', can only be studied after we know what to expect when the individuals are independent.

Suppose the critical distance, d_1, below which an individual will fly off in a certain circumstance is characteristic for that individual, and can be conceived as a random trial from some probability density, $f_1(x)\,dx$. The probability, $F_m(x)$, that the flock of size m does not fly off at distance x equals the probability that all m critical distances less than x, so

$$P\{d_m < x\} \equiv F_m(x) = F_1^m(x) \tag{15.1}$$

where $F_1(x)$ is the distribution function of the critical distance for a single individual, i.e. $F_1(x) = \int_0^x f_1(y)\,dy$. The derivation of densities of extremes is easy by using distribution c.q. survivor functions. When evaluating expected values, we use the property for non-negative random variables, that the expected values equals the integral (c.q.sum) over the survivor function. The expected critical distance is thus

$$\mathcal{E}d_m = \int_0^\infty (1 - F_m(x))\; dx = \int_0^\infty (1 - F_1^m(x))\; dx \tag{15.2}$$

Since $0 < F_1(x) < 1$, we know that $\mathcal{E}d_m$ must be a non-decreasing function of m. We have to specify F_1, however, before we can tell more about the behaviour of $\mathcal{E}d_m$ as function of m.

Suppose that d_1 follows a nearest neighbour distribution, so

$$F_1(x) = 1 - e^{-sx^2} \tag{15.3}$$

where s is a parameter (the species-specific "shyness-parameter"). Then,

$$\mathcal{E}d_m \;=\; \int_0^\infty \left(1 - \left(1 - e^{-sx^2}\right)^m\right)\; dx$$

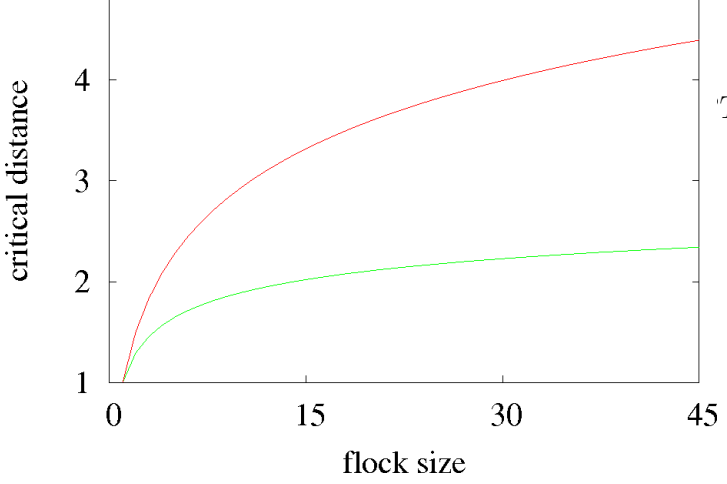

Figure 15.1: The expected critical distance as a function of flock size in units of that of a single individual. The critical distance of a single individuals is assumed to follow a nearest neighbour (green) or an exponential distribution (red).

$$\begin{aligned} &= \int_0^\infty \left(1 - \sum_{i=0}^{m} \binom{m}{i} \left(-e^{-sx^2(m-i)}\right)\right) dx \\ &= \sum_{i=0}^{m-1} \binom{m}{i} (-1)^{m-i+1} \int_0^\infty e^{-sx^2(m-i)}\, dx \\ &= \sum_{i=0}^{m-1} \binom{m}{i} \frac{(-1)^{m-i+1}\sqrt{\pi}}{\sqrt{8s(m-i)}} \\ &= \sqrt{\pi/8s} \sum_{i=1}^{m} \binom{m}{i} (-1)^{i+1}/\sqrt{i} \end{aligned} \tag{15.4}$$

So

$$f(m) \equiv \mathcal{E}d_m \,/\, \mathcal{E}d_1 = \sum_{i=1}^{m} \binom{m}{i} (-1)^{i+1}/\sqrt{i} \tag{15.5}$$

A plot of $f(m)$ against m is given in Fig.15.1. We see that, although $f(m)$ does not have an asymptote, because $F_1(x)$ approaches 1 asymptotically, it increases very slowly for m larger than 8.

If we choose an exponential distribution for d_1, so we replace (15.3) by

$$F_1(x) = 1 - \exp -tx \tag{15.6}$$

we find

$$\mathcal{E}d_m = \int_0^\infty \left(1 - \left(1 - e^{tx}\right)^m\right) dx = t^{-1} \sum_{i=1}^{m} \binom{m}{i} (-1)^{i+1}/i \tag{15.7}$$

So

$$f(m) = \mathcal{E}d_m/\mathcal{E}d_1 = \sum_{i=1}^{m} \binom{m}{i} (-1)^{i+1}/i = \sum_{i=1}^{m} 1/i \tag{15.8}$$

This one has not an asymptote either, but it levels off less rapidly. (see Fig.15.1) This is because the exponential density has a thicker tail compared to the nearest neighbour one.

The first one is proportial to $\exp\{-tx\}$, while the second one is proportial to $\exp\{-sx^2\}$. Tail thickness is thus closely connected with the expected value of the extreme, as function of the number over which the extreme is taken. Indeed, for $F_1(x) = (x > u)$, we have $\mathcal{E}d_m = u$, irrespective of m.

When walking on the beach, we fail to notice that large flocks are much shier than small ones, this does not automatically indicate that their is social interaction, apart from flie when the shiest flies. In order to detect such interaction, we first have to identify the critical distance distribution for single individuals.

Level key

basic

Method keys

variable!random, function!survivor, function!probability density, variable!random, function!distribution, expectation, value!maximum.

Area keys

behavioural sciences

Info

Filename: ex015; Date: 1989/07/01; Author: Bas Kooijman

Chapter 16

The opening and closing behaviour of ion channels

From a cell physiological point of view, the mechanism of the opening and closing of ion channels in nerve cells is very important. However, it is not so easy to perform experiments at molecular level, so these mechanisms must be inferred indirectly from measurements of total cell performance. It is possible to measure the electrical flux between two clamps attached to a dendrite of a single cell. It varies somewhat in time, and the first question is: can we make use of these variations in time to disentangle the opening and closing of individual channels? With aid of a model for the behaviour of these channels, it is possible indeed.

The argument runs as follows. Assume that the electrical flux is proportional to the number of ion channels that are open. Assume further that the probability that a randomly chosen closed channel will open in an incremental time interval Δt equals $\lambda \Delta t$. Similarly, the probability that a randomly chosen open channel will close in that interval is assumed to be $\mu \Delta t$. For the moment we will assume that the probability rates λ and μ are constant and that the probability that a channel opens as well as closes in Δt is negigibly small. When N denotes the number of channels between the clamps, n the number of channels that are open and t the time, the probability that there are n open channels at time t is given by

$$\begin{aligned} P_n(t+\Delta t) &= P_n(t)(1-\mu\Delta t)^n(1-\lambda\Delta t)^{N-n} + \\ &\quad P_{n-1}(t)(1-\mu\Delta t)^{n-1}(1-\lambda\Delta t)^{N-n}\lambda\Delta t(N-n+1) + \\ &\quad P_{n+1}(t)(1-\mu\Delta)^n\mu\Delta t(n+1)(1-\lambda\Delta t)^{N-n-1} \end{aligned} \tag{16.1}$$

To simplify the notation, we assume that $P_{<0}(t) = P_{>N}(t) = 0$. If we let Δt approach to zero, we arrive at

$$\frac{d}{dt}P_n(t) = -P_n(t)(\mu n + \lambda(N-n)) + P_{n-1}(t)\lambda(N-n+1) + P_{n+1}(t)\mu(n+1) \tag{16.2}$$

This equation describes the opening and closing behaviour of ion channels, in which we consider N, λ and μ as parameters to be estimated from a continuous registration of the

electrical flux, so the number of open channels. With a very small probability, all channels are open at a given time, so when we wait long enough, the maximum flux over a very long time bears information about the number of channels N. However, it is very hard to keep conditions constant over such long a period. Therefore we will not make use of this possibility. What we will do is use the mean, the variance and the autocovariance function to lead us to the three parameters. The mean and variance can be deduced from the equilibrium distribution for n, i.e. the case where $\frac{d}{dt}P_n(t) = 0$. Using (16.2) we obtain

$$P_n(\infty) = \left(\begin{array}{c} N \\ n \end{array} \right) \left(\frac{\lambda}{\lambda+\mu} \right)^n \left(\frac{\mu}{\lambda+\mu} \right)^{N-n} \tag{16.3}$$

This we recognize as the binomial distribution with mean $M = \frac{\lambda N}{\lambda+\mu}$ and variance $V = \frac{\lambda\mu N}{(\lambda+\mu)^2}$.

The straightforward way to obtain the covariance function is first to solve $P_n(t)$ from (16.2) from the initial condition $P_m(0) = 1$. Let us call this solution $P_{n,m}(t)$. When we denote the equilibrium distribution by P_n, the (equilibrium) autocovariance function is given by $C(\tau) = \sum_{m,n} mnP_mP_{n,m}(\tau) - M^2$. The problem now is that it is very laborious to obtain $P_{n,m}(\tau)$. In this case it is helpful to note that we do not need it explicitely, we only need it as a weighted sum over all n and m. We therefore try to convert the set of differential equations of all the $P_n(t)$'s into one for the autocovariance function. We note that $\frac{d}{dt}C(\tau) = \sum_{m,n} mnP_m\frac{d}{dt}P_{n,m}(\tau)$, with $C(0) = V$. From (16.2), we obtain

$$\begin{aligned} \sum_{m,n} mnP_m\frac{d}{dt}P_{n,m}(\tau) &= -\sum_{m,n} mnP_mP_{n,m}(\tau)(\mu n + \lambda(N-n)) + \\ &\quad \sum_{m,n} mnP_mP_{n-1,m}(\tau)\lambda(N-n+1) + \\ &\quad \sum_{m,n} mnP_mP_{n+1,m}(\tau)\mu(n+1) \end{aligned} \tag{16.4}$$

After some manipulation, we obtain the simple expression

$$\frac{d}{dt}C(\tau) = -C(\tau)(\lambda+\mu) \tag{16.5}$$

which leads to $C(\tau) = V\exp\{-(\lambda+\mu)\tau\}$. So the autocovariance function decreases exponentially with rate $\lambda+\mu$.

It is instructive to relate this model formulation with a very simple deterministic one, where we assume that n is large enough to allow a continuous approximation. When the opening of channels is proportional to the number of closed channels and the closing of channels is proportional to the number of open channels, we have $\frac{d}{dt}n = \lambda(N-m) - \mu n = \lambda N - (\lambda+\mu)n$. The solution is $n(t) = M - (M-n(0))\exp\{-(\lambda+\mu)t\}$, and we recognize $(\lambda+\mu)^{-1}$ as the relaxation time.

Back to the stochastic model now. The simplest way to proceed is to uncover $\lambda+\mu$ from $C(\tau)$. We can do this e.g. by plotting $\ln C$ against time and fit a straight line. Although this procedure must be classified as "quick and dirty", it is not at all obvious

how to formulate a "clean" procedure. Next we multiply $\lambda + \mu$ by V/M and obtain μ. Subsequently we uncover λ and N.

The ability to disentangle the opening from the closing rate can be very valuable in the experimental research to which (environmental) factors influence both mechanisms. The constraint that λ and μ are constant can be relaxed to the constraint that the rate at which they vary is small with respect to $\lambda + \mu$.

Level key

medium

Method keys

variable!random, process!birth and death, distribution!binomial, function!correlation, state!steady.

Area keys

molecular biology, neuro biology, cell biology.

Info

Filename: ex016; Date: 1990/09/02; Author: Bas Kooijman

Chapter 17

Shape constraints for isomorphs with permanent exoskeletons

Isomorphism is an important property, which can keep life simple for the researcher as well as the organism: When the relative size of the different organs, uncluding the secreting ones, does not change during development a number of regulating mechanisms does not have to change as well.

When isomorphic animals change their outer surface area during development and growth in a way that includes transformation, there are little constraints for their shape. However, when they only add new surface area, leaving the existing surface area untouched, there are rather strong constraints for their shape. The present conjecture is that they are composed of one or more subunits that must belong to one of two 3 parameter families of logarithmic spirals, which are described here.

We focus on animals starting from an infinitesimal size. Theory on energy uptake and use for isomorphs predicts that, when feeding conditions do not change, there exists an ultimate size, which we now use to define the shape. More in particular, we define a three dimensional closed mouth curve, $x(0)$, which is part of the outer surface area and a center point, $f(0)$, which is part of the logarithmic spiral at argument value $l = 0$.

The logarithmic spiral is given by

$$f(l) = c^{l/2\pi}(b, a\sin -l, a\cos -l) \tag{17.1}$$

with $l \in (-\infty, 0]$ and $c > 0$ (see Figure 17.1). It has the important property that $f(l+h) = c^{h/2\pi}R(-h)f(l)$ where R is a rotation matrix around the x-axis

$$R(h) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos h & \sin h \\ 0 & -\sin h & \cos h \end{pmatrix}$$

The mouth curve for argument l is given by

$$\begin{aligned} x(l) &= f(l) + c^{l/2\pi}R(-l)(x(0) - f(0)) \\ &= c^{l/2\pi}((b, a\sin -l, a\cos -l) + R(-l)(x(0) - (b, 0, a)) \end{aligned} \tag{17.2}$$

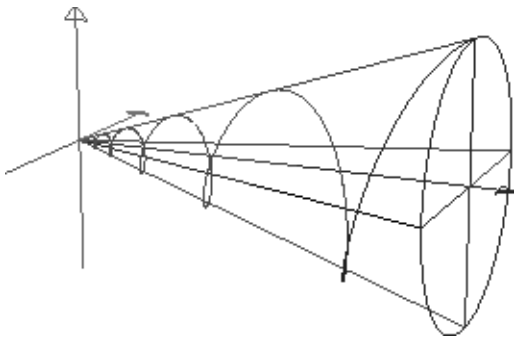

Figure 17.1: The logarithmic spiral lies on a cone around the x-axis with vertex at the origin, and tangent a/b of the divergencing angle with respect to the axis. The normalized direction vector of the spiral from the vertex, $(a^2+b^2)^{-1/2}(b, a\sin -l, a\cos -l)$, describes a circle in the (y,z)–plane at x–value $b/\sqrt{a^2+b^2}$, when we let argument l walk.

The parameters (a,b,c) plus mouth curve together determine the shape.

The curves $x(l)$, describe the outer surface area of the animal, *i.e.* its exosketelon. For isomorphism, it should occupy only the interval $(l-h,l)$ for some $h<\infty$, if $a\neq 0$.

A defining property of isomorphism is that all length measures depend on size in the same way. It is not difficult to show that $\|x_1(l+h)-x_0(l)\| \propto c^{l/2\pi}$, for some h, and $x_0(0), x_1(0)\in x(0)$, where the proportionality constant does not depend on l.

The present class of morphs is too wide for being physically possible. First of all we must exclude negative growth at the mouth curve. The orientation of the mouth curve should be such that a mouth opening results and the shape may not 'bite' itself when walking along the spiral. However, it is extremely tedious to translate these physical contraints into mathematical ones.

In order to construct a particular morph, it might be easy to first orientate the mouth curve, $x^*(0)$, such that the centre point is at $(0,0,0)$, the vertex has a x-value of 0 and the logarithmic spiral starts off in the y-direction, *i.e.* $f'(0)=(0,1,0)$, with $f'(l)\equiv \frac{d}{dl}f(l)/\|\frac{d}{dl}f(l)\|$. We then back transform $x^*(0)$, to $x(0)$ according to $x(0)=(b,0,a)+Qx^*(0)$, where the rotation matrix Q is given by $Q(0,1,0)=(a^2+(a^2+b^2)(\frac{\ln c}{2\pi})^2)^{-1/2}(b\frac{\ln c}{2\pi}, a, a\frac{\ln c}{2\pi})$.

Uptil now, no explicit reference to time has been made. When we assume that a length measure of the animal follows a von Bertalanffy growth pattern, *i.e.* $1-e^{-\gamma t}$ for $t\in(0,\infty)$, we have the relation $c^{l/2\pi}=1-e^{-\gamma t}$. So, $l=\frac{2\pi}{\ln c}\ln\{1-e^{-\gamma t}\}$. This is realistic when food density and temperature remain constant. In winter, when growth ceases in the temperate regions and calcification partially continues in molluscs, a thickening of the shell occurs, which is visible as a ribble. Neglecting the gradual transitions between the seasons, we expect these rings thus at $l=\frac{2\pi}{\ln c}\ln\{1-e^{-\gamma i}\}$, $i=1,2,3,\cdots$, when the unit of time is one growth season. In principle, this offers the possibility to the determine the von Bertalanffy growth rate γ from a single shell found dead along the beach.

Shell height is sometimes taken as a characteristic length of the animal. Since the living animal should be confined to a fixed interval, this length measure includes part of the exoskeleton, which is abandoned. However the length of the interval has no consequences of the shape of the exoskeleton. Irrespective of the actual interval, we can take its length very large, which makes the distance from $x(l-h)$ to the vertex negligibly small. Therefore, shell height will approximate a von Bertalanffy growth curve, when food density and temperature remain constant.

When $a = 0$, so $f(l) = c^{l/2\pi}(b, 0, 0)$, a second family of isomorphs is given by

$$x(l) = c^{l/2\pi}((b, 0, 0) + R(dl)(x(0) - (b, 0, 0)) \tag{17.3}$$

where d is a tordation parameter. For $d = 1$, this family belongs to the first one.

The models can generate complex shapes. Most shapes are simple and correspond with special cases. For $d = 1$ and $b = 0$, we arrive at shapes like *Planorbis* and *Nautilus*. When $a \to 0$, the logarithmic spiral straightens to a line like in *Patella*. When $b \to 0$ as well, we arrive a growing sheet.

Animals like bivalves and brachiopods have two logarithmic spirals, sharing the same mouth curve. One turns clockwise, one anti–clockwise. This can be obtained by deleting the minus signs in (17.1), (17.2) and (17.3). There is no need for both spirals to be identical or symmetric to produce isomorphs. In many species they are different in fact. Isomorphic shapes are possible with more compounds, like in goose barnacles.

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Raup, D. M. (1967). Geometric analysis of shell coiling: Coiling in ammonoids. *J. Paleon.*, 41:43–65.

Level key

medium

Method keys

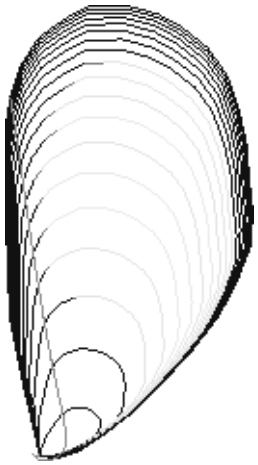
cosine, sine, matrix!rotation.

Area keys

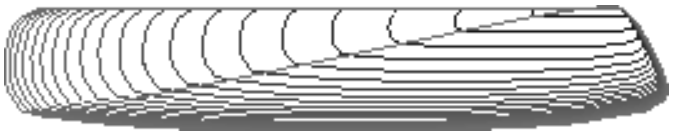
morphology

Info

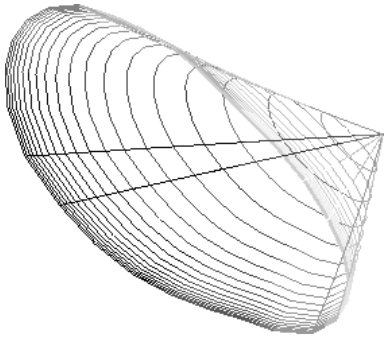
Filename: ex0017; Date: 1991/02/12; Author: Bas Kooijman



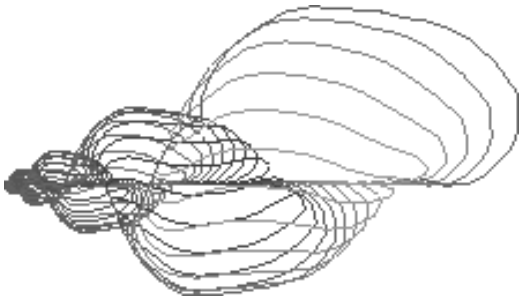
Mytilus, a=0.01, b=0.01, c=10^4



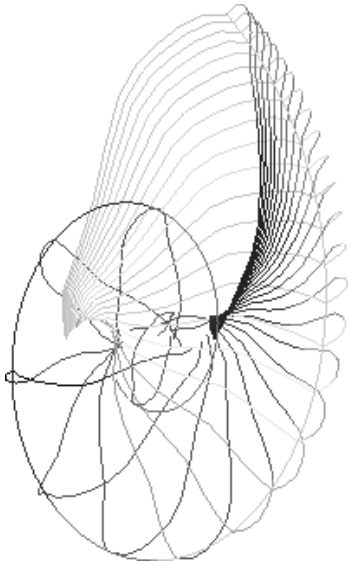
Ensis, a=0, b=0, c=10^5



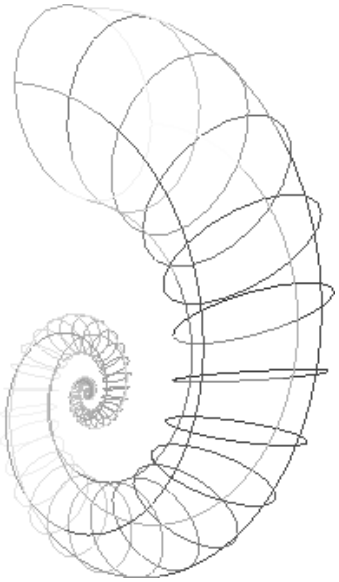
Patella, a=0, b=3, d=0



Lymnaea, a=0.01, b=3.5, c=2



Nautilus, a=0, b=0, c=3



Spirula, a=3, b=0, c=5

Chapter 18

The basis of colours

Colour is a human sensation which has little to do with plain physics and a lot with biology. Every very small (part of an) object around us emits electro magnetic energy, which meets the eye. Its image is projected onto the retina. Because of the rapid elliptical movements of the eye, the image describes an elliptical trajectory on the retina. Let $e(\lambda)$ be the energy density at wavelength λ of the image, so $\int_{\lambda_1}^{\lambda_2} e(\lambda)\, d\lambda$ is the total amount of energy between wave lengths λ_1 and λ_2. Due to the ellitical movements of the eye, the image meets different sensors for electromagnetic radiation, that have different sensitivities for the different wave lengths. For simplicity's sake we here assume that the signal output of the sensor is proportional to the input. Let $w_i(\lambda)$ be the energy signal conversion of sensor i at wavelength λ, so $s_i = \int_0^\infty e(\lambda) w_i(\lambda)\, d\lambda$ is the signal of sensor i, if all the separate contributions of the different wave lengths just add up. The actual signal is approximately hyperbolically transformed, like $\frac{s_i}{K+s_i}$, but this is at present of no importance.

It seems that most of us have got three different types of sensors. So, the total signal we receive can be represented as $\vec{s} \equiv (s_1, s_2, s_3)$, which we call sensation.

The lower end of the sensitivity range is around 420 nm, where we have a sensation which we call violet, and an upper limit of 67 nm, where we have a sensation which we call red. The range has no sharp limits. Every possible sensation can be represented by a point in the three dimensional sensation space. The sensors have a considerable overlap in sensitivities. Therefore it is not possible to stimulate only one sensor, without stimulation the others to some extend. This means that not all points in the sensation space can be reached in practice. Suppose that there exists a fixed minimum threshold of the signal we can detect, the range depends on the energy input E, which we experience as intensity. The relative firing rate of the three sensors we experience as colour.

Any choice of three different colours (i.e. sensations)

$$\vec{c}_i = c_{1i}\vec{s}_1 + c_{2i}\vec{s}_2 + c_{3i}\vec{s}_3 \text{ with } i = 1, 2, 3 \tag{18.1}$$

can in principle be used as a basis for the sensation space, as long the corresponding three vectors are not in the same plane. So all colours, like white, can be obtained by a linear combination of that three colours. That is to say, when we admit subtraction. The sensation $\vec{a}_s = (a_1, a_2, a_3)$ in fact means $a_1\vec{s}_1 + a_2\vec{s}_2 + a_3\vec{s}_3$ when we use the sensors $\vec{s}_1$, $\vec{s}_2$, $\vec{s}_3$

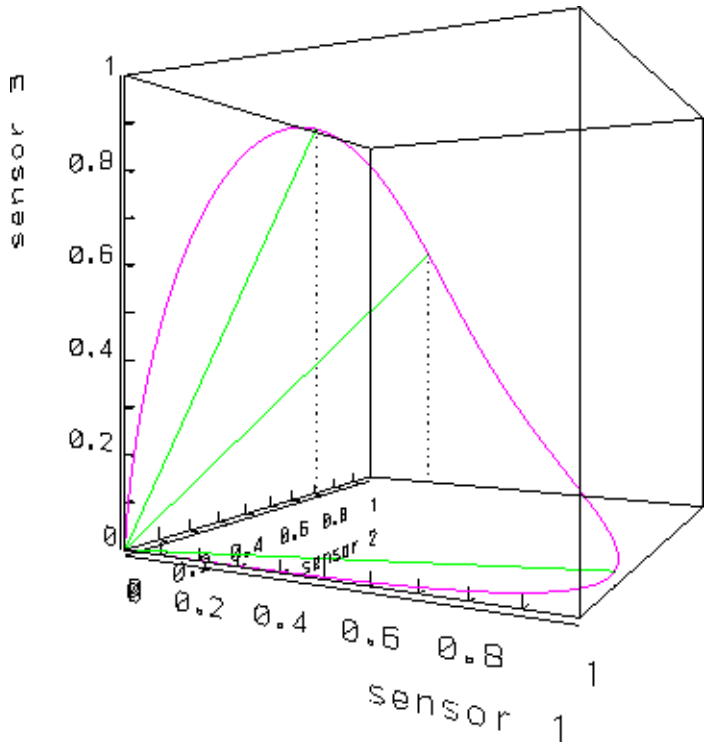


Figure 18.1: When a source emits monochromatic electro-magnetic radiation at wavelength λ_j and energy level E, we have $e(\lambda)\,d\lambda = E(\lambda = \lambda_j)$. The sensation is thus $\vec{s}(\lambda_j) = E(w_1(\lambda_j), w_2(\lambda_j), w_3(\lambda_j))$. When we let λ_j walk from $0 \to \infty$, the sensation $\vec{s}(\lambda_j)$ describes a curve in the three dimensional space spanned up by the sensors. For short as well as long wave lengths, all three sensors are insensitive. Therefore, the curve starts and ends at the origin, where we have sensation "black".

as a basis. It is equivalent to the sensation $\vec{a}_c = (\alpha_1, \alpha_2, \alpha_3)$, which means $\alpha_1\vec{c}_1 + \alpha_2\vec{c}_2 + \alpha_3\vec{c}_3$ when we use the three colours $\vec{c}_1$, $\vec{c}_2$, $\vec{c}_3$ as a basis. Because both expressions are equivalent, we must have that $C\vec{\alpha} = \vec{a}$, or $\vec{\alpha} = C^{-1}\vec{a}$, where

$$C \equiv \begin{pmatrix} c_{11} & c_{12} & c_{13} \\ c_{21} & c_{22} & c_{23} \\ c_{31} & c_{32} & c_{33} \end{pmatrix} \tag{18.2}$$

However, not every choice of the colours as a basis is equally usefull. In the first place, subtraction is cumbersome from a physical point of view. Small errors in the signals of the three sensors are enlarged when the colours are close to each other.

It is useful to realize that the eye reduces the energy density function $e(\lambda)$, consisting of an infinite number of "data- points" to just three values collected in $\vec{s}$. Therefore many different energy density functions are mapped into the same sensation (i.e. colour). It also implies that there are many ways to combine different colours to produce a particular one. The study of different types of colour blindness has contributed a lot in our understanding of colour perception. A particular type is the absence of one sensor, which means that the perception is in two rather than three dimensions. Some species of animals have more than three sensors for electro magnetic radiation. They must be able to distinguish between different sources, that look the same for us.

Level key

basic

Method keys

vector, matrix.

Area keys

physiology

Info

Filename: ex018; Date 1991/04/24; Author: Bas Kooijman