This addendum provides short answers to the questions in the ebook “Biological Modeling of Populations”. Since many of the questions can be approached by using several different models, these answers are typically just one of the many possible answers. When you get stuck on a particular question, you may peek into its answer to obtain a hint enabling you to proceed. When you are done with a question, use this addendum to check if your own answer is correct and complete. Do not give up if your own answer is different, as it could very well be correct (and hopefully even better). Please report errors and suggestions for improvement, for instance by emailing me Rob de Boer at r.j.deboer@uu.nl.

Ebook publicly available at:
https://tbb.bio.uu.nl/rdb/books/bm.pdf and ./bmAnswers.pdf
Answers to Chapter 2

Question 2.1. Red blood cells
Figure made with blood.R:

(a) Since the production of red blood cells relies on a source we use Eq. (2.3), and rewrite that as \( dN/dt = m - dN \).
(b) Donating blood corresponds to Panel (a).
(c) Receiving blood corresponds to Panel (b).

Question 2.2. Pesticides on apples
Figure made with the previous version of Grind:

(a) An expected time course is depicted in Panel (a).
(b) The pesticide concentration would approach its steady state \( \bar{P} = \sigma/\delta \).
(c) The model becomes \( dP/dt = -\delta P \) with the initial condition \( P(0) = \sigma/\delta \). Solving \( P(0)/2 = P(0)e^{-\delta t} \) yields \( t_{1/2} = \ln[2]/\delta \).
(d) From \( dP/dt = 2\sigma - \delta P \) with \( \bar{P} = 2\sigma/\delta \), one obtains the same \( \ln 2/\delta \) days for the half life.
(e) From \( 50 = \ln 2/\delta \) one obtains \( \delta = 0.014 \) per day.

Question 2.3. Bacterial growth
(a) The doubling time is defined as \( t = \ln[2]/r \).
(b) Since the neutrophil have to prevent bacterial growth we require that \( dB/dt < 0 \). Solving \( dB/dt = rB - kNB = 0 \), and neglecting the trivial \( B = 0 \) solution, we obtain \( N = r/k \) for the critical number of neutrophils.
(c) The dimension of \( r \) is per hour. Since the total term \( kNB \) has dimension “number of bacteria per ml per hour”, the dimension of \( k \) should be “per neutrophil per ml per hour”. This can also be checked from the expression \( N = r/k \) that should be “neutrophils per ml” on the both the left- and right-hand side.
(d) “bacteria per neutrophil per hour”. This is the maximum number of bacteria that one neutrophil can encounter and kill per hour.
e. The critical number now depends on the concentration of bacteria, i.e., solving $dB/dt = rB - \frac{kNB}{N+h} = 0$ for $N$ now gives $N = \frac{r}{k}(h+B)$. This is a straight line with slope $r/k$, intersecting the vertical axis at $N = rh/k$. Thus, the larger the infection, the more neutrophils are required. Note that this line is a nullcline: below this line $dB/dt > 0$, and above it $dB/dt < 0$.

f. $h$ has the dimension number of bacteria per ml. When $B = h$ the model is $dB/dt = rB - kN/2$ saying the neutrophils are killing at a rate $k/2$, i.e., half their half-maximal killing rate.

Question 2.4. Physics

a. The dimension of the velocity, $v$, is m/s and that of the acceleration, $a$, is m/s$^2$, which makes perfect sense.

b. For the plastic we write $dp/dt = k(t) = at + k(0)$, and the corresponding solution is $p(t) = \frac{1}{2}at^2 + k(0)t + p(0)$.

c. No, the amount of plastic will continue to increase at an accelerating rate.

Answers to Chapter 3

Question 3.1. Carrying capacity

a. The per capita birth rate is minimal when a population approaches its carrying capacity.

b. the per capita death rate is maximal when a population approaches its carrying capacity.

c. The individual well-being is expected to be best in an expanding population: the per capita birth rate is maximal and the per capita death rate is minimal.

d. With $dN/dt = rN[1 - N/(k\sqrt{N})] = 0$ one obtains the carrying capacity from $N/(k\sqrt{N}) = 1$ or $\sqrt{N} = k$ giving $\bar{N} = k^2$ which is still a finite carrying capacity, at which circumstances are poor. For the best circumstances the population has to remain below its carrying capacity.

Question 3.2. Freitas

a. No, the steady state of $dB/dt = m - dB = \alpha P - dB$ is $\bar{B} = \frac{\alpha P}{d}$. In such a model the number of peripheral B cells remains proportional to the number of bone marrow precursors, $P$.

b. For instance with density dependent death, $dB/dt = m - dB(1 + eB)$, or with density dependent production, $dB/dt = m/(1 + eB) - dB$, because with such a negative density dependence the steady state, $\bar{B}$, will depend less than proportional on $m = \alpha P$. Actually, the steady state of both density dependent models is solved from $m - dB - deB^2 = 0$, i.e.,

$$\bar{B} = \frac{d \pm \sqrt{d^2 + 4edm}}{-2ed} \quad \text{with one positive root} \quad \bar{B} = \frac{\sqrt{d^2 + 4edm}}{2ed} - \frac{1}{2ed},$$

in which we see that steady state depends on the square root of the source $m = \alpha P$. Thus both models allow for some of the saturation observed by Agenes et al. [1], but do not predict a plateau at large numbers of progenitors. You may want to try alternative models starting with the Grind model provided as agenes.R.

c. Yes clearly, in the absence of homeostasis the steady number of peripheral B cells is proportional to the number of bone marrow precursors, and in the data it is not.

d. No, it is accounting for a steady state, but not for density dependent population regulation.

Question 3.3. Overfishing herring

Figure made with the previous version of Grind:
a. Plotting \( \frac{dN}{dt} = f(N) = rN(1 - N/K) \) as a function of \( N \) (or \( y = rx(1 - x/K) \) as function of \( x \)), delivers a parabola crossing the horizontal axis at \( N = 0 \) and \( N = K \). See Panel (a).

b. The maximum of the function, \( f(N) = rN - rN^2/K \), is found by setting its derivative, \( \partial_N f = r - 2rN/K \), to zero. This delivers \( \bar{N} = K/2 \) (see Panel (a)). Substituting this maximum into the population growth function, one obtains the maximum population growth of \( f(\bar{N}) = rK/4 \).

c. The optimal population size is the one yielding maximum growth, i.e., \( N = K/2 \). At this optimal density, the total population growth, \( rK/4 \), could in principle be harvested.

d. We just add the maximum harvest as a negative term to the logistic growth model: \( \frac{dN}{dt} = rN(1 - N/K) - rK/4 \).

e. See Panel (b): at the maximum harvest there is a steady state where \( \frac{dN}{dt} = 0 \) at \( N = K/2 \). Starting at \( N = K \) and allowing for this maximum harvest, one would mathematically expect to approach this equilibrium. However, this steady state is not structurally stable, because any disturbance of the population size, bringing it below the level \( N = K/2 \), will let the fish go extinct, because the population enters the basin of attraction of \( \bar{N} = 0 \).

f. Harvesting less than the maximum yield allows for a structurally stable population size. See Panel (c). The population remains vulnerable to extinction by large perturbations due to the saddle point at low population densities. In the computer practical you will revisit this problem and discover that by catching an optimal fraction of the population one can on average catch this maximum yield, without threatening the population with extinction.

**Question 3.4. Biofilm**

Figures made with the model biofilm.R:

a. The function \( y = \frac{bx}{h + x} \) is an increasing saturation function intersecting the vertical axis in the origin, and the function \( y = d + ex \) is a straight line intersecting the vertical axis in \( y = d \); see Panel (a). When \( d < b \) these lines tend to intersect in two points, where the per capita birth rate equals the per capita death rate. The steady state at low population densities is
unstable, and the one at high densities corresponds to the stable carrying capacity.

b. Because the birth function goes from quadratic to linear, and the death function from linear to quadratic, these tend to intersect three times: in the origin, at a low density and at a high density. See Panels (b) and (c) where (b) is a zoom-in at low population densities.

c. We therefore find three steady states, with a stable origin and a stable carrying capacity, and a saddle point in the middle defining the population threshold corresponding to an Allee effect.

d. When the biofilm enhances survival, one should decreases the death rate, e.g., \( \frac{dB}{dt} = \frac{bB}{1+B/k} - \frac{dB}{1+B/h} \), where we have put the negative density dependence in the birth rate to allow for a carrying capacity (and the Allee effect in the death rate). The per capita death rate is \( d \) when the population is small, decreases to \( d/2 \) when \( B = h \), and approaches zero when \( B \to \infty \).

Question 3.5. Stem cells

The Figure was made with the model `stem.R`:

a. Defining \( p \) as the division rate, and \( d \) as a death rate, a simple model would be \( \frac{dS}{dt} = pS(1 - S/K) - dS \), where we could define a time scale of days, i.e., the dimension of \( p \) and \( d \) are \( d^{-1} \), and that of \( K \) is cells. No, the size of the substrate naturally limits the number of stem cells. Note that this equation corresponds to the logistic growth model of Eq. (3.6).

b. Solving \( \frac{dS}{dt} = 0 \) gives the non-trivial solution \( \bar{S} = K(1 - \frac{d}{p}) \), which is smaller than \( K \) because sites are continuously freed up by cell death.

c. Because the fraction \( S/K \) of the stem cells differentiates one obtains \( \frac{dD}{dt} = \frac{p}{K}S^2 - \delta D \).

d. The production rate is \( \frac{p}{K}S^2 \), which has the parabolic form of \( y = ax^2 \). Note that this despite the quadratic form this production has a correct dimension cells \( d^{-1} \) because \( p \) has a dimension \( d^{-1} \), and \( K \) cells. The production rate remains bounded, however, because there can be no more than \( \bar{S} = K(1 - \frac{d}{p}) \) stem cells, i.e., the maximum production is \( pK(1 - \frac{d}{p})^2 \) cells \( d^{-1} \).

e. The \( \frac{dS}{dt} = 0 \) nullcline is given by \( \bar{S} = K(1 - \frac{d}{p}) \) and the \( \frac{dD}{dt} = 0 \) nullcline by \( D = \frac{p}{K\delta}S^2 \), which is a parabola going through the origin (see the Figure). Since \( \frac{dD}{dt} > 0 \) when \( S \) is large and \( D \) is small the differentiated cells increase on the right-hand side of their nullcline. Stem cells increase below their steady state.

Question 3.6. Generalized logistic growth

a. The per capita growth term in the standard logistic equation is of the form \( r(1 - N/K) = r - kN \), where \( k = r/K \). Summing per capita birth and death rates of the form \( b(1 - N/k_b) \) and \( d(1 + N/k_d) \), respectively, also yields a per capita growth rate of the form \( r - kN \), where \( r = b - d \) and \( k \) is a combination of all four parameters.

b. This would be a per capita birth rate of the form \( b(1 - (N/k)^m) \), which is concave when \( m > 1 \) (like blue red line in Fig. 3.3c), and convex when \( m < 1 \) (like the green line in Fig. 3.3c). The concave shape would mean that the negative density dependence on the birth process kicks
in at relatively high population densities, which would be realistic when resources become limiting only after the population has expanded. The convex shape would imply that effect of competition on the birth rate is steepest at low densities, which would be realistic for a population expanding spatially, and growing at its border. Thus, any positive value of $m$ seems legitimate.

c. The death rate would be of the form $d(1 + (N/k)^m)$, which for $m > 1$ would mean that the increase of per capita death rate keeps accelerating when the population expands. For $m < 1$ the increase of the per capita death rate decelerates with the population size. Both could be realistic and hence any positive value of $m$ seems legitimate.

**Question 3.7. Red blood cells**

Figure made with the model `epo.R`:

![Figure](image)

**Question 3.8. Regression to the mean**
a. Since everything is random, the first expectation is that one should find not correlation between the per capita change, \((N_{t+\Delta} - N_t)/N_t\), and the previous density, \(N_t\).

b. We nevertheless find a significant correlation. Although all \(N_t\) values are random, relatively small \(N_t\) values tend to create a large deviate \(N_{t+\Delta} - N_t\), which is subsequently “boosted” by dividing by a small \(N_t\) value. In statistics this is known as the “regression to the mean” phenomenon. Thus, testing for density dependence in a random time series is expected to lead to statistically significant evidence.

c. This “taught-experiment” illustrating the main message of the Shenk et al. [11] and Freckleton et al. [4] papers tells us that one needs to be careful when searching for evidence for density dependence in time-series data.

Question 3.9. The Fisher equation

a. The model defines a vector of left and right neighbors by initializing two vectors filled with zeros. The left neighbor of compartment \(i\) is then defined as compartment \(i - 1\), and the left neighbor of the first compartment is set as the last compartment. For the right neighbors this is just the other way around. The \(dtN\) line then computes the derivatives for the whole vector of compartments.

b. Starting at position 30, this code creates a wave traveling left- and right-wards. The wave traveling left-wards re-enters the space on the right (see the Figure).

c. If the Allee effect is sufficiently strong and the diffusion sufficiently slow it should be possible to stop the wave. Try this!

Question 3.10. Life stages

Figure made with the previous version of Grind:
a. For the larvae, $L$, and the adults, $A$, one could write

\[
\frac{dL}{dt} = rA - mL - d_1 LA \quad \text{and} \quad \frac{dA}{dt} = mL - d_2 A ,
\]

where $m$ is the maturation of the larvae, and $r$ the reproduction of the adults.

b. The larvae nullcline is solved from $\frac{dL}{dt} = rA - mL - d_1 LA = 0$ giving $A = \frac{mL}{r - d_1 L}$, which is zero when $L = 0$ and has a vertical asymptote at $L = r/d_1$. The slope in the origin is computed from the derivative

\[
\frac{m}{r - d_1 L} + \frac{md_1 L}{(r - d_1 L)^2}
\]

which for $L = 0$ gives $\frac{m}{r}$.

See Panel (a). For the adults $\frac{dA}{dt} = mL - d_2 A = 0$ gives $A = \frac{mL}{d_2}$, which is a line with slope $m/d_2$. If $m/d_2 > m/r$ the two nullclines intersect in a non trivial stable steady state. Otherwise the origin is the only steady state (see Panel (b)). (Also see the online tutorial for sketching nullclines on http://tbb.bio.uu.nl/rdb/bm/clips/nullclines for the a rotated version of the phase space).

c. Assuming a quasi steady state for the larvae, one has to solve $L$ from $\frac{dL}{dt} = 0$, giving $\dot{L} = \frac{rA}{m+d_1 A}$.

d. Substituting $\dot{L}$ into the adult equation gives $\frac{dA}{dt} = \frac{mrA}{m+d_1 A} - d_2 A$ for the quasi steady state model. This is one of the models with a density dependent birth rate (see Table 3.1).

e. From $A = (m/d_2)L$ we get $\frac{dL}{dt} = (r' - m)L - dL^2$ where $r' = rm/d_2$ and $d = d_1m/d_2$, which has the form of a logistic equation.

f. In many insect species the adults live much shorter than the larvae. Then $\frac{dA}{dt} = 0$ would be most realistic.

**Question 3.11. Tumor growth**

Figure made with the previous version of Grind:
a. Since the total biomass is given by $A = c\pi r^2$, one obtains that the radius $r = \sqrt{\frac{A}{c\pi}} = c'\sqrt{A}$, where $c'$ is a new scaling constant. The total growth rate, $G$, is proportional to the circumference, i.e., $G \propto 2\pi r$, which after substituting the radius becomes $G \propto 2\pi c'\sqrt{A}$ or $G = b\sqrt{A}$, where $b$ is a “birth rate” that is proportional to the square root of the biomass. On the other hand, the total death rate should be proportional to the total biomass, $A$. A simple model would therefore be $\frac{dA}{dt} = G - dA = b\sqrt{A} - dA$.

b. The carrying capacity is solved from $b\sqrt{A} - dA = 0$, or $b - d\sqrt{A} = 0$ giving $\bar{A} = (b/d)^2$. There is a trivial steady state, $A = 0$, corresponding to having no tumor.

c. The per capita death rate is $cN$: see Panel (a).

d. The net per capita growth rate is $b - cN$: see Panel (b).

e. The steady state is $\bar{N} = b/c$.

f. Because there is no generation time.

g. The derivative with respect to $N$ is $b - 2cN$. Substituting $N = b/c$ yields $\lambda = -b < 0$. Thus the return time $T_R = 1/b$ is fully determined by the birth rate and is independent of the density dependent death rate $c$.

Answers to Chapter 4

Question 4.1. Density dependent death

Figure made with the previous version of Grind:

![Figure](image_url)

a. The per capita death rate is $cN$: see Panel (a).

b. The net per capita growth rate is $b - cN$: see Panel (b).

c. The steady state is $\bar{N} = b/c$.

d. Because there is no generation time.

e. The derivative with respect to $N$ is $b - 2cN$. Substituting $N = b/c$ yields $\lambda = -b < 0$. Thus the return time $T_R = 1/b$ is fully determined by the birth rate and is independent of the density dependent death rate $c$.

Question 4.2. Return time

a. For $\frac{dN}{dt} = f(N) = bN(1 - N/k) - dN$ there are two steady states, the origin $\bar{N} = 0$, and the carrying capacity $\bar{N} = k(1 - d/b)$. For the return time to the carrying capacity one computes the derivative $\frac{d}{dN}f(N) = b - d - 2bN/k$ and substitutes the steady state value to obtain

$$\lambda = b - d - \frac{2b}{k} k(1 - d/b) = d - b$$ and $T_R = \frac{-1}{\lambda} = \frac{1}{b - d}$.

For $\frac{dN}{dt} = g(N) = bN - dN(1 + N/K)$ there are also two steady states, the origin $\bar{N} = 0$, and the carrying capacity $\bar{N} = k(b/d - 1)$. For the return time to the carrying capacity one

\[ T_R = \frac{-1}{\lambda} = \frac{1}{b - d}. \]
computes the derivative $\partial_{N}g(N) = b - d - 2dN/k$ and substitutes the steady state value to obtain

$$\lambda = b - d - \frac{2d}{k} k(b/d - 1) = d - b \quad \text{and} \quad T_R = -\frac{1}{\lambda} = \frac{1}{b - d}.$$  

Thus, in both models the return time decreases when the net rate of increase, $r = b - d$, increases (which underlies the $r$ versus $K$-selected paradigm).

b. For $dN/dt = f(N) = s - dN$ with steady state $\bar{N} = s/d$, the derivative $\partial_{N}f(N) = -d$, which immediately gives $\lambda = -d$ and $T_R = 1/d$.

c. The $s$ and $k$ parameters are not rates, but have dimension $[N \text{ time}^{-1}]$ and $[N]$, respectively. Because both depend on the units of the population size, one can always scale the population size such that $s = 1$ and $k = 1$. For instance, scaling the non-replicating population by its steady state, $\bar{N} = s/d$, by defining a scaled population as $n = \frac{d}{s} \bar{N}$, and hence substituting $N = \frac{s}{d}n$ into $dN/dt = s - dN$, one obtains the scaled ODE

$$\frac{s}{d} \frac{dn}{dt} = s - \frac{s}{d}dn \quad \text{or} \quad \frac{dn}{dt} = d - dn,$$

see Section 13.4 which has the death rate as its only parameter.

d. The ODE $dN/dt = s(1 - N/k) - dN$ can be written as $dN/dt = s - (s/k + d)N = s - \delta N$, where $\delta = s/k + d$. This is of the same form as $dN/dt = s - dN$, and hence the return time is given by $R_T = \frac{\delta}{s} = \frac{1}{s/k + d}$, which is shorter than $1/d$. Note that the parameter $s$ is now part of the return time because $s/k$ is a rate.

**Question 4.3. Whales**

Figures made with the model *whales.R*:

To develop a proper model for the whales we have to consider three biological processes: birth, death, and the likelihood of finding a male. We write a model for the number of females, $N$, in the population, and assume that there is a similar number of males (the true population size would therefore be similar to $2N$). The probability that an individual female finds a male should increases with the number of males, and approach one at large densities of males. We define a simple saturation function, $p = N/(h + N)$, where $p$ is the probability, and $h$ is the
population size at which there is a 50% probability of finding a male. Note that a sigmoid Hill function would be inappropriate here because at low densities this probability should increase linearly with the density. To allow for a carrying capacity we have to include negative density dependence in either the birth or the death terms.

a. Assuming density dependent birth one would write something like

\[
\frac{dN}{dt} = \frac{bN}{1+N/k} \frac{N}{h+N} - dN, \tag{A.4.1}
\]

and assuming density dependent death one could write

\[
\frac{dN}{dt} = bN \frac{N}{h+N} - dN(1 + (N/k)^2), \tag{A.4.2}
\]

and in reality one could have a combination of the two.

b. The population birth rate (in red) and the death rate (in blue) of Eq. (A.4.1) is depicted in Panel (a). Those of Eq. (A.4.2) are shown in Panel (b).

c. The population growth rates are shown in Panels (c) and (d). The basins of attraction are defined by the intersections by the black line located at \(dN/dt = 0\) (see the arrows).

**Answers to Chapter 5**

**Question 5.1. Sketch the per capita birth rate**

Figure made with the file `birth.R`:

a. Plotting \(y = \frac{b(R_T - cN)}{h+R_T - cN}\) as a function of \(N\) needs to be done in several steps. First, \(y = 0\) when \(N = R_T/c\), i.e., when all of the nutrient is contained in the cells. At low population densities the population approaches the birth rate \(y = \frac{bR_T}{h+R_T}\), and when the saturation constant, \(h\), is much smaller than the total resource density, \(R_T\), this will approach the maximum birth rate \(b\). When \(N\) increases the per capita birth rate will decrease. Since the function is of the form \(y = b(1 - \frac{h}{h+R_T - cN})\), one can see that there is a vertical asymptote at \(N = \frac{h+R_T}{c}\), which is located beyond the point, \(N = R_T/c\), where \(y = 0\). We find the horizontal asymptote by first writing \(y = \frac{bR_T/N - bc}{h/N + R_T/N - c}\), and then taking the limit \(N \to \infty\) to find that \(y \to b\). We therefore obtain the concave hyperbolic function depicted above.

b. This concave shape is what we considered most realistic in Chapter 3. For instance see Fig. 3.3b and Fig. 3.5b.

**Question 5.2. Neutrophils**

Figure made with `neutrophils.R`:
a. The ODE of the bacteria is identical to the prey equation of the Lotka-Volterra model, and hence nullcline is given by the straight declining line \( N = \frac{r}{k}(1 - B/K) \). The nullcline of the neutrophils is defined by the line \( N = \frac{s}{d} \). These lines will only intersect when \( \frac{r}{k} > \frac{s}{d} \).

In Panel (a) the uninfected state is unstable and there is a stable state corresponding to a chronic infection. In Panel (b) the uninfected state is stable, and small infections cannot grow.

b. Comparing Panel (a) with (b) we observe that the previous condition \( kN > r \) now translates into the similar \( ks > r \).

c. The ODE of the bacteria is given by the parabola \( N = \frac{r}{k}(1 - B/K)(h + B) \); see Panels (c)–(e). (It is identical to the prey equation of the Monod-saturated predator-prey model in Chapter 7). The situation in Panel (d) is like that of Panel (b), where small infections cannot grow. In Panel (e) the situation is like that in Panel (a), with a new stable state corresponding to a chronic infection. In Panel (c) the uninfected state, \((\bar{B}, \bar{N}) = (0, s/d)\), is a stable node, the steady state marked by the open circle is a saddle point, and the steady state marked by the bullet is a stable node, corresponding to a chronic infection.

d. The condition for control is that \( s/d \) is larger than the maximum of the parabola (which can be computed by substituting \( B = (K - h)/2 \) into the equation for the nullcline \( N = \frac{r}{k}(h + B)(1 - B/K) \). Additionally, saturated killing creates a threshold density of bacteria above which the bacteria can no longer be controlled, which corresponds to the saddle point indicated by the open circle in Panel (c).

e. Writing \( dB/dt = rB \frac{B}{\alpha + B}(1 - B/K) - \frac{kNB}{k + B} \) makes hardly anything changes around the steady states (see Panels f and g). This is partly because small populations of bacteria were already controlled by the neutrophils, i.e., \((\bar{B}, \bar{N}) = (0, s/d)\) was already stable. Secondly, because the bacteria have no death rate the Allee effect is “weak”, i.e., in the absence of neutrophils small bacteria populations do not decline but grow slowly (which may in fact be realistic).

f. The large transient output from the bone marrow tends to overcome the threshold of the previous model.

**Question 5.3. Lotka-Volterra models**

a. This would indeed be compatible with \( dT/dt = rT(1 - T/K) - kTN \) and \( dN/dt = aTN - dN \) for the tumor, \( T \), and natural killer cells, \( N \), respectively. Here \( k \) is a mass-action killing rate and \( a \) the mass-action activation rate allowing the natural killing cells to divide.
b. In Chapter 6 we will encounter the SI model, \( \frac{dS}{dt} = rS(1 - S/K) - \beta SI \) and \( \frac{dI}{dt} = \beta SI - dI \), for the susceptible individuals, \( S \), and infected individuals, \( I \), respectively. Here \( \beta \) is an infection rate and \( d \) the death rate of infected individuals.

c. The natural killer cells probably have a maximum killing rate, and a maximum rate of activation, which would change the model to \( \frac{dT}{dt} = rT(1 - T/K) - \frac{kTN}{h + T} \) and \( \frac{dN}{dt} = \frac{aTN}{h + T} - dN \) (see Chapter 7). The SI model is frequently written as \( \frac{dS}{dt} = rS(1 - S/K) - \frac{\beta SI}{S + T} \) and \( \frac{dI}{dt} = \frac{\beta SI}{S + T} - dI \), because \( \frac{I}{S + T} \) is the fraction of infected individuals in the population (see Chapter 6). This is a more natural term when the susceptible individuals tend to meet an average number of other people, irrespective of their health status.

**Question 5.4. Desert**

Figures made with the previous version of Grind:

\[ \begin{array}{cc}
\text{(a)} & \text{(b)} \\
\end{array} \]

\[ \begin{array}{cc}
V & V \\
0 & 0.5 \\
W & 0.5 \\
\end{array} \]

\[ \begin{array}{cc}
0 & 0 \\
W & \frac{a}{c} \\
\end{array} \]

\[ \begin{array}{cc}
0 & 0 \\
W & \frac{a}{c} \\
\end{array} \]

a. If there is no vegetation one sets \( V = 0 \) to obtain \( \frac{dW}{dt} = a - cW \) with the steady state \( W = a/c \).

b. If there is twice the amount of rain the parameter \( a \) becomes \( 2a \), which means \( \bar{W} = 2a/c \).

c. The steady state is now solved from the system \( \frac{dW}{dt} = dV/dt = 0 \). Since \( V = 0 \) cancels from \( dV/dt = 0 \) one obtains the steady state \( W = e/d \) from the vegetation equation. This is independent of rain and evaporation!

d. Knowing that \( \bar{W} = \frac{a}{2b} \), we solve \( V \) from \( \frac{dW}{dt} = 0 = a - b \frac{c}{2} V - c \bar{W} \), or \( \bar{V} = \frac{ad}{bc} - \frac{c}{b} \).

e. The steady state remains \( \bar{W} = e/d \) and because \( \bar{V} \) depends on \( a \) we see that the extra water ends up in the vegetation.

f. The vegetation nullcline is solved from \( dV/dt = dWV - eV = 0 \) which means that \( V = 0 \) and \( W = e/d \). The water nullcline is solved from \( dW/dt = a - bWV - cW = 0 \) or \( a - cW = bWV \), i.e., \( V = \frac{a}{bW} - \frac{c}{b} \), which is a decreasing hyperbolic function with horizontal asymptote \( V = -(c/b) \) and vertical asymptote \( W = 0 \). There are two possibilities: See Panel (a) and (b). The vector field shows steady state \( \bar{W} = a/c \) without a vegetation is an unstable saddle in Panel (a) and is stable in Panel (b). For the non-trivial steady state in Panel (a) we can derive the full Jacobian

\[ J = \begin{pmatrix} -b\bar{W} - c & -b\bar{W} \\ d\bar{V} & d\bar{W} - e \end{pmatrix} = \begin{pmatrix} -b\bar{V} - c & -b\bar{W} \\ d\bar{V} & 0 \end{pmatrix}, \]

because \( \bar{W} = \frac{a}{2b} \), and giving \( \text{tr}\, J = -b\bar{V} - c < 0 \) and \( \text{det}\, J = 0 + bd\bar{W}\bar{V} > 0 \). One can also retrieve the graphical Jacobian from the local vector field, i.e.,

\[ J = \begin{pmatrix} - & - \\ + & 0 \end{pmatrix} \] also giving \( \text{tr}\, J < 0 \) and \( \text{det}\, J > 0 \).

Both methods agree that the non-trivial steady state in Panel (a) is stable.

g. Increased rainfall increases \( a \), which will move the water nullcline up and to the right. Since the vertical vegetation nullcline is unaffected, the amount of water in the soil remains the same, and the vegetation increases.
Question 5.5. Biotic and abiotic resources

a. For the abiotic resource, $R$, we first write a source term, $s$, and a loss term, $d$, i.e., $dR/dt = s - dR$. For the consumer we define a per capita birth rate $bR/(k + R)$ that obeys a Monod saturation of the resource concentration. Adding the same loss rate we arrive at $dN/dt = bRN/(k + R) - dN$, where $d$ is the rate of outflow from the chemostat (which we assume to be much larger than the death rate of the consumers), and $h$ is the resource concentration at which the birth rate is half of its maximum. Since the resource is only used when the consumer grows, we add this birth rate as a consumption term to the ODE of the resource, i.e., $dR/dt = s - dR - c(RN)/h + R$, where $c$ is the amount of resource contained in a single consumer individual.

b. The biotic resource maintains itself by growth and because it has a carrying capacity, we write a logistic growth model $dR/dt = rR(1 - R/K)$. Adding mass-action consumption we arrive at $dR/dt = rR(1 - R/K) - aRN$, where $a$ is an attack rate, and $aR$ is the daily consumption per consumer. Since the birth rate is a saturation function of the consumption, we write $dN/dt = bRN/aR - dN$, where $h$ is the level of consumption, $aR$, at which the birth rate is half of its maximum, and $d$ is the death rate of the consumers.

c. The consumer equations are mathematically identical, because both are based upon a saturated birth rate and density independent death rate. The resource equations differ in the form of the consumption term, and in the process whereby the resource is produced.

Question 5.6. Cryptic oscillations

a. Since bacteria readily evolve resistance to bacteriophages, the stable E. coli population is most likely resistant to T4. If the resistant bacteria continue to revert to sensitive bacteria, one could postulate that a small subpopulation of sensitive E. coli maintains the predator-prey oscillations with the T4 phage.

b. This would mean that resistance evolves after about 200h of co-culture.

c. A mathematical model would require four variables: sensitive uninfected bacteria, $S$, resistant bacteria, $R$, infected bacteria, $I$, and phages $P$. In its most simple form it would be something like

$$\frac{dS}{dt} = bBS(1 - B/k) - dBS - \beta SP , \quad \frac{dR}{dt} = bB(1 - s)R(1 - B/k) - dB R ,$$

$$\frac{dI}{dt} = \beta SP - dI I \quad \text{and} \quad \frac{dP}{dt} = bdI I - dP P ,$$

where $B = S + R + I$ is the total number of bacteria, $bB$ is the maximum birth rate of bacteria, $k$ is the bacterial density at which the birth rate vanishes, $s$ is the fitness cost of the resistance, $d_2$ are death rates, and $b$ a burst size. A first model like this, which also allows for resistance mutations of the bacteria is available on the website as phages.R. Note that you may have to change the mass-action infection rate into a saturated term to obtain oscillations (see Chapter 7).
Question 5.8. Return time

We calculate the return time of the non-trivial steady state of the Lotka-Volterra model considering both density dependent birth and density dependent death. For simplicity we do this for the case where this equilibrium is a stable spiral point. To save time we first write the model in a general form and compute the return time for this general model. The two cases of density dependent birth and death can then be “substituted” into the general form. A general form of the Lotka-Volterra model is:

\[
\frac{dR}{dt} = rR - \gamma R^2 - aRN \quad \text{and} \quad \frac{dN}{dt} = caN - \delta N .
\]

a. For the return time of the general form we first solve the non-trivial steady state by setting \(\frac{dN}{dt} = 0 \) and \(\frac{dR}{dt} = 0\), which gives:

\[
\bar{R} = \frac{\delta}{ca} \quad \text{and} \quad \bar{N} = \frac{r}{a} - \frac{\gamma}{a} \bar{R} = \frac{r}{a} - \frac{\gamma \delta}{ca^2} ,
\]

respectively. The Jacobian of the general model is:

\[
J = \begin{pmatrix} r - 2 \gamma \bar{R} - a \bar{N} & -a \bar{R} \\ ca \bar{N} & ca \bar{R} - \delta \end{pmatrix} = \begin{pmatrix} -\frac{\gamma \delta}{ca} & -\frac{\delta}{ca} \\ cr - \frac{\delta}{a} & 0 \end{pmatrix},
\]

where \(cr - \gamma \delta / a > 0\) because \(ca \bar{N} > 0\). The trace of this matrix is negative, i.e., \(\text{tr} = -\frac{\gamma \delta}{ca}\), and the eigenvalues of this Jacobian are given by:

\[
\lambda_\pm = \frac{\text{tr} \pm \sqrt{\text{tr}^2 - 4 \text{det}}}{2} = -\frac{\gamma \delta}{2ca} \pm \frac{\sqrt{D}}{2} ,
\]

where \(D = \text{tr}^2 - 4 \text{det}\) is the discriminant of the matrix (and “det” the determinant). Since we are considering a spiral point, the eigenvalues have to be complex, implying that the discriminant \(D < 0\). The imaginary part of the eigenvalues defines the period of the dampened oscillation, and the real part how fast its amplitude grows or contracts, i.e., the return time depends on the real part only. Thus, for the return time we consider the real part, \(\text{Re}(\lambda) = -\frac{\gamma \delta}{2ca}\), to obtain a return time:

\[
T_R = -\frac{1}{\text{Re}(\lambda)} = \frac{2ca}{\gamma \delta} = \frac{2}{\gamma} \frac{1}{\bar{R}} .
\]

Thus, the return time is independent of the net rate of increase, \(r\), depends on the density dependence parameter, \(\gamma\), and is inversely related to the steady state of the resource.

b. We write the model with density dependent birth as:

\[
\frac{dR}{dt} = bR(1 - R/k) - dR - aRN = bR - bR^2/k - dR - aRN ,
\]

which in the general form means that \(r = (b - d)\) and \(\gamma = b/k\). To obtain the return time of the non-trivial steady state of this model, we only need to substitute \(\gamma = b/k\) into the general expression for the return time, because the return time is independent of \(r\), and because \(\bar{R}\) came from \(\frac{dN}{dt} = 0\), which has not changed. We obtain that:

\[
T_R = \frac{2}{b} \frac{k}{\bar{R}} = \frac{2ca}{b \delta} ,
\]

where \(k/\bar{R}\) is a ratio of resource densities (i.e., \(k\) is the density at which the birth rate become zero). Note that the dimension is correct: \(k/\bar{R}\) is dimensionless and \(2/b\) has the dimension time. Thus, the return time of this density dependent birth depends on the birth rate parameters, \(b\) and \(k\), and not on the density independent death rate, \(d\).
c. We write the model with density dependent death as

$$\frac{dR}{dt} = bR - dR(1 + R/k) - aRN = bR - dR - dR^2/k - aRN,$$

which in the general form means that \( r = (b - d) \) and \( \gamma = d/k \). Now we substitute \( \gamma = d/k \) into \( T_R \) and obtain that

$$T_R = \frac{2}{d/k} \bar{R} = \frac{2cak}{d\delta},$$

where \( k/\bar{R} \) is another ratio of resource densities (i.e., \( k \) is the density at which the death rate doubles). Now the return time depends on the density dependent death rate parameters, \( d \) and \( k \).

d. In both cases the return time is determined by a self-dampening effect of the resource onto itself, i.e., \( \text{Re}(\lambda) = -(\gamma/2) \bar{R} \). Increasing the birth rate, or the death rate, decreases the return time because it speeds up the dynamics around the steady state. Increasing \( k \) increases the return time because it weakens the density dependent regulation. Weakening the consumer, i.e., increasing \( \bar{R} \), decreases the return time because that also increases the self-dampening effect of the resource.

Answers to Chapter 6

Question 6.1. SARS

a. First count the total number of infected patients \( I(t) \). \( R_0 = 3 \) in two weeks means that \( \beta = 1.5 \) per week. For a time scale of weeks the model therefore is \( dI/dt = 1.5I - 0.5I = I \).

The equation to solve is \( 3 \times 10^9 = I(0)e^{rt} \), where \( r = (\beta - \delta) = 1 \), and where one starts with one infected individual, i.e., \( I(0) = 1 \). Solving \( 3 \times 10^9 = e^t \) yields \( t = 22 \) weeks for the time required to have \( I(t) = 3 \times 10^9 \).

For completeness, one could argue that it is more interesting to calculate the time required to have killed half of the population, but this is more difficult. For that one also should keep track of the total number of dead individuals \( dD/dt = \delta I \). With \( I(t) = e^{(\beta-\delta)t} \) and \( D(0) = 0 \) the solution of \( dD/dt = \delta e^{(\beta-\delta)t} \) is \( D(t) = \frac{\delta e^{(\beta-\delta)t} - 1}{\beta-\delta} \). Solving \( I(t) + D(t) = 3 \times 10^9 \) for \( \beta = 1.5 \) and \( \delta = 0.5 \) per week gives a total time of \( t = 21 \) weeks. The difference is small because the number of dead patients approaches a fixed fraction \( \frac{t}{\beta-\delta} = 0.5 \) of the total number of patients that are alive.

b. No, it will go slower because the epidemic will limit itself by depleting the number of susceptibles. Thus it is much better to use an SI model. Because the SARS epidemic is so much faster than the human birth and death rates, Eq. (6.1) would simplify to

$$\frac{dS}{dt} = -\beta IS \quad \text{and} \quad \frac{dI}{dt} = \beta IS - \delta I.$$

You can use the sir.R model to study how rapid SARS would spread in this SI model. Another improvement of the model that would slow down the epidemic is to allow for an incubation period, and use the SEIR model.

Question 6.2. Evolution of virulence
a. Since infected individuals appear at a maximum rate $\beta S$, and have an expected life span of $1/(d + v)$ time units, the $R_0 = \frac{\beta S}{d + v} = \frac{\beta}{d+v} \frac{S}{d}$.

b. Substituting $\beta = cv$ we obtain $R_0 = \frac{cvS}{d + v} = \frac{cv}{d + v} \frac{s}{d}$.

c. The $R_0$ of the infection is a saturation function of the virulence (see Panel (a)). Since one expects the variant with the highest reproductive number, $R_0$, to win the competition, one expects the most virulent variant to win. Virulence is therefore expected to increase over time.

d. When $\beta = \frac{cv}{h + v}$ one obtains $R_0 = \frac{cv}{h + v} \frac{1}{d + v} \frac{s}{d}$.

e. To sketch the latter as a function of the virulence, $v$, we observe that for $v \to 0$ the fitness approaches $R_0 \approx \frac{cK}{h} \frac{1}{d} \frac{s}{d}$, which is an increasing function of $v$. When $v \gg h$, the fitness approaches $R_0 = \frac{c}{d + v} \frac{s}{d}$, which is a decreasing function of $v$. In combination one therefore expects a curve with an optimal virulence (see Panel (b)), where the trade-off between the increased transmission and the decreased life span is balanced (see the tutorial on sketching functions).

**Question 6.3. Sexually transmitted disease (STD)**

Figure made with the model aids.R:

a. In the absence of foreign infections infected individuals appear at a maximum rate $\beta S$, and have an expected life span of $1/\delta$ days, meaning that the $R_0 = \frac{\beta S}{\delta} = \frac{\beta}{\delta} \frac{a}{\delta}$.

b. No the infection will never disappear from this subpopulation because there is always a small source of infected individuals. The steady state number of infected individuals will always be larger than $I = cS/\delta$, which is the minimum approached when $\beta \to 0$.

c. The $dS/dt = 0$ nullcline is defined as $I = \frac{a}{\beta s} - \frac{d + \epsilon}{\beta}$. The nullcline has a vertical asymptote
at $S = 0$ because when $S \to 0$ the first term goes to infinity. The nullcline has a horizontal asymptote because when $S \to \infty$ the number of infected individuals approaches $I = \frac{\epsilon - d}{\beta}$. The nullcline intersects the horizontal axis in the carrying capacity $S = \frac{\delta - d}{\beta}$; see Panel (a) and (b). The $dS/dt = 0$ nullcline is defined by $I = \frac{\epsilon S S}{S + I}$, which has the vertical asymptote at $S = \frac{\delta}{\beta}$. When $S \to 0$ the nullcline approaches $I \approx \frac{\epsilon}{\beta}$, which increases with $S$ (see Panel (a) and (b)). Note that this vertical asymptote corresponds to the classical vertical nullcline of the SI model without a source, i.e., the epidemic grows at the right-hand side of this asymptote. Panel (a) therefore corresponds to the case where $R_0 > 1$ because the epidemic can maintain itself without a source, and Panel (b) reveals the opposite case where $R_0 < 1$ and the source maintains a small infection. In both Panels the Jacobi matrix of the non-trivial steady state is given by

$$J = \begin{pmatrix} -\beta & \epsilon \\ \delta & -\gamma \end{pmatrix}$$

i.e., the endemic state is stable (even if $R_0 < 1$).

d. Because the probability of becoming infected by an HIV-infected partner is relatively low for heterosexual couples, implying that $\beta$ and $R_0$ are small, the situation depicted in Panel (b) is quite realistic for non-promiscuous Dutch subpopulations.

Question 6.4. SIR model

Figure made with the model sir.R:

(a) $\frac{dI}{dt} = \frac{S I}{S + I} - (\delta + r)I = 0$ giving $\frac{\beta S}{\delta + r} = I + S$,

or $I = S(R_0 - 1)$, which is a line through the origin with slope $R_0 - 1$. For the other nullcline we set

$$\frac{dS}{dt} = s - dS - \frac{\beta SI}{S + I} = 0$$

giving $(s - dS)(S + I) = \beta SI$ or $I = \frac{sS - dS^2}{(\beta + d)S - s}$,

which defines a line that is too unpleasant to sketch by hand. Better use the sir.R model (see the Panel (a)).

c. The fact that the $dI/dt = 0$ nullcline goes through the origin means that the epidemic can grow when the susceptible population is extremely small (see the upward arrow near the origin). This is an unpleasant consequence of using the fraction of infected individuals in the number of daily encounters: at low population densities the number of individuals encountered should actually go to zero. Thus, this problem should be solved by realizing that the infection term should depend on the expected number, $n$, of individuals encountered per day, and the
fraction, \( f = \frac{I}{S + I} \), of infected individuals among them. This frequency dependent model only deals with the latter by making the rate at which a susceptible individual is infected directly proportional to the fraction, \( f \), of infected individuals. If one were to write that the expected number of individuals encountered per day should be a saturation function of the population density, e.g., \( n = \frac{S + I}{n^2 + S + I} \), and that the infection rate should be proportional the fraction of infected individuals encountered, i.e., \( fn = \frac{I}{S + I} = \frac{S + I}{n^2 + S + I} \), we obtain from

\[
\frac{dI}{dt} = \frac{\beta SI}{h + S + I} - (\delta + r)I = 0 \quad \text{that the nullcline,} \quad I = S(R_0 - 1) - h ,
\]

is intersecting the horizontal axis at \( S = \frac{h}{R_0 - 1} \) (see Panel (b)).

**Question 6.5. Measles**

- On a logarithmic scale the epidemic first grows linearly and then contracts.
- \( \text{e}[^*\text{i}]<\text{=}\exp(\text{coef}(\text{f})[\text{1}]) \) sets \( I(0) \) to \( e^i \) where \( i \) is the intercept.
- \( \text{p["beta"]<}1+\text{coef(}\text{f}[\text{2}]) \) sets \( \beta \) to one plus the slope because \( r_0 = \beta - r = \beta - 1 \).
- The fit looks reasonable, but the parameter estimates can be very unreasonable with way too large population densities and recovery rates of just a few hours. Starting with different initial guesses different estimates are obtained. The solution is to not estimate the “known” recovery rate, \( r \), i.e., to remove it from the vector of free parameters. Estimating just \( I(0) \) and \( \beta \) works fine. Apparently, many combinations of \( \beta \) and \( r \) can give the same behavior, i.e., a high infection rate combined with a fast recovery rate is the same as a low infection rate with a slow recovery rate.
- Estimating just \( I(0) \) and \( \beta \), the two parameters have reasonable confidence ranges.
- Since \( N = S + I + R \) is not changing over time, this basically scales the \( \beta \) parameter, and nothing should change. However, the frequency dependent formulation better separates the parameters \( S(0) \) and \( \beta \) from each other, which may facilitate the fitting and hence narrow down the confidence intervals.

**Answers to Chapter 7**

**Question 7.1. Michaelis Menten**

- From the conservation equation one obtains that the concentration of freely available enzyme is given by \( E = E_0 - C \). From the reaction scheme one derives for the complexes \( \frac{dC}{dt} = k_1ES - (k_{1-} + k_2)C \), which after substituting the conservation equation becomes

\[
\frac{dC}{dt} = k_1(E_0 - C)S - (k_{1-} + k_2)C .
\]

For the formation of product one simply writes \( \frac{dP}{dt} = k_2C \).
- To solve \( \frac{dC}{dt} = 0 \) we first collect all the terms containing \( C \),

\[
\frac{dC}{dt} = k_1E_0S - (k_1S + k_{1-} + k_2)C .
\]

Because \( \frac{dC}{dt} = 0 \) we obtain \( k_1E_0S = (k_1S + k_{1-} + k_2)C \), and by solving for \( C \)

\[
C = \frac{k_1E_0S}{k_1S + k_{1-} + k_2} = \frac{E_0S}{K_m + S} \quad \text{where} \quad K_m = \frac{k_{1-} + k_2}{k_1} .
\]

Thus, \( C \) as a function of \( S \) looks like a standard Hill function \( y = \frac{x}{x + x} \).
- By defining \( K_m \) the simplification was already done. This means the the product equation can be written as \( \frac{dP}{dt} = \frac{k_2E_0S}{K_m + S} \).
- The beautiful trick of adding \( \frac{dC}{dt} = 0 \) to \( dS/dt \) readily simplifies the substrate equation into \( dS/dt = -k_2C \). Filling in the quasi steady state expression for \( C \) gives \( dS/dt = -\frac{k_2E_0S}{K_m + S} \).
Question 7.2. Parameters
The biological interpretation and dimension of the parameters are:

a. 1. $a_1$: Maximal per capita growth rate ($1/t$)
2. $K$: Carrying capacity (numbers or biomass).
3. $b_1$: Maximal per capita consumption rate ($1/t$).
4. $c_1$: Population density $R$ where $N$ catches/feeds at its half maximal rate (numbers or biomass).
5. $a_2$: per capita death rate ($1/t$).
6. $b_2$: Maximum per capita birth rate ($1/t$).
7. $c_2$: Population $R$ where $N$ grows at half its maximum rate (numbers or biomass).

b. Yes, if this achieved by scaling the variables. Typically, $b_2 = \alpha b_1$ where $\alpha$ is the conversion factor. If population sizes are measured in biomass the normal trophic conversion factor is $\alpha = 0.1$, i.e., typically there is a 90% loss between trophic levels. If the population sizes are measured in numbers $\alpha$ could be anything because small consumers could feed on a large resource.

c. Choosing $c_1 = c_2$ means that the growth of the consumer is proportional to what it eats. Setting $c_1 > c_2$ means that the growth rate saturates earlier than the catching rate, which is to be expected when the birth rate of the consumer saturates as a function of its consumption; see Eq. (7.16). Setting $c_1 < c_2$ therefore seems strange because it means that the catching rate is saturated earlier than the birth rate.

Question 7.3. Nullcline construction
Figures made with chemoMonod.R:

The red line in Panel (a) is the line $y = s - wR$ and the blue lines in depict the consumption term $y = sR/N$ for various values of $N$. At all intersection points $dR/dt = 0$ because for the growth is perfectly balanced by the consumption. Copying the intersection points in Panel (a) for all values of $N$ into a plot with $N$ on the vertical axis delivers the red nullcline depicted in Panel (b).

Question 7.4. Type I functional response
The nullcline of the consumer is only defined when \( R < L \) because \( \frac{dN}{dt} = caNL - dN \) is either positive or negative. Considering \( R < L \) and solving \( \frac{dN}{dt} = caNR - dN = 0 \) delivers the familiar \( R = \frac{d}{ca} \) nullcline. For the resource we consider both cases, i.e.,

\[
\begin{align*}
    \frac{dR}{dt} &= rR(1 - R/K) - aNR \quad \text{when } R < L \text{ and } \\
    \frac{dR}{dt} &= rR(1 - R/K) - aNL \quad \text{otherwise},
\end{align*}
\]

to obtain

\[
\begin{align*}
    N &= \frac{r}{a} (1 - \frac{R}{K}) \quad \text{when } R < L \text{ and } \\
    N &= \frac{rR}{aT} (1 - \frac{R}{K}) \quad \text{otherwise},
\end{align*}
\]

where the former is the straight line intersecting the vertical axis at \( N = \frac{r}{a} \) and the horizontal axis at \( R = K \), and the latter is a parabola intersecting the horizontal axis at \( R = 0 \) and \( R = K \). Putting these together delivers the picture shown above (where we ignore the case that \( \frac{d}{ca} > K \)).

b. The stability of the steady states has not changed because nothing changed in the immediate neighborhood of steady states. Thus, the origin, \((0,0)\), and the carrying capacity, \((K,0)\), remain saddle points, and the non-trivial point is stable like in the Lotka-Volterra model.

c. No, the consumer nullcline has to be located at a resource density where changing the resource density changes \( \frac{dN}{dt} \).

d. No, the non-trivial steady state has to be located in the part where the resource nullcline is a declining straight line (see the answer in b), and there the steady state is stable.

**Question 7.5. Dampened oscillations**

Figures made with hiv.R:

a. The mass-action model is shown in Panel (a) and for large values of the saturation constants the extended model indeed has a very similar behavior (the target cells, \( T \), are called “C” in the figure because “T” also means true in R).
b. The behavior of the saturated model for low saturation constants is depicted in Panel (b). Comparing Panel (a) with (b) we see that the oscillations are dampened by the ‘Beddington’ interaction terms.

c. Yes, if both populations are small their encounters should be proportional to the product of their densities, and in this regime the Beddington term approaches the mass-action term. When only one of the populations is large the Beddington term approach a normal saturation function, whereby the process is limited by the smallest population. All of this seems very reasonable.

d. Yes, the trajectories of the Beddington model approach the steady state asymptotically, whereas those of the Lotka-Volterra model approach it by dampened oscillations. The latter steady state is a stable spiral and the former a stable node.

**Question 7.6. Curvature**

Figure made with hyper.R:

![Curvature Diagram](image)

a. Panel (a) shows that for \( H = h/(1 - \gamma/2) \) all curves cross at \( R = h \), and that the curvature changes smoothly from a conventional saturation function to a discontinuous Holling type-I function. This therefore seems a very useful functional response when data deviate from the usual saturating functions.

b. Panel (b) and (c) show two cases with a stable limit cycle around a stable steady state. Note that it is not possible for the consumer nullcline to intersect at the right-hand side of the maximum of the resource nullcline.

c. It is somewhat disturbing that a somewhat steeper curvature can completely change the behavior of the model. The devil is apparently in the details, which is unfortunate because we typically do not worry about the curvature and just choose a convenient function.

**Question 7.7. Ratio-dependent predation**

Figures made with ratio.R:

![Ratio-dependent Predation Diagram](image)

a. This model has the same two regimes as models based upon the Beddington functional response, with a limited-consumer scenario in Panel (a), and a humped consumer nullcline with a stable steady state in Panel (b), and with an unstable steady state in Panel (c). Panel (c) reveals that the behavior of the model is problematic as all trajectories approach the
origin, which is an unstable steady state. Like in the question on the SIR model, this is a consequence of the consumer nullcline going through the origin.

b. No, by increasing $K$ in Panel (b) one will never find a Hopf bifurcation [8].

**Question 7.8. Eutrophication**

Figures made with the previous version of Grind:

\[
\frac{dA}{dt} = rA(1 - A/K) - bZA^2 \frac{h^2 + A^2}{h^2 + 2h - A^2} \quad \text{and} \quad \frac{dZ}{dt} = cbZA^2 \frac{h^2 + A^2}{h^2 + 2h - A^2} - dZ(1 + eZ),
\]

where $e$ is the extra death due to intra-specific competition. The nullcline for the algae has been constructed in the text. For the zooplankton one obtains from $dZ/dt = 0$ that $Z = 0$ or

\[
Z = \frac{cb}{de} \frac{A^2}{h^2 + 2h - A^2} - \frac{1}{e},
\]

which is a sigmoid function intersecting the vertical axis at $Z = -1/e$, and the horizontal axis at $A = h/\sqrt{R_0 - 1}$, where $R_0 = cb/d$. When $e = 0$ the $Z$-nullcline is a vertical line.

b. The carrying capacity, $K$, of the algae will depend on the total amount of nutrients that are available for the algae. Studying eutrophication therefore corresponds to increasing $K$.

c. There are many possibilities, see Panel (a) and (b). The effect of eutrophication corresponds to moving along a sigmoid zooplankton nullcline from the lowest to the highest algae nullcline. Steady states may stabilize or destabilize, and may appear or disappear.

d. Models suggest that changing a single parameter can have various different effects, depending on the precise initial circumstances. It is difficult to generalize, and reliable predictions are nearly impossible to make. A model plays the important role of suggesting various possible outcomes; possibly including undesired outcomes.

**Question 7.9. Luckinbill**

Figures made with previous version of Grind:
a. The oscillatory behavior suggests a Monod saturation

\[
\frac{dP}{dt} = aP(1 - P/K) - \frac{bDP}{h + P} \quad \text{and} \quad \frac{dD}{dt} = \frac{cDP}{h + P} - dD.
\]

b. Increasing the viscosity of the medium decreases the likelihood of meeting prey, which corresponds to increasing the \( h \) parameter; see Panel (b). Halving the concentration of food decreases the \( K \) parameter; see Panel (c).

c. See Panels (a)–(c).

d. The agreement between model and data seems perfect; a simple Monod saturated functional response provides a good explanation.

e. Formally the populations cannot go extinct in the model; the noise in the data would require stochasticity in the model.

**Question 7.10. Exponential functional response**

Figure made with the previous version of Grind:

\[
\text{a. For } R \to \infty \text{ the functional response } (1 - e^{-\ln[2]R/h}) \to 1, \text{ which means that at high resource densities the consumption of a consumer is } a \text{ per unit of time.}
\]

\[
\text{b. Since one can scale time by the natural rate of increase } r, \text{ the resource density by its carrying capacity, and the consumer by the } a \text{ parameter, the generic form of both models is:}
\]

\[
\frac{dR}{dt} = R(1 - R) - \frac{NR}{h + R} \quad \text{and} \quad \frac{dR}{dt} = R(1 - R) - N(1 - e^{-\ln[2]R/h}),
\]

which has only one parameter \( h \). Panel (a) shows the nullclines for \( h = 0.1, 0.2, 0.4, 0.8 \) and \( h = 1.6 \). The nullclines intersect when \( R = h \) because the functional response then equals 0.5. Since there is no qualitative difference between the two sets of nullclines, we expect similar behavior for these two models.

**Question 7.11. Wolves**

Figure made with the previous version of Grind:
There are many different possibilities. For instance, let $R$ be the prey, and $W$ be the wolves:

a. One could define $\hat{R} = RW/(c + W)$ as the number of prey that can be caught, i.e., if there are enough wolves ($W \gg c$) all prey can be caught ($\hat{R} \to R$). Taking $\hat{R}$ through a normal Monod saturation gives

$$f(R, W) = \frac{\hat{R}}{h + \hat{R}} = \frac{RW}{hc + hW + RW}$$

and

$$\frac{dR}{dt} = rR(1 - R/K) - \frac{aRW^2}{hc + hW + RW} \quad \text{and} \quad \frac{dW}{dt} = \frac{aRW^2}{hc + hW + RW} - dW,$$

with $R_0 = a/d$.

b. To sketch the predator nullcline one solves

$$\frac{aRW}{hc + hW + RW} = d \quad \text{or} \quad W = \frac{hc}{R(R_0 - 1) - h},$$

which has a vertical asymptote at $R = h/(R_0 - 1)$ and a horizontal asymptote at $W = 0$. The only intersection with the vertical axis ($R = 0$) is at the negative value $W = -c$. The prey nullcline is not so easy to sketch. We have drawn it with Grind in the picture above, where it looks like a parabola. From the vector field one can see that the carrying capacity is stable. This is an Allee effect because the wolves cannot invade in small numbers. The upper non-trivial steady state is stable when the intersection points is located at the right hand side of the top of the parabola. The lower intersection point is a saddle point, with a separatrix defining the Allee effect.

Alternatively, one could use a mass action predation term and write a more phenomenological model,

$$\frac{dR}{dt} = rR(1 - R/K) - \frac{aRW^2}{c + W} \quad \text{and} \quad \frac{dW}{dt} = \frac{aRW^2}{c + W} - dW.$$

One could also employ the Beddington functional response and define $f(R, W) = \frac{R}{h(1 - cW) + R}$ as a functional response that decreases the saturation constant when the number of wolves increases (and use a maximum function to prevent that $h(1 - cW)$ becomes negative).

**Question 7.12. Saturation in consumers**

Figure made with the previous version of Grind:

![Figure](image)

a. The prey nullcline is solved from

$$r(1 - R/K) = \frac{aN}{h + N} \quad \text{or} \quad R = K \left(1 - \frac{a/rN}{h + N}\right),$$

which is an inverse Hill function intersecting the vertical $R$-axis at $R = K$. If $a/r < 1$ one obtains a “limited predation” nullcline with an asymptote at $R = K(1 - a/r)$; see Panel (a).
Otherwise the nullcline intersects the horizontal $N$-axis $N = h/(a/r - 1)$; see Panel (b). The consumer nullcline is solved from

$$\frac{aR}{h + N} = d \quad \text{or} \quad R = (d/a)(h + N),$$

which is a straight line with slope $d/a$ that intersects the vertical axis at $R = dh/a$.

b. For the non-trivial steady states in both panels we derive the Jacobian $J = \begin{pmatrix} - & + & - & - & - & - & - \\ - & - & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -(p + d) & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \ldots & 0 & 0 & 2p & -d \end{pmatrix}$, giving $\text{tr} J < 0$ and $\det J > 0$, i.e., they are stable.

**Answers to Chapter 8**

**Question 8.1. Food chain**

a. For $N = M = 0$ one finds $\bar{R} = s/r$. For $M = 0$ one solves $\bar{R} = d/b$ from $dN/dt = 0$ and then $
\bar{N} = s/d - r/b$. When all three species are present, one solves $\bar{N} = e/c$ from $dM/dt = 0$, then $\bar{R} = \frac{\bar{N}}{r + be/c}$ from $dR/dt = 0$, and finally $\bar{M} = (b\bar{R} - d)/c$ from $dN/dt = 0$.

b. Yes, the steady state of $R$ only depends on its source when the length of the chain is odd.

**Question 8.2. Triangular Jacobian**

Since $dN_0/dt$ only depends $N_0$, and $dN_i/dt$ only depends on $N_{i-1}$ and $N_i$, the Jacobi matrix is of the triangular form

$$J = \begin{pmatrix} -(p + d) & 0 & 0 & 0 & \ldots & 0 \\ 2p & -(p + d) & 0 & 0 & \ldots & 0 \\ 0 & 2p & -(p + d) & 0 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \ldots & 0 & 0 & 2p & -d \end{pmatrix}, \quad (A.8.3)$$

with a characteristic equation corresponding to Eq. (8.11).

**Question 8.3. Accumulating mutations**

a. Mathematically this would seem appropriate, and it is similar to Eq. (8.9).

b. The problem with a cascade like this is that the variables described by ODEs are continuous, whereas actual cell numbers cannot become lower than a single cell. Solving this cascade, either mathematically or numerically, would immediately populate all the $N_i$ equations, and hence deliver very small densities into the equations for the senescent and leukemic cells at very early time points. For the senescent cells this is not a problem because they die and disappear, but since the leukemic cells have a growth rate that could be much faster than the division rate of the progenitor cells, they will start to expand much earlier than expected.

c. Note that the vector in the `leukemia.R` document is indexed from 1 to `n.div` (and not from 0 to `n`), and that `R` allows one to write all the ODEs for $dN_i/dt$ as a single (fast) vector operation. The leukemic cells appear way too early in this model.

d. This model violates the constraint that size of a population of cells should be described by an integer number. When populations are large this is typically not a problem, but small populations should be described by stochastic models describing the behavior of individual cells. This problem is also known as the “atto-fox” problem. When $pN_i < 1$ one should define this term as the probability that a single cell divides and delivers exactly two daughter cells in the next generation. The formal procedure to do this is called a Gillespie simulation [7], in which every term of the model is translated into an event happening with a probability
depending on the current population densities. Stochastically executing individual events on the basis of these probabilities, the population densities will only change by a single cell at a time. The ODEs basically describe the average that is expected from running a large number of Gillespie simulations. If you like this question we could turn this model into a project.

e. No the Smith-Martin model would only delay the formation of the leukemic cells by \( n \times \Delta \) days, i.e., by the total time spent in the B-phase division, which is short even if cells divide once per year.

**Question 8.4. Chaos**

Figures made with the previous version of Grind:

![Diagram](image)

a. See Panel (a). Yes, for their values of \( b_1 \) the steady state is unstable.

b. See Panel (b). Yes, the unstable steady state around which the trajectory cycles is located above the nullcline of the top-consumer, and since the average consumer density is expected to be higher than this, we expect the top-consumer to invade.

c. Use Grind for the last 3 items.

**Question 8.5. Detritus**

A simple model would be

\[
\frac{dR}{dt} = [bF - d_R - c_1N]R , \quad \frac{dN}{dt} = [c_1R - d_N - c_2M]N \quad \text{and} \quad \frac{dM}{dt} = [c_2N - d_M]M ,
\]

where \( F = K - R - N - M \). This shows that the \( dN/dt \) and \( dM/dt \) equations do not change. For \( N = M = 0 \) one now obtains \( \bar{R} = K - d_R/b \), which increases linearly with the total amount of nutrients, \( K \), in the system. When \( N > 0 \) and \( M = 0 \), one solves \( \bar{R} = d_N/c_1 \) from \( dN/dt = 0 \), and from \( [b(K - \bar{R} - N) - d_R - c_1N] = 0 \) one solves that

\[
\bar{N} = \frac{c_1bK - bd_N - c_1d_R}{c_1(b + c_1)}
\]

which increases linearly with \( K \), and becomes positive when \( K > (bd_N - c_1d_R)/(c_1b) \). When \( N > 0 \) and \( M > 0 \) one again solves \( \bar{N} = d_M/c_2 \) from \( dM/dt = 0 \), \( \bar{M} = \frac{c_1R - d_N}{c_2} \) from \( dN/dt = 0 \). After substitution of \( \bar{N} \) and \( \bar{M} \) one solves \( \bar{R} \) from \( dR/dt = 0 \), i.e.,

\[
\bar{R} = \frac{b(c_2K + d_N - d_M) - c_1d_M - c_2d_R}{b(c_1 + c_2)} .
\]

Thus, the steady state resource density again only depends on \( K \) when the food chain has an odd length.
Question 8.6. Kinetic proofreading

For receptors having \( n \) different phosphorylation sites one writes
\[
\frac{dC_0}{dt} = k_1 FL - (k_{-1} + k_2)C_0, \quad \frac{dC_i}{dt} = k_2 C_{i-1} - (k_{-1} + k_2)C_i \quad \text{and} \quad \frac{dC_n}{dt} = k_2 C_{n-1} - k_{-1} C_n,
\]
for \( i = 1, 2, \ldots, n - 1 \), with the conservation equation \( F = R - \sum_{i=0}^{n} C_i \). Summing these equations gives an ODE for the total amount of complexes,
\[
\frac{d\hat{C}}{dt} = k_1 FL - k_{-1}\hat{C} = k_1 (R - \hat{C})L - k_{-1}\hat{C},
\]
Setting \( d\hat{C}/dt = 0 \) reveals that
\[
\hat{C} = \frac{k_1 RL}{k_{-1} + k_1 L} = \frac{RL}{K_m + L},
\]
where \( K_m = k_{-1}/k_1 \), which is nothing more than the normal Michaelis Menten expression. This is a natural result because we are just counting the number of phosphorylation steps, and at each step we have the same off rate, \( k_{-1} \). Setting all ODEs in the first equation to zero, one obtains
\[
C_i = \left( \frac{k_2}{k_{-1} + k_2} \right)^i C_0 \quad \text{and} \quad C_n = \frac{k_2}{k_{-1}} C_{n-1} = \frac{k_2}{k_{-1}} \left( \frac{k_2}{k_{-1} + k_2} \right)^{n-1} C_0,
\]
for \( i = 0, 1, \ldots, n - 1 \). Since these ultimately all depend on \( C_0 \) we solve \( dC_0/dt = 0 \),
\[
k_1 (R - \hat{C})L - (k_{-1} + k_2)C_0 = \frac{k_1 K_m RL}{K_m + L} - (k_{-1} + k_2)C_0 = k_{-1} RL \frac{K_m + L}{K_m + L} - (k_{-1} + k_2)C_0 = 0,
\]
to obtain that
\[
C_0 = \frac{k_{-1} RL}{(K_m + L)(k_{-1} + k_2)} = \frac{RL}{K_m + L} \frac{k_{-1}}{k_{-1} + k_2} = \frac{k_{-1}}{k_{-1} + k_2} \hat{C}.
\]

Hence
\[
C_n = \hat{C} \left( \frac{k_2}{k_{-1} + k_2} \right)^n = \frac{RL}{K_m + L} \left( \frac{k_2}{k_{-1} + k_2} \right)^n,
\]
where the first term is the Michaelis-Menten function describing the saturation in the total number of complexes at large ligand concentrations, and the second term provides the fraction of \( C_n \) in this total. The final term introduces a novel dependence of \( C_n \) on the off-rate, \( k_{-1} \), which becomes steep for large \( n \) (when \( k_{-1} \) is sufficiently large).

Answers to Chapter 9

Question 9.1. Migration

Figure made with the previous version of Grind:
a. Scaling the two carrying capacities to one, implies setting $A_{ii} = 1$, and simplifying the notation by defining $\gamma_1 = A_{12}$ and $\gamma_2 = A_{21}$ model would become

$$\frac{dN_1}{dt} = i + r_1N_1(1 - N_1 - \gamma_1N_2)$$

and

$$\frac{dN_2}{dt} = i + r_2N_2(1 - N_2 - \gamma_2N_1),$$

where $i$ is a small immigration rate.

b. For the four panels in Fig. 9.2 one obtains the nullclines in Panels (a)–(c) given that $i \ll 1$ (where we collapse the two cases with non-intersecting nullclines into Panel (b)).

c. From the vector field one can see that the steady states close to the carrying capacity are stable. The steady state in the middle of Panel (a) is stable, whereas that in the middle of Panel (c) is unstable.

d. In Panel (a) there is normal coexistence. In the other Panels there is no true competitive exclusion. However, at the steady state near the carrying capacity the density of the rarest species is so low that one can consider it to be excluded.

Question 9.2. Tilman’s competition model

Figure made with tilmanMin.R:

a. Solving $\alpha_{11}c_{11}R_1 + \alpha_{12}c_{12}R_2 - \delta_1 = 0$ gives $R_{11}^* = \frac{\delta_1}{\alpha_{11}c_{11}}$ and $R_{12}^* = \frac{\delta_1}{\alpha_{12}c_{12}}$. Similarly, solving $\alpha_{21}c_{21}R_1 + \alpha_{22}c_{22}R_2 - \delta_2 = 0$ gives $R_{22}^* = \frac{\delta_2}{\alpha_{22}c_{22}}$ and $R_{21}^* = \frac{\delta_2}{\alpha_{21}c_{21}}$.

b. In Fig. 9.6a $R_{11}^* > R_{21}^*$ and $R_{22}^* < R_{12}^*$, i.e., each consumer requires less than the other consumer of the resource it consumes most. In Fig. 9.6b this is the other way around, which leads to unstable steady state, corresponding to a founder controlled situation. (Note that
Grind indicates the stability of the steady state by a bullet or a circle, and that the fact that the black production vector in Fig. 9.6b falls in between the two colored consumption vectors confirms that the 4-dimensional steady state exists (see the online tutorial)).

c. A consumer always needs both resources but is limited by the resource providing the lowest birth rate, $a_{ij}c_j \vec{R}_j$. If one of the resources were to decline it would ultimately become limiting.

d. To sketch these nullclines one first ignores the minimum function to find that the $d\vec{N}_1/dt = 0$ nullcline is given by the vertical line $R_{11}^* = \frac{\delta_1}{a_{11}c_{11}}$ and the horizontal line $R_{12}^* = \frac{\delta_1}{a_{12}c_{12}}$ (see the green lines in Panel (a)). Only resource densities ($\vec{R}_1, \vec{R}_2$) larger than these two lines allow $d\vec{N}_1/dt > 0$, i.e., $\vec{N}_1$ can only grow in the region defined by the upper-right green square. Similarly, the $d\vec{N}_2/dt = 0$ nullcline is constructed from the lines $R_{22}^* = \frac{\delta_2}{a_{22}c_{22}}$ and $R_{21}^* = \frac{\delta_2}{a_{21}c_{21}}$ (see the orange lines in Panel (a)). Note that the upper circle denotes the point $\vec{R}_1 = \vec{R}_2 = 1$ where both resources are at carrying capacity, $s_i/d_i$.

e. Apparently, the steady state is now stable when $R_{11}^* > R_{21}^*$ and $R_{22}^* > R_{12}^*$. In the stable situation of Panel (b) the steady state is located on the vertical part of the $d\vec{N}_1/dt = 0$ nullcline, i.e., where $\vec{N}_1$ is limited by $\vec{R}_1$, and the horizontal part of the $d\vec{N}_2/dt = 0$ nullcline, i.e., where $\vec{N}_2$ is limited by $\vec{R}_2$. Thus, this still corresponds to a situation where each consumer is limited by the resource it consumes most. Note that in Panels (a) and (b)

\[
\left( \frac{\partial R_1 N_1'}{\partial R_1 N_1'} \right) = \left( \begin{array}{c} 0 \\ + \\ 0 \end{array} \right) \quad \text{and} \quad \left( \frac{\partial R_2 N_2'}{\partial R_2 N_2'} \right) = \left( \begin{array}{c} + \\ 0 \\ + \end{array} \right),
\]

respectively (see the online tutorial on http://tbb.bio.uu.nl/rdb/bm/clips/tilman).

f. The nullclines in Panels (c) and (d) were made the quasi steady state model in tilmanMin.R, and correspond to the Tilman diagrams of Panels (a) and (b), respectively. This confirms that the intersect in Panel (a) corresponds to the classical Lotka-Volterra competition situation with an unstable non-trivial state, and two stable carrying capacities on the axes.

**Question 9.3. Co-existence by trade-offs?**

a. No this is not an appropriate model for substitutable resources because the birth rate increases with every non-essential resource that is added to the ecosystem. Consumers are expected to approach their maximal birth rate at sufficiently high densities of just one resource if these are non-essential.

b. One could argue that this would become a model for essential resources when the birth rates, $\delta_{ij}$, on the individual resources are made smaller than the death rates, $\delta_i$. Consuming a combination of resources then becomes essential, but this interpretation remains somewhat contrived.

c. One can define a trade-off by adding terms like $c_{12}<-c_{11}$; $c_{21}<-c_{22}$; $c_{31}<-c_{32}$ to the model, which defines a total consumption rate, $c$, that is the same for all consumers, and play with the other consumption rates. For substitutable resources defined by Eq. 9.21 (in the file additive.R), one indeed finds that the three consumer nullclines intersect in one steady state in a Tilman diagram spanned up by two resources, but this requires that all other parameters like the saturation constants and the death rates are also the same. For essential resources defined by Eq. 9.24 (in the file essential.R), defining this trade-off is not sufficient to let the three consumer nullclines intersect in one steady state. Thus, the result seems rather artificial: it is not based upon an appropriate model, and requires unreasonable parameter constraints. This would be a good project to study further.

**Question 9.4. Equilibrium co-existence**

Figure made with the previous version of Grind:
a. Since the trees can just overgrow the grass they experience areas occupied by grass as “empty space”, and they do not suffer from the presence of the grass. The grass can only expand into true empty space, which is reflected by the $T - N_1 - N_2$ term, and suffers from the expansion of trees into grassy areas, which is reflected the $b_1 N_1 N_2$ term.

b. The $\frac{dN_1}{dt} = 0$ nullcline corresponds to the line $N_1 = T - \frac{d_1}{b_1} = T \left(1 - \frac{1}{R_{01}}\right)$. The $\frac{dN_2}{dt} = 0$ nullcline is given by $N_2 = T - \frac{d_2}{b_2} - N_1 \left(1 + \frac{b_1}{b_2}\right)$. The vector field demonstrates that the non-trivial steady state is stable, and that the two carrying capacities, $\bar{N}_i = T - d_i/b_i$, are unstable when the nullclines intersect.

c. These lines will intersect, and give rise to the phase space shown above, when $\frac{b_2 T - d_2}{b_1 + b_2} > \frac{b_1 T - d_1}{b_1}$, revealing that the maximum growth rate $r_{\text{max}} = b_2 T - d_2$ of the grass should at least be faster than that of the trees.

d. Yes, this is a counterexample. The reason is that the competition between these two species is not defined by their parameters, but by the structure of the model. Although the trees and the grass compete for the same resource, i.e., space, their competitive relationship is asymmetric just because trees are larger and can shadow the grass. One could argue that the trees and the grass (partly) belong to a different ecological guild, and that the model implicitly adds another resource dimension, i.e., light, allowing the trees to be superior over the grass with respect to this additional resource. For bacteria growing in a petri dish one could envision that $N_1$ produces a toxin killing $N_2$, which would enable the first species to overgrow the second one, irrespective of their respective birth and death rates. Again, the toxin would add another dimension allowing an independent ranking of competitive dominance. Finally, this deepens our understanding of the classical $r$-selected and $K$-selected species, as this model would allow $K$-selected species to invade into areas occupied by $r$-selected species, irrespective of their parameters.

**Question 9.5. Non-equilibrium co-existence**

Figure made with `noneqco.R`:
a. These are the standard phase planes of the Monod-saturated model, and the Lotka-Volterra model, respectively.

b. The initial slope of the saturated functional response should be steeper than that of the linear one (see Panel (a)).

c. The best approach is to first make a system where the Monod saturated consumer co-exists with the resource on a stable limit cycle. Then add the second consumer, and make sure that it can invade on this limit cycle. The nullcline of the Monod saturated consumer has to be located at a lower resource value than that of the linear consumer to enable the Monod saturated consumer to invade in the steady state of the linear consumer with the resource, i.e.,  \( \frac{h}{a_2/d_2-1} < \frac{d_1}{a_1} \) (see Panel (b)), where the red ellipse depicts a stable limit cycle.

d. Yes, one can always give the species with the linear functional response a saturation function with a large saturation constant.

**Question 9.6. Larvae and adults**

a. A simple model would be:

\[
\frac{dL}{dt} = rA - dL(1 + eL) - mL \quad \text{and} \quad \frac{dA}{dt} = mL - \delta A ,
\]

where we assume density dependent death by competition between the larvae. The steady state can be solved by first setting \( \frac{dA}{dt} = 0 \) delivering \( A = mL/\delta \). Substituting this into \( \frac{dL}{dt} = 0 \) gives

\[
\bar{L} = \frac{1}{e} \left[ \frac{m}{d} \left( \frac{r}{\delta} - 1 \right) - 1 \right] , \quad \bar{A} = \frac{m}{\delta} \bar{L} ,
\]

which requires \( \alpha = r/\delta > 1 \) and \( m(\alpha - 1)/d > 1 \). The carrying capacity of this population would be defined as either \( \bar{L} \) or \( \bar{A} \).

b. Adding two predators changes to model into

\[
\frac{dL}{dt} = rA - dL(1 + eL) - mL - c_1LN_1 , \quad \frac{dA}{dt} = mL - \delta A - c_2AN_2 ,
\]

\[
\frac{dN_1}{dt} = (c_1L - d_1)N_1 \quad \text{and} \quad \frac{dN_2}{dt} = (c_2A - d_2)N_2 .
\]

Solving the steady state of the latter two gives \( \bar{L} = d_1/c_1 \) and \( \bar{A} = d_2/c_2 \). Substituting this into \( \frac{dL}{dt} = 0 \) and \( \frac{dA}{dt} = 0 \) gives

\[
\bar{N}_1 = \frac{rd_2}{c_2d_1} - \frac{m}{c_1} - d_1 \left( 1 + \frac{ed_1}{c_1} \right) \quad \text{and} \quad \bar{N}_2 = \frac{md_1}{c_1d_2} - \frac{\delta}{c_2} .
\]

Since one can always choose parameters such that \( \bar{N}_1 > 0 \) and \( \bar{N}_2 > 0 \) co-existence is possible.
Question 9.7. Gradients with sharp borders

![Graph of gradients with sharp borders](image)

a. Solving \( dN_1/dt = N_1(b_1(1 - N_1) - d_1 - d_S) \) gives the trivial \( \bar{N}_1 = 0 \) solution and the carrying capacity \( \bar{N}_1 = 1 - \frac{d_1 + d_S}{b_1} = 1 - 1/R_0 \). This declines when the concentration of salt increases (because \( d_S \) increases with the salt).

b. See Panel (a): \( \bar{N}_1 \) declines linearly with \( d_S \). The species can no longer be maintained when \( 1 - \frac{d_1 + d_S}{b_1} = 0 \), i.e., when \( d_S = b_1 - d_1 \).

c. In the absence of salt the two nullclines are parallel lines with slope \(-1\), \( N_2 = 1 - \frac{d_1}{b_2} - N_1 \) and \( N_2 = 1 - \frac{d_2}{b_2} - N_1 \), respectively. \( N_1 \) will outcompete \( N_2 \) because it has a higher \( R_0 \) at low concentrations of salt. See Panel (b). Along the gradient \( d_S \) will increase, and the \( dN_1/dt = 0 \) nullcline will be given by \( N_2 = 1 - \frac{d_1 + d_S}{b_2} - N_1 \). The nullcline will shift downward and at some value of \( d_S \) cross the \( dN_1/dt = 0 \) nullcline. Beyond that \( N_2 \) will outcompete \( N_1 \) and approach its carrying capacity \( N_2 = 1 - \frac{d_2}{b_2} \).

d. See Panel (c). Along a smooth gradient we expect a sharp transition between the species due to competitive exclusion.

Question 9.8. Density dependent birth rate

Figure made with the previous version of Grind:

![Graph of density dependent birth rate](image)

a. \( R_0 = b/d \) or \( R_0 = \frac{b}{H+a} \), depending on its definition.

b. The QSS of the resource is \( R = 1 - aN \) by substitution gives

\[
\frac{dN}{dt} = \left[ b - a(1-aN) \right] \frac{N}{h+a(1-aN) - d} \cdot
\]

which can be simplified into

\[
\frac{dN}{dt} = \left[ b \frac{1-aN}{H-aN} - d \right] N .
\]

where \( H = 1 + h/a \), which is larger than one.
c. The maximum birth rate is \( \frac{b}{H} = \frac{ab}{a + h} \). Hence \( R_0 = \frac{b}{a + \frac{a}{H}} \), which is the same as the second answer in a.

d. To sketch the per capita birth rate as a function of \( N \) we need to consider the function \( y = \frac{b}{H - a} \) knowing that \( H > 1 \). For \( N = 0 \) this delivers \( y = \frac{b}{H} \), and for \( y = 0 \) we find \( N = 1/a \). A horizontal asymptote is found by dividing numerator and denominator by \( N \), i.e., \( y = \frac{b}{H/\sqrt{\sqrt{N}/a}} \), and letting \( N \to \infty \) to find that \( y \to b \). A vertical asymptote is located at \( N = H/a \). Because \( H > 1 \) we know that the intersections with the horizontal and vertical axis fall below the asymptotes. See the sketch in the Figure above.

e. This concave shape is what we considered most realistic in Chapter 3. For instance see Fig. 3.3c and Fig. 3.5b.

f. The QSS now equals \( R = 1/(1 + aN) \) which gives a per capita birth rate of \( \frac{b}{1 - h/a + hN} \) which is convex. Again the devil is in the details, as the shape of the consumers density dependence depends on the nature of the resource.

**Question 9.9. Fitness**

a. Writing out Eq. (9.12) explicitly, and combining parameters

\[
R^*_i = \frac{h_i}{b_i/d_i - 1} = \frac{h_i}{r_i - 1},
\]

where \( r_i = b_i/d_i \), we have a simple expression for which species wins (i.e., the one with the lowest \( R^*_i \)). Writing

\[
\hat{R}_0 = \frac{b_i}{d_i} \frac{\tilde{R}}{h_i + \tilde{R}} = \frac{r_i}{h_i/\tilde{R} + 1},
\]

we can solve for \( r_i \) and write Eq. (A.9.4) in terms of \( \hat{R}_0 \):

\[
R^*_i = \frac{h_i}{\hat{R}_0 (h_i/\tilde{R} + 1) - 1} \quad \text{where} \quad \tilde{R} = \frac{s}{d}.
\]

The species with the lowest fitness \( \hat{R}_0 \) can therefore be the superior competitor when its \( h_i \) is sufficiently smaller than that of the other competitors. In conclusion, \( \hat{R}_0 \) does not uniquely identify the superior competitor, and the critical resource density, \( R^* \), remains the best indicator.

b. The model competition.R provides an example where an \( r \)-selected species, with the lowest \( \hat{R}_0 \) and carrying capacity, outcompetes a \( K \)-selected species.

**Answers to Chapter 10**

**Question 10.1. Invasion criterion**

Figures made with the model invasion.R:
a. Since the diet of the two established species does not overlap, their resource usage curves should not overlap. The curve of the invading species should be located in the middle, and have an equal overlap with both species (here indicated by the $\alpha$). See Panel (a).

b. Since $N_1$ and $N_3$ do not compete the model simplifies to
\[
\frac{dN_1}{dt} = rN_1(1-N_1-\alpha N_2), \quad \frac{dN_2}{dt} = rN_2(1-N_2-\alpha N_1-\alpha N_3) \quad \text{and} \quad \frac{dN_3}{dt} = rN_3(1-N_3-\alpha N_2),
\]
where we have scaled all carrying capacities to one.

c. Because $N_2 \approx 0$ the steady state before invasion is $\bar{N}_1 = \bar{N}_3 = 1$, and hence $dN_2/dt \simeq rN_2(1-2\alpha)$. For invasion one requires $dN_2/dt > 0$, meaning that $1 - 2\alpha > 0$, giving that $\alpha < 1/2$. Since $N_2$ has an overlap of one with itself, the total overlap with the two other species should be less than the overlap with itself.

d. For $N_2 = 0$ the nullclines of $N_1$ and $N_3$ are perpendicular lines at $N_1 = 1$ and $N_3 = 1$, respectively (see Panel (b)). The $N_2$ nullcline intersects the $N_1$ and the $N_3$ axis at $1/\alpha$. At the critical invasion point the $dN_2/dt = 0$ nullcline should go exactly through the point $N_2 = 0$ and $N_1 = N_3 = 1$ (see Panel (b), where the origin and the carrying capacities are indicated by circles). When $N_2$ can invade the $dN_2/dt = 0$ nullcline will intersect at larger $N_1 = N_3$ values, and then there will be a stable 3-dimensional steady state.

**Question 10.2. Control by parasites**

a. Define $T = S + I$ as the total population size of susceptible and infected birds, and write
\[
\frac{dS}{dt} = bT(1-T) - dS - \beta SI \quad \text{and} \quad \frac{dI}{dt} = \beta SI - \delta I
\]

b. The $R_0$ of the birds is $b/d$ and the carrying capacity is scaled $K = 1 - 1/R_0 < 1$.

c. The $R_0$ of the parasites is $R'_0 = \beta K/\delta$.

d. In the presence of the parasite the number of susceptibles is solved from $dI/dt$ which gives $S = \delta/\beta = K/R'_0$.

e. Defining $O$ as the other species one could write
\[
\frac{dS}{dt} = bT(1-T-O) - dS - \beta SI, \quad \frac{dI}{dt} = \beta SI - \delta I \quad \text{and} \quad \frac{dO}{dt} = bO(1-T-O) - d_0 O,
\]
with $d_0 > d$. Note that the other species can invade whenever $b(1-T)/d_0 > 1$.

f. Thus, if the infection is sufficiently harmful, i.e., $T \ll K$, the other species can invade despite its lower fitness.

g. If each species is sufficiently down-regulated by its parasite the resource density can stay high and many species can be maintained [10].
**Question 10.3. Monopolization**

**a.** Yes, since most competition situations are “founder controlled”, species that grow faster are more likely to outcompete the species that grow slower.

**b.** No, one would still have that species will survive in a few patches just because they arrived there earlier, or in greater numbers, than other species.

**Question 10.4. Symbiosis**

Figures made with the previous version of Grind:

**a.** A simple model makes the birth rate a saturation function of the other species and assumes density dependent death:

\[
\frac{dN_1}{dt} = N_1 \left[ \frac{b_1 N_2}{h + N_2} - d_1 (1 + e_1 N_1) \right] \quad \text{and} \quad \frac{dN_2}{dt} = N_2 \left[ \frac{b_2 N_1}{h + N_1} - d_2 (1 + e_2 N_2) \right].
\]

Note that it is quite natural that the symbiotic effect has some maximum. The \( dN_2/dt = 0 \) nullcline is given by

\[ N_2 = \frac{1}{e_2} \left( \frac{R_0}{R_0 - 1} \right), \]

where \( R_0 = b_2 / d_2 \). This is a saturation function starting at \( N_2 = -1/e_2 \) when \( N_1 = 0 \). See Panel (a). The \( dN_1/dt = 0 \) nullcline is just the mirror image of this (Panel (a)). The nullclines intersect in three steady states. The origin and the system at “carrying capacity” are stable nodes, separated by a saddle point in the middle. The stable manifold of this saddle point defines the separatrix between the two stable steady states.

**b.** When \( N_1 \) is the saprophyte, one would write

\[
\frac{dN_1}{dt} = N_1 \left[ \frac{b_1 N_2}{h + N_2} - d_1 (1 + e_1 N_1) \right] \quad \text{and} \quad \frac{dN_2}{dt} = N_2 \left[ b_2 N_1 + d_2 (1 + e_2 N_2) \right].
\]

The \( dN_1/dt = 0 \) nullcline stays the same (see Panel (a)), and the \( dN_2/dt = 0 \) nullcline is a horizontal line located at its carrying capacity.

**c.** The other species could merely increase the birth rate, e.g.,

\[
\frac{dN_1}{dt} = N_1 \left[ b_1 + \frac{\beta_1 N_2}{h + N_2} - d_1 (1 + e_1 N_1) \right] \quad \text{and} \quad \frac{dN_2}{dt} = N_2 \left[ b_2 + \frac{\beta_2 N_1}{h + N_1} - d_2 (1 + e_2 N_2) \right],
\]

where \( \beta_i \) is the maximum birth rate due to the presence of the symbiont, and \( b_i \) is the maximum birth rate in the absence of the symbiont. The nullclines have been depicted with Grind in Panel (c).

**d.** Yes, just make sure that \( R_0_i = b_i / d_i < 1 \) in the absence of the other species, and \( (b_i + \beta_i) / d_i > 1 \) to enable growth in the presence of the symbiont. Panel (c) depicts the typical phase space when \( R_0_i > 1 \).
Question 10.5. Infinite Niche-matrix

a. The partial derivatives of the off-diagonal elements

\[ \partial_{N_j} N_i - \sum_j A_{ij} N_i N_j \text{ are } 0, 0, \ldots, -A_{ij} N_i, 0, \ldots. \]

Because all populations have the same steady state, \( \bar{N} \), they become \( -\alpha \bar{N}, -\alpha^4 \bar{N}, -\alpha^9 \bar{N} \).

The partial derivatives on the diagonal

\[ \partial_{N_i} N_i - \sum_j A_{ij} N_i N_j \text{ are } 1 - 2\bar{N} - \sum_{j \neq i} A_{ij} \bar{N}, \]

and hence the Jacobian is:

\[
J = \begin{pmatrix}
\ldots & -\alpha \bar{N} & 1 - 2\bar{N} - \sum_{j \neq i} A_{ij} \bar{N} & -\alpha \bar{N} & -\alpha^4 \bar{N} & -\alpha^9 \bar{N} & \ldots \\
\ldots & -\alpha^4 \bar{N} & -\alpha \bar{N} & 1 - 2\bar{N} - \sum_{j \neq i} A_{ij} \bar{N} & -\alpha \bar{N} & -\alpha^4 \bar{N} & -\alpha^9 \bar{N} & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots
\end{pmatrix}
\]

Moving one of the \( 2\bar{N} \) on the diagonal into the sum we obtain

\[
J = \begin{pmatrix}
\ldots & -\alpha \bar{N} & 1 - \bar{N} - \sum_i A_{ij} \bar{N} & -\alpha \bar{N} & -\alpha^4 \bar{N} & -\alpha^9 \bar{N} & \ldots \\
\ldots & -\alpha^4 \bar{N} & -\alpha \bar{N} & 1 - \bar{N} - \sum_i A_{ij} \bar{N} & -\alpha \bar{N} & -\alpha^4 \bar{N} & -\alpha^9 \bar{N} & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots
\end{pmatrix}
\]

Finally because \( \bar{N} = 1/\sum A_{ij} \) all diagonal elements can be simplified as \( -\bar{N} \), i.e.,

\[
J = \begin{pmatrix}
\ldots & -\alpha \bar{N} & -\bar{N} & -\alpha \bar{N} & -\alpha^4 \bar{N} & -\alpha^9 \bar{N} & \ldots \\
\ldots & -\alpha^4 \bar{N} & -\alpha \bar{N} & -\bar{N} & -\alpha \bar{N} & -\alpha^4 \bar{N} & -\alpha^9 \bar{N} & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots
\end{pmatrix}
\]

b. The Jacobian is equal to \( -\bar{N}A \), where \( A \) is the interaction matrix. The signs of the eigenvalues of the Jacobian are equal to those of the interaction matrix.

Question 10.6. Random Jacobian

a. At low connectivities the characteristic equation will tend to be defined by the trace, i.e., \( \lambda = -1 \).

b. For large \( n \) Eq. (10.9) holds, for small \( n \) the dominant eigenvalue tends to be \( \lambda = -1 \).

c. Change the assignments in the for loops and see what happens.

d. Change the definition of the diagonal elements by \( \text{diag()} \) into a for loop setting a fraction of them to \( -1 \). This will markedly decrease the fraction of matrices with a dominant eigenvalues less than zero.

Answers to Chapter 11

Question 11.1. Biomanipulation

Figures made with the previous version of Grind:
a. For $F = 0.15$, $h = 1$, $k = 10$, $m = 0.4$ and $p = 0.5$ the phase space is given by Panel (a), which has three non-trivial steady states. By decreasing the carrying capacity the upper two states disappear.

b. Depleting the fish by setting $F = 0$ will transiently remove the lower two steady states from Panel (a), and the system will approach the attractor located near the top of the parabola. If the fish were to regrow to same $F = 0.15$ density, the two lower steady states would reappear, but the system would remain in the upper attractor because it is locally stable.

c. Changing the carrying capacity $k$ yields the bifurcation diagram of Panel (b). The heavy solid line depicts stable steady states, the light solid line unstable steady states, and the green bullets denote the amplitude of a stable limit cycle. There is a transcritical bifurcation at $k = 4$, a saddle-node bifurcation at $k \approx 9$, a Hopf bifurcation at $k \approx 11.5$, and another saddle-node bifurcation at $k \approx 19.5$. The stable limit cycle that is born at the Hopf bifurcation dies by a so-called “global bifurcation” around $k = 12$, when it “glues” with the stable manifold of the saddle point in the middle.

Question 11.2. Early warning signals

a. Using 

```
continue(state=s,x="c",y="X",xmin=0.1,xmax=3,ymax=10)
```

one obtains the classic picture with two saddle-node bifurcations.

b. Drawing normally distributed disturbances of the population size (with 10% standard deviation) one could run something like the following R-script, where the call to `plot()` depicts $X_{t+1}$ as a function of $X_t$, and the call to `cor()` computes the correlation. One should do this for various values of $c$ to test if the variation and the auto-correlation increases when the saddle-node bifurcation is approached:

```r
after <- "state[1]<-abs(state[1]*rnorm(1,1,0.1))"
p["c"] <- 2; s <- newton(run()) # start at steady state
data <- run(750,after=after,table=TRUE)
plot(data$X[1:nrow(data)-1],data$X[2:nrow(data)],type="p")
cor(data$X[1:nrow(data)-1],data$X[2:nrow(data)])
```

c. Use

```r
after <- "parms[1]<-abs(parms[1]*rnorm(1,1,0.1))"
```

d. Using the parameters in the model defined by `warning.R`, we basically get no early warning signal.

e. No, we learn that one does not always receive an early warning signal when a saddle-node bifurcation is approached. This would then be absent from the return time and from the autocorrelation.

Answers to Chapter 12

Question 12.1. Fishing herring

The first thing to think about is the parameters of the model. For instance, one could consider the Herring population in the North sea, and realize that the population will have a carrying capacity amounting to an enormous number of individuals, or an enormous amount of biomass. Fortunately, one can always scale the population density in a model by the carrying capacity of the population. Thus, we can set the carrying capacity, $k = 1$, realizing that $H = 1$ corresponds to a Herring population at carrying capacity in the North sea. The next parameter is the natural rate of increase, $r$. We first need to define a time-scale, and for a Herring population with a yearly reproduction cycle, a time-scale of years seems a proper choice. If $t$ is measured in years we can think of a growth rate per year, and using our biological intuition about fish or the size of Herring, it seems obvious that a growth rate of 1% per year seems slow and that they will not easily grow faster than 100% per year. Thus, setting $r = 0.1$ per year, or $r = 0.2$ per year, seem reasonable choices. One can actually check this by studying the recovery rate of a crashed Herring population in the absence of fishing: setting $H = 0.01$ and $Q = 0$, and run the model for
a few decades to test how long it takes for the population to recover and approach its carrying capacity. Once you think you have found realistic parameters, you can start on the rest of the exercise.

a. Starting at the carrying capacity, and setting \( Q = rk/4 \) to study the impact of this maximum yearly harvest, one finds that the population approaches \( H = k/2 \) in the absence of noise. However, the population will always go extinct if there is enough noise.

b. Now the population will not go extinct as long as \( f < r \).

c. At the steady state \( dH/dt = rH(1 - H/k) - fH = 0 \), or \( \bar{H} = k(1 - f/r) \), the total harvest is \( f\bar{H} \). Taking the derivative, \( \partial f \), of \( f\bar{H} \), and setting that to zero gives \( k - (2k/r) f = 0 \) or \( f = r/2 \). Substituting that into \( \bar{H} \) gives \( \bar{H} = k/2 \), i.e., half of the carrying capacity.

d. The population will no longer go extinct. Even noise on the “optimal” \( f \) will not drive the population to extinction.

e. The optimal harvest \( f\bar{H} \) at \( f = r/2 \) is \( rk/4 \), which is equal to \( Q \). Thus, catching a fraction of the Herring population on average allows for the same maximum harvest, but is much more robust. Note that a shortcut to the same result is to see that this optimum is reached when the harvest function, \( f\bar{H} \), crosses the growth function, \( rH(1 - H/k) \), in its maximum \( rk/4 \) at \( H = k/2 \).

Question 12.2. Fitting the Gause data from 1934

a. Yes, the fit looks reasonable and starting with the estimates of Gause \([6]\) we obtain very similar estimates for the two growth rates and carrying capacities.

b. For \textit{Paramecium aurelia} we obtain \( \alpha \approx 1.05 \) and for \textit{P. caudatum} we obtain \( \beta \approx 0.64 \). However, this does not mean that \textit{P. aurelia} suffers more from \textit{P. caudatum} than the other way around, because these parameters remain to be divided by the —quite different— carrying capacities. This can easily be checked by calling \texttt{plane(xmax=110,ymax=110,eps=-0.01)} for the estimated parameters, revealing that the nullclines fail to intersect, and that \textit{P. aurelia} is the strongest competitor. Note that this probably the first time in your life that you sketch nullclines based upon measured parameters.

c. Since \textit{P. aurelia} suffers more from \textit{P. caudatum} than from itself, it could be that the species are competing for more than one essential resource, and that \textit{P. caudatum} consumes more than \textit{P. aurelia}. However, also note that \( \alpha \approx 1 \) and that we could be over-interpreting the fact that \( \alpha > 1 \) (see below).

d. Fortunately we find similar results, but this is at least partly due to the fact that by going step wise, and by using Gause’s estimates, we have such a good initial guess. Try other initial guesses to test how much this depends on the guess.

e. Yes, given a good initial guess the confidence intervals suggest that all parameters are identifiable. The confidence intervals for \( \alpha \) and \( \beta \) do overlap, and hence we cannot conclude that \( \alpha > \beta \). Additionally the confidence interval for \( \alpha \) includes \( \alpha = 1 \), so we have indeed over-interpreted the estimate that \( \alpha > 1 \).

f. The more mechanistic model explains the data at least equally good, with similar growth rates, and it may suggest that \textit{P. caudatum} consumes more of the resource. However, when fitting the data where both species are competing we find unexpected estimates for the death rate and consumption of \textit{P. aurelia}. Apparently, there is too much freedom here, meaning that not all parameters are identifiable.

Question 12.3. Paradox of enrichment

a. We could scale the density of the algae at which the birth rate vanishes to \( k = 2 \) and scale time by their expected life span such that \( d_1 = 1 \) (which implies a time scale of about one week). We could give the algae a maximum rate of increase of \( b - d_1 = 1 \) per week by setting \( b = 2 \) per week. Because the carrying capacity \( K = k(1 - 1/R_0) \) (see Table 3.1) we then obtain that \( K = 1 \). (An even simpler alternative approach would be to let the algae be described by logistic growth by setting \( d_1 = 0 \), then set \( b = 1 \) for the weekly time scale, and \( K = k = 1 \) to scale the density, as this leads to the same model, i.e., \( 2R(1 - R/2) - R = R(1 - R) \)).
Because the saturation of the functional response probably occurs at prey densities below the carrying capacity, it seems wise to set $h \ll K$, e.g., $h = 0.1$. We could scale the predator biomass such that its attack rate becomes $c = 1$, and let us give the predators a 2-fold longer life span, i.e., $d_2 = 0.5$. To give the predator an $R_0 = ce/d_2 = c/0.5 > 1$ we could set $c = 0.6$ such that the initial growth rate of the predator at high prey densities is about 0.1, i.e., 10-fold slower than the algae. For these values the predator nullcline is located at $h/(R_0 - 1) = 0.1/(0.6(0.5 - 1)) = 0.5$, which is just at the right hand side of the maximum of the prey nullcline at $(K - h)/2 = 0.45$.

b. Different possibilities for the location of the predator nullcline, without changing that of the prey, can be made by changing the death rate of the predator.

c. The carrying capacity can be changed by altering the density $k$ at which the birth rate of the algae vanishes.

d. First settle into a non-trivial steady state by giving proper initial values and then issuing the command `f<-newton(s)` to define the horizontal axis (where we avoid $h/R_0$). Then call `continue(f,x="k",xmin=0.1,xmax=5,y="N")` to define a horizontal axis (where we avoid $k = 0$ because the model is dividing by $k$), and we keep the predator nullcline at the vertical axis.

e. Replace the death rate of the predators by $d_2(1 + \epsilon N)$.

f. This indeed delivers a phase plane resembling that of consumer-resource model with a sigmoid functional response.

**Question 12.4. Cell division takes time**

a. When $t < \Delta$ the cells in the A-stage disappear at rate $dA/dt = -(d+p)A$, whereas those in the B-phase obey $dB/dt = pA - dB$. Since the two $pA$ terms cancel each other, summing both delivers $dN/dt = -dN$, which is a natural results because the cells can only die before the first divided cells appear at $t = \Delta$. The model with a flexible delay gives very similar results because the $n \Delta (B_i$ terms cancel each other when the $dB_i/dt$ equations are summed and $n$ is sufficiently large such that $B_n \approx 0$.

b. $dA/dt = -(p+d)A$ in the Smith-Martin model at early time points, i.e., the cells in the A-stage are declining until $t = \Delta$. Running the Smith-Martin model for a short period of time readily confirms this.

c. The expected time between divisions in the ODE model is $1/p'$, and in the Smith-Martin model it is the sum of the length of the A-stage and B-phase, i.e., $1/p + \Delta$. To compute the corresponding division rate, $p'$, in the simplest ODE model, $dN/dt = (p' - d)N$, we take the inverse of division time in the Smith-Martin model, i.e., $p' = 1/(p + \Delta)$.

d. No, cells dividing according to the Smith-Martin model will expand slower because they have a minimum interdivision time $\Delta$. Consider for simplicity that the cells do not die, i.e., $d = 0$. Cells in the ODE will then expand at a rate $r' = p'$, which for $p = 1$ and $\Delta = 0.5$ gives $r' = 1/(1 + 0.5) = 2/3$. The ultimate growth rate, $r$, of cells in the Smith-Martin model is given by Eq. \[12.3\]. Evaluating this numerically for $d = 0, p = 1$ and $\Delta = 0.5$, we obtain $r = 0.53$, which is slower than $r' = 2/3$. When cells die, those in the ODE also grow faster those in the Smith-Martin model (just test a few examples with $d > 0$).

e. The Smith-Martin model approaches the exponential growth model $dN/dt = rN$, which is not different from the $dN/dt = (p' - d)N$ model when the parameters are set by Eq. \[12.3\]. When the B-phase is short compared to the length of the A-stage the models will be very similar. The Smith-Martin model is therefore most appropriate for rapidly dividing cells with a division time dominated by the length of the B-phase. An example would be proliferating tumor cells, or lymphocytes during their clonal expansion phase [3].

**Question 12.5. Lymphocyte migration**

a. Because the total number of cells is not changing the number of cells in the blood can be described with a conservation equation. The ODE would have been $dB/dt = eS + dL - (i_S + ni_L)B$, and replacing the conservation equation with this ODE gives exactly the same
model. Numerically, the version with the conservation equation is more stable because small numerical errors could make \( dB/dt + dS/dt + dL/dt \neq 0 \).

b. The steady state is \( \bar{S} \approx 22, \bar{D} \approx 1.9, \) and \( \bar{L} \approx 72.4 \) cells, and hence there will be \( B \approx 3.7 \) cells in the blood. Every lymph node is expected to contain \( 72.4/38 = 1.9 \) cells, which is also revealed by \( \bar{D} \approx 1.9 \).

c. The only term missing in the denominator is the \( e_{LS}S \) term, and hence \( \bar{B} = \frac{e_{LS}}{e_{LS} + e_{LS} + e_{S}S + e_{S}S} \)

The recurrent pattern in the expression is that \( \bar{S} \) and \( \bar{L} \) increase with their own influx times the efflux of the other compartment. It makes sense that increasing the rate of efflux from the lymph nodes increases the number of cells in the spleen (and similarly in the blood).

d. Running the model for several days reveals that one needs 20 days of capturing cells to exceed \( D(t) = 50 \). Waiting for almost three weeks to recruit just 50% of the cognate naive T cells would be dangerously long.

e. Adding on a \( f_i = 9 \) fold increase in the influx to the draining lymph nodes reveals that it would take about 2.5 days to accumulate 50% of the cells. Note that this still requires that cognate cells do not egress from the draining lymph node: otherwise a new steady state is established where most of the cells reside in the other lymph nodes (because \( f_i < n - 1 \)).

f. To model infection with a gradual angiogenesis, one could replace the \( f_i i_L B \) term by \( \frac{1}{1 + e} (f_i - 1)i_L B + i_L B \) to define that at \( t = 0 \) the influx is \( i_L B \), at \( t = h \) the influx is \( \frac{(f_i - 1)i_L B}{2} + i_L B \), and that when \( t \to \infty \) the influx approaches the previous \( f_i i_L B \).

Question 12.6. Stem cell renewal

a. When on average half of the stem cell divisions deliver a new stem cell, their cell division is not changing the density of stem cells, and on average delivers a single daughter cell into the population of differentiated cells:

\[
\frac{dS}{dt} = -dS S \quad \text{and} \quad \frac{dD}{dt} = p_S S - d_D D ,
\]

where \( p_S \) is the fixed division rate of the stem cells, and the \( d \) parameters are death rates. This illustrates that the stem cell population will go extinct and that more than half of their divisions have to be asymmetric to compensate for their death rate (many models therefore set \( d_S = 0 \)). Thus, if \( f \) is the fraction of asymmetric divisions, and one needs to solve

\[
\frac{dS}{dt} = -p_S S + 2f p_S - d_S S = p_S(2f - 1)S - d_S S = 0 \quad \text{with} \quad \frac{dD}{dt} = 2p_S(1 - f)S - d_D D ,
\]

to derive that the stem cells will be at steady state when \( f = \frac{1}{2} + \frac{d_S}{2p_S} \) (which indeed approaches \( f \to 1/2 \) when \( d_S \ll p_S \)). Note that it is very unlikely that stem cells “know” this parameter expression for \( f \), which strongly suggests that the fraction of asymmetric divisions has to be regulated by the (local) environment.

b. The previous equation was already written with a free parameter, \( f \), for the fraction of asymmetric divisions, and we only need to rewrite that into a function, \( 0 < f(D) \leq 1 \), that should should decline with the density \( D \). A general choice would be a Hill function, e.g.,

\[
\frac{dS}{dt} = p_S[2f(D) - 1]S - d_S S = 0 \quad \text{and} \quad \frac{dD}{dt} = 2p_S[1 - f(D)]S - d_D D \quad \text{with} \quad f = \frac{1}{1 + D/h_f} .
\]

c. To allow for a density dependent division rate of the stem cells one multiplies the parameter \( p_S \) with another function, \( g(D) \) for growth rate, also declining as a function of \( D \):

\[
\frac{dS}{dt} = p_S g(D)[2f(D) - 1]S - d_S S = 0 \quad \text{and} \quad \frac{dD}{dt} = 2p_S g(D)[1 - f(D)]S - d_D D ,
\]

with \( f = \frac{1}{1 + D/h_f} \) and \( g = \frac{1}{1 + D/h_g} \). We have now arrived at the full, and quite complicated terms of the Lander et al. [9] model. Note that reading this equation is almost more difficult than deriving it.
d. If differentiated cells also divide we can add a similar growth term to $dD/dt$:

$$\frac{dS}{dt} = ps_g(D)[2f(D) - 1]S - dsS = 0 \quad \text{and} \quad \frac{dD}{dt} = 2ps[1 - f(D)]g(D)S + pDg(D) - dD,$$

where $G = \frac{1}{1 + h/D}$. There will be two dynamical regimes because the differentiated cells only strictly depend on the stem cells when $p_D < d_D$, i.e., if their maximal self-renewal rate cannot fully compensate for their death rate. Note that Lander et al. [9] also allow for asymmetric division in the early stages of the differentiated cells.

e. Yes in that model the fraction of asymmetric divisions depended almost linearly on the stem cell density.

**Question 12.7. Sexual reproduction**

Figure made with the previous version of Grind:

A model with density dependent death rates would be something like

$$\frac{dN_1}{dt} = N_1 \left[ \frac{b_1 N_1}{h + N_1} - d_1(1 + e_1N_1 + c_1N_2) \right] \quad \text{and} \quad \frac{dN_2}{dt} = N_2 \left[ \frac{b_2 N_2}{h + N_2} - d_2(1 + e_2N_2 + c_2N_1) \right]$$

This model is available as the file sexual.R. Note that one has to separate birth from death because the sexual reproduction should only affect reproduction, and not the death. Assuming that the chance to find a mate approaches one when the population is close to its carrying capacity, i.e., assuming $h \ll K$, the carrying capacity is approximately $K_i \approx (R_{0i} - 1)/e_i$. In the absence of sexual reproduction, i.e., when $h \to 0$, the nullclines are solved from $b_i - d_i(1 + e_iN_i + c_iN_j) = 0$ delivering the normal straight lines

$$N_2 = \frac{R_{01} - 1}{c_1} - \frac{e_1}{c_1}N_1 \quad \text{and} \quad N_2 = \frac{R_{02} - 1}{e_2} - \frac{c_2}{e_2}N_1 ,$$

which may or may not intersect, intersect in a stable state when there is resource competition, and intersect in an unstable steady state when there is interference competition. From these three situations one can sketch the three Panels depicted above. For instance, the $dN_1/dt = 0$ nullcline is given by

$$N_2 = \frac{1}{c_1} \left[ \frac{R_{01} N_1}{h + N_1} - 1 \right] - \frac{e_1}{c_1}N_1 ,$$

which resembles the straight line with slope $-e_1/c_1$ for $N_1 \gg h$, and which gives $N_2 = -1/c_1$ when $N_1 = 0$. Panel (a) would correspond to non-intersecting nullclines, Panel (b) to resource competition (i.e., $c_i < e_i$), and Panel (c) to resource competition (i.e., $c_i > e_i$). Note that sexual reproduction implies an Allee effect, and that (0,0), and the two carrying capacities are always stable (stable states are marked by closed boxes, unstable states by open boxes).
Question 12.8. Improving HIV therapy?

a. To check the growth rate one could run the model starting from \( s \leftarrow c(T=1,I1=0,I2=0,V=1) \) for ten days and compute from \( V(10) = V(0) e^{r10} = e^{r10} \) that \( r = \log[V(10)]/10 \simeq 1.5 \text{ d}^{-1}. \) The dominant eigenvalue of the infected steady state is \( \lambda \simeq 1.4 \) which is close to the desired growth rate of \( r = 1.5 \text{ d}^{-1}. \) This is natural because this eigenvalue gives the growth rate along the only eigenvector pointing outwards.

b. Running `continue(s,x="beta",y="V",ymin=-0.01)` one finds that the uninfected steady state becomes stable at \( \beta \simeq 2.2, \) which corresponds to \( R_0 = 1. \) This means that when \( (1 - \epsilon_\beta) \times 9.1 < 2.2 \) or \( \epsilon_\beta > 1 - 2.2/9.1 = 0.76 \) the virus should be eradicated in this model. This obviously does not happen in reality because there are latently infected cells.

c. A therapy correspond to \( \epsilon_\beta = 0.9 \) does give a slope close to \( \delta = 1 \text{ d}^{-1}. \) Because Gadhamsetty et al. \cite{5} change \( d_1 \) and \( d_2 \) when they consider early or late killing, their parameterization is designed to deliver the desired \( \delta \simeq 1 \) in both cases. Note that during perfect therapy the decline rate of the viral load ultimately approaches the slowest of the two infected cell populations.

d. In the early killing regime, adding on an efficacious therapy blocking \( \gamma \) steepens the initial downslope of the viral load, but slows down the late phase. In the end it takes much longer before the virus is “eradicated”. Adding an efficient therapy can therefore worsen the outcome \cite{2}, and the reason is that the slowest compartment, \( I_1, \) has become even slower, and will keep on producing \( I_2 \) cells over a much longer period of time. The same unexpected outcome does not happen in the early killing scenario. Since we do not know where the killing takes place, one should read the Cardozo et al. \cite{2} before taking this drug.

e. Implementing the immune response used by Gadhamsetty et al. \cite{5} reveals how the onset of the immune response reduces the set point viral load that is approach after the acute phase of the infection. Because it delivers similar killing rates at steady state the treatment results are hardly affected.
Answers to Chapter 13

Question 13.1. Sketch a few functions
Figures made with the previous version of Grind:

(a) First note that \( y = \frac{h}{x + h} = 1 \) when \( x = 0 \). Second, we see that for \( x \to \infty, y \to 0 \), and similarly that for \( x \to -\infty, y \to 0 \). There is a vertical asymptote at \( x = -h \). See Panel (a).

(b) First note that \( y = \frac{x}{x + h} = 0 \) when \( x = 0 \). Second, we see that for \( x \to \infty, y \to 1 \), and similarly that for \( x \to -\infty, y \to 1 \). There is a vertical asymptote at \( x = -h \). See Panel (b).

(c) Plotting \( L = \frac{aA}{c + bA} \) we first rewrite this into \( L = \frac{a}{c/A} \), to see that there is a horizontal asymptote at \( L = \frac{a}{b} \) (see Panel (c)). If we were to plot \( A = \frac{cL}{a-bL} \) this would become a vertical asymptote at \( L = a/b \) (not shown).

(d) Remove the \( Y = 0 \) solution and observe that \( X = (a/b)(1-Y)(c+Y) \) is the parabola shown in Panel (d).

(e) The intersection with the \( x \)-axis corresponds to \( x = \frac{ak-dq-dk}{a-d} \), and that with the \( y \)-axis to \( y = \frac{ak}{q+k} - d \). Rewriting the function as \( y = a\frac{k}{x} - \frac{k}{x-1} - d \) and sending \( x \to \infty \) we see that \( y \to a - d \), meaning that there is a horizontal asymptote at \( y = a - d \). There is a vertical asymptote at \( x = q + k \). See Panel (e), where the dashed lines denote the two asymptotes.

Question 13.2. Linearization

(a) The derivative is \( \partial_x x^2 = 2x \).

(b) Filling in \( f(x) \simeq f(\bar{x}) + \partial_x f(\bar{x}) (x - \bar{x}) \) we obtain that \( f(3.1) = 9 + 0.1 \times 2 \times 3 = 9.6 \). The true value is \( 3.1^2 = 9.61 \).

Question 13.3. Scaling
The Lotka-Volterra equations are
\[
\frac{dR}{dt} = [r(1 - R/K) - aN]R \quad \text{and} \quad \frac{dN}{dt} = [caR - d]N
\]

a. Defining \( x = R/K \) and dividing all rates by \( r \) one obtains
\[
\frac{dKx}{dt} = [(1 - Kx/K) - aN/r]Kx \quad \text{and} \quad \frac{dN}{dt} = \left[\frac{ca}{r}Kx - d/r\right]N
\]
and by defining \( \alpha = a/r \) this simplifies into
\[
\frac{dx}{dt} = [(1 - x) - \alpha N]x \quad \text{and} \quad \frac{dN}{dt} = [\alpha Kx - d/r]N
\]
with only one parameter in the resource equation. Defining \( y = \alpha N \), i.e., \( N = y/\alpha \), we remove that parameter from \( dx/dt \)
\[
\frac{dx}{dt} = [(1 - x) - y]x \quad \text{and} \quad \frac{1}{\alpha} \frac{dy}{dt} = [\alpha Kx - \frac{d}{r}] \frac{y}{\alpha}
\]
where \( dy/dt \) can be simplified by lumping the parameters
\[
\frac{dy}{dt} = [\gamma x - \delta]y ,
\]
where \( \gamma = \alpha K = cKa/r \) and \( \delta = d/r \).

b. We went from five to two parameters for which we even know that is a scaled fitness \( R_0 = \gamma/\delta \), and that \( \gamma/\delta > 1 \) is required for co-existence.
Bibliography


