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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.

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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 \( \frac{dN}{dt} = m - dN \).
(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 \( \frac{dP}{dt} = -\delta P \) 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 \( \frac{dP}{dt} = 2\sigma - \delta P \) 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 of the concentration of bacteria, i.e., solving \( \frac{dN_B}{dt} = rB - \frac{kN_B}{N+B} = 0 \) 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 \( d\bar{B}/dt > 0 \), and above it \( d\bar{B}/dt < 0 \).

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. ATP**

a. Since \( dA/dt \) is measured in grams per day, \( p \) would be grams of ATP produced per day.

Note that ADP and ATP cycle, according to the reaction \( \text{ADP} + \text{P} \xrightleftharpoons[\delta]{k} \text{ATP} \), meaning that ATP is resynthesized when its end-product ADP spends energy to bind phosphate. Thus, the parameter \( p \) combines the mass-action parameter \( k \) and the concentrations of ADP and phosphate.

b. The steady state \( \bar{A} = p/\delta \) g, and because we know there is 60 g of ATP we know that \( p/\delta = 60 \) g.

c. When \( \delta A = \delta 60 = 60 \times 10^3 \) g of ATP per day, we estimate that \( \delta = 10^3 \) per day, or \( \delta = 0.69 \) per minute. The expected ‘life span’ on an ATP molecule would therefore be about \( 1/0.69 = 1.44 \) minutes.

**Question 2.5. 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 \( N = k^2 \) 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. Homeostasis**

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 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.,

\[
\bar{B} = \frac{d \pm \sqrt{d^2 + 4edm}}{-2ed}
\]

with one positive root \( \bar{B} = \frac{\sqrt{d^2 + 4edm}}{2ed} - \frac{1}{2ed} \),

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, \( \frac{\partial f}{\partial N} = r - 2rN/K \), to zero. This delivers \( \hat{N} = K/2 \) (see Panel (a)). Substituting this maximum into the population growth function, one obtains the maximum population growth of \( f(\hat{N}) = rK/4 \).

(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 expects 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 \( \hat{N} = 0 \).

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 \( y = \frac{bx}{x+a} \) 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 (c) 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., \( dB/dt = \frac{bB}{1+\frac{B}{k}} - \frac{dB}{1+\frac{B}{h}} \), 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 \( dS/dt = pS(1 - S/K) - dS \), 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 \( dS/dt = 0 \) 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 \( dD/dt = \frac{p}{K} S^2 - \delta D \).

**d.** The production rate is \( \frac{p}{K} S^2 \), which has the parabolic form of \( y = ax^2 \). Note that this
Question 3.6. Red blood cells
Figure made with the model `epo.R`

(a) Scaling the maximum concentration of EPO to one, we write the declining Hill function $E = \frac{1}{1 + (B/h)^m}$. Because this should be a steep sigmoid function we set $n = 5$; see Panel (a) where $h = 2.5 \times 10^{11}$ (see below).

(b) We need a minimum production rate, $s_0 \simeq 10^9$ cells kg$^{-1}$ d$^{-1}$, in the absence of EPO. Since the concentration of EPO is scaled, $0 < E \leq 1$, we could define the RBC production due to EPO as $s_1 = E^m$, where $s_1$ is the maximum obtained when $E = 1$, and $m$ can be used to make this a linear ($m = 1$), concave ($m > 1$), or convex ($m < 1$) function. Because the maximum production $s_0 + s_1 = 10^{10}$ we obtain that $s_1 \simeq 9 \times 10^9$. The total production, $s_0 + s_1 E^m$ is plotted in Panel (b) for $m = 1$ (black), $m = 2$ (red), and $m = 0.5$ (blue). Plotting the same production as a function of the RBC count, $B$, for $m = 1$ we obtain Panel (c).

c. Together this leads to $dB/dt = s_0 + s_1 E^m - dB$, where $E = \frac{1}{1 + (B/h)^m}$, $s_0 \simeq 10^9$, $s_1 \simeq 9 \times 10^9$, and $d = 1/120$. For estimating the $h$ parameter, we start by considering the model in the absence of EPO because it then simplifies to $dB/dt = s_0 - dB$, with steady state $\bar{B} = s_0/d = 1.2 \times 10^{11}$ cells kg$^{-1}$. Since the effect of EPO should high at the lowest RBC density, we have to set $h > 1.2 \times 10^{11}$ cells kg$^{-1}$. When we make $h$ twice as large, $h = 2.4 \times 10^{11}$, we obtain at the lowest RBC count that $E = \frac{1}{1 + 0.5^m} = 0.97$, which is close the maximum, $E = 1$, and hence a good choice. Rounding this, we therefore set $h = 2.5 \times 10^{11}$ cells kg$^{-1}$.

d. Running the model for these parameters leads to a steady state of $\bar{B} = 3.31 \times 10^{11}$ cells kg$^{-1}$, which should correspond to the healthy steady state. Patients not producing EPO have the steady state of $\bar{B} = 1.2 \times 10^{11}$ cells kg$^{-1}$, which is almost 3-fold lower than the normal number of RBC.

e. Running the model after halving $s_1$ only leads to a 12% loss of the RBC in the blood, i.e., for $s_1 = 4.5 \times 10^9$ one find $\bar{B} = 2.91 \times 10^{11}$ cells kg$^{-1}$. This is just a modest decrease. One can also decrease $s_1$ continuously to see that $\bar{B}$ hardly decreases (see the `epo.R` file).

Question 3.7. 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 3.8. Regression to the mean**

a. Since everything is random, the first expectation is that one should find no 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:

\[ \frac{dL}{dt} = rA - mL - f(A)L = rA - mL - d_1(1 + \epsilon A)L \quad \text{and} \quad \frac{dA}{dt} = mL - d_2A , \]

where \( m \) is the maturation rate of the larvae, and \( r \) the rate of reproduction by the adults.

b. To simplify the algebra we rewrite the ODE for the larvae into 
\[ \frac{dL}{dt} = \frac{m'L}{r - d'_1L} + \frac{m'd'_1L}{(r - d'_1L)^2} \]

which for \( L = 0 \) gives \( \frac{m'}{r} \).

See Panel (a). For the adults \( \frac{dA}{dt} = mL - d_2A = 0 \) gives \( A = \frac{mL}{d_2} \), which is a straight line through the origin with slope \( m/d_2 \). If \( m/d_2 > m'/r = (m + d_1)/r \) 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 [tbb.bio.uu.nl/rdb/bm/clips/nullclines](http://tbb.bio.uu.nl/rdb/bm/clips/nullclines) for the a rotated version of the same phase space).

c. Assuming a quasi steady state for the larvae, one has to solve \( L \) from 
\[ \frac{dL}{dt} = 0, \]
giving \( \dot{L} = \frac{rA}{m+d_1A} \).

d. Substituting \( \dot{L} \) into the adult equation gives 
\[ \frac{dA}{dt} = \frac{mrA}{m+d_1A} - d_2A \]
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 growth 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:

![Graph showing tumor growth](image)

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 $dA/dt = G - dA = b\sqrt{A} - dA$.

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 growth $dA/dt = \frac{b}{\sqrt{A}} - d$. Which for $A \rightarrow \infty$ approaches the horizontal asymptote $-d$, which seems perfectly reasonable (see the Figure). However, for small population sizes, i.e., $A \rightarrow 0$, the per capita growth rate blows up, which is not a good property of the model.

**Question 3.12. Seedlings over-shadowed by adult plants**
Figure made with the model seedling.R:

![Graph showing seedling growth](image)

a. A natural model would look like:

\[
\frac{dJ}{dt} = s - d_1 J - mJ(1 - A/k) \quad \text{and} \quad \frac{dA}{dt} = mJ(1 - A/k) - d_2A .
\]
For the nullcline of the seedlings we set \( \frac{dJ}{dt} = 0 \), i.e.,

\[
s - d_1 J - mJ + \frac{m}{k} JA = 0 \leftrightarrow s - d_1 J - mJ = -\frac{mJ}{k} A \leftrightarrow A = \frac{s}{mJ} \frac{k(d_1 + m)}{m} \leftrightarrow A = \alpha \frac{\beta}{J},
\]

where \( \alpha = \frac{k(d_1 + m)}{m} \) and \( \beta = sk/m \). To sketch this we define \( A \) as the vertical axis and \( J \) as the horizontal axis. Next we
1. find the intersection with \( x \)-axis by solving \( A = 0 \), i.e.,

\[
\alpha = \beta/J \quad \text{or} \quad J = \beta/\alpha = \frac{sk}{m(d_1 + m)} = s/d_1 + m,
\]

2. find a horizontal asymptote by sending \( J \to \infty \), which gives \( A \to \alpha \), or \( A \to k + \frac{k\theta}{m} \),
3. find a vertical asymptote by sending \( J = 0 \), which gives \( A \to -\infty \),
4. and compute the derivative, \( A' = \frac{\beta}{J^2} \), to find out that the slope is always positive, i.e., there are no minima and maxima,

(see the online tutorial on sketching functions). So this is a hyperbola approaching the negative \( y \)-axis, intersecting the \( x \)-axis, and approaching the horizontal asymptote \( A = k + \frac{k\theta}{m} \); see the Figure. For the nullcline of the adult plants one sets \( \frac{dA}{dt} = 0 \):

\[
mJ - \frac{m}{k} JA - d_2 A = 0 \leftrightarrow mJ = A(d_2 + mJ/k) \leftrightarrow A = \frac{mJ}{d_2 + mJ/k} = \frac{kJ}{kd_2/m + J} \frac{kJ}{h + J}
\]

where \( h = kd_2/m \), and which is a Hill function when plotting \( A \) and a function of \( J \). Indeed,
1. setting \( J = 0 \) gives \( A = 0 \), which is the origin of the phase space,
2. letting \( J \to \infty \) gives \( A \to k \), which is a horizontal asymptote,
3. we ignore the vertical asymptote at \( J = -h \), because one can safely ignore negative population densities,
4. we fill in the special point \( J = h = kd_2/m \) because that gives \( A = k/2 \).

(see the online tutorial on sketching functions). So this is an increasing Hill function starting in the origin and approaching the horizontal asymptote \( A = k \); see the Figure.

b. Yes, these nullclines cross whenever \( k + \frac{k\theta}{m} > k \), which is always true. Intuitively, this can be understood because the seed bank always allows some seedlings to be present, and some of these should always mature to become adult plants. The population cannot become infinitely large because the seedlings are limited by the seed bank, and on top of that the adult plants are limiting their own production.

c. Yes, the vector field points towards the steady state in every section of the phase space. Note that arrows point rightwards on the left-hand side of the \( \frac{dJ}{dt} = 0 \) nullcline because \( \frac{dJ}{dt} > 0 \) for small values of \( J \), and that arrows point upwards below the \( \frac{dA}{dt} = 0 \) nullcline because \( \frac{dA}{dt} > 0 \) for small values of \( A \).

d. Yes, this model allows for homeostasis because there is a negative density dependence from adults onto juveniles: the higher the adult density the more juveniles die (the minimum fraction being \( \frac{d_1}{d_1 + m} \)).

Answers to Chapter 4

Question 4.1. Density dependent death

Figure made with the previous version of Grind:
The per capita death rate is \(cN\): see Panel (a).

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

The steady state is \(N = b/c\).

Because there is no generation time.

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**

For \(dN/dt = f(N) = bN(1 - N/k) - dN\) 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 \(\partial_{N}f(N) = b - d - 2bN/k\) and substitutes the steady state value to obtain

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

For \(dN/dt = g(N) = bN - dN(1 + N/K)\) 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 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).

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 \(T_R = 1/d\).

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 \(n = \frac{s}{d}N\), and hence substituting \(N = \frac{s}{d}n\) into \(dN/dt = s - dN\), one obtains the scaled ODE

\[
\frac{\dot{n}}{d} = s - \frac{s}{d}d = s - d
\]

or

\[
\frac{dn}{dt} = d - dn,
\]

see Section [14.4] which has the death rate as its only parameter.

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 \(R_T = \frac{1}{\delta} = \frac{1}{s/k + d}\), 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`:

(a) Birth and death rate

(b) Birth and death rate

(c) Growth rate \( \frac{dN}{dt} \)

(d) Growth rate \( \frac{dN}{dt} \)

After defining the probability that an individual female finds a male as the simple saturation function, \( p(N) = \frac{N}{h + N} \), one needs to allow for a carrying capacity by including negative density dependence in the birth and/or the death terms:

**a.** Assuming density dependent birth one would write something like

\[
\frac{dN}{dt} = \frac{bN}{1 + N/K} \left( \frac{N}{h + N} - dN \right),
\]

(A.4.1)

and assuming density dependent death one could write

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

(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 \( \frac{dN}{dt} = 0 \) (see the arrows).

Answers to Chapter 5

Question 5.1. Sketch the *per capita* birth rate
Figure made with the file `birth.R`:

![Graph](image)

a. Plotting \( y = \frac{b(R_T - cN)}{h + R_T} \) 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. 3.3c and Fig. 3.5b.

**Question 5.2. Neutrophils**

Figure made with `neutrophils.R`:

![Images of neutrophils](image)

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 \( N = \frac{r}{B}(1 - B/K) \). The nullcline of the neutrophils is defined by the line \( N = \frac{s}{d} \). These lines will only intersect when \( \frac{r}{B} > \frac{s}{d} \). 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 $k_s > r$.

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 $dB/dt = rB \frac{B}{a + B}(1 - B/K) - \frac{kNB}{K + B}$ 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, $dS/dt = rS(1 - S/K) - \beta SI$ and $dI/dt = \beta SI - dI$, 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 $dT/dt = rT(1 - T/K) - \frac{kTN}{h + T}$ and $dN/dt = \frac{aTN}{h + T} - dN$ (see Chapter 7). The SI model is frequently written as $dS/dt = rS(1 - S/K) - \frac{\beta SI}{S + I}$ and $dI/dt = \frac{\beta SI}{S + I} - dI$, because $\frac{I}{S + I}$ 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:

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

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

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

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

e. The steady state remains \( \hat{W} = e/d \) and because \( \hat{V} \) 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., \( V = \frac{a}{bW} - \frac{\hat{W}}{c} \), 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 \( \hat{W} = a/c \) without a vegetation is a 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

\[
J = \begin{pmatrix}
-b\hat{V} - c & -b\hat{W} \\
\frac{d\hat{V}}{d\hat{W}} & d\hat{W} - e
\end{pmatrix}
\]

because \( \hat{W} = \frac{\hat{W}}{a} \), and giving \( \text{tr}J = -b\hat{V} - c < 0 \) and \( \text{det}J = 0 + bd\hat{V} \hat{W} > 0 \). 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. Kingfishers**

Figures made with the model `kingfisher.R`:

\[
\frac{dF}{dt} = rF(1 - F/K) - aFB \quad \text{and} \quad \frac{dB}{dt} = i(B_T - B)F - aFB - eB
\]
for the fish, $F$, and the birds, $B$. The nullcline of the fish is a conventional straight Lotka-Volterra nullcline going from $B = r/a$ when $F = 0$ to $F = K$ when $B = 0$. The nullcline of the birds is solved from $0 = i(B_T - B)F - aFB - eB$, which has only one solution

$$B = \frac{iB_T F}{iF + aF + e},$$

which is a saturation of $F$, i.e., $B = 0$ when $F = 0$ and $B \rightarrow \frac{iB_T}{i+a}$ when $F \rightarrow \infty$. Plotting the fish on the horizontal axis and the birds on the vertical axis we obtain Panel (a) depicted above, which has two steady states, the origin and a non-trivial steady state. Note that the fish at carrying capacity is not a steady state because the birds increase by immigration when $B = 0$. The Jacobian of the non-trivial steady state is $J = \begin{pmatrix} -a & -b \\ +c & -d \end{pmatrix}$, showing that it is stable because the trace, $-a - d$, is negative and the determinant, $ad + bc$, is positive. The origin is unstable because both the birds and the fish increase in its neighborhood.

a. This phase portrait looks very reasonable, suggesting that the model is fine.

b. In the absence of the $eB$ term, $F$ cancels from the $dB/dt = 0$ equation, leading to $B = \frac{iB_T}{i+a}$, which is independent of $F$. Thus, the model would have a non-zero steady state of the birds when $F = 0$.

c. If we had chosen the model where the immigration is a saturation function of the fish, we would have obtained Panel (b) depicted above, which brings little novelty, and is equally reasonable.

**Question 5.7. 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

$$\frac{dS}{dt} = b_BS(1 - B/k) - d_BS - \beta SP, \quad \frac{dR}{dt} = b_B(1 - s)R(1 - B/k) - d_BR,$$

$$\frac{dI}{dt} = \beta SP - d_I I \quad \text{and} \quad \frac{dP}{dt} = bd_I I - d_PP,$$
where $B = S + R + I$ is the total number of bacteria, $b_B$ 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, $d_x$ 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. Phages and bacteria**

a. The lagvalue(tlag) function returns the values of all 5 variables at time $t - \Delta$.

b. The fig2B0 data correspond to bacterial growth in the absence of phages, and the fig2B data comes from an experiment with phages.

c. Fitting the first data provides a very similar estimate for the consumption rate, $v$.

d. Yes, this looks like a good fit, and the parameter estimates are similar. Since the resistant bacteria are growing slower than predicted, it would have been better to also estimate a fitness cost.

e. No the data are equally well described with an ODE model without a fixed time delay. The value of the eclipse time, $1/\lambda$, is much longer now because it is exponentially distributed.

f. The model has no death rate of the bacteria and no clearance of the phages. Given the short time scale of the experiment this is probably not important.

**Question 5.9. 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

$$\frac{dR}{dt} = rR - \gamma R^2 - aRN$$
$$\frac{dN}{dt} = caRN - \delta N .$$

a. For the return time of the general form we first solve the non-trivial steady state by setting $dN/dt = 0$ and $dR/dt = 0$, 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

$$J = \left( \begin{array}{cc} r - 2\gamma \bar{R} - a\bar{N} & -a\bar{R} \\ ca\bar{N} & ca\bar{R} - \delta \end{array} \right) = \left( \begin{array}{cc} -\frac{\gamma \delta}{ca} & -\frac{\delta}{c} \\ cr - 2\frac{\delta}{a} & 0 \end{array} \right) ,$$

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

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

where $D = tr^2 - 4\det$ 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, $\Re(\lambda) = -\frac{\gamma \delta}{2ca}$, to obtain a return time

$$T_R = \frac{-1}{\Re(\lambda)} = \frac{2ca}{\gamma \delta} = \frac{2}{\gamma} \frac{1}{\bar{R}} .$$
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 \( dN/dt = 0 \), which has not changed. We obtain that

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

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

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

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

\[
T_R = \frac{2}{d} \frac{k}{\bar{R}} = \frac{2cak}{d\delta} ,
\]

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 \( D(t) = \frac{\delta}{\beta - \delta} e^{(\beta - \delta)t} - 1 \).

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 \( \frac{\delta}{\beta - \delta} = 0.5 \) 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**

Figure made with the script `virulence.R`:

(a) 

(b)

![Graph](image)

\[ R_0 \]

\[ v \]

\[ R_0 \]

\[ v \]

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

b. Substituting \( \beta = cv \) we obtain \( R_0 = \frac{cvS}{d + v} = \frac{cv}{d + v} \frac{S}{S} \).

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 expect to increase over time.

d. When \( \beta = \frac{cv}{h + v} \) one obtains \( R_0 = \frac{cv}{h + v} \frac{1}{d + v} \frac{S}{S} \).

e. To sketch the latter as a function of the virulence, \( v \), we observe that for \( v \to 0 \) the fitness approaches \( R_0 \approx \frac{cv}{h} \frac{1}{d} \frac{S}{S} \), which is an increasing function of \( v \). When \( v \gg h \), the fitness approaches \( R_0 = \frac{cv}{d + v} \frac{S}{S} \), 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) 

(b) 

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

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 $I = \epsilon \bar{S}/\delta$, which is the minimum approached when $\beta \to 0$.

c. The $\frac{dS}{dt} = 0$ 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 $I = \frac{d - \beta S}{\beta}$. The nullcline intersects the horizontal axis in the carrying capacity $S = \delta \beta + \epsilon$; see Panel (a) and (b). The $\frac{dI}{dt} = 0$ nullcline is defined by $I = \frac{\epsilon S}{\delta - \beta S}$, 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

$$J = \begin{pmatrix} - & - \\ + & - \end{pmatrix}$$
giving $\text{tr}J < 0$ and $\det J > 0$,

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) The $R_0 = \frac{\beta}{\delta + r}$ and the initial growth rate $r_0 = \beta - \delta - r$.

(b) Because $\bar{S} = N$ in the uninfected steady state the Jacobian is

$$J = \begin{pmatrix} -d & -\beta \\ 0 & \beta - \delta - r \end{pmatrix},$$

and hence the largest eigenvalue $\lambda_1 = \beta - \delta - r$. This eigenvalue indeed defines the initial growth rate $r_0$, and since requiring instability means $\lambda_1 > 0$, or $\beta > \delta + r$, this also corresponds to requiring $R_0 > 1$.

c. Setting

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

gives $\frac{\beta S}{\delta + r} = I + S$,

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

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

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

d. 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 a 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., $n = \frac{S + I}{S + S^2}$, and that the infection rate should be proportional the fraction of infected individuals encountered, i.e., $fn = \frac{I}{S + I} \frac{S + I}{h + S + I} = \frac{I}{h + S + I}$, we obtain from

$$\frac{dI}{dt} = \frac{\beta SI}{h + S + I} - (\delta + r)I = 0$$

that the nullcline, $I = S(R_0 - 1) - h$,

is intersecting the horizontal axis at $S = \frac{h}{R_0 - 1}$ (see Panel (b)).
Question 6.5. Measles

a. On a logarithmic scale the epidemic first grows linearly and then contracts.

b. \( s[^*]\left< \exp(\text{coef}(f)[1]) \right> \) sets \( I(0) \) to \( e^i \) where \( i \) is the intercept.

c. 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.

d. Estimating just \( I(0) \) and \( \beta \), the two parameters have reasonable confidence ranges.

e. 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.

Question 6.6. Influenza virus infecting epithelial cells

Figures made with the model \texttt{epithelial.R}:

Assuming \( dV/dt = dF/dt = 0 \) in the first ODE for the virus and the factor leads to \( V = \frac{p_v}{c_V} I \) and \( F = \frac{p_F}{c_F} I \), showing that the QSSA virus and factor densities are both proportional to the infected cells. The QSSA model therefore becomes

\[
\frac{dE}{dt} = bE(1 - (E + I)/K) - dE - \beta EI(1 - I/h') \quad \text{and} \quad \frac{dI}{dt} = \beta EI(1 - I/h') - \delta I ,
\]

where \( \beta' = \beta p_V/c_V \) and \( h' = h c_F/p_F \). For convenience, we drop the primes when performing the phase plane analysis. For the nullcline of the healthy cells one sets \( dE/dt = 0 \) giving \( E = 0 \) and

\[
E = K(1 - d/b) - I - \frac{K \beta}{b} I(1 - I/h) = \kappa - I - \alpha I(1 - I/h) ,
\]

where \( \kappa \) is the carrying capacity of the healthy epithelium, and \( \alpha = K \beta / b \). When the infection rate is very low, i.e., when \( \alpha \to 0 \), this is a declining straight line starting at \( E = \kappa \) when \( I = 0 \), and ending at \( I = \kappa \) when \( E = 0 \) (see the dotted line in Panel (a)). From that line one subtracts a parabola, \( \alpha I(1 - I/h) \), that is zero when \( I = 0 \) or \( I = h \), and has a maximum, \( \alpha h^2/4 \), that is attained at \( I/h \). Since one has to preclude negative infection rates by setting \( (1 - I/h) \) to zero whenever \( I > h \), the \( dE/dt = 0 \) nullcline coincides with the dotted line whenever \( I > h \) (see Panel (a) where we have set \( h \simeq \kappa/2 \)). For the nullcline of the infected cells one sets \( dI/dt = 0 \) giving \( I = 0 \) and

\[
E = \frac{\delta/\beta}{1 - I/h} = \frac{1}{R_0 t (1 - I/h)} ,
\]
which starts at \( E^* = \frac{\delta}{\beta} = \frac{1}{R_0} \) and approaches a vertical asymptote at \( I = h \) (see the dashed line in Panel (a)). Around the origin \( \frac{dE}{dt} \approx (b - d)E > 0 \), i.e., below the blue line the healthy epithelial cells grow. The infected cells increase above the red \( \frac{dI}{dt} = 0 \) nullcline because they require a minimum number, \( E^* \), of target cells. The origin is an unstable steady state because the trivial nullclines intersect and \( \frac{dE}{dt} > 0 \) in its neighborhood. These nullclines will at least intersect in one non-trivial steady state (when \( \kappa > \delta/\beta \), which is anyway required for successful infection), because the \( \frac{dI}{dt} = 0 \) nullcline starts below the \( \frac{dE}{dt} = 0 \) nullcline and approaches infinitely high values when \( I \to h \). This intersection is the state approached by the trajectory corresponding to an infection in Panel (a), and is indeed a stable points because the vector field points towards it in all regions.

Next, consider an alternative model using a declining Hill function for the effect of interferon on the infection rate. A QSSA version of that model would look like

\[
\frac{dE}{dt} = bE(1 - (E + I)/K) - dE - \frac{\beta EI}{1 + (I/h)^n} \quad \text{and} \quad \frac{dI}{dt} = \frac{\beta EI}{1 + (I/h)^n} - \delta I ,
\]

where we have already dropped the primes. This QSSA model readily reveals that choosing \( n = 1 \) would not allow for a large the effect of interferon because the infection term would just become a saturation function of \( I \), and not decline at maximum interferon levels. Choosing \( n \geq 2 \) would suffice because \( x/(1 + x^2) \) is a function with an optimum. Sketching the nullclines follows a similar procedure because the non-trivial \( \frac{dE}{dt} = 0 \) nullcline now is the same dotted line minus this optimum function (see Panel (b)), i.e.,

\[
E = K(1 - d/b) - I - \frac{(K\beta/b)I}{1 + (I/h)^n} = \kappa - I - \frac{\alpha I}{1 + (I/h)^n} ,
\]

giving \( E = \kappa \) when \( I = 0 \) and \( E = \kappa - I \) when \( I \to \infty \) (see the dotted line in Panel (b)). For the nullcline of the infected cells one sets \( \frac{dI}{dt} = 0 \) giving \( I = 0 \) and

\[
E = \frac{\delta}{\beta} (1 + (I/h)^n) = \frac{1}{R_0} (1 + (I/h)^n) ,
\]

which is an increasing parabola starting at \( E^* = \frac{\delta}{\beta} = \frac{1}{R_0} \) when \( I = 0 \) (see Panel (b)). The similarity between Panels (a) and (b) is reassuring as it suggests that these results do not depend on the shape of the function defining the effect of interferon of the infection rate. One can create more steady states by making this function steeper (which need not be realistic). For a high exponent, \( n \), of the Hill function one can indeed obtain a stable steady state corresponding to an infection limited by the availability of target cells, and a saddle point separating the two basins of attraction (see Panel (c)).

**Answers to Chapter 7**

**Question 7.1. Michaelis Menten**

a. 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 \( \frac{dC}{dt} = k_1 ES - (k_{-1} + k_2)C \), 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 \( \frac{dP}{dt} = k_2 C \).
b. To solve $\frac{dC}{dt} = 0$ we first collect all the terms containing $C$,

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

Because $\frac{dC}{dt} = 0$ we obtain $k_1 E_0 S = (k_1 S + k_{-1} + k_2)C$, and by solving for $S$

$$C = \frac{k_1 E_0 S}{k_1 S + k_{-1} + k_2} = \frac{E_0 S}{K_m + S} \text{ where } K_m = \frac{k_{-1} + k_2}{k_1}.$$ 

Thus, $C$ as a function of $S$ looks like a standard Hill function $y = \frac{x}{k + x}$.

c. By defining $K_m$ the simplification was already done. This means that the product equation can be written as $\frac{dP}{dt} = \frac{k_2 E_0 S}{K_m + S}$.

d. The beautiful trick of adding $\frac{dC}{dt} = 0$ to $\frac{dS}{dt}$ readily simplifies the substrate equation into $\frac{dS}{dt} = -k_2 C$. Filling in the quasi steady state expression for $C$ gives $\frac{dS}{dt} = -\frac{k_2 E_0 S}{K_m + S}$.

**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. (7.17). 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 $y = \frac{aRN}{k + R}$ for various values of $N$. At all intersection points $\frac{dR}{dt} = 0$ 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**

Figure made with the previous version of Grind:

\[ \begin{aligned}
&\begin{align*}
  &\text{a.} \quad \text{The nullcline of the consumer is only defined when } R < L \text{ because } dN/dt = caNL - dN \text{ is either positive or negative. Considering } R < L \text{ and solving } dN/dt = caNR - dN = 0 \text{ delivers the familiar } R = \frac{d}{ca} \text{ nullcline. For the resource we consider both cases, i.e.,} \\
  &\left\{ \\
  &\begin{aligned}
  &dR/dt = rR\left(1 - R/K\right) - aNR \quad \text{when } R < L \text{ and} \\
  &dR/dt = rR\left(1 - R/K\right) - aNL \quad \text{otherwise ,}
  \\
  &\end{aligned}
  \\
  \\
  &\right.
\end{align*}
\end{aligned} \]

\[ \begin{aligned}
&\begin{align*}
  &\text{to obtain} \\
  &\left\{ \\
  &\begin{aligned}
  &N = \frac{r}{a} \left(1 - \frac{R}{K}\right) \quad \text{when } R < L \text{ and} \\
  &N = \frac{rR}{aL} \left(1 - \frac{R}{K}\right) \quad \text{otherwise ,}
  \\
  &\end{aligned}
  \\
  \\
  &\right.
\end{aligned} \]

\[ \begin{aligned}
&\begin{align*}
  &\text{where the former is the straight line intersecting the vertical axis at } N = \frac{r}{a} \text{ and the horizontal axis at } R = K, \text{ and the latter is a parabola intersecting the horizontal axis at } R = 0 \text{ and } R = K. \text{ Putting these together delivers the picture shown above (where we ignore the case that } \frac{d}{ca} > K). \\
  &\text{b.} \quad \text{The stability of the steady states has not changed because nothing changed in the immediate neighborhood of steady states. Thus, the origin, } (0,0), \text{ and the carrying capacity, } (K,0), \text{ remain saddle points, and the non-trivial point is stable like in the Lotka-Volterra model.} \\
  &\text{c.} \quad \text{No, the consumer nullcline has to be located at a resource density where changing the resource density changes } dN/dt. \\
  &\text{d.} \quad \text{No, the non-trivial steady state has to be located in the part where the resource nullcline is a declining straight line (see the answer in b), and there the steady state is stable.}
\end{aligned} \]
**Question 7.5. Dampened oscillations**

Figures made with *hiv.R*:

![Figure](image_url)

(a) Time Density (b) Time

**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. Eutrophication**

Figures made with the previous version of Grind:

![Figure](image_url)

(a) Time (b) Time

**a.** For the algae, $A$, and the zooplankton, $Z$, one writes something like

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

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

$$\frac{cb}{h^2 + A^2} - d - deZ = 0 \quad \text{or} \quad Z = \frac{cb}{de h^2 + A^2} - \frac{1}{e},$$

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.

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 7.7. Luckinbill**

Figures made with previous version of Grind:

(a) $D = \frac{h}{h_0 - 1}$, $P = \frac{h}{h_0 - 1}$, $K = \frac{h}{h_0 - 1}$

(b) $D = \frac{h}{h_0 - 1}$, $P = \frac{h}{h_0 - 1}$, $K = \frac{h}{h_0 - 1}$

(c) $D = \frac{h}{h_0 - 1}$, $P = \frac{h}{h_0 - 1}$, $K = \frac{h}{h_0 - 1}$

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

b. Since one can scale time by the natural rate of increase $r$, the resource density by its carrying capacity, and the consumer by the $a$ 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 7.9. Wolves**

There are many different possibilities. For instance, let $R$ be the prey, and $W$ be the wolves:

a. One could define $\hat{R} = \frac{RW}{c + W}$ 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

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

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

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 \( f(R,W) = \frac{R}{(1 - cW) + R} \) 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 7.10. Saturation in consumers**

Figure made with the previous version of Grind:

![Graph showing saturation in consumers](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

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

i.e., they are stable.

**Question 7.11. Curvature**

Figure made with `hyper.R`:
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 7.12. Ratio-dependent predation
Figures made with ratio.R:

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.

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 $\bar{R} = s r + be/c$ 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

\[
J = \begin{pmatrix}
-(p + d) & 0 & 0 & 0 & \ldots & \ldots & 0 \\
2p & -(p + d) & 0 & 0 & \ldots & \ldots & 0 \\
0 & 2p & -(p + d) & 0 & \ldots & \ldots & 0 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & \ldots & 0 & \ldots & 0 & 2p & -d \\
\end{pmatrix},
\]

(A.8.4)

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 \( N \) 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 \( n_{\text{div}} \) (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:

![Figure a](image_a.png)

![Figure b](image_b.png)

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 \( dM/dt = 0 \), \( \bar{M} = \frac{c_1R - d_M}{c_2} \) 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. Maintenance and reproduction
Figures made with the model \texttt{daphnia.R}:

\[\begin{align*}
\text{(a)} & \quad \text{\begin{tikzpicture}[scale=0.7]
\draw[thick,red] (-2,0) -- (2,0);
\draw[thick,blue] (0,-2) -- (0,2);
\draw[thick,red] (0,0) circle (0.5);
\end{tikzpicture}} \\
\text{(b)} & \quad \text{\begin{tikzpicture}[scale=0.7]
\draw[thick,red] (-2,0) -- (2,0);
\draw[thick,blue] (0,-2) -- (0,2);
\draw[thick,red] (0,0) circle (0.5);
\end{tikzpicture}}
\end{align*}\]

Making the QSSA
\[
\frac{dE}{dt} = \frac{e(aA - k)D}{H + aA - k} - mE = 0 \quad \text{leads to} \quad E = \frac{(e/m)(aA - k)D}{H + aA - k},
\]
and substituting this into the ODE for the adult \textit{Daphnias} gives
\[
\frac{dD}{dt} = \frac{e(aA - k)D}{H + aA - k} - d_0D - \frac{d_1D}{1 + aA/h}.
\]
This looks complicated, but its nullclines solved by setting $dD/dt = 0$ corresponds to $D = 0$ and $A = c$, where $c$ is a constant, because the ODE becomes independent of $D$ when the $D = 0$ solution is factored out. Since the ODE for the algae was just a Lotka-Volterra prey equation, one obtains a classic Lotka-Volterra phase portrait. The nullclines of this QSSA model are depicted with a trajectory of the QSSA model in Panel (a) and with a trajectory of the full model in Panel (b). Note that the time scale of Daphnia is much slower in the full model and that the trajectory hence hovers around the nullcline, i.e., the quasi state state, of the algae.

**Question 8.7. 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 $dC_0/dt = 0$,

$$k_1 (R - \hat{C}) L - (k_{-1} + k_2) C_0 = \frac{k_1 K_m RL}{K_m + L} - (k_{-1} + k_2) C_0 = \frac{k_{-1} RL}{K_m + L} - (k_{-1} + k_2) C_0 = 0,$$

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

$$\frac{dN_1}{dt} = i + r_1 N_1 (1 - N_1 - \gamma_1 N_2) \quad \text{and} \quad \frac{dN_2}{dt} = i + r_2 N_2 (1 - N_2 - \gamma_2 N_1),$$

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. 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 $dN_1/dt = 0$ nullcline corresponds to the line $N_1 = T - \frac{d_1}{b_1} = T \left(1 - \frac{1}{R_01}\right)$. The $dN_2/dt = 0$ 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, $N_i = T - d_i / b_i$, are unstable when the nullclines intersect.

c. These lines will intersect, and give rise to the phase space shown above, when $\frac{b_2T - d_2}{b_1+b_2} > \frac{b_1T - d_1}{b_1}$, revealing that the maximum growth rate $r_{\text{max}} = b_2T - d_2$ 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 9.3. Non-equilibrium co-existence**

Figure made with `noneqco.R`:

![noneqco figure](image)

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., $\frac{h}{a_2d_2 - 1} < \frac{d_2}{a_1}$ (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 9.4. 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

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

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

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

Since one can always choose parameters such that $\bar{N}_1 > 0$ and $\bar{N}_2 > 0$ co-existence is possible.

**Question 9.5. Gradients with sharp borders**

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

a. Solving $\frac{dN_1}{dt} = N_1(b_1(1 - N_1) - d_1 - d_S)$ gives the trivial $\bar{N}_1 = 0$ solution and the carrying capacity $\bar{N}_1 = 1 - d_1 + \frac{d_S}{b_1} = 1 - 1/R_0$. 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 $-1$, $N_2 = 1 - \frac{d_1}{b_1} - N_1$ 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 $\frac{dN_1}{dt} = 0$ nullcline will be given by $N_2 = 1 - \frac{d_1+d_S}{b_1} - N_1$. The nullcline will shift downward and at some value of $d_S$ cross the $\frac{dN_1}{dt} = 0$ nullcline. Beyond that $N_2$ will outcompete $N_1$ and approach its carrying capacity $\bar{N}_2 = 1 - \frac{d_2}{b_2}$.

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

**Question 9.6. Density dependent birth rate**

Figure made with the previous version of Grind:
a. $R_0 = b/d$ or $R_0 = \frac{b - a}{2H + a}$, depending on its definition.

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

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

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 $b/H = \frac{ab}{a+H}$. Hence $R_0 = \frac{b - a}{2H + a}$, 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 $y = b \frac{1-aN}{H-aN}$ knowing that $H > 1$. For $N = 0$ this delivers $y = b/H$, and for $y = 0$ we find $N = 1/a$. A horizontal asymptote is found by dividing numerator and denominator by $N$, i.e., $y = \frac{b}{H+1}$, 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 9.7. 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 $R_{21}^* = \delta_2$.

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, $a_{ij}c_{ij}R_j$. 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 $dN_1/dt = 0$ nullcline is given by the vertical line $R_{11}^* = \frac{\delta_1}{\alpha_{11}c_{11}}$ and the horizontal line $R_{12}^* = \frac{\delta_1}{\alpha_{12}c_{12}}$ (see the green lines in Panel (a)). Only resource densities $(R_1, R_2)$ larger than these two lines allow $dN_1/dt > 0$, i.e., $N_1$ can only grow in the region defined by the upper-right green square. Similarly, the $dN_2/dt = 0$ nullcline is constructed from the lines $R_{22}^* = \delta_2$ and $R_{21}^* = \frac{\delta_2}{\alpha_{22}c_{22}}$ (see the orange lines in Panel (a)). Note that the upper circle denotes the point $R_1 = R_2 = 1$ 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 $dN_1/dt = 0$ nullcline, i.e., where $N_1$ is limited by $R_1$, and the horizontal part of the $dN_2/dt = 0$ nullcline, i.e., where $N_2$ is limited by $R_2$. 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)
\[
\left( \frac{\partial R_1}{\partial N_1^l} \frac{\partial R_2}{\partial N_2^l} \right) = \left( + 0 \right) \quad \text{and} \quad \left( \frac{\partial R_1}{\partial N_1^l} \frac{\partial R_2}{\partial N_2^l} \right) = \left( 0 + \right),
\]
respectively (see the online tutorial on [bb.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 9.8. 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, \( \beta_{ij} \), 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 \( c_{12} < c - c_{11}; c_{21} < c - c_{22}; c_{31} < c - c_{32} \) 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 9.9. 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
\[
\hat{R}_{0i} = \frac{b_i}{d_i} \frac{\bar{R}}{h_i + \bar{R}} = \frac{r_i}{h_i/R + 1},
\]
we can solve for \( r_i \) and write Eq. [A.9.5] in terms of \( \hat{R}_{0i} \):
\[
R_i^* = \frac{h_i}{\hat{R}_{0i} (h_i/R + 1) - 1} \quad \text{where} \quad \bar{R} = \frac{s}{d}.
\]
The species with the lowest fitness \( \hat{R}_{0i} \) can therefore be the superior competitor when its \( h_i \) is sufficiently smaller than that of the other competitors. In conclusion, \( \hat{R}_{0i} \) 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 \( R_0 \) 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 $\frac{dN_2}{dt} \simeq rN_2(1-2\alpha)$. For invasion one requires $\frac{dN_2}{dt} > 0$, 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 $\frac{dN_2}{dt} = 0$ 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 $\frac{dN_2}{dt} = 0$ 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 $\frac{dI}{dt}$ 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:

- **Panel (a)**: 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.

- **Panel (b)**: When $N_1$ is the saprophyte, one would write

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

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.

- **Panel (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 $R_0 = b_i/d_i < 1$ 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 $R_0 > 1$.

**Question 10.5. Infinite Niche-matrix**

a. Every single ODE of this system is a function of all variables of the system, i.e., $dN_i/dt = f(N) = N_i - \sum_j A_{ij}N_iN_j$, where $N$ is a vector $(N_1, N_2, \ldots, N_i, \ldots, N_j, \ldots)$. For the off-diagonal elements of the Jacobi matrix we observe that for every $j \neq i$ the partial derivative, $\partial_{N_j}$, of $f(N)$ corresponds to the simple $-A_{ij}N_i$. Further, because all populations have the same steady state, $N_i = \bar{N}$, these off-diagonal elements become $-\alpha \bar{N}$, $-\alpha^4 \bar{N}$, $-\alpha^9 \bar{N}$. For the partial derivatives on the diagonal we write that the partial derivative, $\partial_{N_i}$, of $f(N)$ correspond to

$$1 - 2N_i - \sum_{j \neq i} A_{ij}N_j = 1 - 2\bar{N} - \sum_{j \neq i} A_{ij}\bar{N},$$

where we pull the $i = j$ term out of the sum term, and the factor two is due to the fact that $A_{ii} = 1$ and the partial derivative, $\partial_{N_i}$, of $-N_i^2$ equals $2N_i$. Hence the Jacobian is:

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

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

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

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

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

b. The Jacobian is equal to $-\bar{N}A$, where $A$ is the interaction matrix. The 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 largest 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 largest eigenvalue 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 `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 \( H = k(1 - f/r) \), the total harvest is \( fH \). Taking the derivative, \( \partial f \), of \( fH \), and setting that to zero gives \( k - (2k/r)f = 0 \) or \( f = r/2 \). Substituting that into \( H \) gives \( H = k/2 \), 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 \( fH \) 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, \( fH \), 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 we obtain very similar estimates for the two growth rates and carrying capacities.

b. For Paramecium aurelia we obtain \( \alpha \approx 1.05 \) and for P. caudatum we obtain \( \beta \approx 0.64 \). However, this does not mean that \( P. aurelia \) suffers more from \( P. caudatum \) 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 plane(xmax=110,ymax=110,eps=-0.01) for the estimated parameters, revealing that the nullclines fail to intersect, and that \( P. aurelia \) is the strongest competitor. Note that this probably the first time in your life that you sketch nullclines based upon measured parameters.

c. Since \( P. aurelia \) suffers more from \( P. caudatum \) than from itself, it could be that the species are competing for more than one essential resource, and that \( P. caudatum \) consumes more than \( P. aurelia \). 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 *P. caudatum* consumers 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 *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 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 $e = 1$, 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 `f<-newton(s)` command. 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 on 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 $dN/dt = −dB$, 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 $\frac{A}{K}$ (Bi terms cancel each other when the $dB_i/dt$ equations are summed and $n$ is sufficiently large such that $B_0 \approx 0$.

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., $\frac{1}{p'} + \Delta$. 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., $p' = \frac{1}{1/p + \Delta}$.

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 \( dN/dt = (\rho' - d)N \) 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.

**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 \( dB/dt = e_S S + e_L L - (i_S + n_i L)B \), 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 missing term in the denominator is the \( e_L e_S \) term, and hence \( \bar{B} = \frac{e_L e_S}{e_L e_S + e_L + e_S} \).

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 \( f_i L B \) term by \( \frac{L}{h + t} (f_i - 1) i_L B + i_L B \) to define that at \( t = 0 \) the influx is \( i_L B \), at \( t = h \) the influx is \( (f_i - 1) i_L B / 2 + i_L B \), 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:

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

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

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

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 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 decline with the density \( D \). A general choice would be a Hill function, e.g.,

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

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. 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 \( \frac{dD}{dt} \):

\[
\frac{dS}{dt} = p_s g(D)[2f(D) - 1]S - d_s S = 0 \quad \text{and} \quad \frac{dD}{dt} = 2p_s [1 - f(D)] g(D)S + p_D G(D) - d_D D ,
\]

where \( G = \frac{1}{1 + D/h_G} \). 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. 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

\[
\frac{dN_1}{dt} = N_1 \left[ \frac{b_1 N_1}{h + N_1} - d_1 (1 + e_1 N_1 + c_1 N_2) \right] \quad \text{and} \quad \frac{dN_2}{dt} = N_2 \left[ \frac{b_2 N_2}{h + N_2} - d_2 (1 + e_2 N_2 + c_2 N_1) \right]
\]

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 \( K_1 \approx (R_0 - 1)/e_1 \). In the absence of sexual reproduction, i.e., when \( h \to 0 \), the nullclines are solved from \( b_i - d_i (1 + c_i N_i + e_i N_j) = 0 \) delivering the normal straight lines

\[
N_2 = \frac{R_{01} - 1}{c_1} - \frac{e_1}{c_1} N_1 \quad \text{and} \quad N_2 = \frac{R_{02} - 1}{c_2} - \frac{e_2}{c_2} N_1 ,
\]
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 \(\frac{dN_1}{dt} = 0\) nullcline is given by

\[
N_2 = \frac{1}{c_1} \left[ R_0 \frac{N_1}{h+N_1} - 1 \right] - \frac{c_1}{c_1} N_1,
\]

which resembles the straight line with slope \(-c_1/c_1\) 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. Linear models**

The steady state is \(x = y = 0\) and the Jacobian, \(J = \begin{pmatrix} a & b \\ c & d \end{pmatrix}\), is the same as the interaction matrix. Use Fig. 14.6 to create an interaction matrix with the eigenvalues corresponding to the different types of steady states.

**Question 12.9. Noise and \(r\) and \(K\)-selected species**

\(r\)-selected species recover more quickly from disturbances of the population density, but can also fluctuate more than \(K\)-selected species by tracing the variation in parameter values.

**Question 12.10. 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 \(V(10) = V(0)e^{10} = e^{10}\) that \(r = \log[V(10)]/10 \simeq 1.5\) d\(^{-1}\). The largest eigenvalue of the infected steady state is \(\lambda \simeq 1.4\) which is close to the desired growth rate of \(r = 1.5\) 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 \(\delta = 1\) d\(^{-1}\). Because Gadhamssetty et al. [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 \[2\], 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. \[2\] before taking this drug.

e. Implementing the immune response used by Gadhamssetty et al. [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. Seedlings over-shadowed by adult plants**

Start by assuming that the density of seeds, seedlings and adult plants is distributed evenly over the field. This allows one to write ODEs for the change in the number of seedlings and the number of adult plants in the field. Call them $J$ for juveniles and $A$ for adults, respectively. Because the time scale at which the number of seeds in the seed bank changes is so slow, we can define a constant, $S$, for the number (or the density) of seeds in the seed bank underlying the field. Seedlings can only be produced when a seed sprouts. Seedlings do not replicate, they can only mature or die. For the production of seedlings we therefore write a term, $pS$, where $p$ is the probability that a single seed sprouts. For the death of the seedlings and the adults plants one could write $d_1J$ and $d_2A$, respectively, whereby we assume that these death rates remain independent of the plant densities. Since the maturation rate of the seedlings depends on the adult plant densities, we need a term like $mJf(A)$ for the flux of seedlings from the juvenile to the adult population (where $f(A)$ is a declining function of $A$). Combining these four terms we arrive at the following model

$$\frac{dJ}{dt} = pS - d_1J - mJf(A) \quad \text{and} \quad \frac{dA}{dt} = mJf(A) - d_2A ,$$

composed of the processes sprouting, death and maturation. Finally, we need to define how the maturation rate declines with the number of adult plants, i.e., we need to sketch $mf(A)$ as a function of $A$. Defining $m$ as the maximum maturation rate, one can define a simple non-dimensional function, $f(A)$, that equals one when $A = 0$ and declines when $A$ increases (one may sketch a few alternatives). The most simple choice would be a linear decline, e.g.,

$$f(A) = 1 - A/k ,$$

where $k$ is the adult density where the maturation rate becomes zero. Another natural choice would be a declining Hill function,

$$f(A) = \frac{1}{1 + (A/k)^n} ,$$

where $h$ defines the adult density at which the maturation rate is $m/2$, and $n$ can be used to define a sigmoid decline (when maturation only slows down at high adult densities). The former choice would lead to the simplest model

$$\frac{dJ}{dt} = s - d_1J - mJ(1 - A/k) \quad \text{and} \quad \frac{dA}{dt} = mJ(1 - A/k) - d_2A ,$$

where $s = pS$. Because $1 - A/k$ can be interpreted as the probability that a seedling is growing at spot not covered by an adult plant, this simple model may actually be the most natural one.

**Question 13.2. Whales**

To develop a proper model for the whales we have to consider three biological processes: birth, death, and the likelihood of finding a male. One could 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 then 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 here opt for a simple saturation function, $p(N) = \frac{N}{k+N}$, where $p(N)$ is the probability, and $h$ is the population size at which there is a 50% probability of finding a male. This (daily) probability, $p(N)$, needs to be multiplied with the birth rate (that itself could also be a density dependent function). Indeed, to allow for a carrying capacity we have to include negative density dependence in either the birth or the death terms. Starting with the latter, one could define a minimum death rate, $d$, defining their maximum life span, $1/d$, of several decades, and let the death rate increase with the whale density, e.g., write $d(1 + (N/k)^n)$ for the per capita death rate. When $N = k$ the death rate has doubled, and when $n = 1$ the death rate increases linearly with the density $N$. This increase can be made steeper than linear by setting $n > 1$, or slower than linear by choosing $n < 1$. If the birth rate were to be density dependent, e.g., because the probability that calves survive and mature is low when food (krill) availability is low, we could pick one of the declining density-dependent functions, e.g.,

$$f(N) = \frac{1}{1 + (N/K)^n} ,$$

where $K$
defines the whale density at which the birth rate has halved, and \( n > 1 \) can be used to make this function sigmoid. Combining these three functions, one obtains

\[
\frac{dN}{dt} = \left[ \frac{b}{1 + (N/K)^n} \frac{N}{h + N} - d(1 + (N/k)^n) \right] N ,
\]

where one could let \( K \to \infty \), or let \( k \to \infty \), to only consider density-dependent birth, or density-dependent death, respectively. Note that by treating each process independently we were able to write three fairly simple terms, that together form a quite complicated ODE.

PS. Our choice of a simple saturation function, \( p(N) = \frac{N}{K + N} \), is somewhat phenomenological here. Importantly, a sigmoid Hill function would have been inappropriate because at low densities this probability should increase linearly with the density. Puristically, an exponential function, \( p(N) = 1 - e^{-aN} \), would have the best choice, because the probability of finding at least one male whale in a particular area can be described as a Poisson process that can be approximated with an exponential function.

**Question 13.3. Kingfishers**

Since the density of kingfishers in the area is assumed to be constant, we define \( B_T \) as the total density of birds in the area. Defining \( B \) as the number kingfishers at the lake, we obtain that there should be \( B_E = B_T - B \) kingfishers elsewhere. Since these fly in at a rate depending on the fish density in the lake, one would obtain \( iB_E f(F) \) for the immigration of birds at the lake, where \( f(F) \) is an increasing function of the density of fish, \( F \), in the lake. One could sketch a few functions for the per capita immigration rate, \( iF(F) \), of kingfishers elsewhere into the lake surroundings. For simplicity, we could choose for a linear increase, \( iF(F) = iF \), and hence write a mass-action term \( iB_E F = i(B_T - B)F \) term to define the immigration. The maximum per capita immigration rate would then be \( iK \), where \( K \) is the carrying capacity of the fish in the lake, which is bounded and therefore seems fine. Alternatively, one could assume that the immigration rate is a saturation function of the local fish density, and write \( iF(F) = \frac{iF}{N + F} \), where \( i \) would be the maximum per capita immigration rate, and then write \( \frac{i(B_T - B)F}{h + F} \) for the immigration term in the model. For the emigration rate of birds from the lake we read that they leave after catching fish. If we were to write a simple mass-action predation term, i.e., \( aFB \) in the fish equation, the emigration term in the bird equation would also be \( aFB \), because we loose both a fish and a bird when a kingfisher catches a fish. However, this would lead to the strange situation that birds never leave if there is no fish at the lake, which implies that one has to define an additional emigration term, e.g., \( eB \), allowing birds to give up and leave after catching too little. Arbitrarily, choosing for the simplest emigration term, and adding both emigration terms to \( dB/\text{dt} \), one obtains

\[
\frac{dF}{dt} = rF(1 - F/K) - aFB \quad \text{and} \quad \frac{dB}{dt} = i(B_T - B)F - aFB - eB ,
\]

which also adopts the logistic growth given by the story for the fish. Note the birds leaving the lake immediately arrive “elsewhere” thanks to the conservation equation \( B_E = B_T - B \).

**Question 13.4. Influenza virus infecting epithelial cells**

Consider a tissue of a certain size by defining \( K \) as the maximum of cells that be packed in this tissue. Uninfected epithelial cells, \( E \), will divide when they find empty space around them, which is expected to happen with probability \( (K - E - I)/K = 1 - (E + I)/K \), where \( I \) is the number of infected cells. Defining a maximum division rate, \( b \), and a death rate, \( d \) (such that \( 1/d \) corresponds to a few weeks), one would start by writing \( dE/\text{dt} = bE(1 - (E + I)/K) - dE \). Epithelial cells are infected by virus, which could be modeled with a mass-action term, \( \beta EV \)
(where $V$ represent virus), and the infection rate declines when there is interferon, $F$. If the effect of interferon is modeled with a declining Hill function one would write $f(F) = \frac{1}{1+(F/h)^n}$, where $h$ is the interferon concentration at which the infection rate is halved. If the effect of interferon were modeled with a declining linear function one would write $f(F) = 1 - F/h$, where $h$ is the interferon concentration at which the infection rate becomes zero. Multiplying the infection term, $\beta EV$, with either of these two non-dimensional functions, allows interferon to reduce the infection rate, where $\beta$ remains the maximum mass-action infection rate. Arbitrarily, choosing for the linear function one obtains

$$\frac{dE}{dt} = bE(1 - (E + I)/K) - dE - \beta EV(1 - F/h),$$

and since infected cells appear by successful infection and die at a faster rate, one readily writes for the infected cells, $I$,

$$\frac{dI}{dt} = \beta EV(1 - F/h) - \delta I,$$

where $\delta \gg d$, and we assume that infected cells do not divide. Finally, infected cells produce virus and interferon, which both should decay, e.g.,

$$\frac{dV}{dt} = pV - cV V \quad \text{and} \quad \frac{dF}{dt} = pF - cF F,$$

where the $p$ parameters are production rates, the $c$ parameters clearance rates. For completeness one could allow virus and interferon to be absorbed to the healthy cells,

$$\frac{dV}{dt} = pV I - cV V \quad \text{and} \quad \frac{dF}{dt} = pF I - cF F - aF FA,$$

where the $a$ parameters are mass-action absorption rates.

**Question 13.5. Maintenance and reproduction**

Since we learn little about the algae in this system, one could assume a simple mass-action consumption rate, and conventional logistic growth for the algae, to write

$$\frac{dA}{dt} = rA(1 - A/K) - aAD,$$

where $aA$ is the *per capita* consumption rate of *Daphnia*, $D$. Since the death rate of the zooplankton declines as a function of their *per capita* consumption, we could sketch a declining Hill function $f(aA)$ starting at a maximum death rate, $d_1 + d_0$, when $aA = 0$, and approaching a minimum death rate, $d_0$, when $aA \to \infty$, e.g.,

$$f(aA) = d_0 + \frac{d_1}{1+aA/h}.$$ 

Since the production of eggs should only start at consumption levels at which the organisms become long-lived, i.e., when $aA > h$, one could sketch an increasing Hill function, $g(aA)$, with a saturation constant, $k$, exceeding $h$. One could even choose for a sigmoid function to define that virtually no eggs are produced at low consumption levels, e.g.,

$$g(aA) = \frac{e(aA)^n}{k^n + (aA)^n},$$

where $e$ is maximum rate at which eggs can be produced, $k > h$, and $n > 1$. An alternative would be a shifted Hill function,

$$g(aA) = \frac{e(aA - k)}{H + aA - k},$$
where \( k \) is the consumption level at which eggs begin to be produced, and \( H \) is a saturation constant. Arbitrarily choosing for the latter, one would write for the eggs, \( E \), and the \textit{Daphnia}, \( D \),

\[
\frac{dE}{dt} = \frac{e(aA - k)D}{H + aA - k} - mE \quad \text{and} \quad \frac{dD}{dt} = mE - d_0D - \frac{d_1D}{1 + aA/h},
\]

where \( m \) is the rate at which eggs hatch to form novel \textit{Daphnia}s. Note that this remains a phenomenological model because we are not distributing the consumed resources over the maintenance and reproduction processes in a conserved manner, and note that one should make sure that \( aA - k \geq 0 \) when analyzing the model.

Answers to Chapter 14

Question 14.1. Sketch a few functions

Figures made with the previous version of Grind:

![Graphs](image)

\( \text{a.} \) First note that \( y = \frac{h}{n+x} = 1 \) 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).

\( \text{b.} \) First note that \( y = \frac{x}{n+x} = 0 \) 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).

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

\( \text{d.} \) 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 \( y = a \frac{k}{q/x+k/x-1} - d \) 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 14.2. 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 14.3. 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 \( dx/dt \)

\[
\frac{dx}{dt} = [(1 - x) - y]x \quad \text{and} \quad \frac{1}{\alpha} \frac{dy}{dt} = [\alpha Kx - \frac{d}{r}]y/\alpha
\]

where \( dy/dt \) can be simplified by lumping the parameters

\[
\frac{dy}{dt} = [\gamma x - \delta]y,
\]

where \( \gamma = \alpha K = cK/a/r \) 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


