Mathematical Methods in Biology
Part 4: Differential equations with several variables

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Contents

1 Introduction

Differential equations are the most frequently used tools to understand how variables such as population densities or concentrations of biomolecules change in time. We introduced differential equations already in Part 1, but now we can considerably extend the analysis of such models. The reason why this had to be delayed until now is that when the model has more than one variable, then we need matrix techniques (in particular, eigenvalues) for the analysis. And of course almost all interesting models capture interactions between several populations or several kinds of molecules, and as such, have more than one variable.

In the first half of this part, I shall use a series of infectious disease models as running examples. The simplest SIS model in the next section serves to briefly recap ideas from Part 1, and to provide a springboard towards more elaborate models and techniques.

2 Recap of models with a single variable: The SIS model of infectious diseases

The simplest model of an infectious disease divides the population of the host organism into just two groups: those susceptible to the disease and those infected (and infectious). Susceptible individuals may become infected and thus move from the susceptible class to the infected class. Infected individuals can recover, whereby they become susceptible again; this model thus assumes no acquired immunity. The name SIS model refers to the sequence of being susceptible (S), infected (I) and susceptible again. Further, the model assumes that the epidemic plays out quickly, so that the number of births and deaths is negligible during the time interval we consider. In the SIS model thus only two processes occur:

1. Susceptibles become infected when they interact with infected individuals. Interactions occur according to mass action (Part 1, section 3.1) and the disease is transmitted at rate β. This means that in a short time interval Δt, a *single* susceptible individual encounters a *specific* infected individual and pick up the disease from him with probability $\beta\Delta t$. If there are not one but I infected individuals in the population, then the probability that a given susceptible gets infected is $\beta\Delta t \cdot I$. Finally, with S susceptibles present, the number of new infections in Δt time is given by $\beta\Delta t \cdot I \cdot S = \beta SI\Delta t$.

2. Infected individuals recover at rate v. This means that in a short time interval Δt, each infected recovers with probability $v\Delta t$; and with I infected individuals present, the number of recoveries is $v\Delta t \cdot I$. Notice that we assume a constant recovery rate (i.e., independent from how long the infection has lasted). This results in an exponential recovery process (see Part 1, section 1.4), which is not very realistic for real infections, but here we prefer the mathematically simplest assumption.

How the numbers of susceptibles (S) and infected (I) change follows directly from the above two processes. In a short time Δt, the number of susceptibles decreases by $\beta SI\Delta t$ and increases by $vI\Delta t$, hence the net change is

$$\Delta S = -\beta SI\Delta t + vI\Delta t$$

Similarly, the number of infected individuals increases by $\beta SI\Delta t$and decreases by $vI\Delta t$ such that we have

$$\Delta I = \beta SI\Delta t - vI\Delta t$$

By dividing with Δt and taking $\Delta t \to 0$ (as in Part 1, sections 1.4 and 2.3), we arrive at the system of differential equations

$$\frac{dS}{dt} = -\beta SI + vI \tag{1a}$$

$$\frac{dI}{dt} = \beta SI - vI \tag{1b}$$

Strictly speaking, in these equations one should write $S(t)$ and $I(t)$ instead of S and I, because they change with time and at any time point t we should use their current values, but this is often suppressed for brevity.

It is conspicuous that ΔI is the negative of ΔS such that $\Delta S + \Delta I = 0$; and, consequently, the sum of equations (1a) and (1b) is also zero. This is because the total number of individuals $N = S + I$ is constant (i.e., $\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} = 0$; in the terminology of Part 1, $S + I = N = const$ is a conservation law). The model assumes no births and no deaths, which would change the total number of individuals; all what happens is that individuals move between the classes S and I, but their total number does not change. We can thus express S as $S = N - I$ with N being a constant. This allows us to rewrite equation (1b) into

$$\frac{dI}{dt} = \beta(N - I)I - vI \tag{2}$$

which is a differential equation for a single variable, I.

Exercise 1. Rearrange equation (2) to show that it is identical to the logistic model of population growth, i.e., equation (2) could be written as $\frac{dI}{dt} = rI[1 - I/K]$, with r and K being some combinations of the parameters of the SIS model, β, v and N.

Exercise 2. Assume that initially only a few individuals are infected in a large population, i.e., $I(0) \ll N$. Show that if $N < v/\beta$, then I will not increase, i.e., there will be no epidemic outbreak.

Exercise 3. Suppose that a fraction p of N individuals are vaccinated against the disease. Since vaccinated individuals cannot contract and transmit the disease, they are effectively absent from the infection's point of view. Determine

the minimum fraction of individuals to be vaccinated to prevent an epidemic outbreak. *Hint:* use the result of the previous exercise. Populations where the vaccination fraction exceeds this minimum are said to exhibit *herd immunity*. In such a population random sporadic cases of the disease might occur, but these will not lead to a major outbreak.

The analysis of a model with a single differential equation, such as the SIS model in equation (2), usually follows three steps (see also Part 1, section 3.5):

1. *Find all equilibria of the model.* At equilibrium, the change of the variable must be zero ($\frac{dI}{dt} = 0$) such that from equation (2), we obtain

$$\beta(N - I)I - vI = 0 \tag{3}$$

The equilibrium equation in (3) has two solutions, and therefore the SIS model has two equilibria: the trivial equilibrium $\hat{I}_1 = 0$ (obviously, if no one is infected now then no one will ever be infected if the population is closed to the outside) and the nontrivial equilibrium $\hat{I}_2 = N - v/\beta$.

Exercise 4. Check that the last statement is true.

Exercise 5. Calculate the equilibrium number of susceptibles. Compare to the result of exercise 2: Can you explain why the number of susceptibles equilibrates to the critical value of population size, below which there is no epidemic outbreak? What happends when $N < v/\beta$ such that $\hat{I}_2$ is negative?

2. *Local stability analysis.* The next step is to establish the stability of the equilibria. Let $f(I)$ denote the entire right hand side of the differential equation in (2). The equilibrium $\hat{I}$ is stable if $f'(\hat{I}) < 0$ (cf. Part 1, section 3.5). With $f(I) = \beta(N - I)I - vI$, the derivative evaluates to $f'(I) = \beta N - 2\beta I - v$. The trivial equilibrium is stable if $f'(0) = \beta N - v < 0$, whereas the nontrivial equilibrium is stable if $f'(N - \frac{v}{\beta}) = -\beta N + v < 0$. The latter is equivalent to $\beta N - v > 0$, i.e., the nontrivial equilibrium is stable when the trivial equilibrium is unstable.

Exercise 6. Show that the nontrivial equilibrium of the SIS model is stable whenever it is positive.

3. *Bifurcation diagram.* Finally, we investigate how the equilibria change when changing the model parameters. Figure 1 shows $\hat{I}_1$ and $\hat{I}_2$ with their stability (thick line when stable, dashed line when unstable) against total population size N. As derived in exercise 6, $\hat{I}_2$ is stable when it is positive; and $\hat{I}_1$ is stable when $\hat{I}_2$ is not. At $N = v/\beta$, the equilibria undergo a transcritical bifurcation, i.e., they cross each other and exchange their stability (cf. Part 1, section 3.7).

Exercise 7. Suppose a medical treatment makes recovery faster such that the recovery rate v becomes higher. How does this change the bifurcation diagram in Figure 1?

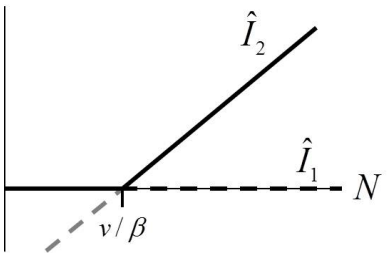


Figure 1: The bifurcation diagram of the equilibria of the SIS model. Thick and dashed lines represent stable and unstable equilibria, respectively. Negative values are shown in grey because these are biologically irrelevant. At $N = v/\beta$ a transcritical bifurcation occurs, i.e., the two equilibria cross each other and exchange their stability.

The analysis outlined above concentrates on equilibria. Models with a single differential equation (such as the SIS model in equation (2)) can behave in only two ways: either their variable grows unboundedly (at some time it becomes larger than any fixed large number; or it becomes ever more negative in a similar fashion) or they approach an equilibrium. Since the former possibility is biologically unrealistic, we expect an equilibrium or several equilibria in biologically well justified models. As we shall see, models with several variables can have also other types of dynamics (cycles and chaos), yet equilibria are the simplest and generally it is a good idea to start the analysis of any model with investigating its equilibria.

Exercises

Exercise 8. *Medicine concentration.* The concentration of a medicine decays in the body as the liver metabolizes the medicine and/or the kidneys excrete it. At low concentrations of the medicine, this is approximately an exponential decay process. At higher concentrations, however, the amount of medicine removed per unit of time saturates since the body cannot remove more than a certain amount per unit of time. This saturating removal process can be modelled with the equation

$$\frac{dx}{dt} = -\frac{cx}{k+x}$$

where x is the concentration of the medicine, c is the maximum amount removed per unit time (as x goes to infinity, the right hand side goes to $-c$),

and k is the half-saturation value (when $x = k$, removal occurs at speed $c/2$; cf. section 1.2 of Part 1). If the medicine is infused at a constant rate u, then the infusion and the decay together yield the dynamics

$$\frac{dx}{dt} = u - \frac{cx}{k+x}$$

Find all equilibria of this model and establish their stability.

Exercise 9. *Prebiotic replicators.* It is thought that before the emergemce of life proper, RNA-like molecules were replicating themselves in an autocatalytic reaction, where one RNA molecule is copied by another (identical) RNA molecule acting as a ribozyme ("RNA-enzyme"). In this autocatalytic reaction, the replication rate of a given copy of the RNA molecule, bx, is proportional to the concentration of RNA, x, because to replicate one copy, another is needed as a ribozyme. The speed of replication is also proportional to the concentration of the monomers from which RNA is synthesized, c. The RNA molecules decay at a constant rate d. The concentration of RNA therefore changes according to

$$\frac{dx}{dt} = [bxc - d]x$$

The monomer concentration c varies in time depending on how many monomers are incorporated into RNA molecules. Suppose that monomers are not destroyed and not synthesized anew, so that their concentration changes only by being built into RNA and released when RNA decays. If one RNA molecule contains k monomers, then a unit volume contains $c_0 = c + kx$ monomers either free (c) or part of an RNA molecule (kx). Since the total number of monomers does not change, $c_0 = c + kx = const$ is a conservation law and we can substitute c with $c = c_0 - kx$ to obtain the equation

$$\frac{dx}{dt} = [bx(c_0 - kx) - d]x$$

where b, c_0, k and d are constants.
(a) Find all equilibria of this model.
(b) Establish the stability of the trivial equilibrium $\hat{x} = 0$ and deduce the stability of all other equilibria. *Hint:* recall that stable and unstable equilibria alternate (see section 3.5 of Part 1).
(c) Draw a bifurcation diagram to show how the equilibria change when the decay rate d is varied.
(d) In reality, there is a very low rate a of spontaneous, non-catalysed RNA-replication. This changes the dynamics into

$$\frac{dx}{dt} = [(a + bx)(c_0 - kx) - d]x$$

How does this change the stability of the trivial equilibrium? How does the bifurcation diagram change?

3 Phase plane analysis: The SIR and SI models

The SIS model in the previous section assumed that individuals who recover from the disease return to the susceptible state. Because recovery replenishes the susceptibles, the disease always finds new hosts to infect; the disease can thus be present permanently at the nontrivial equilibrium found above. The outcome of an epidemics will however be rather different if recovering individuals acquire immunity to the disease such that they cannot be infected again. In this case the population is divided into three groups: susceptible (S), infected (I), and recovered (R), giving this model the name SIR model. Since the recovered individuals no longer participate in the disease dynamics, we can consider them as having been removed from the system (R may also stand for "removed"). In fact, the same SIR model applies also to a disease that kills its victims, with R representing the dead.

The model equations are constructed similarly to the SIS model in equations (1), except that the recovering individuals are not put back in S (the last term of the fisrt equation is missing),

$$\frac{dS}{dt} = -\beta SI \tag{4a}$$

$$\frac{dI}{dt} = \beta SI - vI \tag{4b}$$

but are moved to R,

$$\frac{dR}{dt} = vI$$

We still have that the total population size $N = S + I + R$ is constant, but the sum $S + I$ is not constant any more. Hence we have to analyze the two equations (4a,b).

A quick graphical method to gain insight into the behaviour of a model with two differential equations is to draw how the variables change on the phase plane (Figure 2. The phase plane is a coordinate system with the two variables (S and I) on the two axes. For each point on this plane, we can evaluate the right hand side of the first differential equation (4a), and decide whether it is positive or negative; accordingly, we see whether the first variable (S) increases or decreases. This amounts to moving horizontally to the right or to the left on the phase plane (marked with horizontal arrows). Similarly, we can decide using the second differential equation (4b) whether the second variable (I) is increasing or decreasing, and mark this vertical movement on the phase plane.

In the case of the SIR model, the right hand side of dS/dt in equation (4a) is negative whenever S and I are positive; hence S always decreases (horizontal arrows to the left in Figure 2). dI/dt in equation (4b) is positive if $\beta SI > vI$. Assuming that I is

positive, this simplifies to $\beta S > v$ or, equivalently, to $S > v/\beta$. Hence I increases when S exceeds v/β (vertical arrow up in the right half of Figure 2), but I decreases when S is below v/β (vertical arrow down in the left half of Figure 2). The line across which the direction changes is referred to as an *isocline*. In the SIR model, the vertical line at $S = v/\beta$ is an isocline for the variable I; and S has no isocline because it always decreases.

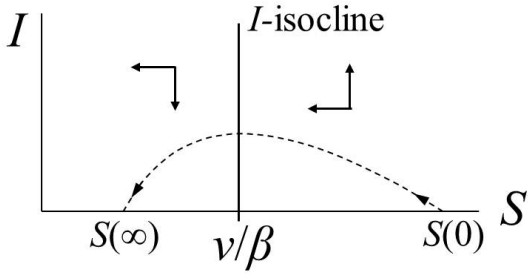


Figure 2: Phase plane analysis of the SIR model; see the text for explanation.

The dashed curve in Figure 2 shows the trajectory the system follows when the initial population has $S(0)$ susceptibles and a very small number of infected. At the outbreak of the epidemic, the number of infected increases and the number of susceptibles decreases (movement up and to the left). When the trajectory crosses the I-isocline, the direction of vertical movement changes such that I starts to decrease, whereas S continues to decrease (movement down and to the left). Notice that the trajectory crosses the I-isocline horizontally; this is because at this point it no longer moves upwards but does not yet move downwards. Eventually the disease disappears (I becomes zero), even though some susceptibles remain (their number is marked with $S(\infty)$ in Figure 2). The number of individuals who got infected during the epidemic can be obtained as $S(0) - S(\infty)$, which is called the *final size* of the epidemic.

Figure 2 shows just one trajectory, but of course a separate trajectory may be drawn starting from any values of $S(0)$ and $I(0)$ we may choose. When sketching possible trajectories, it is useful to keep in mind that *trajectories cannot intersect*. This is because the differential equations unequivocally prescribe at any point of the phase plane how the system will move on. For example in the SIR model, S increases by $dS = -\beta SIdt$ and I increases by $dI = [\beta SI - vI]dt$ in the next short time interval dt, such that the system moves from the point (S, I) along the tangent $dI/dS = -1 + v/\beta S$. If two trajectories intersected, then from the point of intersection they would continue in two different ways; but that is impossible because the differential equations give always one tangent for the trajectory.

Exercise 10. Sketch several more trajectories of the SIR model in Figure 2, assuming realistically that the initial number of infected, $I(0)$, is small. Use these trajectories to argue that in a population of fewer susceptibles, the epidemic leaves more individuals uninfected (i.e., $S(\infty)$ is higher when $S(0)$ is smaller).

Exercise 11. Solve the SIR model in equations (4) numerically with parameter values $\beta = 1$, $v = 1$, and $N = 1.2$; 1.5; 1.7; 2; 2.5; 3; 4; 5, assuming that initially 1% of the population is infected. Plot the final number of susceptibles $S(\infty)$ againts N.

Exercise 12. At the onset of an epidemic outbreak, all but the few initially infected individuals are susceptible so that $S(0) \approx N$. Show that no epidemic outbreak occurs (the number of infected does not increase) if $N < v/\beta$. This is the same threshold as in the SIS model (cf. exercise 2); explain why the SIR and SIS models have the same threshold for an outbreak.

Exercise 13. Calculate the minimum fraction of individuals to be vaccinated in order to avoid an outbreak of an epidemic in the SIR model; explain why it is the same as in the SIS model (exercise 3).

In the basic SIR model in equations (4), we neglect the birth and (not disease-related) death of the hosts. This is justified for short epidemic outbreaks during which the number of births and deaths is negligible (such as an influenza epidemic), but not for endemic diseases that are permanently present (such as measles and other childhood diseases in unvaccinated human populations). A disease can be permanently present precisely because the birth of new hosts replenishes the susceptibles, such that the disease can always infect new hosts. In the remainder of this section, we develop and analyze a model for an endemic disease with births and deaths included.

Before turning to the dynamics of an endemic disease, we need a model for the host population dynamics in absence of the disease. Since the host population cannot grow indefinitely, the birth rate or the death rate (or both) of the host must be density-dependent (see section 3.4 of Part 1). Here I assume that the birth rate is given by

$$b\left[1 - \frac{N}{M}\right] \tag{5}$$

where N is the host population size and b and M are constants. This birth rate is linearly decreasing with the host population size. A simple justification for this formula is if we assume that the hosts live in individual sites (patches of the habitat able to support only one individual), and newborns disperse randomly to one of these sites. If there is a total of M sites and N of these are occupied, then a randomly dispersing newborn lands in an

occupied site with probability $\frac{N}{M}$, in which case it perishes; and it lands in an empty site with probability $\left[1-\frac{N}{M}\right]$, in which case it survives. If each host produces newborns at a constant rate b but only the fraction $\left[1-\frac{N}{M}\right]$ of the newborns is added to the population, then the *per capita* rate of offspring production is as given in formula (5). Assuming a constant death rate μ, the host population dynamics in absence of the disease is given by

$$\frac{dN}{dt} = b\left[1-\frac{N}{M}\right]N - \mu N \tag{6}$$

Exercise 14. Show that the host population is has a stable positive equilibrium when $b > \mu$ and dies out when the opposite holds.

Exercise 15. Rearrange equation (6) to show that it is identical to the logistic model of population growth, $\frac{dN}{dt} = rN(1-N/K)$, and express r and K with the parameters b, M and μ.

To add birth and death to the SIR equations, assume that all hosts can reproduce (including the infected), and all newborns are susceptible (there is no vertical transmission from an infected parent to its offspring and there is no vaccination). This means that the birth term $b\left[1-\frac{N}{M}\right]N$ is added to $\frac{dS}{dt}$. All S, I and R individuals suffer disease-unrelated death at the rate μ, and infected individuals die due to the disease at a rate α, the virulence of the disease ($\alpha = 0$ corresponds to a harmless disease). This leads to the equations

$$\frac{dS}{dt} = b\left[1-\frac{N}{M}\right]N - \mu S - \beta SI \tag{7a}$$

$$\frac{dI}{dt} = \beta SI - vI - \mu I - \alpha I \tag{7b}$$

$$\frac{dR}{dt} = vI - \mu R \tag{7c}$$

Note that due to the births and deaths, the total population size $N = S + I + R$ is no longer constant, and therefore in this model there is no conservation law we could use to reduce the number of equations.

The analysis of the full model in equations (7) is hindered by the difficulty of visualizing the dynamics in a 3-dimensional phase space (with axes for S, I and R). In order to simplify, I make the new assumption that infected individuals never recover ($v = 0$). With this assumption R is always zero (no one ever enters the class of recovered), so that the model becomes the 2-dimensional SI model

$$\frac{dS}{dt} = b\left[1-\frac{N}{M}\right]N - \mu S - \beta SI \tag{8a}$$

$$\frac{dI}{dt} = \beta SI - \mu I - \alpha I \tag{8b}$$

with $N = S + I$.

It is easier to carry out the phase plane analysis of the SI model if we rewrite the equations such that we use the total population size N and the number of infected I as the two variables. Adding (8a) and (8b) yields the equation

$$\frac{dN}{dt} = b\left[1 - \frac{N}{M}\right] N - \mu N - \alpha I \tag{9a}$$

whereas substituting $S = N - I$ into (8b) and factoring I out gives

$$\frac{dI}{dt} = [\beta(N - I) - (\mu + \alpha)]I \tag{9b}$$

The two equations in (9a) and (9b) we use to obtain the isoclines, find the equilibria and establish their stability as far as possible with a phase plane analysis. Throughout, we assume that the host population is viable ($b > \mu$, cf. exercise 14).

The N-isocline consists of the points where $\frac{dN}{dt} = 0$, and hence, from equation (9a),

$$b\left[1 - \frac{N}{M}\right] N - \mu N - \alpha I = 0$$

With N on the horizontal axis and I on the vertical axis as in Figure 3, the isocline is plotted easiest if we express I from the above equation:

$$I = \frac{b\left[1 - \frac{N}{M}\right] - \mu}{\alpha} N \tag{10}$$

The graph of I as a function of N is the "upside down" parabola in Figure 3 (notice the negative sign of the N^2 term). The parabola goes through the origin because at $N = 0$, the isocline equation (10) gives $I = 0$. The other zero of the parabola is where the numerator in equation (10) vanishes; I shall denote N at this point with K.

> **Exercise 16.** Show that $N = K$ is the equilibrium size of the disease-free host population, i.e., the carrying capacity of the logistic model in exercise 15.

On the I-isocline $\frac{dI}{dt} = 0$, and hence, from equation (9b),

$$[\beta(N - I) - (\mu + \alpha)]I = 0$$

This equation has two solutions. The first is $I = 0$, which means that the N-axis of Figure 3 is itself an I-isocline. The second solution is where the expression in the brackets is zero, i.e.,

$$I = N - \frac{\mu + \alpha}{\beta} \tag{11}$$

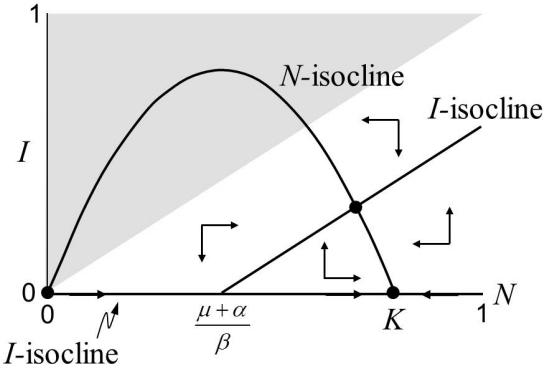


Figure 3: Phase plane analysis of the SI model with births and deaths. Dots denote equilibria (irrespective of stability). In the grey area $I > N$, which is biologically impossible. See the text for further explanation. Parameter values: $b = 5$, $M = 1$, $\mu = 1$, $\beta = 5$, $\alpha = 1$

The I-isocline corresponding to this second solution is a straight line with slope 1, which intersects the horizontal axis at $N = \frac{\mu+\alpha}{\beta}$.

To draw the N- and I-isoclines in the same figure, we need to know their positions relative to each other. More precisely, what important is the position of the intersection of the second I-isocline with the horizontal axis, $\frac{\mu+\alpha}{\beta}$ relative to K, the nontrivial zero of the N-isocline. Figure 3 shows the isoclines assuming $\frac{\mu+\alpha}{\beta} < K$; the opposite case is analyzed in exercise 18.

The isoclines divide the phase plane in Figure 3 into areas with different directions of movement. To find these directions (i.e., to draw the arrows of Figure 3), it is easiest to start on the horizontal axis, where the disease is absent. In this case the host population tends to its disease-free stable equilibrium at $N = K$, i.e., moves to the right if we start below K and moves to the left if we start above K. The same directions hold also when I is not zero but small (because then the last term in (9a) is, even though not zero, but negligible), i.e., the same horizontal arrows apply in the phase plane just above the N-axis. The horizontal arrows change only when we cross the N-isocline; hence at every point below the parabola the horizontal arrow points to the right, and at every point above the parabola it points to the left. To see the directions of the vertical arrows, notice in equation (9b) that $\frac{dI}{dt}$ is negative when N is small and positive when N is large. Hence on the left of the second I-isocline (where the small values of N are) the number of infected decreases and the vertical arrow points downward; and on the right side of the second I-isocline the vertical arrows point upward. (The first I-isocline coincides with the horizontal axis, so that it does not divide the positive, biologically meaningful part of the phase plane.) This completes drawing the phase plane diagram in Figure 3.

We can find the equilibria of the model as the intersections of N- and I- isoclines. On the N-isocline the change in N is zero (equation (9a) evaluates to zero); and on the I-isocline the change in I is zero (equation (9b) evaluates to zero). The intersection point is a point on both isoclines where neither N nor I changes (both differential equatiions evaluate to zero), i.e., an equilibrium.

In Figure 3, there are three equilibrium points:

- The origin, where the parabola-shaped N-isocline intersects the horizontal axis, which is the first I-isocline. This represents the trivial equilibrium of not having a population at all.
- The point K on the horizontal axis, where the N-isocline intersects the horizontal axis (the first I-isocline) again. This represents the disease-free equilibrium of the host.
- The interior equilibrium where the N-isocline intersects the second I-isocline. This is an equilibrium where the disease is endemic.

To see the stability of an equilibrium, we investigate a trajectory starting from the vicinity of that equillibrium. If all trajectories starting from near the equilibrium tend back to the equilibrium, then the equilibrium is (locally) stable. Since we have three equilibria in the SI model, we have to investigate the stability of each:

- When the system starts from near the origin, it will move down and to the right (cf. arrows). This means that it will move towards the horizontal axis (returning towards $I = 0$), but also towards the right along the horizontal axis. This latter movement will take it away from the origin, i.e., the equilibrium at the origin is unstable.
- When the system starts from near the disease-free equilibrium, then horizontal movement tends to push it towards K, but vertically it moves upwards and hence away from the equilibrium. The disease-free equilibrium is therefore also unstable.
- In the vicinity of the endemic equilibrium, the arrows suggest the possibility of a spiralling movement. It is unfortunately not possible to say just from the directions of the arrows whether the system is indeed spiralling around the endemic equilibrium, and whether such spirals lead closer ("spiralling in") or further away ("spiralling out") from the equilibrium.

  Exercise 17. Sketch an example where the configuration of isoclines and arrows is as near the endemic equilibrium in Figure 3, yet the trajectory is not spiralling. *Hint*: consider the case when movement is much faster horizontally that vertically (or *vice versa*).

The failure to establish the stability of the endemic equilibrium highlights that we need also more sophisticated methods for stability analysis. However, we can make an important conclusion based on Figure 3: if $\frac{\mu+\alpha}{\beta} < K$ (this is the case for which Figure 3 is drawn), then the disease will remain endemic either at the endemic equilibrium or exhibiting some non-equilibrium behaviour. The disease cannot disappear because then the system should settle on the horizontal axis; and on the horizontal axis all trajectories go to K, which in turn is unstable such that the disease can spread again once the population is near K. In many other models, a simple phase plane analysis suffices also to establish the stability of all equilibria (see the exercises below).

Exercise 18. Carry out the phase plane analysis of the SI model assuming $\frac{\mu+\alpha}{\beta} > K$, i.e., that the second I-isocline intersects the horizontal axis to the right of K. Show that (i) no endemic equilibrium exists, and (ii) the disease-free equilibrium is stable.

Exercise 19. Sketch a few examples for the isoclines of the SI model starting with Figure 3 and assuming smaller and smaller values for the transmission rate β. How does the endemic equilibrium change? How does Figure 3 transform into the figure obtained in exercise 18? What happens when β is such that $\frac{\mu+\alpha}{\beta} = K$? The phenomenon observed there is a transcritical bifurcation in a 2-dimensional system (compare with section 2).

Exercise 20. In the SI model, the disease is endemic when $\frac{\mu+\alpha}{\beta} < K$ (cf. Figure 3) or, equivalently, $\beta K/(\mu+\alpha) > 1$. Show that $\beta K/(\mu+\alpha)$ is the expected number of new infections a single infected individual makes before it dies in the equilibrium population of susceptible hosts (*hint:* recall the expected lifetime in an exponential decay process from section 1.4 of Part 1). This quantity is known as R_0, the *basic reproduction number* of the infection (see also section 1.3 of Part 3). When $R_0 > 1$, then each infected makes on average more than 1 new infections in an all-susceptible population, which means that the infection spreads and an outbreak ensues.

Exercises

Exercise 21. *The SI model with frequency-dependent transmission.* The epidemic models we have studied so far assume that the individuals make contact with each other according to mass action, i.e., the number of contacts one individual makes per unit time is directly proportional to population size. This is however not a realistic assumption for animals living in herds, where the number of contacts one individual makes is approximately constant. A constant number of contacts per unit time is also a better approximation for humans. Assume thus that a susceptible individual makes βdt contacts in dt time, and if the partner contacted is infected, then contracts the disease. The probability

that a randomly chosen partner is infected equals the frequency of the infected, I/N, such that the probability that a given susceptible becomes infected in dt time is given by $\beta(I/N)dt$. This is called frequency-dependent transmission (or standard incidence); the difference from the mass action model is the division by N. With frequency-dependent transmission, the SI model in equations (9a,b) becomes

$$\begin{aligned} \frac{dN}{dt} &= b\left[1-\frac{N}{M}\right]N-\mu N-\alpha I \\ \frac{dI}{dt} &= \beta(N-I)\frac{I}{N}-(\mu+\alpha)I \end{aligned}$$

Investigate this model using phase plane analysis. In particular, show that with frequency-dependent transmission, a deadly disease ($\alpha > 0$) can drive the host population extinct.

Exercise 22. *The SI model with Allee effect in the host.* Suppose that in a sexual host species the number of births is limited by how often the females encounter males, such that the birth rate is proportional to the density of males. Assume 1:1 sex ratio such that the density of males equals the density of females, N. (Since the total population size is now $2N$, we have to change the number of living sites to $2M$, too, such that the fraction of occupied sites remains $\frac{2N}{2M}=\frac{N}{M}$.) The *per capita* birth rate of females is then $bN(1-\frac{N}{M})$ (as in equation (9a), but with bN in place of b) and the SI model in equations (9a,b) becomes

$$\begin{aligned} \frac{dN}{dt} &= b\left[1-\frac{N}{M}\right]N^2-\mu N-\alpha I \\ \frac{dI}{dt} &= [\beta(N-I)-(\mu+\alpha)]I \end{aligned}$$

(a) Study the dynamics of this model in absence of the disease. Find all erquilibria and establish their stability.
(b) Perform the phase plane analysis of the full model with parameter values $b=2$, $M=10$, $\mu=3$, $\alpha=3$ and (i) $\beta=2$ or (ii) $\beta=6$. Find out whether an endemic equilibrium exists, and if not, what happens if an epidemic breaks out.
(c) Suppose that a fraction p of the newborns are vaccinated and therefore cannot contract the disease. Modify the model equations and sketch the isoclines on the phase plane for increasing values of p. Discuss how the equilibria change.

Exercise 23. *Competition between two strains of a pathogen.* Consider the SIS model in equations (1) but with two strains of the pathogen, which differ in their transmission rates (β_1 vs β_2) and recovery rates (v_1 vs v_2). Assuming

that once an individual is infected with one strain of the pathogen, it cannot be infected with the other (cross-immunity), the two-strain SIS model becomes

$$\begin{aligned}\frac{dS}{dt} &= -\beta_1 S I_1 - \beta_2 S I_2 + v_1 I_1 + v_2 I_2 \\ \frac{dI_1}{dt} &= \beta_1 S I_1 - v_1 I_1 \\ \frac{dI_2}{dt} &= \beta_2 S I_2 - v_2 I_2\end{aligned}$$

where I_1 and I_2 denote the number of hosts infected with strain 1 and strain 2, respectively, and $N = S + I_1 + I_2$ is constant. Use this conservation law to rewrite the model with only two equations, and perform a phase plane analysis to show that (i) the two strains do not coexist unless $\frac{\beta_1}{v_1} = \frac{\beta_2}{v_2}$ (which is very unlikely); and (ii) strain 1 outcompetes strain 2 if $\frac{\beta_1}{v_1} > \frac{\beta_2}{v_2}$, whereas strain 2 outcompetes strain 1 if the opposite inequality holds.

Exercise 24. *The Lotka-Volterra competition model.* The simplest model for competition between two species is

$$\frac{dN_1}{dt} = r_1[1 - \alpha_{11}N_1 - \alpha_{12}N_2]N_1 \tag{12a}$$

$$\frac{dN_2}{dt} = r_2[1 - \alpha_{21}N_1 - \alpha_{22}N_2]N_2 \tag{12b}$$

where N_1 and N_2 are the population densities of species 1 and 2, respectively, r_1 and r_2 are their intrinsic growth rates, and α_{ij} measures the competitive effect of species j on species i. Perform the phase plane analysis of this model: find all equilibria and if possible, establish their stability for all possible combinations of the competition coefficients:

(i) $\alpha_{11} > \alpha_{21}$, $\alpha_{22} > \alpha_{12}$

(ii) $\alpha_{11} < \alpha_{21}$, $\alpha_{22} < \alpha_{12}$

(iii) $\alpha_{11} < \alpha_{21}$, $\alpha_{22} > \alpha_{12}$

(iv) $\alpha_{11} > \alpha_{21}$, $\alpha_{22} < \alpha_{12}$

Optional: Show that the Lotka-Volterra competition model can be written in the form

$$\frac{dN_1}{dt} = r_1 N_1 \left[1 - \frac{N_1 + a_{12}N_2}{K_1}\right] \tag{13a}$$

$$\frac{dN_2}{dt} = r_2 N_2 \left[1 - \frac{N_2 + a_{21}N_1}{K_2}\right] \tag{13b}$$

and calculate the parameters of equations (12) if the parameters of equation (13) are known. Most textbooks display the Lotka-Volterra competition model

in the form of equations (13), but the analysis is more transparent when using equations (12). In equations (13), it is easy to see that the Lotka-Volterra competition model is a straightforward extension of the logistic model (see section 3.4 of Part 1).

Exercise 25. *A genetic switch.* To differentiate into different tissues during ontogenesis, cells need to switch certain sets of genes on or off. The genetic switch must be inducable (so that with different initial conditions, cells with the same genome can arrive at different final states) and must also be stable against random perturbations of the concentrations of the regulating molecules. Whether a certain set of genes is active or not depends on the presence of transcription factors, proteins that bind to regulating DNA-sequences upstream from the structural genes and determine whether the genes are being transcribed or not. The simplest genetic switch consists of two sets of genes. Each set of genes includes the gene of a transcription factor (U and V, respectively) and each set of genes is preceded by a separate regulating DNA-sequence (R_U and R_V, respectively). Both regulating sequences can bind one transcription factor at a time. If the regulating sequence R_U binds transcription factor U, then the genes regulated by R_U are active; these genes include the gene for U. Hence U must be present for its own production. The alternative transcription factor, V, can also bind to R_U, but binding V does not activate R_U. R_U is thus inactive so that U is not produced if either R_U is free or V is bound to R_U; and V can prevent activation simply by taking the place of U (this is called *competitive inhibition* by V). The regulating sequence R_V works analogously: it can bind either U or V but it is activated only when V is bound to it, and it controls, among other genes, the gene producing V.

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

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

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

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

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

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

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

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

$$\frac{dx}{dt} = k_1(1-x-y)u - k_{-1}x \tag{14a}$$

$$\frac{dy}{dt} = k_2(1-x-y)v - k_{-2}y \tag{14b}$$

Binding unbinding the transcription factors are simple chemical reactions that play out much faster than the synthesis and decay of the transcription factors (large proteins), hence these processes attain a quasi-equilibrium in such a short time while the total amounts of U and V can be considered (almost) constants. To determine the quasi-equilibrium of equations (14a,b), we set the right hand sides to zero to obtain

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

The easiest way to solve these equations for x and y is to multiply the first equation with $k_2 v$ and the second equation with $k_1 u$ so that the left hand sides of the two equations become the same:

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

Because $k_{-1}k_2vx$ and $k_1k_{-2}uy$ are equal to the same quantity, they must be equal to each other. From $k_{-1}k_2vx = k_1k_{-2}uy$, we obtain $y = \frac{k_{-1}k_2vx}{k_1k_{-2}u}$. Finally,

we substitute this into the first equation $k_1(1-x-y)u = k_{-1}x$ to obtain

$$k_1\left(1 - x - \frac{k_{-1}k_2vx}{k_1k_{-2}u}\right)u = k_{-1}x$$

$$k_1u = x\left[k_1u + \frac{k_{-1}k_2v}{k_{-2}} + k_{-1}\right]$$

$$x = \frac{k_1u}{k_1u + \frac{k_{-1}k_2v}{k_{-2}} + k_{-1}}$$

The result becomes more transparent if we divide both the numerator and the denominator with k_{-1}; then everywhere we see *ratios* of reaction rates:

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

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

$$x = \frac{\alpha u}{\alpha u + \beta v + 1} \tag{15}$$

Now we turn to the slow processes of the production and decay of U and V. U is produced at a constant rate a when R_U is active, which occurs in the fraction x of time; hence the speed of production is ax. U decays at a constant rate μ. U is also binding to and dissociating from R_U and R_V, but these fast processes are at their quasi-equilibrium where binding balances dissociation and therefore they cause no net change in the concentration of U. u thus changes according to

$$\frac{du}{dt} = ax - \mu u$$

By substituting the quasi-equilibrium value of x from equation (15), we arrive at

$$\frac{du}{dt} = \frac{a\alpha u}{\alpha u + \beta v + 1} - \mu u \tag{16a}$$

and, assuming that the production and decay rates a and μ are the same for both U and V, an analogous derivation shows that v changes according to

$$\frac{dv}{dt} = \frac{a\alpha v}{\beta u + \alpha v + 1} - \mu v \tag{16b}$$

Perform the phase plane analysis of the model in equations (16a,b) to find all equilibria and their stability (assume $a\alpha > \mu$). You will need to distinguish the two cases $\alpha > \beta$ and $\alpha < \beta$; in which case does this system work as a genetic switch? What conditions should the binding/unbinding reaction rates k_1, k_{-1}, k_2 and k_{-2} satisfy for having a genetic switch (recall the definitions of α and β)?

4 Local stability of equilibria

This section explains the method of local (or linear) stability analysis of equilibria in models with several differential equations. What we obtain in this section is a generalization of the stability condition for a single variable (see section 2 and section 3.5 of Part 1): if the model is written in the form $\frac{dx}{dt} = f(x)$ (where x is the variable and $f(x)$ represents whatever expression is on the right hand side of the differential equation), then a point $\hat{x}$ is a locally stable equilibrium if $f(\hat{x}) = 0$ (it is an equilibrium) and $f'(\hat{x}) < 0$ (the equilibrium is stable). The basic idea behind the stability analysis with multiple variables is the same as with a single variable, but technically the analysis is more complicated. Because the stability analysis is our main tool in exploring the behaviour of differential equation models, it is important to understand it in detail, and therefore this section presents all derivations behind the method in a step-by-step fashion in sections 4.1-4.3. Yet at the end, the method boils down to a straightforward recipe, summarized in section 4.4. Section 4.5 contains a shortcut that is valid when the model has two variables (which is very often the case).

4.1 Linearization

The method of local stability analysis is applicable to models with any number of differential equations. However, to ease the notation, I present the method with only two differential equations; the generalization to more equations is straightforward. (Only section 4.5 is specific to the case of two differential equations.)

We start with a model written in the form

$$\frac{dx_1}{dt} = f_1(x_1, x_2) \tag{17a}$$

$$\frac{dx_2}{dt} = f_2(x_1, x_2) \tag{17b}$$

where x_1 and x_2 are the two variables, and $f_1(x_1, x_2)$ and $f_2(x_1, x_2)$ are the expressions on the right hand sides of the model equations. For example in the SIS model in equations (1a,b) of section 2, $x_1 = S$, $x_2 = I$, $f_1(S, I) = -\beta SI + vI$, and $f_2(S, I) = \beta SI - vI$.

Suppose that we have an equilibrium in the model, the stability of which we want to establish (recall that if the model has several equilibria, the stability of each must be investigated separately). Let $\hat{x}_1$ and $\hat{x}_2$ denote the equilibrium values of the variables. Because this is an equilibrium, we must have that

$$f_1(\hat{x}_1, \hat{x}_2) = 0 \tag{18a}$$

$$f_2(\hat{x}_1, \hat{x}_2) = 0 \tag{18b}$$

As the first main step, we approximate $f_1(x_1, x_2)$ and $f_2(x_1, x_2)$ for values of x_1 near $\hat{x}_1$ and for values of x_2 near $\hat{x}_2$. This approximation is easier to visualize for a function

of a single variable (see Figure 4). If we have some function $f(x)$, we can approximate it with a straight line tangent to the function at $\hat{x}$; this approximation is of course not good at all points but it is good as long as we look at values of x near $\hat{x}$. Using the definition of the derivative, the tangent line is given by $f(\hat{x}) + f'(\hat{x}) \cdot (x - \hat{x})$. We thus have $f(x) \approx f(\hat{x}) + f'(\hat{x})(x - \hat{x})$ as the linear approximation of the function in the neighbourhood of $\hat{x}$. This linear approximation takes the value $f(\hat{x})$ as the baseline and adds how much the function changes when x is different from $\hat{x}$, estimating the latter from the slope (derivative) of the function.

Exercise 26. Verify the formula for the tangent line.

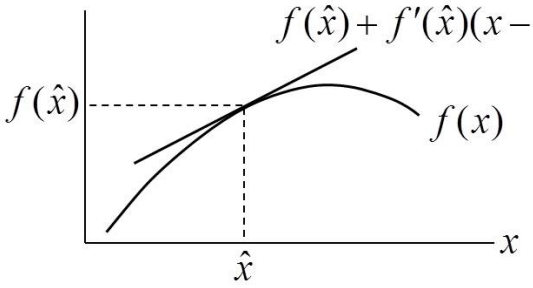


Figure 4: Linear approximation of a function near $\hat{x}$.

The extension of the linear approximation to two variables is straightforward, because we have to do the same as above for each variable separately; only the notation becomes more cumbersome. Near the point $(\hat{x}_1, \hat{x}_2)$, a function $f(x_1, x_2)$ is approximated as

$$f(x_1, x_2) \approx f(\hat{x}_1, \hat{x}_2) + \left.\frac{\partial f}{\partial x_1}\right|_{\hat{x}_1, \hat{x}_2} (x_1 - \hat{x}_1) + \left.\frac{\partial f}{\partial x_2}\right|_{\hat{x}_1, \hat{x}_2} (x_2 - \hat{x}_2)$$

The partial derivative $\frac{\partial f}{\partial x_1}$ means that the function is differentiated with respect to the variable x_1 (i.e., differentiated as if x_2 were simply a constant; see section 2.11 of Part 1), and the subscript that follows the partial derivative indicates that after differentiation, the result is evaluated at $x_1 = \hat{x}_1$ and $x_2 = \hat{x}_2$ (this is the same as in Figure 4, where the derivative f' had to be evaluated at $\hat{x}$).

Returning to the model in equations (17a,b), we approximate both functions f_1 and f_2 just as above:

$$\begin{aligned} f_1(x_1, x_2) &\approx f_1(\hat{x}_1, \hat{x}_2) + \left.\frac{\partial f_1}{\partial x_1}\right|_{\hat{x}_1, \hat{x}_2} (x_1 - \hat{x}_1) + \left.\frac{\partial f_1}{\partial x_2}\right|_{\hat{x}_1, \hat{x}_2} (x_2 - \hat{x}_2) \\ f_2(x_1, x_2) &\approx f_2(\hat{x}_1, \hat{x}_2) + \left.\frac{\partial f_2}{\partial x_1}\right|_{\hat{x}_1, \hat{x}_2} (x_1 - \hat{x}_1) + \left.\frac{\partial f_2}{\partial x_2}\right|_{\hat{x}_1, \hat{x}_2} (x_2 - \hat{x}_2) \end{aligned}$$

Because we do this approximations near the equilibrium, we have from equations (18a,b) that the first term on the right hand side of each approximation is zero. To ease the notation, we introduce abbrieviations for the derivatives: let J_{ij} denote the partial derivative of the ith function with respect to the jth variable evaluated at the equilibrium (hence $J_{11} = \partial f_1/\partial x_1|_{\hat{x}_1,\hat{x}_2}$, $J_{12} = \partial f_1/\partial x_2|_{\hat{x}_1,\hat{x}_2}$, $J_{21} = \partial f_2/\partial x_1|_{\hat{x}_1,\hat{x}_2}$, and $J_{22} = \partial f_2/\partial x_2|_{\hat{x}_1,\hat{x}_2}$). With these, the approximations become

$$\begin{aligned} f_1(x_1, x_2) &\approx J_{11}(x_1 - \hat{x}_1) + J_{12}(x_2 - \hat{x}_2) \\ f_2(x_1, x_2) &\approx J_{21}(x_1 - \hat{x}_1) + J_{22}(x_2 - \hat{x}_2) \end{aligned}$$

so that we write the model equations (17a,b) as

$$\frac{dx_1}{dt} = J_{11}(x_1 - \hat{x}_1) + J_{12}(x_2 - \hat{x}_2) \tag{19a}$$

$$\frac{dx_2}{dt} = J_{21}(x_1 - \hat{x}_1) + J_{22}(x_2 - \hat{x}_2) \tag{19b}$$

These equations are *much* simpler than the original model, because here the right hand sides of the differential equations are just linear functions of x_1 and x_2, whereas $f_1(x_1, x_2)$ and $f_2(x_1, x_2)$ in equations (17a,b) may stand for very complicated functions. This linearized version of the model is, however, valid only near the equilibrium $(\hat{x}_1, \hat{x}_2)$.

We can make one more simple change to bring out the essential features of equations (19a,b). Let us introduce the new variable y_1 to denote the difference between x_1 and its equilibrium value $\hat{x}_1$: $y_1 = x_1 - \hat{x}_1$, and the same for $y_2 = x_2 - \hat{x}_2$. Since the equilibrium values are constants, the derivative of y_1 is the same as the derivative of x_1, and the derivative of y_2 is the same as the derivative of x_2. Hence instead of equations (19a,b), we can write

$$\frac{dy_1}{dt} = J_{11}y_1 + J_{12}y_2 \tag{20a}$$

$$\frac{dy_2}{dt} = J_{21}y_1 + J_{22}y_2 \tag{20b}$$

The goal of the local stability analysis is to see whether the system converges to the equilibrium if started from a point nearby; in other words, whether the difference from the equilibrium, measured by y_1 and y_2, decays to zero. We need to solve the differential equations (20a,b) to see whether this is the case.

4.2 Diagonalization

To solve equations (20a,b), we shall need to work with the matrix

$$\mathbf{J} = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix}$$

called the *Jacobi matrix* or *Jacobian*, and use matrix-vector notation for equations (20),

$$\begin{pmatrix} dy_1/dt \\ dy_2/dt \end{pmatrix} = \mathbf{J} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} \tag{21}$$

Exercise 27. Verify that equation (21) is indeed tha same as equations (20a,b).

There is one special case when it is easy to solve equation (21), and even though this case rarely occurs in practice, it will be useful to deal with this case first. Suppose that the Jacobian is a diagonal matrix (J_{12} and J_{21} are zero). The equation then simplifies into

$$\begin{aligned} \begin{pmatrix} dy_1/dt \\ dy_2/dt \end{pmatrix} &= \mathbf{J} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{bmatrix} J_{11} & 0 \\ 0 & J_{22} \end{bmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \\ &= \begin{pmatrix} J_{11}y_1 \\ J_{22}y_2 \end{pmatrix} \end{aligned} \tag{22}$$

which is just the vector notation for

$$\begin{aligned} \frac{dy_1}{dt} &= J_{11}y_1 \\ \frac{dy_2}{dt} &= J_{22}y_2 \end{aligned}$$

Each of these equations contains only one variable, hence they can be solved separately, one by one; and they are akin to the familiar equation for exponential growth or decay (see section 1.4 of Part 1), the solution of which is

$$\begin{aligned} y_1(t) &= y_1(0)e^{J_{11}t} \\ y_2(t) &= y_2(0)e^{J_{22}t} \end{aligned}$$

Here $y_1(0)$ is the difference between the first variable x_1 and its equilibrium value at time 0; and similarly $y_2(0)$ is the difference between the second variable x_2 and its equilibrium value at time 0. If J_{11} and J_{22} are both negative, then the difference from the equilibrium decreases with time, and eventually both $y_1(t)$ and $y_2(t)$ converge to zero, which means that the system goes to the equilibrium. If however J_{11} or J_{22} is positive (or both), then $y_1(t)$ or $y_2(t)$ is increasing such that the system gets more and more away from the equilibrium in the direction of the x_1- or x_2-axis (or both). The equilibrium is therefore stable if both J_{11} and J_{22} are negative.

Exercise 28. Generalize this result to a model with three (or an arbitrary number n) differential equations: Write down the corresponding Jacobian, assume that it is a diagonal matrix, and show that the equilibrium is stable if all diagonal elements of the Jacobian are negative.

In most models, the Jacobian is not a diagonal matrix, but a matrix we can diagonalize[1] (see section 5.5 of Part 3). This means that we can write the Jacobian as the product of three matrices,

$$\mathbf{J} = \mathbf{C}\mathbf{\Lambda}\mathbf{C}^{-1}$$

where $\mathbf{\Lambda}$ is a diagonal matrix with the eigenvalues of $\mathbf{J}$ as the diagonal elements, $\mathbf{C}$ is a matrix the columns of which are the eigenvectors of $\mathbf{J}$, and $\mathbf{C}^{-1}$, the inverse of $\mathbf{C}$, is a matrix the rows of which are the left eigenvectors of $\mathbf{J}$. We can now substitute this into equation (21),

$$\begin{pmatrix} dy_1/dt \\ dy_2/dt \end{pmatrix} = \mathbf{C}\mathbf{\Lambda}\mathbf{C}^{-1} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

and pre-multiply both sides with $\mathbf{C}^{-1}$ (which removes $\mathbf{C}$ on the right hand side),

$$\mathbf{C}^{-1} \begin{pmatrix} dy_1/dt \\ dy_2/dt \end{pmatrix} = \mathbf{\Lambda}\mathbf{C}^{-1} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

On the right hand side of this equation, we have the diagonal matrix $\mathbf{\Lambda}$ multiplied with the vector $\left(\begin{smallmatrix} z_1 \\ z_2 \end{smallmatrix}\right) = \mathbf{C}^{-1} \left(\begin{smallmatrix} y_1 \\ y_2 \end{smallmatrix}\right)$; and on the left hand side, there is the derivative of this same vector (because $\mathbf{C}^{-1}$ is a constant matrix, it can be factored out of the differentiation). Hence we have

$$\begin{aligned} \begin{pmatrix} dz_1/dt \\ dz_2/dt \end{pmatrix} &= \mathbf{\Lambda} \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} = \\ &= \begin{pmatrix} \lambda_1 z_1 \\ \lambda_2 z_2 \end{pmatrix} \end{aligned} \tag{23}$$

Notice that this is the same result as what we had for the special case in equation (22), only the variables z_1 and z_2 replace y_1 and y_2, and the eigenvalues of $\mathbf{J}$ (i.e., λ_1 and λ_2) replace J_{11} and J_{22}. The solution of equation (23) is therefore analogous to the solution of equation (22):

$$z_1(t) = z_1(0)e^{\lambda_1 t} \tag{24a}$$

$$z_2(t) = z_2(0)e^{\lambda_2 t} \tag{24b}$$

We can draw similar conclusions as in the special case above: If both λ_1 and λ_2 are negative, then both z_1 and z_2 converge to zero. This implies that y_1 and y_2 in $\left(\begin{smallmatrix} y_1 \\ y_2 \end{smallmatrix}\right) = \mathbf{C} \left(\begin{smallmatrix} z_1 \\ z_2 \end{smallmatrix}\right)$ also converge to zero, i.e., the difference between the variables x_1, x_2 and their equilibrium values disappears and the system goes to the equilibrium. If λ_1 or λ_2 is positive (or both), then the system gets more and more away from the equilibrium. (Note that if the Jacobian is a diagonal matrix as in the special case above, then its eigenvalues are the diagonal elements, i.e., $\lambda_1 = J_{11}$ and $\lambda_2 = J_{22}$; and $\left(\begin{smallmatrix} z_1 \\ z_2 \end{smallmatrix}\right)$ equals $\left(\begin{smallmatrix} y_1 \\ y_2 \end{smallmatrix}\right)$ because $\mathbf{C}$ and $\mathbf{C}^{-1}$ equal the identity matrix.)

[1] In fact, the results we derive are valid also when the Jacobian cannot be diagonalized. This is however an exceptional case (most matrices are diagonalizable), and the derivation becomes much more complicated without diagonalization.

Exercise 29. Suppose that λ_1 is positive and λ_2 is negative. Show that y_1 and y_2 increase such that eventually the vector $\binom{y_1}{y_2}$ will point in the direction of the first eigenvector of the Jacobian. (*Hint:* recall that the columns of $\mathbf{C}$ are the eigenvectors.)

Exercise 30. Suppose now that both λ_1 and λ_2 are negative, but λ_2 is much more negative than λ_1 (i.e., $\lambda_2 \ll \lambda_1$). Show that y_1 and y_2 decrease such that eventually the system approaches the equilibrium in the direction of the first eigenvector of the Jacobian. (*Hint:* solving the previous exercise helps.)

Figure 5 summarizes our findings so far. If both λ_1 and λ_2 are negative, then trajectories starting from the neighbourhood of the equilibrium converge to the equilibrium as shown in Figure 5a; this type of equilibrium is called a *stable node*. Note that when λ_2 is more negative than λ_1, then convergence is faster in the direction of $\mathbf{u}_2$ than in the direction of $\mathbf{u}_1$ (cf. exercise 30), such that eventually the trajectory approaches the equilibrium along the $\mathbf{u}_1$-direction. If λ_2 is negative but λ_1 is positive, then the trajectories converge in the $\mathbf{u}_2$-direction but diverge (leave) in the $\mathbf{u}_1$-direction; the result is a *saddle point* (or *saddle*; Figure 5b), where the trajectories go away in the direction of the eigenvector that corresponds to the positive eigenvalue (cf. exercise 29). Finally if both λ_1 and λ_2 are positive, then the trajectories are the reverse of those of a stable node, and the equilibrium is an *unstable node* (Figure 5c). (The trajectories reverse because in equations (24a,b), taking the opposite sign for the eigenvalues is equivalent to replacing t with $-t$, which amounts to running time backwards. If the backwards trajectories converge to the equilibrium as in Figure 5a, then the forward trajectories diverge from the equilibrium as in Figure 5c.) Of the three types of equilibria shown in Figure 5, only the stable node is stable.

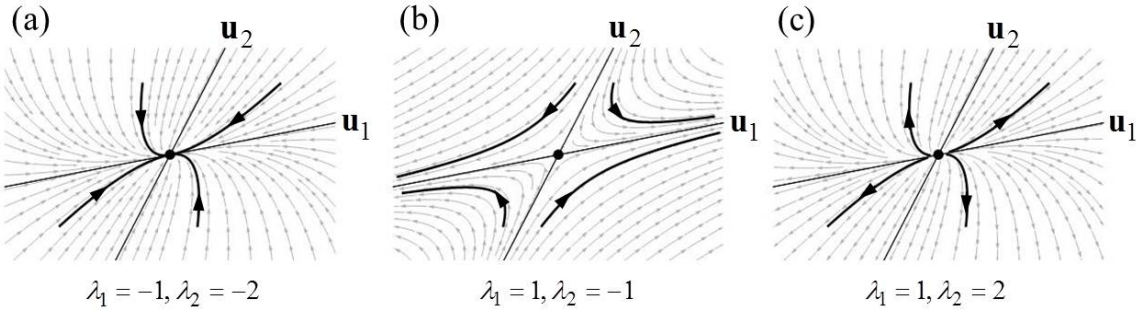


Figure 5: Types of equilibria when the eigenvalues of the Jacobian are real. The dots are the equilibria, the thick curves are typical trajectories, and the gray lines in the background show many more trajectories (i.e., the "phase portrait"). The straight lines represent the eigenvectors of the Jacobian. (a) $\lambda_1, \lambda_2 < 0$, stable node; (b) $\lambda_1 > 0, \lambda_2 < 0$, saddle point; (c) $\lambda_1, \lambda_2 > 0$, unstable node.

Exercise 31. Sketch some trajectories near a stable node assuming that (i) $\lambda_2 \ll \lambda_1$, i.e., convergence in the direction of the second eigenvector is *much* faster; (ii) $\lambda_1 < \lambda_2$, i.e., convergence in the direction of the first eigenvector is faster; (iii) $\lambda_1 = \lambda_2$, i.e., the speed of convergence is the same in all directions.

The above results extend naturally to models with more than two variables. If the model has n differential equations for n variables, then the $n \times n$ Jacobian has n eigenvalues. If one (or more) of these is positive, then there is a direction (given by the eigenvector(s) that corresponds to the positive eigenvalue(s)) where the trajectories leave the neighbourhood of the equilibrium, i.e., the equilibrium is unstable. If all eigenvalues are negative, then the equilibrium is stable. There is however a complication (also with only two variables): the eigenvalues may not only be negative or positive (or zero), but may also be complex numbers. This possibility is treated in the next section.

4.3 Complex eigenvalues

It is often the case that some of the eigenvalues of the Jacobian are complex numbers[2]. As the following example illustrates, complex eigenvalues arise because of taking the square root of a negative number while solving the characteristic equation in order to obtain the eigenvalues (see section 5.2 of Part 3).

Example. The eigenvalues of the matrix

$$\mathbf{J} = \begin{bmatrix} 1 & 4 \\ -2 & -3 \end{bmatrix}$$

are the solutions of its characteristic equation,

$$\begin{vmatrix} 1-\lambda & 4 \\ -2 & -3-\lambda \end{vmatrix} = \lambda^2 + 2\lambda + 5 = 0$$

given by

$$\lambda_{1,2} = \frac{-2 \pm \sqrt{4-20}}{2} = -1 \pm \frac{\sqrt{16 \cdot (-1)}}{2} = -1 \pm 2\sqrt{-1} = -1 \pm 2i$$

Since we can write the square root of any negative number (such as $\sqrt{-16}$ in the above example) as the square root of a positive number times the square root of -1 ($\sqrt{-16} = \sqrt{16}\sqrt{-1}$), all complex numbers can be expressed using just $\sqrt{-1}$, the *imaginary unit*, which is denoted by i. Any complex number z can therefore be written in the form

$$z = a + bi$$

[2]In Part 3, we did not have to work with complex eigenvalues because we were concerned with the dominant eigenvalue of a non-negative matrix. In contrast, here we need to consider all eigenvalues of the Jacobian, which may be any matrix and does not have to be e.g. non-negative.

where a and b are "ordinary", real numbers. a is called the *real part* of z ($Re(z)$), whereas b is called the *imaginary part* ($Im(z)$; note that the imaginary part is a real number!). The basics of working with complex numbers are summarized in Box 1.

Box 1: Working with complex numbers

To add (or subtract) complex numbers, add the real part to the real part and the imaginary part to the imaginary part:

$$(2 + 3i) + (5 + i) = 7 + 4i$$

To multiply complex numbers, multiply them as multiplying sums, and use that $i^2 = (\sqrt{-1})^2 = -1$:

$$(2 + 3i) \cdot (5 + i) = 2 \cdot 5 + 2i + 3i \cdot 5 + 3i^2 = 10 + 17i - 3 = 7 + 17i$$

To take exponentials of complext numbers, first use that $e^{a+bi} = e^a e^{bi}$. Here e^a is a real number. e^{bi} is evaluated using *Euler's formula:*

$$e^{bi} = \cos(b) + i \sin(b)$$

where b is in radians (2π radians equal 360°, set the calculator to radians).

> A particularly beautiful equation results when taking $b = \pi$ in Euler's formula. Since $\cos(\pi) = -1$ and $\sin(\pi) = 0$, we get $e^{\pi i} = \cos(\pi) + i \sin(\pi) = -1$, which yields the relationship
>
> $$e^{\pi i} + 1 = 0$$
>
> between the five most important numbers of mathematics, π, e, i, 0 and 1.

Two complex numbers that differ only in the sign of their imaginary part,

$$a + bi \quad \text{and} \quad a - bi$$

are called *complex conjugates*. As the above example illustrates, complex eigenvalues always come in complex conjugate pairs; if a complex number $a + bi$ is an eigenvalue of the Jacobian, then $a - bi$ is also an eigenvalue.

> To see that this is indeed so also for any large Jacobian with a high-degree characteristic equation, suppose that the we substitute the eigenvalue $a + bi$ into the characteristic equation. The result must equal the zero on the right hand side, therefore the imaginary parts must cancel in the characteristic equation. If we substitute $a - bi$, then the imaginary parts

are exactly the same as for $a + bi$, only with a minus sign. If the imaginary parts cancel with a plus sign, they also cancel with a minus sign (+0 is the same as −0); therefore $a - bi$ is also a solution of the characteristic equation, i.e., an eigenvalue.

Exercise 32. Carry out the multiplications to show that the following is true:

$$(a + bi)(c + di) + (a - bi)(c - di) = 2(ac - bd)$$

i.e., when the product of two complex numbers is added to the product of their complex conjugates, the result is a real number. Intuitively, this is so because for every term that contains i after opening the parentheses in $(a+bi)(c+di)$, there is the same term but with a minus sign in $(a - bi)(c - di)$.

Exercise 33. Show that

$$\begin{gathered}(a + bi)(c + di)(\gamma + \delta i) + (a - bi)(c - di)(\gamma - \delta i) = \\ = 2[c(a\gamma - b\delta)) - d(a\delta + b\gamma)]\end{gathered}$$

(This result will be used later in section 4.3.)

Now we return to the linearized model in equation (23) and to its solution

$$z_1(t) = z_1(0)e^{\lambda_1 t} \tag{25a}$$
$$z_2(t) = z_2(0)e^{\lambda_2 t} \tag{25b}$$

taking the case that λ_1 and λ_2 are complex conjugate eigenvalues, i.e., they can be written as

$$\lambda_1 = \alpha + \beta i \quad \text{and} \quad \lambda_2 = \alpha - \beta i$$

Substituting λ_1 into equation (25a) and using Euler's formula (see Box 1) gives

$$z_1(t) = z_1(0)e^{(\alpha+\beta i)t} = z_1(0)e^{\alpha t}e^{\beta i t} = z_1(0)e^{\alpha t}[\cos(\beta t) + i\sin(\beta t)]$$

Analogously, substituting λ_2 into equation (25b) yields $z_2(t) = z_2(0)e^{\alpha t}[\cos(\beta t)+i\sin(-\beta t)]$; and finally note that $\sin(-\beta t) = -\sin(\beta t)$ (cf. Figure 6) so that we have

$$z_1(t) = z_1(0)e^{\alpha t}[\cos(\beta t) + i\sin(\beta t)] \tag{26a}$$
$$z_2(t) = z_2(0)e^{\alpha t}[\cos(\beta t) - i\sin(\beta t)] \tag{26b}$$

Notice that the expression in the brackets, $\cos(\beta t) + i\sin(\beta t)$, is a complex number such that its real part, $\cos(\beta t)$, is between -1 and 1 (because the cosine function can take only these values; see Figure 6) and also its imaginary part, $\sin(\beta t)$, is between -1 and 1 (because the sine function can take only these values). Hence the complex number in the brackets cannot become very large. Whether or not $z_1(t)$ and $z_2(t)$ converge to zero depends on the factor before the brackets, $e^{\alpha t}$. If α is negative, then $e^{\alpha t}$ decays exponentially toward zero, so that $z_1(t)$ and $z_2(t)$ converge to zero and the equilibrium is stable;

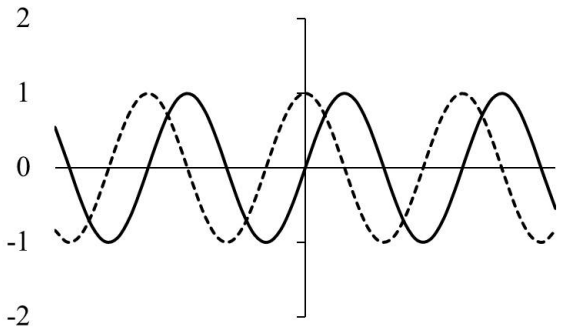


Figure 6: $\sin(\beta t)$ (continuous line) and $\cos(\beta t)$ (dashed line) plotted against time.

if however α is positive, then the equilibrium is unstable. The stability of the equilibrium thus depends on the sign of α, which is the real part of the two eigenvalues ($\alpha = Re(\lambda)$).

To see in detail how the system converges to or diverges from the equilibrium, recall from section 4.2 that the elements of the vector $\binom{y_1}{y_2} = \mathbf{C}\binom{z_1}{z_2}$ measure the distance to the equilibrium horizontally and vertically. The columns of $\mathbf{C}$ are the eigenvectors $\mathbf{u_1}$ and $\mathbf{u_2}$ that belong to the eigenvalues λ_1 and λ_2, respectively. When the two eigenvalues are complex conjugates, then also the eigenvectors are complex conjugates so that we can write them as

$$\mathbf{u_1} = \begin{pmatrix} \gamma_1+\delta_1 i \\ \gamma_2+\delta_2 i \end{pmatrix} \quad \text{and} \quad \mathbf{u_2} = \begin{pmatrix} \gamma_1-\delta_1 i \\ \gamma_2-\delta_2 i \end{pmatrix}$$

Similarly, $z_1(0)$ and $z_2(0)$ are complex conjugates,

$$z_1(0) = a + bi \quad \text{and} \quad z_2(0) = a - bi$$

because $\begin{pmatrix} z_1(0) \\ z_2(0) \end{pmatrix} = \mathbf{C}^{-1}\begin{pmatrix} y_1(0) \\ y_2(0) \end{pmatrix}$; the rows of $\mathbf{C}^{-1}$ are the left eigenvectors, which are complex conjugates, so that the product of the first row with the real vector $\begin{pmatrix} y_1(0) \\ y_2(0) \end{pmatrix}$ is the complex conjugate of the same with the second row. Substituting equation (26) as well as the complex conjugate pairs into $\begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix} = \mathbf{C}\begin{pmatrix} z_1(t) \\ z_2(t) \end{pmatrix}$, we obtain

$$\begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix} = \begin{bmatrix} \gamma_1 + \delta_1 i & \gamma_1 - \delta_1 i \\ \gamma_2 + \delta_2 i & \gamma_2 - \delta_2 i \end{bmatrix} \begin{pmatrix} (a+bi)e^{\alpha t}[\cos(\beta t) + i\sin(\beta t)] \\ (a-bi)e^{\alpha t}[\cos(\beta t) - i\sin(\beta t)] \end{pmatrix}$$

Let us calculate $y_1(t)$ explicitly:

$$y_1(t) = e^{\alpha t}\Big((\gamma_1 + \delta_1 i)(a+bi)[\cos(\beta t) + i\sin(\beta t)] + (\gamma_1 - \delta_1 i)(a-bi)[\cos(\beta t) - i\sin(\beta t)]\Big)$$

The expression in the big parentheses is the product of three complex numbers plus the product of their complex conjugates. Using the result of exercise 33 (with $c = \cos(\beta t)$ and $d = \sin(\beta t)$), the above equation simplifies to

$$y_1(t) = 2e^{\alpha t}\Big((a\gamma_1 - b\delta_1)\cos(\beta t) - (a\delta_1 + b\gamma_1)\sin(\beta t)\Big) \tag{27a}$$

and, analogously, we have

$$y_2(t) = 2e^{\alpha t}\Big((a\gamma_2 - b\delta_2)\cos(\beta t) - (a\delta_2 + b\gamma_2)\sin(\beta t)\Big) \tag{27b}$$

Admittedly, these equations still do not look very simple. However, there are only two simple things we need to notice. Firstly, all symbols in equations (27a,b) represent real numbers, so that we have got a valid result for how far the system is from its equilibrium measured in horizontal ($y_1(t)$) and vertical directions ($y_2(t)$). Secondly, the expression in the big parentheses depends on time t only via $\sin(\beta t)$ and $\cos(\beta t)$. These functions are *periodic*: if we increase βt with 2π (which amounts to 360°), then the values of the cosine and the sine do not change (cf. Figure 6). In other words, if we wait $T = 2\pi/\beta$ time longer (such that $\beta(t+T) = \beta t + 2\pi$), then the value of the big parenthesis is exactly the same as T time before. If $\alpha = 0$ such that the factor $e^{\alpha t}$ in front of the parenthesis is constant 1, then T time later the system is exactly at the same position as before. The expression in the parenthesis thus describes a cyclic (or periodic) movement. When this is multiplied with $e^{\alpha t}$, then the size of the cycles shrink with time (when $\alpha < 0$ so that $e^{\alpha t}$ represents exponential decay) or grow with time (when $\alpha > 0$ so that $e^{\alpha t}$ gives exponential growth). The result is a spiral movement towards or away from the equilibrium, as shown in Figures 7a and 7b, respectively.

To summarize briefly, complex eigenvalues indicate that the system undergoes oscillations, such that both variables are sometimes below and sometimes above their equilibrium values (Figure 7). These oscillations are however damped and the system converges to the equilibrium if the real part of the eigenvalues is negative ($Re(\lambda) < 0$, Figure 7a), in which case the equilibrium is a *stable focus*. The oscillations grow and the trajectory diverges from the neighbourhood of the equilibrium if the real part of the eigenvalues is positive ($Re(\lambda) > 0$, Figure 7b), in which case the equilibrium is an *unstable focus*.

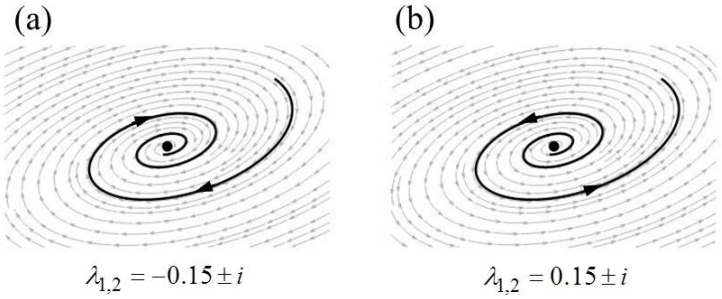


Figure 7: Types of equilibria when the eigenvalues of the Jacobian are complex. The dots are the equilibria, the thick curves are typical trajectories, and the gray lines in the background show many more trajectories (i.e., the "phase portrait"). The eigenvectors of the Jacobian are complex and therefore cannot be shown. (a) $Re(\lambda) < 0$, stable focus; (b) $Re(\lambda) > 0$, unstable focus.

Exercise 34. Redraw the trajectory of Figure 7a assuming that (i) the real part of the eigenvalues is strongly negative ($Re(\lambda) \ll 0$)) and (ii) the real part of the eigenvalues is negative but close to zero.

Exercise 35. Explain why the trajectory of Figure 7b is the reverse of the one in 7a.

Since complex eigenvalues always come as complex conjugate pairs, there is always an even number of complex eigenvalues. In a higher dimensional model, there can be several pairs of complex eigenvalues, and each pair describes a damped or amplified oscillation as in Figure 7. The pairs of complex eigenvalues can also combine with real eigenvalues, which correspond to monotone (non-oscillating) convergence or divergence as shown in Figure 5. A 3-dimensional example is shown in Figure 8. Here there is a pair of complex eigenvalues with negative real part, hence the oscillations are damped, but the third eigenvalue (which must be real since it cannot have a conjugate pair) is positive, hence the system diverges in the direction of the (real) eigenvector that belongs to the positive eigenvalue.

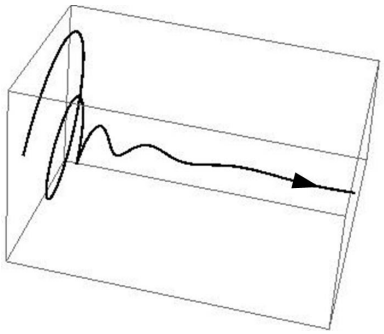


Figure 8: A trajectory in a 3-dimensional model that has a pair of complex eigenvalues with negative real part and a positive eigenvalue. The equilibrium point (not shown) is in the middle of the left face of the cubiod.

4.4 Summary and recipe for local stability analysis in practice

In local stability analysis, we linearize the original equations (i.e., we replace their right hand sides with linear functions that are valid approximations near the equilibrium but not further away; see section 4.1) and solve the linearized equations (here we did this using diagonalization in sections 4.2-4.3). Naturally, these derivations do not have to be repeated every time we use stability analysis. The steps that need to be carried out in practice are as follows. We start with the model

$$\frac{dx_1}{dt} = f_1(x_1, x_2)$$
$$\frac{dx_2}{dt} = f_2(x_1, x_2)$$

where $f_1(x_1, x_2)$ and $f_2(x_1, x_2)$ stand for any (possibly complicated) formula on the right hand side of the equations (the details obviously depend on the model at hand).

1. Find all equilibria of the model by solving the equations

$$f_1(x_1, x_2) = 0$$
$$f_2(x_1, x_2) = 0$$

for the equilibrium values $\hat{x}_1$ and $\hat{x}_2$. There may be several solutions and hence several equilibria; the stability analysis must be carried out for each of them separately.

2. Calculate the Jacobian matrix

$$\begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \end{bmatrix}$$

where all derivatives are evaluated at the equilibrium values obtained in step 1, $x_1 = \hat{x}_1$ and $x_2 = \hat{x}_2$.

3. Calculate the eigenvalues of the Jacobian matrix, λ_1 and λ_2 (see section 5.2 of Part 3).

4. If all real eigenvalues are negative and the real part of all complex eigenvalues are negative, then the equilibrium is stable. If there is a positive eigenvalue, or an eigenvalue with a positive real part, then the equilibrium is unstable.

   Since the real part of a real eigenvalue is the eigenvalue itself (the real part of $-5 = -5 + 0i$ is -5), we can state the condition for stability as follows:

- if $Re(\lambda) < 0$ holds for each eigenvalue, then the equilibrium is stable
- if there is an eigenvalue with $Re(\lambda) > 0$, then the equilibrium is unstable

Note the following points:

(i) This stability analysis is *local*, i.e., it tells us whether the system goes to the equilibrium if it starts in a close enough neighbourhood of the equilibrium. The starting point must be close enough to the equilibrium because we have aproximated the original model with its linearized version (section 4.1), and this approximation is valid only in the neighbourhood of the equilibrium. Local stability is best thought of whether the system returns to the equilibrium after a small perturbation has removed it from the equilibrium. As perturbations occur in all natural systems, we can expect to see a system only at stable equilibria, where they return to after being perturbed.

(ii) A model may have several stable equilibria. It is then true for each of them that after small perturbations the system returns to the equilibrium where it was perturbed from. Large perturbations may cause the system to converge to another equilibrium (or other type of attractor to be explored later); large perturbations cannot be handled with local stability analysis.

(iii) If there is an eigenvalue with $Re(\lambda) = 0$ and all others have negative real parts, then the linear stability analysis is inconclusive: The equilibrium may be stable, may be unstable, or may even be stable in certain directions and unstable in others, depending on higher derivatives. This fact we have encountered also in the case of a single differential equation, see section 3.5 of Part 1. If there is an eigenvalue with $Re(\lambda) = 0$ and some other eigenvalue has a positive real part, then of course the equilibrium is unstable; but even then, the local stability analysis cannot fully determine the dynamics near the equilibrium, because it is unclear how the system moves in the direction(s) corresponding to $Re(\lambda) = 0$.

(iv) If there is only one differential equation for a single variable, $\frac{dx}{dt} = f(x)$, then the Jacobian is the 1×1 "matrix" $[\frac{\partial f}{\partial x}|_{x=\hat{x}}] \equiv f'(\hat{x})$, i.e., a number. The eigenvalue of this "matrix" is its only entry ($\lambda = f'(\hat{x})$), which is of course a real number, so that we recover the result of section 3.5 of Part 1: the equilibrium $\hat{x}$ is stable if $f'(\hat{x}) < 0$.

(v) The equilibrium equations in step 1 above may be hard to solve. If this is the case in a model with two equations, then it is helpful to draw the isoclines on the phase plane and read the approximate locations of the equilibria from the plot (see section 3).

(vi) Obtaining the Jacobian matrix in step 2 is routine and never poses a problem. Calculating its eigenvalues in step 3 may be possible only numerically if the matrix is large (see section 5.2 of Part 3 for a graphical solution for real eigenvalues). However, many models of interest have just two differential equations, and calculating the eigenvalues of a 2×2 Jacobian is never a problem (see the next section for a shortcut). Note that the eigenvectors are not needed to establish the stability of an equilibrium.

The method of local stability readily extends to any number of variables and differential equations, and the criteria for stability stated above hold for models of any dimension. In the next section, however, we focus on the special (but frequent) case of two variables.

4.5 A shortcut for the case of two variables

With only two variables, the Jacobian is a 2×2 matrix. In this section, we calculate the eigenvalues of a general 2×2 Jacobian, and find simple rules to establish the stability of equilibria without calculating the eigenvalues each time we perform a local stability analysis in a model with two variables.

The eigenvalues of a 2×2 Jacobian

$$\mathbf{J} = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix}$$

are the solutions of its characteristic equation,

$$\begin{vmatrix} J_{11} - \lambda & J_{12} \\ J_{21} & J_{22} - \lambda \end{vmatrix} = \lambda^2 - (J_{11} + J_{22})\lambda + J_{11}J_{22} - J_{12}J_{21} = 0$$

In this equation, we recognize $J_{11}J_{22} - J_{12}J_{21}$ as the determinant of the Jacobian matrix itself; let thus denote it with Det. The sum of the diagonal elements $J_{11} + J_{22}$ is called the trace of the matrix, Tr. With these shorthands, the characteristic equation is

$$\lambda^2 - Tr\lambda + Det = 0$$

which has the solutions

$$\lambda_{1,2} = \frac{Tr \pm \sqrt{Tr^2 - 4Det}}{2}$$

We can judge the sign of the (real part of the) eigenvalues from Tr and Det as follows.

- If $Det < 0$, then $Tr^2 - 4Det$ under the square root is certainly positive, and larger than Tr in absolute value; hence the "+" solution is a positive eigenvale and the "−" solution is a negative eigenvalue. $Det < 0$ hence corresponds to a saddle.

- If $Det > 0$ but $Det < Tr^2/4$, then the expression under the square root is still positive, but smaller than Tr in absolute value. The eigenvalues are therefore real, and their sign is given by the sign of Tr (adding and subtracting a number small compared to Tr will not change its sign). In this case the equilibrium is a node, and it is a stable node if $Tr < 0$ but an unstable node if $Tr > 0$.

- If $Det > Tr^2/4$, then the expression under the square root is negative and the eigenvalues are complex. The real part of these eigenvalues is $Re(\lambda) = Tr/2$, which has the same sign as Tr. Hence in this case the equilibrium is a focus, and it is a stable focus if $Tr < 0$ and an unstable focus if $Tr > 0$

Figure 9 summarizes these conclusions visually. In practice, we may want to focus only on stability and ignore the type of equilibria. Collecting the stable equilibria from the above list (or noticing that in Figure 9, the equilibria in the upper left part are stable), we see that

the equilibrium is stable if $Tr < 0$ and $Det > 0$

These conditions are known as the Routh-Hurwitz criteria for 2×2 matrices[3]. Since it is easier to calculate the trace and the determinant of a matrix than to calculate its eigenvalues, using these criteria spares some work when we apply local stability analysis to concrete models of two differential equations.

[3]Similar conditions are known also for larger Jacobians, but they quickly get very complicated. It is however important to stress that the simple conditions derived here are valid only for 2×2 matrices, not for larger ones.

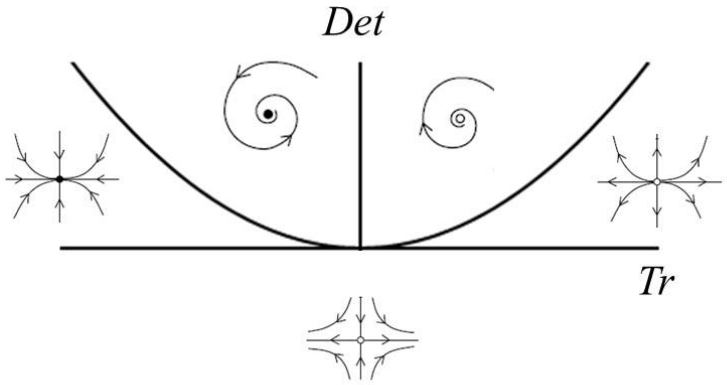


Figure 9: Stability of equilibria in two dimensions. The axes are for the trace (Tr) and the determinant (Det) of the Jacobian, the parabola is given by $Det = Tr^2/4$. Below the horizontal axis ($Det < 0$), the equilibrium is a saddle; above the horizontal axis but below the parabola ($0 < Det < Tr^2/4$) the equilibrium is a node, stable in the left ($Tr < 0$) and unstable in the right ($Tr > 0$); above the parabola ($Det > Tr^2/4$) the equilibrium is a focus, stable in the left ($Tr < 0$) and unstable in the right ($Tr > 0$). The stable equilibria are in the upper left part ($Tr < 0, Det > 0$). In the insets, stable and unstable equilibria are marked with filled dots and empty circles, respectively. For simplicity, in the insets the eigenvectors are drawn horizontally and vertically, but this need not be the case (see Figure 5).

4.6 A worked example: The Brusselator

For a chemical reaction that does not exist, the Brusselator is pretty well known. It is a theoretical reaction scheme inspired by the famous (and real) Belousov-Zhabotinsky reaction, a chemical reaction that exhibits periodic oscillations where the colour of the reaction mixture changes back and forth[4]. The Belousov-Zhabotinsky reaction is very complicated, so a group of chemicists in Brussel (hence the name), fascinated by the possibility of non-equilibrium reactions, invented the Brusselator to serve as a simple example:

$$\begin{aligned} A &\xrightarrow{k_1} X \\ B + X &\xrightarrow{k_2} Y + C \\ 2X + Y &\xrightarrow{k_3} 3X \\ X &\xrightarrow{k_4} D \end{aligned}$$

[4]Time lapse photos and videos are easy to find on the Internet.

The concentrations of X and Y are the variables (x and y, respectively), whereas the concentrations of A and B are kept constants respectively at a and b. C and D are decay products that do not participate in further reactions, hence their concentrations are unimportant. Note the reaction involving three molecules in the third row; in reality all reactions are betwen only two molecules at a time (because it is infinitely unlikely that three molecules would hit each other at exactly the same instant), so that a trimolecular reaction may only be an approximation. By mass action, the equations governing the concentrations x and y are (cf. section 3.1 of Part 1):

$$\frac{dx}{dt} = k_1 a - k_2 b x + k_3 x^2 y - k_4 x = \alpha - \beta x + k_3 x^2 y - k_4 x \tag{28a}$$

$$\frac{dy}{dt} = k_2 b x - k_3 x^2 y = \beta x - k_3 x^2 y \tag{28b}$$

where at the end we use the shorthand notation $\alpha = k_1 a$ and $\beta = k_2 b$.

We shall use this model to illustrate the technique of local stability analysis and also later as an example in section 6.1 for its simplicity, while we leave many interesting biological examples for the exercises.

To analyze the Brusselator model in equations (28a,b), we follow the steps outlined in section 4.4, but use the shortcut of section 4.5. Let me point out that although this example is our first, it is not a particularly simple example; the analysis below is representative for many models we may come accross.

1. Find the equilibria. At equilibrium the differential equations equal zero, i.e.,

$$\alpha - \beta x + k_3 x^2 y - k_4 x = 0$$
$$\beta x - k_3 x^2 y = 0$$

   It is easiest to solve these equations using their sum and the second equation:

$$\alpha - k_4 x = 0$$
$$\beta x - k_3 x^2 y = 0$$

   From the first of these equations we have $\hat{x} = \alpha/k_4$; and substituting this into the second equation we obtain $\hat{y} = \beta k_4/\alpha k_3$. Hence the model has only one equilibrium, which is always positive.

2. Calculate the Jacobian matrix. In the Brusselator model, $f_1(x,y) = \alpha - \beta x + k_3 x^2 y - k_4 x$ and $f_2(x,y) = \beta x - k_3 x^2 y$. Taking the derivatives and evaluating them at the equilibrium, we obtain

$$\mathbf{J} = \begin{bmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{bmatrix} = \begin{bmatrix} -\beta + 2k_3\hat{x}\hat{y} - k_4 & k_3\hat{x}^2 \\ \beta - 2k_3\hat{x}\hat{y} & -k_3\hat{x}^2 \end{bmatrix} = \begin{bmatrix} \beta - k_4 & k_3(\alpha/k_4)^2 \\ -\beta & -k_3(\alpha/k_4)^2 \end{bmatrix}$$

   where in the last step, I substituted $\hat{x} = \alpha/k_4$ and $\hat{y} = \beta k_4/\alpha k_3$ from step 1 and simplified.

3. We use the shortcut of section 4.5: Instead of calculating the eigenvalues, we calculate only the trace and the determinant of the Jacobian,

$$Tr = \beta - k_4 - k_3(\alpha/k_4)^2$$
$$Det = (\beta - k_4)(-k_3(\alpha/k_4)^2) - (k_3(\alpha/k_4)^2)(-\beta) = \alpha^2 k_3/k_4$$

4. The determinant is always positive, but the trace may be either positive or negative, hence the equilibrium may be stable or unstable depending on the values of the parameters. In particular, if β takes the critical value $\beta_{crit} = k_4 + k_3(\alpha/k_4)^2$, then the trace is zero, i.e., the equilibrium is on the borderline between a stable and an unstable focus (see Figure 9). For values of β below the critical value, the equilibrium is stable. Increasing β beyond the critical value destabilizes the equilibrium such that it becomes an unstable focus, and the concentrations of X and Y start to oscillate. Since $\beta = k_2 b$ is proportional to the constant concentration of B, in a real system the equilibrium could be destabilized and oscillatory behaviour be observed simply by keeping B at a higher concentration.

This example raises the question what happens to the concentrations in the long run when the trajectory spirals away from an unstable focus. The concentrations obviously cannot increase without bound, so that one may suspect that that eventually the system may settle on a large periodic oscillation. (By "large", I mean a distance from the equilibrium where the linearized dynamics is no longer valid; as long as the linearized equations describe the dynamics satisfactorily, the trajectory keeps spiralling away.). This question we shall pursue in section 6.1.

4.7 A second worked example: The SI model revisited

In the phase plane analysis of the SI model in section 3, we found that if the disease remains endemic, then there is one nontrivial equilibrium where both variables are positive; the stability of this equilibrium was however not obvious from the graphical analysis (see Figure 3). Here we carry out the local stability analysis of the endemic equilibrium. This example will illustrate how one can get around some technical difficulties when the equilibria are given by unwidely formulas.

The SI model with births and deaths has been given in equations (9a,b), which were

$$\begin{aligned} \frac{dN}{dt} &= b\left[1 - \frac{N}{M}\right] N - \mu N - \alpha I \\ \frac{dI}{dt} &= [\beta(N - I) - (\mu + \alpha)]I \end{aligned}$$

From the second equation, we easily get the non-zero equilibrium density of the infected as $\hat{I} = \hat{N} - \frac{\mu+\alpha}{\beta}$. Substituting this into the first equation, the equilibrium value of N has

to satisfy the quadratic equation

$$b\left[1-\frac{N}{M}\right]N-\mu N-\alpha\left[N-\frac{\mu+\alpha}{\beta}\right]=0$$

Solving a quadratic equation is not a problem, but the result is a big formula:

$$\hat{N}=\frac{\beta M(b-\mu-\alpha)+\sqrt{(\beta M(b-\mu-\alpha))^2+4\alpha b\beta M(\mu+\alpha)}}{2b\beta}$$

(the other root is negative).

To establish the stability of this equilibrium, we calculate the Jacobian,

$$\mathbf{J}=\begin{bmatrix}\frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y}\\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y}\end{bmatrix}=\begin{bmatrix} b\left(1-2\frac{\hat{N}}{M}\right)-\mu & -\alpha\\ \beta\hat{I} & -\beta\hat{I}\end{bmatrix}$$

and its trace and determinant,

$$\begin{aligned} Tr &= b\left(1-2\frac{\hat{N}}{M}\right)-\mu-\beta\hat{I}\\ Det &= \beta\hat{I}\left[\mu+\alpha-b\left(1-2\frac{\hat{N}}{M}\right)\right]\end{aligned}$$

Substituting the equilibrium values $\hat{N}$ and $\hat{I}$ would be very unpleasant. Hence we try to establish the signs of the trace and of the determinant knowing that $\hat{N}$ and $\hat{I}$ are positive. Two more considerations will help (these could be proven analytically, but should be clear also from verbal reasoning):

(i) If the disease were not present, then the number of births would match the number of natural deaths at equilibrium, so that $b\left(1-\frac{N}{M}\right)=\mu$ would hold. If *all* individuals were infected, then the same would hold but with the death rate of the infected, $\mu+\alpha$, instead of μ. At equilibrium, however, all individuals cannot be infected (explain why!), so that the birth rate must be lower than $\mu+\alpha$; therefore $b\left(1-\frac{\hat{N}}{M}\right)\leq\mu+\alpha$ must hold at the equilibrium value $\hat{N}$ (the equality applies when the disease does not cause extra deaths, i.e., $\alpha=0$). The difference $\mu+\alpha-b\left(1-\frac{\hat{N}}{M}\right)$ is thus positive (or zero at worst). The determinant has a similar expression in its brackets, and if we write

$$Det=\beta\hat{I}\left[\mu+\alpha-b\left(1-2\frac{\hat{N}}{M}\right)\right]=\beta\hat{I}\left[\mu+\alpha-b\left(1-\frac{\hat{N}}{M}\right)+b\frac{\hat{N}}{M}\right]$$

then we see that the expression in the brackets is the sum of the positive difference $\mu+\alpha-b\left(1-\frac{\hat{N}}{M}\right)$ and another positive term. The determinant is therefore positive.

(ii) Susceptible individuals contract the disease at a *per capita* rate $\beta\hat{I}$ at the equilibrium. If the infected were immediately dead, then the rate of infection would just be added to the death rate, and the births would balance the deaths if $b\left(1-\frac{\hat{N}}{M}\right)$ equalled $\mu+\beta\hat{I}$. This is of course not the case, so the birth rate at the equilibrium density $\hat{N}$ must be smaller than this; hence we have $b\left(1-\frac{\hat{N}}{M}\right) < \mu+\beta\hat{I}$. The difference $b\left(1-\frac{\hat{N}}{M}\right) - (\mu+\beta\hat{I})$ is therefore negative. Writing the trace as the sum of this negative difference and the rest of the terms,

$$Tr = b\left(1-2\frac{\hat{N}}{M}\right) - \mu - \beta\hat{I} = b\left(1-\frac{\hat{N}}{M}\right) - (\mu+\beta\hat{I}) - b\frac{\hat{N}}{M}$$

we see that the trace is negative.

Since the determinant is positive and the trace is negative, the endemic equilibrium of the SI model is always stable. We could establish this fact without actually substituting the equilibrium values of the variables into the Jacobian; it was enough to know that they are positive. This example was actually quite challenging, it is often much easier to see the signs of the trace and of the determinant also without calculating their values explicitly at the equilibrium. If however a model has several positive equilibria, then the trace and the determinant of the Jacobian will have different signs for these (since not all positive equilibria will have the same stability properties), so that it will not be enough to know that they are positive.

Exercises

The first four of the following exercises can be done already after section 4.2, and in these it will be easy to calculate the eigenvalues of the Jacobian explicitly. For the rest, keep two hints in mind:

- For 2×2 Jacobians, use the trace and the determinant instead of the eigenvalues (section 4.5).
- Try to obtain the signs of the trace and of the determinant of the Jacobian without substituting the equilibrium values explicitly (as in section 4.7), especially if the equilibrium values are complicated formulas. This is not always possible, but worth a try.

Exercise 36. *A simple enzyme-product system.* An enzyme X is produced by the cell at a constant rate a and decays exponentially at a rate μ. The enzyme converts a substrate S into the product Y at a rate k. The substrate concentration, s, is regulated by the cell such that it remains constant, whereas the product is used in other biochemical reactions and therefore it is depleted

exponentially at a rate δ. The concentrations of the enzyme (x) and the product (y) therefore change according to

$$\begin{aligned} \frac{dx}{dt} &= a - \mu x \\ \frac{dy}{dt} &= cx - \delta y \end{aligned}$$

where the constant $c = ks$ combines the reaction rate and the constant substrate concentration. Find the equilibrium of this model and establish its stability analytically.

Exercise 37. *Viability of a pathogen.* Investigate analytically the stability of the disease-free equilibrium of the host in the SI model in equations (9a,b). When the disease-free equilibrium is *not* stable, then the pathogen can spread when introduced at a low density, i.e., the pathogen is viable. Study how the viability of the pathogen depends on the parameters of the host (b, M, μ) and of the disease (β, α).

Exercise 38. *The SIS model of a harmless disease with births and deaths.* Include births and deaths into the SIS model in equations (1) with the same assumptions we used for including births and deaths into the SIR model in equations (7), except that assume no disease-related mortality ($\alpha = 0$). Find the nontrivial equilibrium of this model, investigate under which conditions it is positive, and investigate its stability. *Hint:* rewrite the model for the total population size (N) and the number of infected (I) as we did for the SI model in equations (9).

Exercise 39. *A predator-prey model.* In absence of predators, a population of prey grows according to the logistic model with parameters r and K. The predators catch prey according to mass action at rate β, and convert the captured prey into predator offspring with efficiency γ. The predators die at a constant rate δ. These simple assumptions lead to the model

$$\begin{aligned} \frac{dN}{dt} &= rN\left(1 - \frac{N}{K}\right) - \beta NP \\ \frac{dP}{dt} &= \gamma\beta NP - \delta P \end{aligned}$$

where N and P are respectively the population density of prey and predator. Find all equilibria and establish their stability for the parameter values $r = 1$, $K = 1$, $\beta = 1$, $\gamma = 1$, and $\mu = 0.9$. (Note that the results may be different for different parameter values; we shall revisit this model to investigate it in more detail in exercise 71).

Exercise 40. *The Lotka-Volterra competition model revisited.* Carry out the local stability analysis of those equilibria in the Lotka-Volterra competition model where both species are present (see exercise 24), and compare the result to the phase plane analysis.

Exercise 41. *Bacterial growth limited by the accumulation of a toxin.* Suppose that a population of bacteria would grow exponentially at a rate $r > 0$, but the bacteria produce a toxin at a *per capita* rate p, and the toxin kills the bacteria proportionally to its concentration T, i.e., it leads to a *per capita* death rate cT. The toxin decays at a constant rate α. The population density of the bacteria (N) and the concentration of the toxin (T) thus obey the equations

$$\begin{aligned} \frac{dN}{dt} &= rN - cTN \\ \frac{dT}{dt} &= pN - \alpha T \end{aligned}$$

(a) Show that this model has a single nontrivial equilibrium, which is always stable.
(b) Investigate when the nontrivial equilibrium is a stable node and when it is a stable focus. Interpret the result biologically: do oscillations occur when the toxin decays fast or when it decays slowly? Can you explain why?
(c) Perform the phase plane analysis of this model. Sketch several trajectories for increasingly fast toxin production and decay (i.e., assume that both p and α double etc. such that p/α remains the same, and redraw the trajectory for the faster toxin).
(d) Suppose now that the production and the decay of the toxin is much faster than the population growth of the bacteria, i.e., p and α are large compared to r and cT. Analyze the model using time-scale separation (see section 3.9 of Part 1). Show that in this case, the bacteria follow logistic population growth, and derive the carrying capacity.

Exercise 42. *The SEIS model of infectious diseases.* An infectious disease spreads as described by the SIS model of section 2, except that newly infected hosts are not immediately infectious, but first become only "exposed" (the letter E in "SEIS" refers to the exposed state). Exposed individuals incubate the disease and become infectious (I) at a rate γ. This yields the following model (compare with equations (1a,b)):

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + vI \\ \frac{dE}{dt} &= \beta SI - \gamma E \\ \frac{dI}{dt} &= \gamma E - vI \end{aligned}$$

(a) This model assumes no birth and death for the host. Use the conservation law $N = S + E + I = constant$ to reduce the number of equations to two (retain the variables E and I).
(b) What condition the parameters should satisfy for the disease-free equilibrium ($E = 0, I = 0$) to be unstable? Explain why this is the same as the viability condition of the disease in the SIS model (see section 2).
(c) Suppose that the disease is viable. Find all equilibria where the disease is present and establish their stability.

Exercise 43. *A consumer-resource model.* Assume that a resource flows into a system at a constant rate α. The resource is used by a consumer, which eats the resource with capture rate β and converts the consumed resource into offspring with a conversion efficiency γ. The death rate of the consumer is δ, whereas the spontaneous decay rate of the resource is ϵ. Let x and y be the density of the resource and of the consumer, respectively. The above assumptions lead to the model

$$\begin{aligned} \frac{dx}{dt} &= \alpha - \epsilon x - \beta xy \\ \frac{dy}{dt} &= \gamma\beta xy - \delta y \end{aligned}$$

Find all equilibria of this model and establish their stability.

Exercise 44. *Enzyme kinetics: Allosteric product inhibition.* In allosteric product inhibition, the product of the reaction inhibits the reaction itself in order to prevent making too much of the product. To achieve this, the product molecule binds to the enzyme molecule and thereby inactivates the enzyme; this binding occurs at a site different from the catalytic active site of the enzyme, hence the inhibition is called "allosteric".

The enzyme molecules are divided into active enzyme (with concentration a) and inactive enzyme (with concentration $e - a$, where e is the total enzyme concentration, which is constant). The active enzyme molecules are lost due to binding the product (the concentration of which is p) according to mass action with a reaction rate γ, and are recovered as the inactive enzyme-product complex dissociates at a rate δ. This yields the equation

$$\frac{da}{dt} = -\gamma pa + \delta(e - a)$$

for the concentration of the active enzyme.

If the substrate is present in a high concentration, then the active enzyme is working at maximum speed, so that the product accumulates at a speed

proportional to the concentration of the active enzymes (this is a limiting, or "extreme", case of the Michaelis-Menten kinetics discussed in section 3.9 of Part 1). Suppose that the product decays (or is used up in other reactions) at a rate μ. In addition, the free product molecules disappear when they bind to the enzyme and inactivate it, and appear again when they dissociate from the enzyme-product complex. Hence the concentration of the product changes according to

$$\frac{dp}{dt} = ka - \mu p - \gamma pa + \delta(e - a)$$

Find the equilibrium concentrations and establish the stability of the equilibrium. (Heed the advice above: do not substitute the equilibium concentrations explicitly into the Jacobian, it would be quite obviously futile!)

Exercise 45. *The SIR model with demographic turnover.* In this model, we consider a non-lethal disease in a host population in demographic equilibrium, where the number of births balances the number of deaths.The newborns are susceptible to the disease, whereas those who have recovered from the disease are immune. The demographic turnover (immune hosts dying and susceptible hosts being born) will affect the disease, even though the total population size $N = S + I + R$ is constant. The dynamics of susceptibles (S), infected (I) and recovered (R) are given by

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \mu S - \beta SI \\ \frac{dI}{dt} &= \beta SI - vI - \mu I \\ \frac{dR}{dt} &= vI - \mu R \end{aligned}$$

where μ is the death rate of the host (all hosts die equally), and the other parameters are as in the standard SIR model in section 3. In the first equation, the birth term μN is such that it balances the deaths, $\mu S + \mu I + \mu R$.

(a) Investigate the stability of the disease-free equilibrium. Show that the disease is viable if $\frac{\beta N}{v+\mu} > 1$. (NB. This condition means that the R_0 of the disease is greater than 1, see section 1.3 of Part 3).
(b) Suppose that the disease is viable. Find the equilibrium where the disease is present, and establish its stability.

Exercise 46. *Medicine concentration.* A medicine is administered by the continuous infusion of m milligrams per hour. The concentration of the medicine in the body fluids (x_1) and within the cells (x_2) changes according to the compartment model shown in Figure 10.

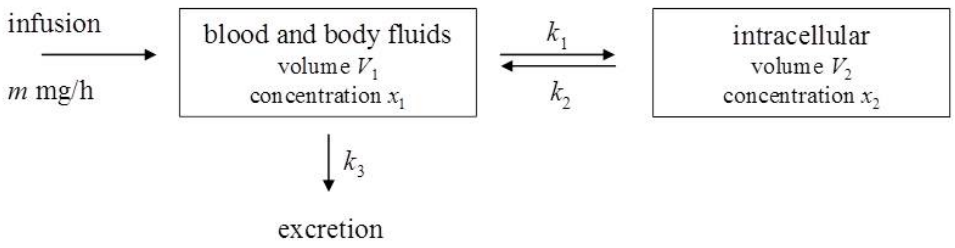


Figure 10: The flow of a medicine in the body.

To write the corresponding differential equations, we must be careful to note that when a certain *mass* of the medicine moves from the body fluids into the cells (or *vice versa*), then the changes in the *concentrations* (=mass/volume) depend on the volumes of the body fluids and of the cells, respectively. (Moving a small mass from a small volume into a large volume can change the concentration in the small volume considerably, but will not change the concentration in the large volume by much.) For this reason, it is best to start with equations for the masses present in the body fluids (x_1V_1) and in the cells (x_2V_2). Hence we write

$$\begin{aligned} \frac{dx_1V_1}{dt} &= m - (k_1 + k_3)x_1V_1 + k_2x_2V_2 \\ \frac{dx_2V_2}{dt} &= k_1x_1V_1 - k_2x_2V_2 \end{aligned}$$

Since V_1 and V_2 are constant volumes, we can factor them out of the derivatives. Dividing with the volumes yields differential equations for the concentrations,

$$\begin{aligned} \frac{dx_1}{dt} &= \frac{m}{V_1} - (k_1 + k_3)x_1 + k_2x_2\frac{V_2}{V_1} \\ \frac{dx_2}{dt} &= k_1x_1\frac{V_1}{V_2} - k_2x_2 \end{aligned}$$

(a) Find the equilibrium concentrations and establish the stability of the equilibrium.
(b) Can this system have a focus, i.e., can the concentrations of the medicine exhibit any oscillations?

Exercise 47. *The Lotka-Volterra predator.prey model.* A famous, historically very important, if over-simplistic model of a prey population and its predator is given by

$$\begin{aligned} \frac{dN}{dt} &= aN - bNP \\ \frac{dP}{dt} &= cNP - dP \end{aligned}$$

where N and P are respectively the population densities of the prey and the predator. In absence of the predator ($P = 0$), the prey grows exponentially at a rate a (which is of course unrealistic, and makes this model significantly different from the one in exercise 39 also mathematically). The predator catches the prey at a rate b, and converts the consumed prey into predator offspring with an efficiency e such that the bNP prey eaten per unit time results in the birth of $ebNP$ predators; in the above equations, the constant eb is denoted with c. Predators die at at rate d.

(a) Find the nontrivial equilibrium of this model and perform its local stability analysis. Can this analysis prove the stability or the instability of the equilibrium?
(b) Solve the differential equations numerically with various initial points (see section 3.3 of Part 1). Plot the solutions on the phase plane together with the isoclines.
(c) Let the function $V(t)$ be defined as the following quantity calculated from the population densities of the prey and of the predator:

$$V(t) = a \ln P(t) + d \ln N(t) - bP(t) - cN(t)$$

The value of $V(t)$ depends on the values of $P(t)$ and $N(t)$, which change in time according to the differential equations. Calculate the change of $V(t)$ in time (differentiate $V(t)$ with respect to t, and substitute $\frac{dN}{dt}$ and $\frac{dP}{dt}$ from the differential equations). You should get that $\frac{dV}{dt} = 0$, i.e., $V(t)$ is constant in time; thus V is a so-called *constant of motion*. Use this fact to interpret the numerical results obtained in (b) (*hint:* it may help to visualize V as a function of N and P, and imagine the curve $N(t)$ and $P(t)$ must trace on the surface of V).

Exercise 48. *Cyclic competition.* The Lotka-Volterra competition model we analyzed in exercises 24 and 40 extends naturally to three competing species as

$$\begin{aligned}
\frac{dN_1}{dt} &= r_1[1 - \alpha_{11}N_1 - \alpha_{12}N_2 - \alpha_{13}N_3]N_1 \\
\frac{dN_2}{dt} &= r_2[1 - \alpha_{21}N_1 - \alpha_{22}N_2 - \alpha_{23}N_3]N_2 \\
\frac{dN_3}{dt} &= r_3[1 - \alpha_{31}N_1 - \alpha_{22}N_2 - \alpha_{33}N_3]N_3
\end{aligned}$$

The three- (and higher) dimensional Lotka-Volterra competition model exhibits surprisingly rich dynamics, its behaviour is still not understood in full. Here we consider a special case of cyclic competition, i.e., a situation where species 1 beats species 2; species 2 beats species 3; and species 3 beats species 1. This is analogous to the famous Rock-Scissors-Paper game (Rock beats

Scissors; Scissors beat Paper; Paper beats Rock). Antibiotic-producing bacteria provide a biological example, where the three "species" are a strain that produces the antibiotic, a sensitive strain and a strain that is resistant to the antibiotic but does not produce it. Here the producer strain beats the sensitive strain; the sensitive strain beats the resistant strain (when the two are pitted against each other, there is no antibiotic production, but the resistant strain bears the cost of maintaining the resistance mechanism); and the resistant strain beats the producer strain (both are resistant, and the producer has the cost of antibiotic production).

To keep the model as simple as possible, we assume $r_1 = r_2 = r_3 = 1$, $\alpha_{11} = \alpha_{22} = \alpha_{33} = 1$, and equal interspecific competition coefficients arranged such that each species is affected only by the one that beats it, not by the one it beats. This leads to the model

$$\begin{aligned} \frac{dN_1}{dt} &= [1 - N_1 - aN_3]N_1 \\ \frac{dN_2}{dt} &= [1 - aN_1 - N_2]N_2 \\ \frac{dN_3}{dt} &= [1 - aN_2 - N_3]N_3 \end{aligned}$$

where we shall assume $a > 2$.

(a) This model has three equilibria where only one species is present and the other two are absent. Show that none of these single-species equilibria is stable.
(b) Show that there is no equilibrium where two species are present and the third is absent.
(c) Find the equilibrium where all three species coexist. Calculate the corresponding Jacobian matrix and show that the eigenvalues of the Jacobian are the solutions of the characteristic equation

$$[(1 + a)\lambda + 1]^3 = -a^3$$

One solution of this equation we get when $(1 + a)\lambda + 1 = -a$, which yields $\lambda_1 = -1$. A 3×3 Jacobian must however have three eigenvalues (see section 5.5 of Part 3). Check that the complex numbers

$$\lambda_{2,3} = \frac{a - 2 \pm \sqrt{3}ai}{2(1 + a)}$$

satisfy the characteristic equation so that these are the other two eigenvalues. Assuming $a > 2$, the real part of these eigenvalues is positive. The equilibrium where all three species coexist is unstable, so that the model has no stable equilibrium at all (cf. (a) and (b)).

(d) Solve the differential equations numerically for $a = 2.1$. Confirm that this system oscillates such that (after some time) it approaches the equilibrium where only species 1 is present; but then species 3 starts growing and takes over such that the system moves to the neighbourhood of the species 3-only equilibrium; but then species 2 starts growing and the system moves over to the species 2-only equilibrium; but then species 1 starts growing and the system moves back to the neighbourhood of the species 1-only equilibrium, where the cycle starts again. This is however not a regular cycle where we would periodically see the same population densities. Instead, the system gets a little closer to the equilibria at each repetition, and therefore it takes ever longer to get away and move to the next equilibrium (if the system ever reached the equilibrium, it would take infinitely long to get away). Hence the system spends increasingly long times near each equilibrium, and these almost-static periods are interspersed with fast movements to the next equilibrium. The circular chain of unstable equilibria (saddle points) we found here is called a *heteroclinic cycle*. The possibility of heteroclinic cycles raises management problems, beacuse the fast changes after long almost-static periods are very difficult to control. In real ecosystems, species would easily go extinct while they are at low population densities, and it would be nearly impossible to predict which species will be lost.

5 Limit cycles

5.1 Theory

In the Brusselator model of section 4.6, we had an example where the only equilibrium of the model was an unstable focus, which trajectories cannot converge to. Even in models that have a locally stable equilibrium, we know only for trajectories starting in the vicinity of the stable equilibrium that they will converge to it; trajectories starting further away might do something else. What can happen to a trajectory if it does not approach an equilibrium? There is a number of possibilities:

- The trajectory may escape to infinity (i.e., one or several variables may go to infinity as time goes to infinity). Exponential population growth is an example: the model

$$\frac{dN}{dt} = \rho N$$

has only the trivial equilibrium $\hat{N} = 0$, which is unstable when $\rho > 0$. In this case, the population size grows exponentially with time,

$$N(t) = N(0)e^{\rho t}$$

so that the population becomes arbitrarily large if we wait long enough (see section 3.4 of Part 1). This is however biologically impossible; a finite world cannot support an infinitely large population. Other variables of biological interest, such as concentrations, cannot become infinitely large either. In biologically realistic models, therefore, there must be a (possibly large but finite) a "box" in the coordinate system of the trajectories, such that if the system starts within the box or enters the box, then it will always remain within the box. I shall refer to this "box" as a trapping region.

- The trajectory may form a tangled jumble, curling around itself like a long spaghetti in a big knot (although nearby parts of the trajectory run along each other for a while before they separate, because small differences in the variables cause only small differences in the direction of the trajectory). Moving along such a trajectory, the system never visits the same point again. This happens when a 3- or higher dimensional model has a chaotic trajectory[5]. In a 2-dimensional phase plane, however, the trajectory cannot be a jumble without crossing itself. And trajectories may not cross; at every point on the phase plane, the differential equations of the model unequivocally determine[6] how the trajectory must continue, hence it is impossible that at a crossing point the trajectory would continue in two different ways.

- The system may exhibit periodic oscillations, usually in the form of limit cycles[7]. A *limit cycle* is a closed "loop" to which the system either converges to (stable limit cycle) or diverges from (unstable limit cycle). Figure 11 shows a stable limit cycle from the Brusselator model of section 4.6. On the limit cycle, the system keeps moving around forever. This cyclic movement corresponds to periodic oscillations of the variables in time (Figure 12).

Exercise 49. Solve the differential equations of the Brusselator model numerically and reproduce Figure 11.

[5]The Lorenz-attractor is a famous example of chaos in a simple 3-dimensional model; you can find animated figures of the Lorenz-attractor in Wikipedia.

[6]This is true for autonomous ordinary differential equations (the only kind of differential equations we consider) and under some technical conditions; it is sufficient if the right hand sides of the differential equations are continuously differentiable in all their variables, which is the case in models of biological interest.

[7]Exercise 47 shows an example for cycles that are not limit cycles. In the Lotka-Volterra predator-prey model investigated in this exercise, there are infinitely many cycles such that every starting point is on one of the cycles, and every trajectory continues on the cycle where its starting point is on. These cycles are not limit cycles because trajectories do not converge to or diverge from them.

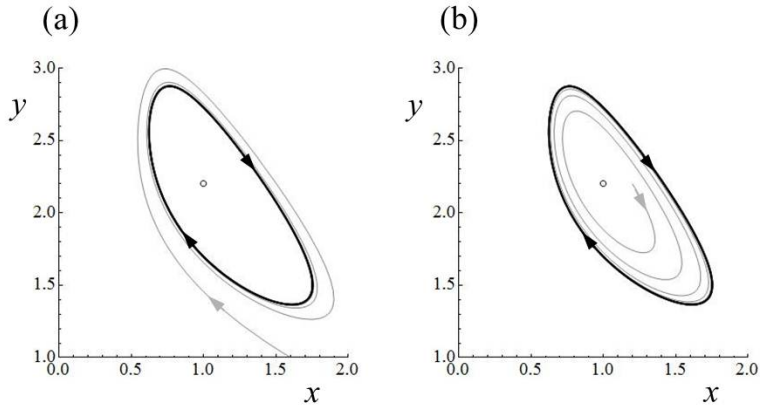


Figure 11: Limit cycle in the Brusselator model (equations (28) with parameters $\alpha = 1$, $\beta = 2.2$, $k_3 = 1$, $k_4 = 1$). The thick black "loop" is the limit cycle. The grey lines are trajectories starting outside (in panel (a)) and inside (in panel (b)) of the limit cycle; both converge to the limit cycle, i.e., the limit cycle is stable. The empty dots mark the position of the unstable equilibrium.

Limit cycles are of great interest for understanding the oscillatory behaviour intrinsic to many biological systems. The cell cycle, the biological clock behind circadian rythms, and the heart beat are obvious examples, but many ecological systems also exhibit a significant cyclic component in their observed dynamics. For a complete understanding of a biological model, it is important to find out whether it has limit cycles. Unfortunately, however, the mathematical tools that can be used to investigate limit cycles are less powerful than the tools for equilibria. Usually it is not possible to find the position of a limit cycle analytically. For equilibria, we solve the equilibrium equations to see how many equilibria the model has and where they are (as in step 1 of section 4.4); for limit cycles, there is no analogous procedure. In practice, limit cycles are located by solving the differential equations numerically (see section 3.3 of Part 1) and checking whether the solution revisits (approximately) the same point again and again. (To plot the limit cycle as the black loop in Figure 11, one computes the trajectory for a long time, and plots only the last part of it, so that the *transient*, the part of the trajectory where it is still at a noticeable distance from the limit cycle (gray in Figure 11), is not shown.)

Exercise 50. The above procedure will find only stable limit cycles, to which the trajectory converges as time goes on. Convince yourself that unstable limit cycles can be found by running time backwards, i.e., substituting $-dt$ in place of dt in the differential equations. (This is equivalent to multiplying the right hand side of each equation with -1.)

Exercise 51. Explain why a model with a single differential equation cannot have a limit cyce.

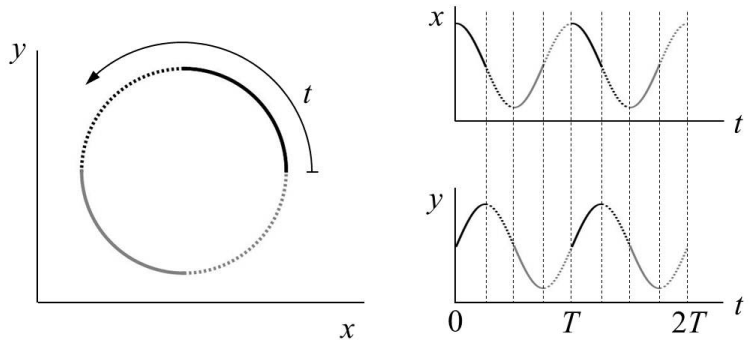


Figure 12: This schematic figure illustrates how a cyclic movement on the phase plane (left) translates into periodic oscillations in time (right). As the system moves along the limit cycle (indicated by the time arrow), first it moves to the left and upwards (thick black line), i.e., x decreases and y increases (see the first part of the diagrams on the right). Next, the system keeps on going left but turns downward (dashed black line), i.e., x still decreases and now also y decreases. Then the trajectory turns to the right while it still goes downwards (thick gray line) such that x increases whereas y decreases. Finally, the trajectory goes right and upwards (dashed gray line), which means that both x and y increase. After T time (the period) the system is back at the starting point, and afterwards the same cycle repeats again and again. The direction of the rotation may of course be also the opposite (see Figure 11).

In the remainder of this section, we consider models with only two variables. For these (but only these) models, there are two useful tools to investigate whether a model has a limit cycle. The first tool builds on the three possibilities what can happen to a trajectory if it does not go to an equilibrium: escape to infinity, exhibit chaotic behaviour or go to a cycle. As we have seen above, in 2-dimensional, biologically justified models we can discount the first two of these, such that only periodic oscillations remain. This is formulated in a famous theorem:

Poincaré-Bendixson theorem. *If a two-dimensional system has a finite trapping region and a trajectory in the trapping region does not go to a small neighbourhood of any equilibrium, then it goes to (or is already on) a periodic solution, generically a stable limit cycle.*

If a model has no stable equilibrium at all, then by the Poincaré-Bendixson theorem, we expect that the trajectories converge to a stable limit cycle[8]. This is the most common

[8]There is however a fine detail here (and this is the reason why in the Poincaré-Bendixson theorem we have to say "does not go to a small neighbourhood of an equilibrium" rather than saying simply that the model has no stable equilibrium). It is possible that the model has several saddle points (see Figure 5b) connected to each other in such a way that when the trajectory leaves from one saddle point along its "outgoing" eigenvector, it approaches the neighbourhood of the next saddle point near its "incoming" eigenvector; then as the trajectory leaves the second saddle point, this repeats until the

way of discovering limit cycles. For example, the Brusselator model has only one equilibrium, and with the parameters used in Figure 11, this equilibrium is an unstable focus. Clearly, trajectories will not go to the vicinity of this equilibrium; to the contrary, they leave the neighbourhood of the unstable focus. The model has a finite trapping region (the concentrations will not become infinite), hence the conditions of the Poincaré-Bendixson theorem are satisfied. As expected, the model has a stable limit cycle (Figure 11).

A stable limit cycle may however exist also if the model does have a stable equilibrium. Figure 13 shows a hypothetical example, where a stable equilibrium is surrounded with an unstable limit cycle, which again is surrounded with a stable limit cycle. Trajectories starting outside the stable limit cycle and trajectories starting inbetween the two limit cycles converge to the stable limit cycle. trajectories starting inside the unstable limit cycle converge to the stable equilibrium.

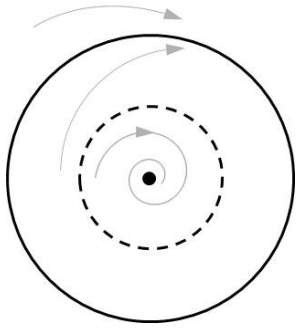


Figure 13: Nested limit cycles. Filled dot: stable equilibrium; dashed line: unstable limit cycle; thick line: stable limit cycle; gray arrows: trajectories

The second tool for investigating whether a model has limit cycles aims at proving that the model has none. This method is applicable only in two-dimensional systems, and it gives only a *sufficient* condition to exclude limit cycles. This means that if the condition is satisfied, then we know that the model has no limit cycle; but if the condition is not satisfied, then the model may or may not have a limit cycle, we still don't know. This sufficient condition is known as

trajectory gets back to the first saddle point. Such a loop of connecting saddles is called a *heteroclinic cycle*. A heteroclinic cycle contains no stable equilibrium, yet the trajectory visits the neighbourhoods of equilibria (the saddle points). Heteroclinic cycles are uncommon, but there is a famous example shown in exercise 48. There can also be a loop between the "outgoing" and "incoming" directions of a single saddle point, but such a *homoclinic cycle* exists only for specific parameter values and disappears upon the slightest change of parameters.

Bendixson's negative criterion. *If, in the two-dimensional system*

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2) \end{aligned}$$

the quantity

$$\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}$$

has the same sign at every point, then the system has no limit cycle (neither stable nor unstable).

The expression $\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}$ is reminiscent of the trace of the Jacobian, but here it is not evaluated at an equilibrium point (as in the Jacobian); rather, here we check whether it is always positive or always negative for any x_1 and x_2. The quantity $\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}$ is called the *divergence* and denoted with $\mathrm{div}(f_1, f_2)$.

Bendixson's negative criterion is based on a simple geometrical argument. Place a small rectangle of size $dx_1 \times dx_2$ on the phase plane such that its lower left corner is at the point (x_1, x_2), as in Figure 14. Start four trajectories from the four corners of the rectangle; the arrows in Figure 14 indicate how these trajectories go in a short time interval dt. The parallelogram drawn with dashed lines connects the four trajectories after dt time. All trajectories that start from within the original rectangle end up on the dashed parallelogram dt time later. If the area of the dashed parallelogram is greater than the original rectangle, then the area is expanded under the flow of the trajectories; and conversely, if the parallelogram is smaller than the rectangle, then the area is contracted under the flow. A somewhat tedious calculation shows that the area of the parallelogram is $\left[1 + (\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2})dt\right]dx_1 dx_2$, whereas the area of the rectangle is $dx_1 dx_2$. The difference is therefore $(\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}) \cdot dt \cdot dx_1 dx_2$, or $\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2}$ per unit time and unit area. This quantity is the divergence defined above and used in Bendixon's negative criterion.

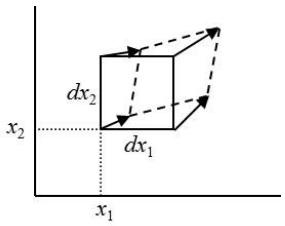


Figure 14: Change of area under the flow of trajectories (see text for explanation).

Suppose now that the system has a limit cycle. The limit cycle itself is a trajectory; if we start exactly on the limit cycle, then the trajectory follows the limit cycle (even if the limit cycle is unstable). Since trajectories may not cross each other, every trajectory that starts inside the limit cycle will remain inside the limit cycle, and every trajectory that starts outside will remain outside. If we divide the area inside the limit cycle into many small rectangles and follow how each of those expand or contract under the flow, then the resulting parallelograms must exactly cover the area inside the limit cycle. This means that the total area of the parallelograms must equal to the total area of the rectangles, which is possible

only if some rectangles expand and some rectangles contract. If we find that the divergence is everywhere positive, then every rectangle expands; and if the divergence is everywhere negative, then every rectangle contracts. Both cases are impossible if the system has a limit cycle; hence if the divergence is always positive or always negative, then no limit cycle can exist. Note, however, that the divergence may switch sign also if the system has no limit cycle. Bendixson's negative criterion works only in one direction: if the criterion is satisfied, then we have excluded any limit cycle, but if the criterion is not satisfied, then we haven't learned anything.

To illustrate the use of Bendixson's negative criterion, we investigate whether the following resource-consumer model may have a limit cycle. Let x and y denote the population density of resource and consumers, respectively, and suppose that the resource is provided at a constant rate α. The consumer captures the resource at a rate β according to mass action, and converts the resource into consumer offspring with a conversion factor γ. This means that in dt time, each consumer captures βx resources and gives birth to $\gamma\beta x$ consumer offspring. Finally, assume that the resource decays at a constant rate ϵ and the consumer dies at a constant rate δ. These assumptions lead to the consumer-resource model

$$\frac{dx}{dt} = \alpha - \epsilon x - \beta xy \tag{29a}$$

$$\frac{dy}{dt} = \gamma\beta xy - \delta y \tag{29b}$$

The results of exercise 43 show that this model has a locally stable equilibrium, but this does not exclude that the model may also have a limit cycle (cf. Figure 13). To see if we can exclude limit cycles, we calculate the divergence

$$\frac{\partial[\alpha - \epsilon x - \beta xy]}{\partial x} + \frac{\partial[\gamma\beta xy - \delta y]}{\partial y} = -\epsilon - \beta y + \gamma\beta x - \delta$$

Unfortunately, this quantity may be both positive and negative; for example, if we take small values for both x and y then $-\epsilon - \beta y + \gamma\beta x - \delta \approx -\epsilon - \delta$ is negative, but if we take small y and very large x, then $-\epsilon - \beta y + \gamma\beta x - \delta \approx \gamma\beta x$ is positive. Hence Bendixon's criterion does not hold, so that we cannot exclude limit cycles based on the divergence.

There is, however, a nice trick to make Bendixon's method much more powerful. Whether or not the model has a limit cycle depends on the *shape* of the trajectories, not on the speed how fast the system moves along them. The shape of the trajectory is characterized locally by its slope, dy/dx, which we obtain from the differential equations as

$$\frac{dy}{dx} = \frac{\frac{dy}{dt}}{\frac{dx}{dt}} = \frac{\gamma\beta xy - \delta y}{\alpha - \epsilon x - \beta xy}$$

This quotient remains the same if we multiply both the numerator and the denominator with the same positive function[9] $h(x, y)$:

$$\frac{dy}{dx} = \frac{[\gamma\beta xy - \delta y] \cdot h(x, y)}{[\alpha - \epsilon x - \beta xy] \cdot h(x, y)}$$

This means that the trajectories of the original model in equations (29a,b) and of an alternative model

$$\frac{dx}{dt} = [\alpha - \epsilon x - \beta xy] \cdot h(x, y) \tag{30a}$$

$$\frac{dy}{dt} = [\gamma\beta xy - \delta y] \cdot h(x, y) \tag{30b}$$

have exactly the same shape, only the speed of moving along the trajectory is different. If the alternative model has no cycle-shaped trajectory, then the original model has none either. It is therefore enough to exclude limit cycles in the alternative model of equations (30). Now the trick is to find a function $h(x, y)$ so that the divergence of the alternative model is always positive or always negative — if there is any such function. Nobody can give a recipe for how to find a suitable function, but often quite simple functions help. Let us try $h(x, y) = \frac{1}{xy}$ in the consumer-resource model. The alternative model is then

$$\begin{aligned} \frac{dx}{dt} &= [\alpha - \epsilon x - \beta xy] \cdot \frac{1}{xy} = \frac{\alpha}{xy} - \frac{\epsilon}{y} - \beta \\ \frac{dy}{dt} &= [\gamma\beta xy - \delta y] \cdot \frac{1}{xy} = \gamma\beta - \frac{\delta}{x} \end{aligned}$$

and if we calculate the divergence from this model, we get

$$\frac{\partial[\frac{\alpha}{xy} - \frac{\epsilon}{y} - \beta]}{\partial x} + \frac{\partial[\gamma\beta - \frac{\delta}{x}]}{\partial y} = -\frac{\alpha y}{(xy)^2} + 0 = -\frac{\alpha}{x^2 y}$$

which is obviously negative. Since the alternative model in equations (30) has no limit cycle, we can conclude that the original consumer-resource model has no limit cycle either. Since the model has a single locally stable equilibrium (cf. exercise 43), and we have excluded any limit cycle, we can conclude that all trajectories that start with positive resource and consumer densities (i.e., not only those that start near the equilibrium) must converge to the equilibrium, so that the equilibrium is *globally stable*.

The fact that we may multiply the right hand sides of both equations with the same function $h(x, y)$ before calculating the divergence is referred to as *Dulac's Lemma*, and $h(x, y)$ is called a *Dulac function*.

[9] $h(x, y)$ must also be continuous and differentiable so that its derivatives with respect to x and y are also continuous, but in practice this condition is usually satisfied.

Exercise 52. Exclude limit cycles in the consumer-resource model in equations (29) using $h(x, y) = \frac{1}{y}$ as a Dulac-function (this is a constant function of its first variable, x). As you will see, this choice also works; hence there can be several simple choices for a Dulac function.

Exercise 53. Exclude limit cycles
(i) in the model for allosteric product inhibition in exercise 44;
(ii) the model for medicine concentrations in exercise 46.
These models do not need a Dulac function.

Exercise 54. Exclude limit cycles
(i) in the Lotka-Volterra competition model in exercises 24;
(ii) in the model for bacterial growth in exercise 41;
(iii) in the model for a genetic switch in exercise 25.
Find simple Dulac functions similar to the worked example above.

5.2 Example: The cell cycle

This section gives a brief illustration of limit cycles in higher dimensional models via Goldbeter's[10] classic model for the cell cycle. To explain the mitotic cycle, we need two key elements: (i) an oscillating molecular system that acts as a "clock" and initiates periodic division as it occurs e.g. during embyonic development; and (ii) a way to switch these cycles off when necessary (unregulated growth yields only cancer, not normal development). Goldbeter's minimal model explains these with only a few biochemical reactions.

Mitosis is initiated by a protein kinase called cdc2 (in fission yeast; the nomenclature varies between organisms). cdc2 phosphorilates other enzymes and thereby triggers the breakdown of the nuclear envelope, the condensation of the chromosomes, the formation of the mitotic spindle, etc. cdc2 itself is activated by a protein called cyclin. Cyclin is produced at a constant rate but its decay is variable, because it is ultimately a consequence of high cdc2 concentrations: Among many other proteins, cdc2 also activates the enzyme called cyclin protease, which destroys cyclin.

Goldbeter's mechanism for the cell cycle thus involves just three main players, cyclin (with concentration C), cdc2 (M), and cyclin protease (X). The concentration of cyclin changes according to

$$\frac{dC}{dt} = v_i - k_d C - v_d X \frac{C}{K_d + C} \tag{31a}$$

where v_i is the constant rate of cyclin production, k_d is the rate of spontaneous decay, and the last term is the amount of cyclin destroyed by cyclin protease. This is proportional to the amount of cyclin protease present (X), but saturates as a function of C according to the Michaelis-Menten enzyme kinetics (see section 3.9 of Part 1; briefly, saturation occurs

[10] Goldbeter 1991, Proc. Narl. Acad. Sci., USA

because a given amount of cyclin protease cannot destroy more than a certain number of cyclin molecules per unit of time even if the number of cyclin molecules is very large).

The number of cdc2 molecules is assumed to be constant, but only a fraction M of the molecules is activated. cdc2 is directly activated by a not identified "activase", which is in turn activated by cyclin. Assume that the total concentration of "activase" molecules is constant, but within this, the fraction of active "activase" is a saturating function of cyclin and is proportional to $C/(K_c + C)$. Because the "activase" is also an enzyme, it is assumed to follow the Michaelis-Menten kinetics where the substrate is the inactive form of cdc2, present in concentration $1 - M$. This gives the first term in equation

$$\frac{dM}{dt} = V_1 \frac{C}{K_c + C} \frac{1 - M}{K_1 + 1 - M} - V_2 \frac{M}{K_2 + M} \tag{31b}$$

The second term describes how cdc2 is inactivated by an enzyme which is present in constant concentration (and hence its concentration can be absorbed into the constant V2).

The last equation describes the activation and deactivation of cyclin protease similarly to equation (31b). Like cdc2, the total number of cyclin protease molecules is assumed to be constant, but only fraction X of them are active. Cyclin protease is activated by cdc2 itself and deactivated by a phosphatase present in constant concentration, yielding

$$\frac{dX}{dt} = V_3 M \frac{1 - X}{K_3 + 1 - X} - V_4 \frac{X}{K_4 + X} \tag{31c}$$

Equations (31a,b,c) constitute the minimal model of the cell cycle. Let us fix the parameters as

$$\begin{aligned}
&K_1 = K_2 = K_3 = K_4 = 0.005 \\
&V_2 = 1.5/\text{min},\ V_3 = 1/\text{min},\ V_4 = 0.5/\text{min} \\
&v_i = 0.025\,\mu\text{M/min},\ v_d = 0.25\,\mu\text{M/min} \\
&K_c = 0.5\,\mu\text{M},\ K_d = 0.02\,\mu\text{M} \\
&k_d = 0.01/\text{min}
\end{aligned}$$

which leaves only V_1 to vary. V_1 is proportional to the number of "activase" molecules, hence by regulating the concentration of "activase", the cell can tune the value of V_1.

As Figure 15(a) shows, the concentrations settle on a stable limit cycle for high values of V_1 (i.e., when the "activase" is present in sufficiently high concentration). This limit cycle corresponds to the cell cycle; at the point where the concentration of active cdc2 (M) is high, the cell undergoes mitosis. The model has also an equilibrium point, but at high concentrations of V_1 it is not stable.

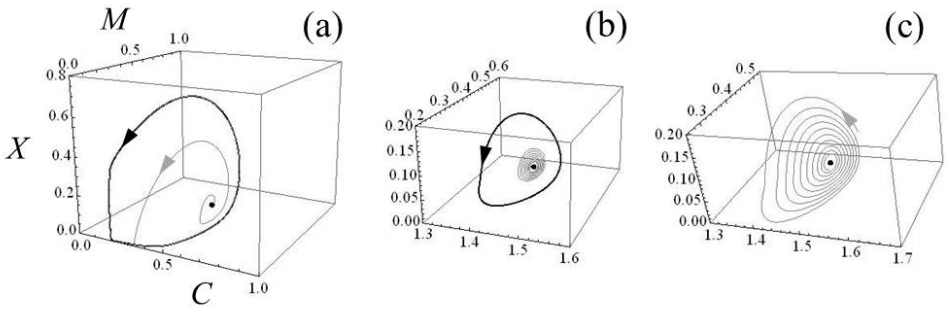


Figure 15: Equilibria (dots) and limit cycles (thick black lines) in the Goldbeter model of the cell cycle. (a) $V_1 = 3$/min. The equilibrium is at $\hat{C} = 0.500$, $\hat{M} = 0.474$ and $\hat{X} = 0.083$; the eigenvalues of the Jacobian are $\lambda_1 = -0.85$ and $\lambda_{2,3} = 0.23 \pm 0.60i$, i.e., the equilibrium is an unstable focus. As the gray trajectory indicates, the limit cycle is stable. (b) $V_1 = 2.017$/min. The equilibrium is at $\hat{C} = 1.440$, $\hat{M} = 0.450$ and $\hat{X} = 0.043$; the eigenvalues of the Jacobian are $\lambda_1 = -1.14$ and $\lambda_{2,3} = -0.0086 \pm 0.24i$, i.e., the equilibrium is a stable focus. The limit cycle is also stable. (c) $V_1 = 2$/min. The equilibrium is at $\hat{C} = 1.488$, $\hat{M} = 0.448$ and $\hat{X} = 0.041$; the eigenvalues of the Jacobian are $\lambda_1 = -1.23$ and $\lambda_{2,3} = -0.014 \pm 0.23i$, i.e., the equilibrium is a stable focus. There is no limit cycle.

For somewhat lower values of V_1 the stable limit cycle is still there, but the previously unstable equilibrium turns into a stable focus (Figure 15(b)). If V_1 is decreased further, then the limit cycle disappears and the trajectories converge to the stable focus; the cell cycle is then switched off (Figure 15(c)).

Exercise 55. Solve the differential equations of the model numerically (see section 3.3 of Part 1) for $V_1 = 3$/min and plot the concentrations C, M and X against time. Compare the result to Figure 15(a). Study the shape of the cycle in time: Where do the concentrations change quickly? Where do they change slowly? Why is there such a sharp turning point on the limit cycle near the lower left corner of Figure 15(a)?

Exercise 56. Plot the equilibrium concentration M as a function of C (pretending that C is not a variable) from equation (31b), and plot the equilibrium concentration X as a function of M from equation (31c) with the parameters as above. Use these plots, and the fact that cyclin (C) is produced at a constant but low speed, to explain verbally how the cell cycle works.

Exercise 57. By experimenting with the numerical solution of the differential equations, explore the range of V_1 where the model has both a stable equilibrium and a stable limit cycle as in Figure 15(b) (*hint:* this range is rather narrow). How do the limit cycles disappear as V_1 decreases? Do they become small before they vanish?

6 Bifurcation analysis

With bifurcation analysis, we explore how the behaviour of a model depends on its parameters. In particular, we are interested in qualitative changes in the behaviour: For example, a model may exhibit a stable equilibrium for certain parameter values, whereas a stable limit cycle for others. Or a model may have a single equilibrium for some parameter values, but multiple equilibria for others. Such qualitative changes are called bifurcations (cf. sections 3.7 and 3.8 of Part 1). Within the domain of parameters where the qualitative outcome is the same (e.g. where the model has a single stable equilibrium), the quantitative predictions of the model still vary (as the equilibrium values of the model variables change with the model parameters), and this of course may also be of interest. However, relatively little can be said about quantitative changes in general; each model needs to be analyzed separately to make quantitative predictions. In contrast, most qualitative changes in the model behaviour are described by only a few types of bifurcations, and the bifurcations act as "organizing centres" for the exploration of a model. In this chapter, we investigate the most common bifurcations directly via the analysis of a few worked examples. The boxes included in the text provide the theory and the last section summarizes the technique of bifurcation analysis; these parts can be used as quick references not cluttered by the details of the examples. Throughout, we consider models with two differential equations, although the methods can easily be extended to larger models.

6.1 The Brusselator revisited

In section 4.6, we introduced the Brusselator model for a chemical reaction that may exhibit sustained oscillations in the form of limit cycles (see Figure 11 in section 5.1). Whether or not limit cycles occur depends on the values of the model parameters. Here we focus on the parameters α and β; since these are proportional to the concentrations of molecules A and B, respectively (cf. section 4.6), these would be easy to manipulate experimentally.

In section 4.6, we found that the Brusselator model has a single equilibrium and that the trace and the determinant of the Jacobian at that equilibrium are

$$Tr = \beta - k_4 - k_3(\alpha/k_4)^2$$
$$Det = \alpha^2 k_3/k_4$$

The determinant is always positive. This means that the stability of the equilibrium depends on the trace; the equilibrium is stable when the trace is negative and unstable when the trace is positive. At the point where the trace flips between negative and positive (i.e., where the trace is zero), the stability of the equilibrium changes and a bifurcation occurs.

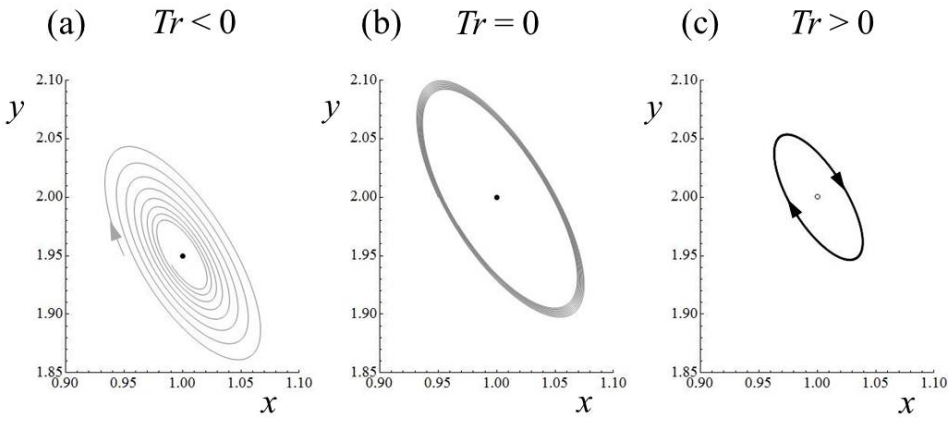


Figure 16: Hopf bifurcation in the Brusselator model. The parameters $\alpha = 1, k_3 = 1, k_4 = 1$ are held constant, such that the trace of the Jacobian is $Tr = \beta - k_4 - k_3(\alpha/k_4)^2 = \beta - 2$. (a) $\beta = 1.95$, $Tr = -0.05$. The equilibrium (filled dot) is a stable focus. (b) $\beta = 2$, $Tr = 0$. The equilibrium is still stable, although the local stability analysis is inconclusive ($Re(\lambda) = 0$) and the trajectory converges very slowly. (c) $\beta = 2.0005$, $Tr = 0.0005$. The equilibrium is an unstable focus (empty circle), surrounded with a small limit cycle (black), which is stable.

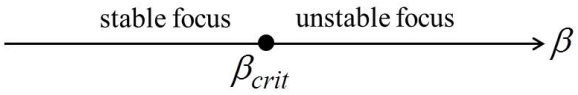
First I vary the parameter β while keep all the others fixed, i.e., I use β as a *bifurcation parameter*. The trace of the Jacobian is negative and therefore the equilibrium is stable when $\beta < k_4 + k_3(\alpha/k_4)^2$, and the equilibrium is unstable when the opposite holds. Hence there is a threshold at

$$\beta_{crit} = k_4 + k_3(\alpha/k_4)^2$$

such that if β is below this critical value, then the equilibrium is stable, whereas if β is above the critical value, then the equilibrium is unstable. The critical value is referred to as the *bifurcation point*.

Figure 16 shows the dynamics of the model for β below its critical value (such that the trace is negative), at its critical value (such that the trace is exactly zero), and slightly above its critical value (such that the trace is slightly positive). With a positive trace, the only equilibrium is unstable, and hence by the Poincaré-Bendixson theorem, we expect the model to have a limit cycle. Indeed, exactly as the equilibrium loses its stability, a small limit cycle is "born" around the equilibrium (Figure 16c). At the bifurcation point itself (Figure 16b), we can think of the model as having a limit cycle of zero size exactly on top of the equilibrium; and as the trace of the Jacobian becomes positive, this limit cycle grows first into a small ellipse, and then into a larger cycle of gradually different shape (compare with Figure 11, where β is greater than in Figure 16c).

The bifurcation seen in the Brusselator model is called a *Hopf bifurcation*. We can summarize the qualitative changes at a Hopf bifurcation in the following *bifurcation diagram*:



Near the Hopf bifurcation point at β_{crit}, the equilibrium is always a focus; this follows from the fact that with (almost) zero trace and with a positive determinant, the eigenvalues $\lambda_{1,2} = \frac{Tr \pm \sqrt{Tr^2 - 4Det}}{2}$ are complex numbers due to the negative term $-4Det$ under the square root. Further away from the bifurcation point, the equilibrium may turn into a node, but this means no change in its stability and therefore this does not count as a bifurcation.

We can naturally extend the above analysis to include a second (etc.) bifurcation parameter. Let us therefore vary α as well as β in the Brusselator model. The trace of the Jacobian is zero and therefore a Hopf bifurcation occurs when $\beta = k_4 + k_3(\alpha/k_4)^2$ or, equivalently, when $\alpha = k_4\sqrt{(\beta - k_4)/k_3}$. The curve depicting this relationship between α and β is shown in Figure 17. When crossing this *Hopf bifurcation line*, a Hopf bifurcation occurs such that the equilibrium is stable on the left of the curve (i.e., for values of β that are below the critical value corresponding to the given value of α) whereas the equilibrium is unstable on the right of the curve. As the grey cross-sections indicate, the 2-dimensional bifurcation diagram in Figure 17 is simply the one-dimensional bifurcation diagram shown above, repeated for a range of values of α.

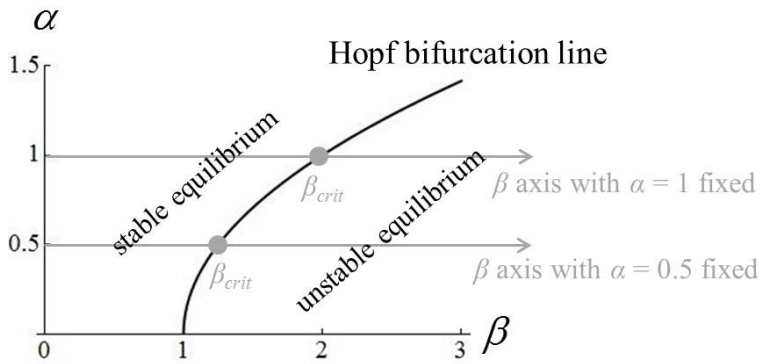


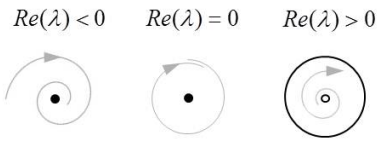
Figure 17: Bifurcation diagram of the Brusselator model. The parameters $k_3 = 1, k_4 = 1$ are held constant.

Box 2: The Hopf bifurcation

A Hopf bifurcation occurs when the real part of a complex pair of eigenvalues of the Jacobian is zero as it crosses between negative and positive values. In a model with two differential equations, this happens when the trace of the Jacobian switches sign while the determinant is positive; with $Tr = 0$ and $Det > 0$, the eigenvalues of the Jacobian simplify to $\lambda_{1,2} = \frac{Tr \pm \sqrt{Tr^2 - 4Det}}{2} = \pm\sqrt{-Det}$, i.e., $Re(\lambda_{1,2}) = 0$.

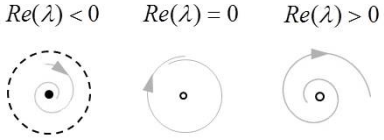
At a Hopf bifurcation, a stable focus bifurcates into an unstable focus (or *vice versa*). The Hopf bifurcation has two types:

(i) At a *supercritical Hopf bifurcation*, a stable limit cycle is born when the equilibrium loses its stability:



Notice that in this case, the equilibrium is stable also at the bifurcation point (although the local stability analysis is inconclusive with $Re(\lambda) = 0$).

(ii) At a *subcritical Hopf bifurcation*, an unstable limit cycle exists around the stable equilibrium. This unstable limit cycle shrinks onto the equilibrium, and the equilibrium becomes unstable when the unstable limit cycle disappears:



In this case, the equilibrium is unstable at the bifurcation point.

The subcritical Hopf bifurcation is also called a *catastrophic* Hopf bifurcation. This is because there is a drastic change in the local behaviour of the model: before the bifurcation trajectories converge to the stable equilibrium, but immediately after the bifurcation, the trajectories leave the neighbourhood and go to a widely different place. In contrast, when the Hopf bifurcation is supercritical (or *non-catastrophic*), the trajectories go to a small limit cycle around the equilibrium that has lost its stability, i.e., they remain in the neighbourhood.

The Brusselator model has a supercritical Hopf bifurcation, which appears to be more common in relatively simple models. The analytic tools that distinguish the two types of the Hopf bifurcation are rather complicated, but one can solve the differential equations numerically and see whether a small stable limit cycle appears when the equilibrium becomes unstable.

Exercise 58. Suppose that we add a catalyst to the Brusselator reaction that speeds up the removal of X in the last reaction, i.e., increases the reaction speed constant k_4. To explore the possible consequences, perform a bifurcation analysis of the Brusselator model with respect to k_4. Extend the analysis to include β as well as k_4 as bifurcation parameters, and construct a bifurcation diagram akin to Figure 17 with fixed parameters $k_3 = 1$ and $\alpha = 1$.

Exercise 59. Increasing temperature speeds up chemical reactions. Although in reality different reactions may respond differently to changes in temperature, assume now that in the Brusselator, all reaction speed constants (k_1, k_2, k_3, k_4) increase by the same factor (e.g. double). Can this change in the parameters lead to a bifurcation? Explain why or why not.

Exercise 60. Which type of bifurcation can explain the change the cell cycle model exhibits between Figures 15a and 15b?

6.2 Predator-prey dynamics

This section investigates one of the most famous ecological models for the joint dynamics of a prey species and its specialist predator. Suppose that in absence of the predator, the prey population follows the logistic model of population growth (see section 3.4 of Part 1):

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

This prey population is exploited by a predator with Holling II functional response. The Holling type II functional response means that each predator captures $\frac{\beta N}{1+\beta TN}$ prey individuals per unit of time, where β is the capture rate of searching predators and T is the handling time the predator spends eating and digesting an individual prey. The formula of the Holling type II functional response was derived in section 1.2 of Part 1. With P predators present, the total number of prey killed is $P \cdot \frac{\beta N}{1+\beta TN}$ per unit time, so that the prey dynamics becomes

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - \frac{\beta N}{1+\beta TN}P$$

In section 3.8 of Part 1, we investigated this model assuming that the predator population size, P, is constant. This assumption approximates the situation when the predator is a generalist that consumes a great variety of prey, so that the one prey species our model focuses on does not influence the number of predators appreciably. In contrast, here we shall consider a specialist predator, which depends on the single prey our model includes. We assume that the predator converts the consumed prey into predator offspring, such that from the $\frac{\beta N}{1+\beta TN}$ prey eaten by one predator per unit time, there are $\gamma \cdot \frac{\beta N}{1+\beta TN}$ new predators born (γ is a conversion factor that shows how many offspring can be produced from one prey eaten). For simplicity, the death rate of the predator, δ, is assumed to be

constant (although in reality, it would also depend on how much prey the predator can consume). With these assumptions, the joint dynamics of the prey and the predator are given by

$$\frac{dN}{dt} = rN\left(1-\frac{N}{K}\right) - \frac{\beta N}{1+\beta T N}P \tag{32a}$$

$$\frac{dP}{dt} = \gamma\frac{\beta N}{1+\beta T N}P - \delta P \tag{32b}$$

This model is known as the *Rosenzweig-MacArthur* model of predator-prey dynamics.

6.2.1 Scaling (or nondimensionalization)

The Rosenzweig-MacArthur model has six model parameters $(r, K, \beta, T, \gamma, \delta)$ — quite many. Obvipusly, it is easier to understand how the behaviour of a model depends on its parameters if the number of parameters is small. It is therefore of interest to see how we can reduce the number of parameters without compromising the generality of the model. This is possible using a technique called *scaling* the model variables and parameters.

Let us start with the size of the prey population, N. We can measure N as the number of individuals; for example, we may have $N = 1200$ individuals. But we can also express the same population size in dozens of individuals, and having $N = 100$ dozens means exactly the same as having $N = 1200$ individuals. Or we may count prey in units of 100 individuals, in which case the size of the same population is $N = 12$ units. Since K is the equilibrium population size of the logistic model, K must be measured in the same units what we use for N. Hence if $K = 2400$ individuals, but we want to count the prey in dozens rather than in individuals, then we must use $K = 200$ dozens[11].

The freedom of choosing the unit to measure prey population size gives a neat possibility: we may decide to measure prey density in units of K. This means that if in our model the carrying capacity is $K = 2400$ individuals, then we decide that we count the prey population in units of 2400 individuals (1 unit = 2400 individuals), and instead of writing $N = 1200$ individuals, we write $N = 0.5$ units, which is the same. We must express K also in the unit of 2400 individuals, which means that $K = 1$ unit. This was the goal of the exercise: by choosing the appropriate unit, we can achieve that the numerical value of K is 1. This we can always do, whatever the original value of K is, provided that it is positive (which is of course the only biologically relevant case); zero would remain zero in any unit and changing units would not make a negative parameter positive. The usual phrase to refer to this procedure is to say that "without loss of generality, we set $K = 1$". "Without loss of generality" emphasises that we have not made a particular assumption

[11] Strictly speaking, N is population density, i.e., the number of individuals per unit area. However, if the area occupied by the population is fixed, then total population size (= density × area) is simply proportional to population density.

about the magnitude of K, just chose the units such that its numerical value is 1. With $K = 1$, we can rewrite equation (32a) as

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

which does not contain K as a free parameter, i.e., it has one parameter less.

To see which parameters we may set to 1 without loss of generality (i.e., via a clever choice of units), it is useful to start with a list all parameters in equations (32a,b) with their units (or "dimensions"). From equation (32a), it is easy to see that N and K must have the same units, because N/K must be a unitless ("dimensionless") number to be subtracted from the (unitless) number 1. (Adding or subtracting quantities with different units would of course be like adding apples and oranges.) To figure out what is the unit of the parameter r, note that the left hand side of equation (32a), dN/dt, is in units of prey population size per time. Hence the term $rN\left(1 - \frac{N}{K}\right)$ must also be measured in units of prey population size per time. The expression in the parenthesis is unitless; N is in units of prey population size; and this leaves r to be in units 1/time (for example, 1/day) in order to match the units of the left hand sise. Proceeding analogously, we arrive at the following list of parameters:

r	1/time
K	prey population size
β	1/(time $\times$ predator population size)
T	time $\times$ predator population size/prey population size
γ	predator population size/prey population size
δ	1/time

Exercise 61. Verify the above list.

We have seen above that by choosing the appropriate unit of prey population size, we can set $K = 1$ without loss of generality. In the same way, we can choose the time unit so that $r = 1$ is set without loss of generality (assuming only that r is positive). For example if $r = 12$/day, then let 2 hours be the time unit (1 unit = 2h), and using this unit, we have $r = 1$/unit time. By now, we have decided which prey population size and time units we want to use. The only remaining unit to choose is the unit of predator population size; and by choosing this appropriately, we can set one of those parameters equal 1 that contain predator population size and are positive (i.e., one of β, γ or T). Here I assume that β is positive (otherwise the predator could not reproduce at all) and set $\beta = 1$. With this, all units are fixed and the remaining parameters cannot be eliminated.

In summary, the Rosenzweig-MacArthur model in equations (32a,b) with positive r, K and β can be simplified by setting $r = 1, K = 1$ and $\beta = 1$ without loss of generality,

which yields the scaled model equations[12]

$$\begin{aligned}\frac{dN}{dt} &= N(1-N) - \frac{NP}{1+TN} \\ \frac{dP}{dt} &= \frac{\gamma NP}{1+TN} - \delta P\end{aligned}$$

These equations contain only three parameters (T, γ, δ), and are fully equivalent to the original equations with positive r, K and β, only the units of measurements have been changed. Therefore the variables and the remaining parameters must be expressed in the new units: for example if $\delta = 0.6$/day, but we have decided to use 2h as the time unit so as to achieve $r = 1$, then we must use the numerical value $\delta = 0.05$, since 0.05/2h is the same as 0.6/day.

6.2.2 Analysis of the Rosenzweig-MacArthur model

Here we proceed with the analysis of the Rosenzweig-MacArthur model in equations (32) assuming $r = 1, K = 1$ and $\beta = 1$ without loss of generality (as explained in the previous section), i.e., using the equations

$$\frac{dN}{dt} = N(1-N) - \frac{NP}{1+TN} \tag{33a}$$

$$\frac{dP}{dt} = \frac{\gamma NP}{1+TN} - \delta P \tag{33b}$$

As a first step, we perform the phase plane analysis of this model.

Exercise 62. Let us draw the phase plane such that N is on the horizontal axis and P is on the vertical axis.

(a) Confirm that

(i) the N-isoclines are the vertical axis and an "upside down" parabola with zeros at $N = -\frac{1}{T}$ and at $N = 1$;

(ii) the P-isoclines are the horizontal axis and a vertical line at $N = \frac{\delta}{\gamma - \delta T}$.

(b) Confirm that the arrows are shown correctly in Figure 18.

[12] These equations are also called *nondimensionalized* equations, loosely speaking because the freedom of choosing the units ("dimensions") has been exchanged for setting some parameters equal to 1. This in effect removes all units (or dimensions) from the model. Here the word "dimension" is a synonym of "unit", and does not refer to the number of variables or to the number of axes of the coordinate system where the trajectories are drawn.

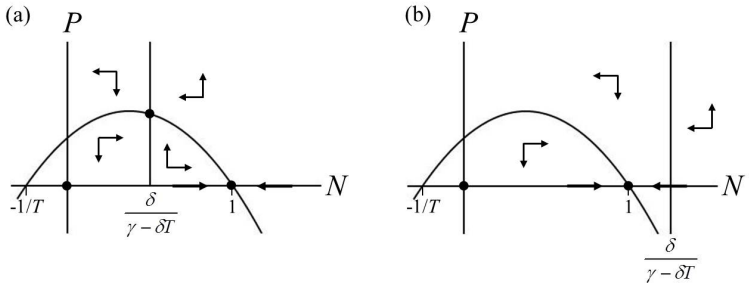


Figure 18: Phase plane analysis of the Rosenzweig-MacArthur model. Dots denote equilibria irrespective of their stability. Parameter values: $r = 1$, $K = 1$ and $\beta = 1$ from scaling (see section 6.2.1); $T = 4$, $\gamma = 0.6$ and (a) $\delta = 0.1$, (b) $\delta = 0.125$.

The model has three equilibrium points:

- the trivial equilibrium $\hat{N} = 0$, $\hat{P} = 0$;
- the prey-only equilibrium $\hat{N} = 1$, $\hat{P} = 0$ (recall that $K = 1$);
- the coexistence equilibrium $\hat{N} = \frac{\delta}{\gamma - \delta T}$, $\hat{P} = (1 - \hat{N})(1 + T\hat{N})$.

Exercise 63. Investigate the equilibria and their stability. In particular,

(a) Verify $\hat{N}$ and $\hat{P}$ at the coexistence equilibrium, and show that these are positive if $\gamma > \delta(1 + T)$.

(b) Show that the trivial equilibrium is always unstable. (This is because we have assumed that r is positive.)

(c) Show that the prey-only equilibrium is unstable (and therefore the predator is viable) if $\gamma > \delta(1 + T)$. This is the same condition as in (a), and therefore the predator is viable precisely when there is a biologically meaningful coexistence equilibrium.

(d) Calculate the Jacobian matrix at the coexistence equilibrium and show that its determinant is always positive (when the equilibrium is positive). Show that the trace of the Jacobian is negative, and therefore the coexistence equilibrium is stable, if $\delta > \gamma \frac{T-1}{T(1+T)}$.

With the help of the results obtained in exercises 62 and 63, we perform a bifurcation analysis of the Rosenzweig-MacArthur model using δ, the predator death rate, as bifurcation parameter. In Figure 18, changing δ influences only the position of the predator isocline (i.e., the vertical isocline). Suppose first that δ is very large ($\delta > \frac{\gamma}{T}$). In this case $\frac{\delta}{\gamma - \delta T}$, the position of the vertical isocline, is negative, so that no predator isocline appears in the biologically relevant positive part of the phase plane. For somewhat smaller but still large values of δ, the denominator of $\frac{\delta}{\gamma - \delta T}$ is a small positive number, so that the vertical isocline appears at the far right as in Figure 18b. In either case, the predator goes extinct (draw trajectories in Figure 18b).

Exercise 64. Show that $\frac{\delta}{\gamma-\delta T}$ decreases with decreasing δ, i.e., in Figure 18, the predator isocline (the vertical isocline) moves to the left as the predator death rate decreases. Show also that $\frac{\delta}{\gamma-\delta T} = 1$, i.e., the predator isocline crosses the prey-only equilibrium at $N = 1$, when $\delta = \frac{\gamma}{1+T}$.

Exercise 64 shows that starting with a high predator death rate and decreasing δ gradually, an important change occurs at $\delta = \frac{\gamma}{1+T}$. When $\delta > \frac{\gamma}{1+T}$, then the N- and P-isoclines do not intersect in the positive part of the phase plane, hence there is no biologically meaningful coexistence equilibrium, and, by exercise 63(c), the predator is not viable; but when $\delta < \frac{\gamma}{1+T}$, then there is a coexistence equilibrium and the predator is viable. When $\delta < \frac{\gamma}{1+T}$ holds but just barely (i.e., shortly after the coexistence equilibrium appears), then this inequality will reverse if we multiply the right hand side with a number less than 1. Since $\frac{T-1}{T}$ is less than 1, we have that $\delta > \frac{\gamma}{1+T}\frac{T-1}{T}$, which, by exercise 63(d), means that the coexistence equilibrium is stable when it appears.

Figure 19 shows the neighbourghood of the prey-only equilibrium for δ slightly below, at, and above the critical value $\delta = \frac{\gamma}{1+T}$. For mathematical completeness, also negative values of P are shown in this figure (the horizontal line is the N-axis). As δ decreases (i.e., from right to left), a negative equilibrium crosses the prey-only equilibrium and enters the positive part of the figure as a coexistence equilibrium; and at the moment of crossing, the two equilibria exchange stability such that when the coexistence equilibrium moves into the positive part, the prey-only equilibrium becomes unstable (cf. exercise 63(c)) and the coexistence equilibrium is stable. This is the two-dimensional version of the *transcritical bifurcation* we have seen in section 2, Figure 1 (and also in section 3.7 of Part 1).

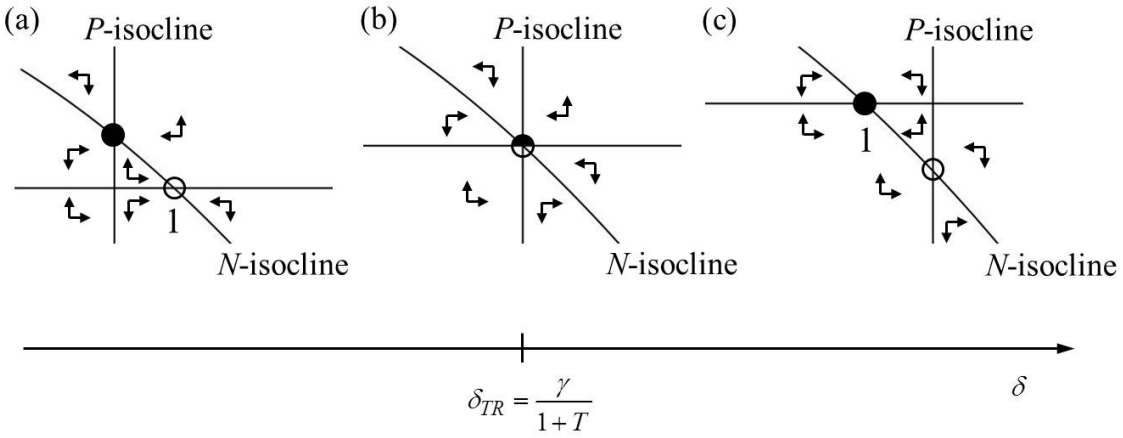
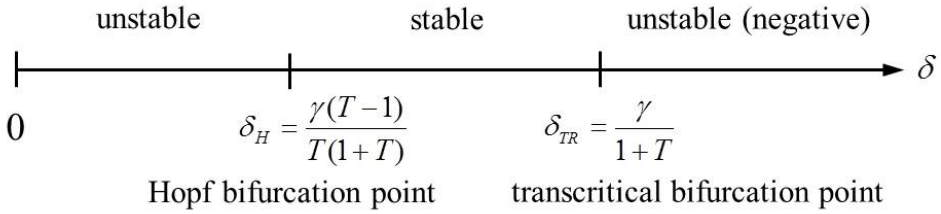


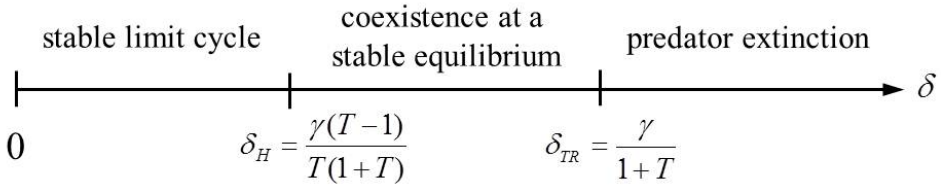
Figure 19: Transcritical bifurcation in two dimensions. Filled dots are stable equilibria, empty circles denote unstable equilibria. δ increases from (a) to (c). At the transcritical bifurcation point δ_{TR}, the only equilibrium is unstable towards negative values of the variables, but all trajectories starting in the positive part converge to the equilibrium on the horizontal axis.

The transcritical bifurcation explains the change in the stability of the prey-only equilibrium found in exercise 63(c). Part (d) of the same exercise shows that the coexistence equilibrium loses its stability when δ dips below $\gamma\frac{T-1}{T(1+T)}$. At this point, the trace of the Jacobian changes its sign while the determinant is positive, hence a Hopf bifurcation occurs (cf. section 6.1). Naturally, $\delta < \gamma\frac{T-1}{T(1+T)}$ is possible only if the right hand side of this inequality is positive, i.e., if $T > 1$. Therefore the Rosenzweig-MacArthur model exhibits a Hopf bifurcation only if T, the handling time of the predator, is sufficiently large. The full bifurcation diagram of the coexistence equilibrium for $T > 1$ is therefore as follows:



whereas for $T < 1$, the Hopf bifurcation point is not in the positive range of δ.

For $\delta < \gamma\frac{T-1}{T(1+T)}$, all equilibria are unstable, and the trajectories converge to a stable limit cycle. This limit cycle is born at the Hopf bifurcation (see section 6.1). Figure 20 shows the dynamics for two values of δ on either side of the Hopf bifurcation point $\delta_H = \gamma\frac{T-1}{T(1+T)}$; for δ above this threshold the trajectory converges to the stable coexistence equilibrium (Figure 20a), whereas for δ below the bifurcation point the model exhibits a limit cycle (Figure 20b). We can thus summarize the predictions made for the Rosenzweig-MacArthur model as the following diagram shows:



Exercise 65. As Figure 19 shows, the coexistence equilibrium is a stable node when δ is only slightly below the transcritical bifurcation point δ_{TR}; but for the Hopf bifurcation to happen, it must be a stable focus when δ is only slightly above δ_H. Hence between the two bifurcation points, the coexistence equilibrium changes between a stable node and a stable focus. Find out at which value of δ this happens when the other parameters are as in Figure 20. (This is not a bifurcation point because the stability of the equilibrium does not change.)

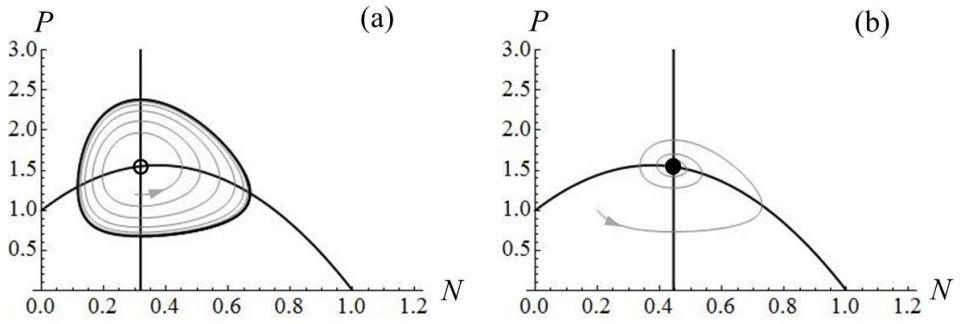


Figure 20: The dynamics of the Rosenzweig-MacArthur model with parameters $r = 1, K = 1, \beta = 1, T = 4, \gamma = 5$ and (a) $\delta = 0.7$, (b) $\delta = 0.8$. Thick lines show the isoclines (cf. Figure 18) and the limit cycle, the empty circle and the filled dot indicate the unstable and stable coexistence equilibria, respectively.

Exercise 66. Show that the Hopf bifurcation occurs precisely when the vertical predator isocline intersects the parabola of the prey isocline at its top. Hence the predator-prey system settles at a stable equilibrium when the predator isocline is to the right of the maximum of the parabola, so that the prey isocline intersects the predator isocline with a negative slope; and the system has an unstable equilibrium and a stable limit cycle when the predator isocline is to the left of the maximum, so that the prey isocline intersects the predator isocline with a positive slope (cf. Figure 20). (This relationship between the slope of the prey isocline at the equilibrium and the stability of the equilibrium holds also for other predator-prey models where the *per capita* growth rate of the predator depends only on the prey, and therefore the predator isocline is vertical.)

Exercise 67. Figure 18 was drawn with $T > 1$. Redraw this figure for $T < 1$, when a Hopf bifurcation is not possible. (Exercise 66 shows how one can see in the phase plane analysis of the Rosenzweig-MacArthur model whether the coexistence equilibrium is stable, or whether it can undergo a Hopf bifurcation.)

Exercise 68. What outcome do you predict of the Rosenzweig-MacArthur model for parameters $r = 1, K = 1, \beta = 1, T = 3, \delta = 0.1$ and (i) $\gamma = 0.55$; (ii) $\gamma = 0.62$? Solve the differential equations numerically with these parameters, and plot the trajectories on the phase plane together with the isoclines. Next, investigate what happens if you gradually increase γ from 0.55 to 0.62 and beyond.

Exercise 69. Draw a 2-dimensional bifurcation diagram of the Rosenzweig-MacArthur model using γ and δ as bifurcation parameters for $T = 4$.

Exercise 70. Analyze the Rosenzweig-MacArthur model with T as bifurcation parameter.

Exercise 71. *A predator-prey model with linear functional response.* A predator-prey model simpler than the Rosenzweig-MacArthur model assumes that the number of prey captured by a predator per unit time is simply proportional to prey density, i.e., the functional response is the linear function βN. With a logistic prey, this yields the model

$$\begin{aligned} \frac{dN}{dt} &= rN\left(1-\frac{N}{K}\right)-\beta NP \\ \frac{dP}{dt} &= \gamma\beta NP-\delta P \end{aligned}$$

where the notation is analogous to the one used in the Rosenzweig-MacArthur model in section 6.2. Scale out as many parameters as possible, and perform the full bifurcation analysis with respect to all remaining parameters. (A special case of this model was treated in exercise 39.)

6.3 Competition with Allee effect

The logistic model of population growth

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

may be derived from assuming that each individual reproduces at a constant rate b and dies at a density-dependent rate $\delta + cN$. Indeed, since population growth is given by the difference between the number of births and the number of deaths, we have

$$\frac{dN}{dt} = bN-(\delta+cN)N = [b-\delta-cN]\,N \tag{34}$$

which is the same as the logistic model with $r = b-\delta$ and $K = (b-\delta)/c$.

Exercise 72. Show that this last statement is true.

The density-dependent death rate may be the consequence of resource depletion; the more individuals are competing for the resources, the less resource each individual can get, so that each individual has a higher death rate due to the lack of necessary resources. Alternatively, the density-dependent death rate may be interpreted as the consequence of aggressive interactions. If individuals encounter each other randomly according to mass action, then the number of opponents encountered per unit time is proportional to N; and if a fixed fraction of these encounters ends with death, then each individual faces a death rate cN in addition to a background mortality δ due to causes other than aggression. In equation (34), the difference between the birth and the death rate, $[b-\delta-cN]$,

is the *per capita* rate of population growth (such that population growth is N times the *per capita* growth). In the logistic model, the *per capita* rate of growth is the highest when population density is the smallest, either because at low population density each individual gets plenty of resources, or because they face little risk from aggression. It is a basic feature of the logistic model that the *per capita* growth rate always decreases with population density (and that this decrease is linear).

In reality, however, individuals of a low-density population may not enjoy the best possible circumstances. The most obvious problem they face is that it may be difficult to find mates, and therefore their birth rate may be low compared to the birth rate in more dense populations. The individuals of a low-density population may also suffer from the lack of shared vigilance and defence against predators as well as the lack of other social interactions, which means that their birth rate is lower and/or death rate is higher than it would be in a somewhat more dense population. The mechanisms that make the *per capita* growth rate low at low population densities are collectively called *Allee effects*.

To incorporate an Allee effect into the dynamics of the population, here we assume that the birth rate increases with increasing population density, e.g. because it is easier to find mates when more individuals are around. However, a female cannot produce an arbitrarily large number of offspring even if finding mates is no problem. Hence we need a birth rate function that increases with population density but also saturates with increasing density, such that it does not get higher than a certain value. The hyperbolic function

$$b(N) = \frac{\beta N}{a + N} \tag{35}$$

will serve this purpose well.

Exercise 73. Figure 21 shows the density-dependent birth rate function given in equation (35). Verify that the saturation value is indeed β.

Incorporating the density-dependent birth rate into equation (34), we arrive at the model

$$\frac{dN}{dt} = \left[\frac{\beta N}{a + N} - \delta - cN\right] N \tag{36}$$

Exercise 74. Show that next to the trivial equilibrium $\hat{N} = 0$, the model in equation (36) has two positive equilibria if $\beta > ca + 2\sqrt{ca\delta} + \delta$ and no positive equilibrium if the opposite of this inequality holds. Moreover, show that when the model does have two positive equilibria, then the smaller of these is unstable and the larger is stable. *Hint:* check the stability of the trivial equilibrium and use that in one-dimensional models, stable and unstable equilibria alternate (see section 3.5 of Part 1).

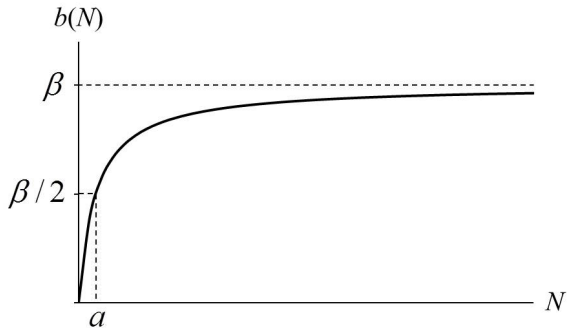


Figure 21: The density-dependent birth rate given in equation (35). When $N = 0$, mating is impossible and hence the birth rate is zero. The birth rate saturates with increasing population density, and for sufficiently large values of N, the birth rate is approximately constant (limited by the capacity of the female to produce eggs, not by the availability of mates).

Next, we extend this model for competition between two species. For simplicity, we assume that only the first species is affected by the Allee-effect, and the second species has a constant *per capita* birth rate. This leads to the two-species model

$$\frac{dN_1}{dt} = \left[\frac{\beta N_1}{a + N_1} - \delta_1 - c_{11}N_1 - c_{12}N_2\right] N_1 \tag{37a}$$

$$\frac{dN_2}{dt} = \left[b - \delta_2 - c_{21}N_1 - c_{22}N_2\right] N_2 \tag{37b}$$

where the coefficients c_{11} and c_{12} describe respectively the effect of species 1 and species 2 on the death rate of species 1, and c_{21} and c_{22} are the same for species 2.

> **Exercise 75.** The competition model in equations (37) is similar to the Lotka-Volterra competition model in exercises 24 and 40, except for the Allee effect in the birth rate of the first species. How do the coefficients c_{11}, c_{12}, c_{21}, c_{22} relate to the coefficients of the equations in exercise 24?

In the analysis below, we shall focus on exploring how the joint dynamics of the competing species given in equations (37) depends on the birth rate of species 2, b. we therefore fix the values of the other parameters as

$$\beta = 8,\ a = 1.5,\ c_{11} = 1,\ c_{12} = 0.5,\ c_{21} = 0.5,\ c_{22} = 1,\ \delta_1 = 1,\ \delta_2 = 1 \tag{38}$$

This choice of parameters ensures that species 1 can persist when species 2 is absent. As exercise 74 has shown, species 1 has two positive equilibria in absence of species 2, an unstable equilibrium that we shall denote with A and a stable equilibrium that we denote with K. If species 2 is absent and the population density of species 1 exceeds the *Allee threshold* given by A, then it will grow until it equilibrates at K. If however the

population density of species 1 is below A, it will die out even in absence of species 2.

First we perform a phase plane analysis. The N_1-isoclines are the vertical axis ($N_1 = 0$) and the curve given by

$$N_2 = \frac{1}{c_{12}} \left(\frac{\beta N_1}{a + N_1} - \delta_1 - c_{11} N_1 \right) \tag{39}$$

This formula is the sum of a saturating function akin to the one in Figure 21 and a linearly decreasing function, and hence it is like the curve in Figure 22. Note that the N_1-isocline must cross the horizontal axis (where species 2 is absent) at the equilibrium points A and K. The N_2-isoclines are the horizontal axis ($N_2 = 0$) and the straight line given by

$$N_2 = \frac{1}{c_{22}} (b - \delta_2 - c_{21} N_1) \tag{40}$$

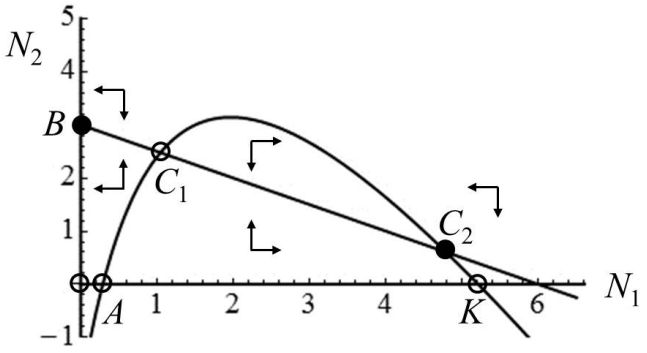


Figure 22: Phase plane analysis of the two-species competition model in equations 37. Filled dots mark stable equilibria, empty circles are unstable equilibria. Parameter values as given in (38) and $b = 4$.

The number of equilibria depend on how the N_1- and N_2-isoclines are placed relative to each other. With the choice of parameters in (38), the straight line of the N_2-isocline is not very steep; and with $b = 4$, its position is such that the isoclines intersect as shown in Figure 22. In this case, the model has six equilibria:

- The trivial equilibrium $\hat{N}_1 = 0$, $\hat{N}_2 = 0$ (no population is present).
- The species 1-only equilibrium A.
- The species 1-only equilibrium K.
- The species 2-only equilibrium marked B in Figure 22.
- The coexistence equilibrium marked C_1 in Figure 22.
- The coexistence equilibrium marked C_2 in Figure 22.

As Figure 22 shows (and as it can be confirmed with local stability analysis), equilibria B and C_2 are stable and the others are unstable. If the initial density of species 1 is large enough but the initial density of species 2 is not too large, i.e., if the trajectory starts under the N_1-isocline, then the two species settle at the stable coexistence equilibrium C_2. If N_1 starts from a low value, or if it becomes small due to strong competition from a large population of species 2, then species 1 goes extinct due to the Allee-effect (which hinders its reproduction at low densities), and the trajectory converges to the species 2-only equilibrium B.

To explore how the behaviour of the model changes with b, we start with the situation in Figure 22 and first gradually increase b (the case of decreasing b is left for exercises 76 and 77). As b increases, the N_2-isocline shifts upward (since the first term in equation (40) increases) and therefore the two coexistence equilibria C_1 and C_2 slide towards each other on the N_1-isocline (which does not depend b). At a critical value of b, the two equilibria collide with each other, and as b increases further, the two equilibria disappear because the isoclines no longer intersect (Figure 23). C_1 is a saddle and C_2 is a stable node before the collision. The collision and disappearance of a saddle and a node is called a *saddle-node* bifurcation. Notice the sudden change in the behaviour of the model: Whereas for b even slightly below the bifurcation point the two species can coexist at a stable equilibrium with $\hat{N}_1$ far from zero (as in Figure 23a), for b slightly above the bifurcation point there is no coexistence equilibrium and species 1 goes extinct (see Figure 23c). The possibility of a saddle-node bifurcation is of obvious importance for management and conservation biology; when a saddle-node bifurcation occurs, then a small change in the environment (harvesing, management policies, climate change, etc.) leads to a large and often catastrophic consequence.

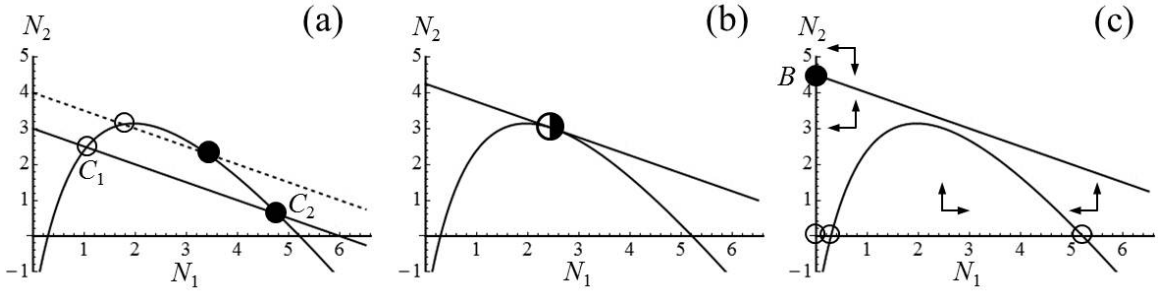


Figure 23: Saddle-node bifurcation in the two-species competition model with an Allee effect. For clarity, only the coexistence equilibria C_1 and C_2 are shown in (a) and (b). Parameter values as given in (38). (a) With increasing b (solid isocline: $b = 4$, dotted isocline: $b = 5$), the coexistence equilibria slide towards each other. (b) At the critical value $b_{SN} = 5.25$, the two coexistence equilibria collide (the subscript SN refers to the saddle-node bifurcation). (c) When b is above its critical value ($b = 5.5$), there are no coexistence equilibria and the only stable equilibrium is the species 2-only equilibrium B.

We can easily determine the critical value b_{SN} where the saddle-node bifurcation happens. Notice in Figure 23b that when $b = b_{SN}$, then the two isoclines are tangent to each other. This means that they have a common point where both equations (39) and (40) hold, so that

$$\frac{1}{c_{12}}\left(\frac{\beta N_1}{a+N_1} - \delta_1 - c_{11}N_1\right) = \frac{1}{c_{22}}(b_{crit} - \delta_2 - c_{21}N_1)$$

and that they have the same slope at the common point, i.e., the derivatives of equations (39) and (40) are equal,

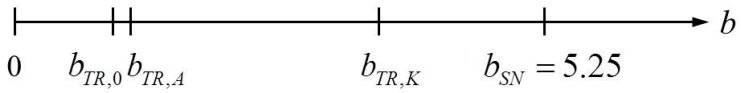
$$\frac{d\left[\frac{1}{c_{12}}\left(\frac{\beta N_1}{a+N_1} - \delta_1 - c_{11}N_1\right)\right]}{dN_1} = \frac{d\left[\frac{1}{c_{22}}(b_{crit} - \delta_2 - c_{21}N_1)\right]}{dN_1}$$

These two equations can be solved for the critical value b_{crit} and N_1, which is the position where the two equilibria collide (the N_2-coordinate can be obtained from substituting the solution into equation (39) or (40)).

Exercise 76. Redraw the isoclines of Figure 22 for gradually decreasing values of b. Investigate the transcritical bifurcations that happen
(i) when C_2 collides with K;
(ii) when C_1 and collides with A;
(iii) when B collides with the trivial equilibrium at the origin.
How does the stability of the equilibria change at these bifurcations?

Exercise 77. For the parameters given in (38), the species 1-only equilibria A and K are at $\hat{N}_A = 0.288$ and $\hat{N}_K = 5.212$, respectively. Determine the critical values $b_{TR,K}$, $b_{TR,A}$ and $b_{TR,0}$ where the transcritical bifurcations (i)-(iii) listed in exercise 76 occur. (You can also confirm the values of $\hat{N}_A$ and $\hat{N}_K$.)

We can summarize the results in the bifurcation diagram



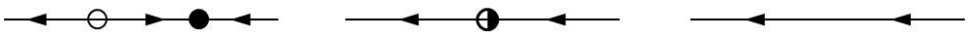
(The value of b_{SN} is from Figure 23, see the small print above for how it can be calculated. $b_{TR,K}$, $b_{TR,A}$ and $b_{TR,0}$ are to be determined in exercise 77.)

Exercise 78. Describe the predictions of the competition model for each interval of b in the above bifurcation diagram. Which species may be present at equilibrium for various values of b?

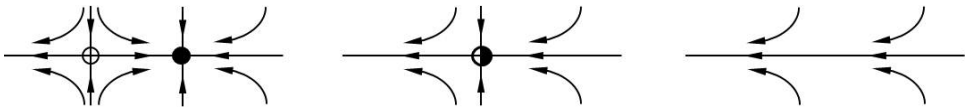
Exercise 79. With the parameter values given in (38), the N_2-isocline is not too steep. Redraw the isoclines when c_{22} is smaller (this makes the N_2-isocline steeper, cf. equation (40)). Use the parameter values as in (38) but $c_{22} = 0.2$, and start with $b = 3$. Investigate the equilibria and their stability based on the phase plane analysis. Next, determine which bifurcations happen by sketching the isoclines for increasing and decreasing b. Why is there no saddle-node bifurcation? Can you determine for which values of c_{22} does a saddle node bifurcation happen when varying b?

Box 3: The saddle-node bifurcation

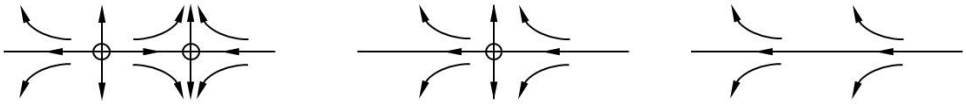
A saddle-node bifurcation occurs when a real eigenvalue becomes zero. This is possible also in models with a single differential equation, where the same bifurcation is referred to as a fold bifurcation (since there are no saddle points in one-dimensional systems). As we have seen in section 3.8 of Part 1, a fold bifurcation means that an unstable and a stable equilibria collide and disappear:



The saddle-node bifurcation is the same in two (or higher) dimensions, where the trajectories approach the equilibria in the other (vertical) direction such that a saddle and a stable node collide and disappear:



or the trajectories diverge in the other direction such that an unstable node and a saddle collide and disappear:



In higher dimensions, the trajectories may approach the equilibria in some directions but diverge in other directions.

The saddle-node bifurcation of a stable node and a saddle (just as the one-dimensional fold bifurcation) is a *catastrophic bifurcation*, which causes a sudden large change in the behaviour of the model: All trajectories that start to the right of the saddle lead to the stable equilibrium before the bifurcation happens, but trajectories starting at the same points leave the neighbourhood and go to some possibly very different endpoint (such as extinction) after the bifurcation.

In a model with two differential equations, a saddle-node bifurcation happens when the determinant of the Jacobian is $Det = 0$, such that the two eigenvalues are $\lambda_{1,2} = \frac{Tr \pm \sqrt{Tr^2 - 4Det}}{2} = \frac{Tr \pm \sqrt{Tr^2}}{2}$. If the trace is negative, then the "+" eigenvalue is zero; and if the trace is positive, then the "−" eigenvalue is zero.

Box 4: The transcritical bifurcation

The transcritical bifurcation may be seen as a special form of the saddle-node bifurcation. As Figure 19 shows, two equilibria collide at the transcritical bifurcation, but they cannot disappear, because one of the equilibria is on the axis; and this trivial equilibrium must always be there in all models that describe a closed system (if a population is absent now, it will always be absent).

To demonstrate the relationship between the transcritical bifurcation and the saddle-node bifurcation in a one-dimensional model (where the saddle-node is actually a fold), consider the harvested logistic model in section 3.7 of Part 1,

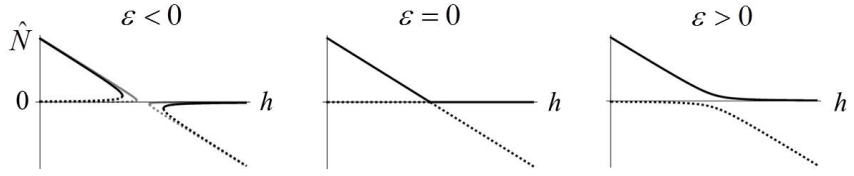
$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - hN$$

where h is the harvesting rate. At $h = 0$ we have the basic logistic model, whereas at large values of h, population growth cannot compensate for harvesting and the population goes extinct. From a mathematical point of view, this equation is special (or "degenerate"), because $\hat{N} = 0$ is always an equilibrium. The general case would be to add a constant ϵ to the right hand side of the equation:

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - hN + \epsilon$$

Biologically, a positive ϵ describes immigration, whereby individuals appear independently of the reproduction of individuals already present (and hence the system is not closed anymore). A negative ϵ readily leads to negative values of N, which is impossible, and therefore the above equation with negative ϵ is not a biologically valid model[a].

The following figures show the equilibria for ϵ slightly below, at, and above zero. With $\epsilon < 0$, there are two fold bifurcations (black lines of the first panel). As ϵ aproaches zero, the two folds approach each other (gray lines in the first panel), and at $\epsilon = 0$, they merge (middle panel). This special case of $\epsilon = 0$ is the transcritical bifurcation. With $\epsilon > 0$, the transcritical bifurcation splits up such that no bifurcation occurs at all; with immigration, the population is never extinct.



[a]One might think that a negative ϵ means the removal of a constant number of individuals per unit time. However, one cannot remove 50 individuals in the next day when only 30 are there, and therefore it is biologically impossible to maintain constant removal at all N.

6.4 Overview of bifurcations

Bifurcation points of equilibria are critical values of a model parameter where the number of equilibria or their stability changes. This happens when one of the eigenvalues of the Jacobian is zero, or the real part of a pair of complex eigenvalues is zero. These are the cases when the local stability analysis cannot determine the dynamics near the equilibrium (see section 4.4). A slight change in a parameter of the model changes the eigenvalues only slightly, and therefore if the real part of an eigenvalue is negative (or positive), then after a sufficiently small change of the parameter it will still be negative (or positive). The qualitative properties of the equilibria can change therefore only at those critical parameter values where an eigenvalue has zero real part.

In models with only two differential equations, the stability of an equilibrium is determined by the sign of the trace and of the determinant of the Jacobian. When a parameter of the model is varied, the trace and the determinant change. Bifurcations happen when the trace or the determinant of the Jacobian becomes zero (Figure 24); a Hopf bifurcation occurs when the trace is zero (see Box 2), and a saddle node or (when the equilibrium is on the axis) a transcritical bifurcation occurs when the determinant is zero.

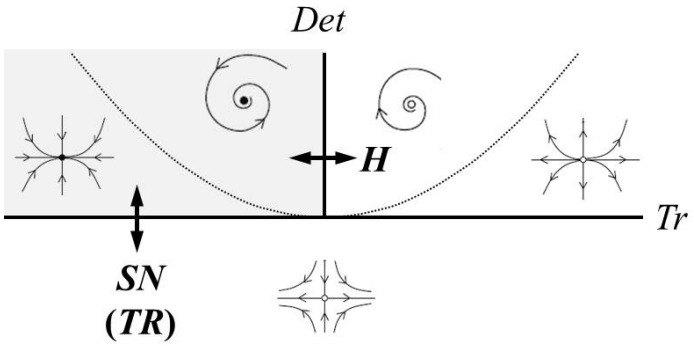


Figure 24: Stability of equilibria in two dimensions shown in terms of the trace and the determinant of the Jacobian (as in Figure 9). Gray shading marks the area where the equilibrium is stable. The system may leave the area of stability to the left (Hopf bifurcation, H) or downwards (saddle-node bifurcation, SN, and, in models of closed systems, also transcritical bifurcation, TR).

Bifurcations that can occur when varying a single model parameter are called *codimension 1* bifurcations. In models of arbitrarily many ordinary differential equations only two types of codimension 1 bifurcations can happen, the Hopf bifurcation and the saddle-node bifurcation. In biological models of closed systems, the transcritical bifurcation is also a codimension 1 bifuraction, although from a pure mathematical point of view it is not. (In the figures of Box 4, the transcritical bifurcation happens at some critical value of h only when $\epsilon = 0$, i.e., two parameters must take critical values; but for biological reasons, the special ase of $\epsilon = 0$ may be the only case of interest, and then a transcritical

bifurcation occurs while varying only one parameter.)

Bifurcations with higher codimension require that several parameters are at critical values simultaneously. In bifurcation diagrams drawn for a single parameter, only codimension 1 bifurcations show up (unless the figure is drawn for an exceptional set of values for the other parameters). In bifurcation diagrams with two parameters, such as in Figure 17, codimension 1 bifurcations correspond to lines; for an arbitrary value of one parameter, there is a critical value of the other (in Figure 17, grey dots show the critical value of parameter β for various values of α). Codimension 2 bifurcations would appear as points in this figure, where both parameters must assume their specific critical values. Codimension 2 bifurcations are useful for understanding how the lines of codimension 1 bifurcations connect to each other.

Limit cycles may also undergo bifurcations. As a parameter is varied, it may happen that a stable and an unstable limit cycle approach each other and finally collide and disappear; this is known as the fold bifurcation of limit cycles (Figure 25a). In more than two dimensions, another possibility is that after a parameter crossed its critical value, the trajectory does not return to the same point after one revolution, but makes another revolution before closing the cycle (period doubling bifurcation, Figure 25b).

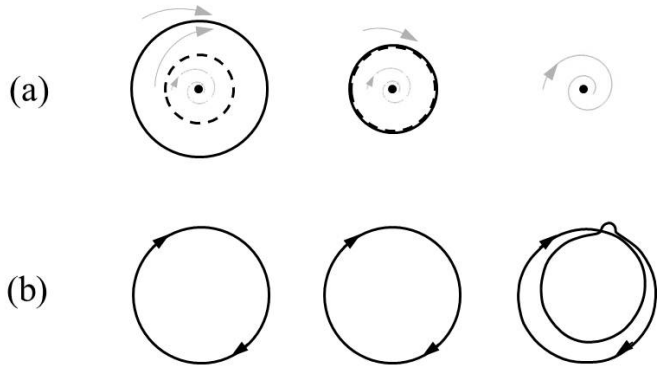


Figure 25: (a) Fold bifurcation of limit cycles. (b) Period-doubling bifurcation of a limit cycle (the "jump" is to denote that the limit cycle does not cross itself, which is possible in 3 and higher dimensions).