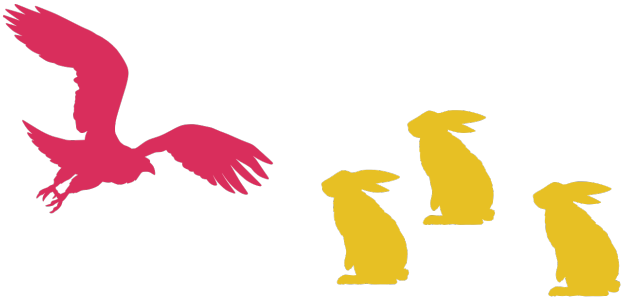
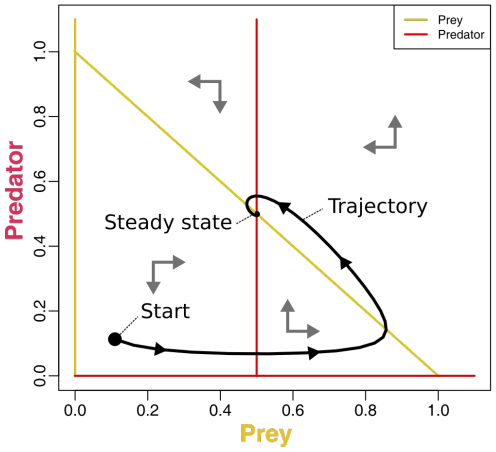
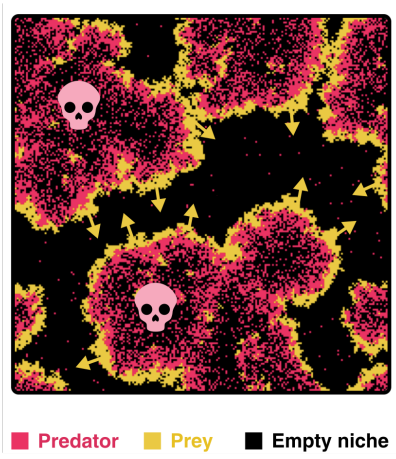
Theoretical Biology

2024







A guide to systems thinking by

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Theoretical Biology & Bioinformatics

Ebook publically available at: https://tbb.bio.uu.nl/bvd/tb.pdf

Preface

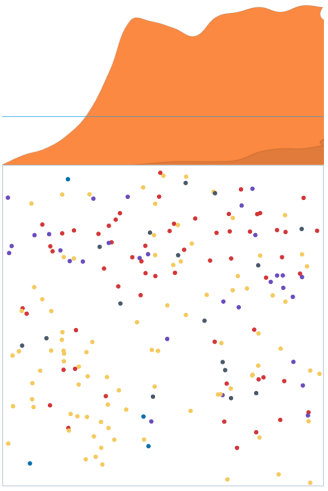
The COVID-19 pandemic – despite already feeling like such a long time ago – has significantly impacted all of our lives. While this time was difficult and confusing for many of us, it has also made some things more clear: *the importance of statistics and modelling in the life sciences*. The critical difference between linear and exponential growth, the reproduction number (R_0), and the impact of distance on the spread of infections have all frequently made the news. These are all components that we can model, that is to say, study them under simplified assumptions as done in the COVID-19 simulation shown below. This is at the core of Theoretical Biology.

During this course, you will learn about simple *mathematical models* describing, for example, the dynamics shown in these simulations. Besides mathematics, you will also dip your toes into simulations, more formally referred to as a *computational model*. By studying these different models, you will grow an intuition on how you expect complex biological systems to behave, without ever setting foot in the lab. The skills you learn in this course should help you to critically assess and interpret numerical data and models, be it on the spread of infections, the level of harvesting a population can undergo without going extinct, or how cardiac arrhythmias arise and can be stopped.

After this course, when you overhear someone say "*one ill person only infects 2 new persons, so how bad can it be?*", or "*exponential functions, who ever needs those?*", or "*biodiversity, why do we care?*", you should be able to give the perfect rebuttal.

I hope you will enjoy this course.

Bram van Dijk



A simple computational model of a spreading infection, and the effects of various measures (hygiene, social distancing, *etc.*). Try it yourself on `lab.kelvinzhao.com/stopit`.

Credits and Feedback

The reader you have before you has a long history. It is worth crediting everyone who has contributed to it over the years. The current reader found its origin many years ago when Paulien Hogeweg first started teaching an introductory course on Theoretical Biology at Utrecht University. When Rob de Boer took over teaching this course this resulted in the first versions of the "Theoretical Biology" reader.

In parallel, Alexander Panfilov developed the complementary reader "Qualitative Analysis of Differential Equations" (Panfilov, 2010), used to teach the mathematical basis of the techniques used in Theoretical Biology. Then, when Kirsten ten Tusscher took over teaching this part of the course she used his reader as a basis, adding chapters about spatial patterns, action potentials in nerve tissues, and much more. Around the same time, Levien van Zon also contributed substantially to the development of the reader.

Now, the Theoretical Biology part of the course will be given by me, Bram van Dijk. As I introduce new material (and leave out other bits), I will without a doubt make mistakes and typos. Feedback from teaching assistants and students is fundamental to the continued improvement of the course materials. I very much appreciate such feedback and suggestions, and I encourage you to send me your remarks. You can do so by sending an email to `b.vandijk@uu.nl`.

I hope you have a great time in this course!

Bram van Dijk

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Chapter 1

Introduction

What is Theoretical Biology?

Why does the abundance of predators and their prey oscillate? If a pathogen is extra deadly, do we need to vaccinate more people? Why do individuals in populations cooperate, rather than taking everything for themselves? How come ecosystem undergo "tipping points", where suddenly everything collapses? Why does social distancing work so well to stop the spread of a disease? How do we know how much we can fish without destroying marine ecosystems? As a biologist, we often ponder such questions, some of which are highly relevant for society. But finding the answers is not always easy. Biological systems are not always intuitive, as our ape-brains did not evolve to comprehend the mind-boggling complexity of nature. In the field of Theoretical Biology, we overcome these challenges by **modelling**: creating and analysing abstract representations of biological systems. If done right, modelling allows us to improve our understanding and therewith make better predictions on how biological systems behave.

This course is meant as an introduction to biological modelling, using simple *mathematical models* and *computational models*. Before I get into that, however, I want to stress one very important thing: **this course is about biology**. Although you will use some basic algebra and learn some computer programming, these are just the tools we will use. Theoretical Biology is as much about palm trees, cats, rats, bats, fungi, butterflies, microbes, DNA, proteins, and cellular physiology, as any other field in biology. The goal is to show you that one can learn a lot about biology by studying *interesting simplifications*.

1.1 Learning objectives

This first chapter serves as an introduction to models in biology. What are models for, how are they conceived, and when is a model "good"? After studying this chapter, you should know about the following learning objectives:

Explain why models are important in biology

Explain what model variables are, and give examples

Explain what model assumptions are, and give examples

Explain what model parameters are

Understand the difference between discrete- and continuous time

Understand the difference between deterministic- and stochastic models

When can we speak of a "good" model?

1.2 What is modelling?

There are many definitions of modelling, but in this course we will stick with the following:

Modelling involves creating and studying useful simplifications of real-world systems

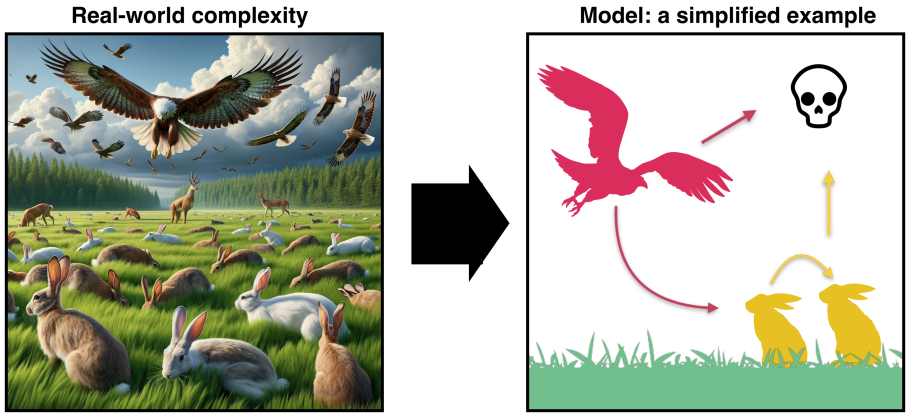


Figure 1.1: Modelling is the art of "leaving things out" and nevertheless learning about biology.

Note that the definition above does not include the words "math" or "computer simulation", and that Fig. 1.1 does not show any equations or computer code. Instead, modelling is about "useful simplifications", and how one can create and study them. Let's unpack those words. To make a simplification, one needs to make **assumptions**: things that are accepted to be true (or true enough) for a given system. For example, if we were to study the interactions between the rabbits and birds of prey in Fig. 1.1, we may safely ignore the deer and trees in the background. Sometimes our assumptions change if our experiments change. For example, bacterial growth in a mixing flask gives

all bacteria equal access to resources, but that same assumption may not hold when bacteria are grown on an agar plate. Another example of an assumption is that all individuals (rabbits, bacteria) are identical, which is not entirely true (individual differences occur) but depending on your research question, may safely be assumed. By being explicit about everything we assume, we can conceive of a simplified "toy" version of our real-world system.

But when is this simplification also "useful"? The answer to that is quite simple: a biological model is useful, if by studying the model, you gain new insights about biology.

1.3 A different model for every scenario

In this course, you will get to know three types of models, all of which make different types of assumptions. These three are by no means the only types of models, but together they cover the majority of models you are likely to encounter in the future. Instead of explaining all the technical details behind these models, let me introduce them to you by giving biologically relevant examples. In all these examples, I will highlight which **variable** are being modelled, and what assumptions are being made.

Scenario A) Enzymatic reactions

Suppose we want to measure the rate at which an enzyme converts a substrate into a product. We add both the substrate and the enzyme into a shaker flask, and wait. Suppose we would want to model the chemical reactions that occur such that we can predict how long we would have to wait for all substrate to be consumed. Because the flask contains millions of substrate molecules and millions of enzymes, it seems unnecessary to model them all individually. Instead, it may be better to choose *concentrations* as our model variable. Next, we have to think about assumptions. Since we keep all other things (temperature, light) constant in the lab, we assume the *reactions happen smoothly* with very little noise, and that there is a very large number of molecules in our flask. We assume the reaction to occur following Michaelis-Menten dynamics: the enzyme binds the substrate and forms a complex, and only then catalyses the reaction into the product. We assume the flask is *well-mixed*, such that the reaction rates are directly proportional to the concentrations of all the components (this is known as a *mass-action* assumption). Since we are thinking in terms of rates (*e.g.* the catalysis rate of the enzyme, k_{cat}), the most fitting modelling strategy for this is using **Ordinary Differential Equations (ODEs)**, where one mathematically describes the speed at which variables change. Because thinking in terms of "rates of change" comes very naturally, ODEs are by far the most common model formalism in biology. With an ODE, you combine the variables of interest (*e.g.* C_{ES}) with simple **parameters** like k_{cat} into an equation. Note that to fully describe the enzymatic reaction, the single equation shown in Fig. 1.2A is not enough, as one should also write an equation for the other variables E, S, and P. We will practice with many types of ODEs throughout the course.

Scenario B) Endangered species

As a second example, let us take something that is not often as smooth as chemical reactions: population dynamics. Especially for endangered species (*e.g.* butterflies), the precise number of

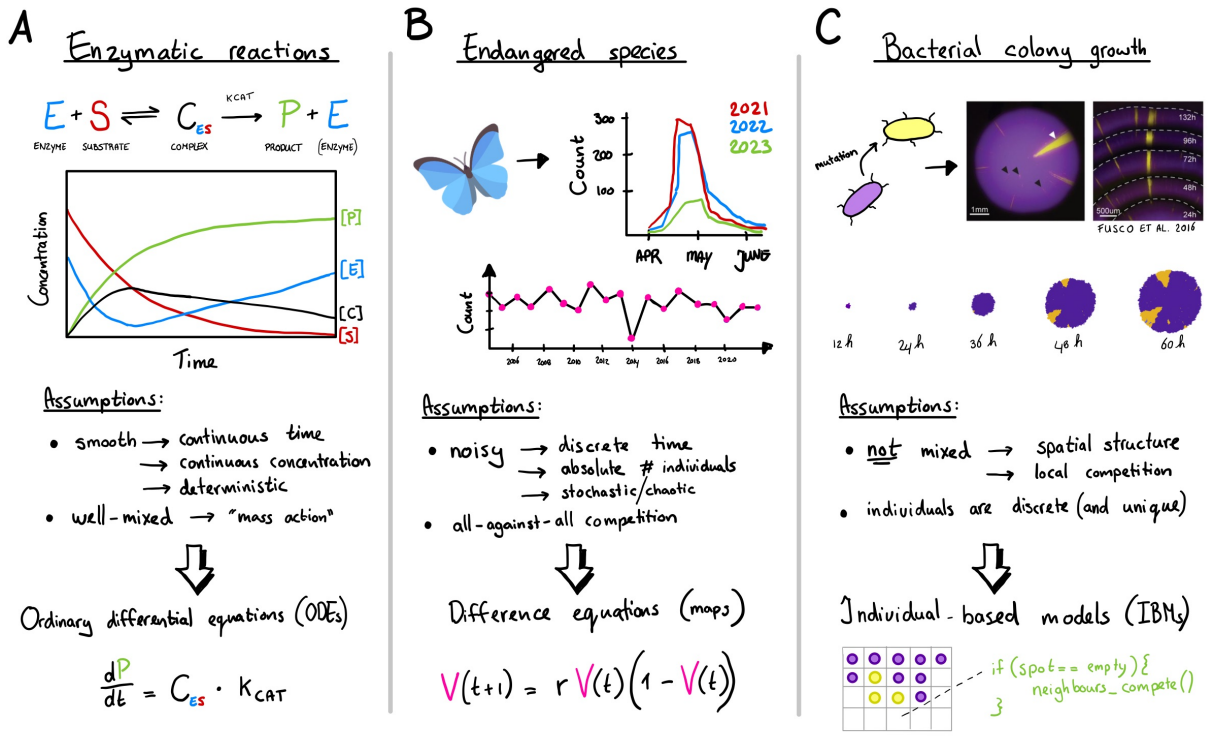


Figure 1.2: Depending on the biological scenario, different types of models can be used

individuals obviously matters a lot! Because of this, it is no longer safe to assume the "concentration" of individuals is a reasonable estimate, because we may need to know when the number will be below some critical threshold. So instead, our model variable will be the *absolute number of individuals*. Because many animals are seasonal (*e.g.* butterflies reproduce in spring), it does not seem necessary to model time as a continuous variable (it would be a waste to model the eggs doing nothing all winter). Instead, we can model it in discrete steps (year 1, year 2, *etc.*). We may also want to introduce some *stochastic events*, such as extremely cold winters that occur at a certain probability. Finally, because butterflies fly and disperse around, let us assume there is *all-against-all competition* (note that this is similar to the aforementioned well-mixed assumption), and that *all butterflies are identical* (no individual differences). Since we are now looking at the absolute numbers and how it differs from one year to the next, we can use simple **difference equations** (often referred to as maps). With this model strategy, we directly "map" how the future population size of butterflies ($V(t+1)$) depends on the current population size ($V(t)$). Just like with ODEs, we can combine our variable (population size) with simple parameters, such as the *intrinstic growth rate* (r) shown in Figure Fig. 1.2B. You will learn more about the intrinsic growth rate and maps in the next chapter, and will also see that this model type does not need noise or extreme winters to see large fluctuations in the population size!

Scenario C) Bacterial colony growth

As a final example, let us look at something quite different. Suppose we are interested in how beneficial mutations spread in a growing bacterial colony. Clearly, the aforementioned *well-mixed assumption* and *all-against-all competition* are a problem. We instead want to learn about the spatial distribution of wild-type bacteria (shown in purple) and its mutants (shown in yellow). Moreover, we may need to assume *individual differences* in growth rates due to access to nutrients (at the edge), and want (beneficial) mutations to be inherited from one individual to the next. For this,

we move away from the mathematical descriptions from scenario A and B, and instead use what is known as **Individual-based models (IBMs)**, sometimes referred to as agent-based models (ABMs). For this, we can simulate discrete entities (individuals) in space, for example by putting them on a grid, and program them to compete locally for nutrients and available space. While the previous models only had abundances or populations sizes as variables, spatially structured models also have the *emergent spatial patterns* as an interesting output variable. In this course, you will get a few examples of models like the one shown in Fig. 1.2C. Although I will not ask you to build these complex models yourselves[1], you should be able to highlight important differences between *spatially structured simulations*, and *mathematical models* that instead assume populations are well-mixed.

1.4 Which model is "good"?

As discussed above, there are many ways to make a model. Perhaps you are inclined to pick the model that most closely approximates reality. Perhaps you don't feel safe to assume butterflies disperse enough to call them "well-mixed", or you want to add more life stages to their growth (egg, caterpillar, *etc.*). However, the more closely you approximate reality, the more complex your model will be. Such a complex model will be increasingly hard to study and may take weeks to compute even on powerful supercomputers. Instead of thinking about the model's realism, let's think about goals. For this, models generally come in two forms: predictive models and exploratory models. With predictive models, the goal is self-explanatory. As long as your model reliably predicts something (*e.g.* a future flu pandemic), the model is good. If your predictions break down, you know you have to go back to the drawing board and revise your model. For exploratory models, however, the goal is not to make predictions, but to study how certain complex processes interact to begin with. The insights gained from such an exploratory "toy" model, may later be applied to make better predictive models, *etc.* In either case, we learn interesting lessons when our model is *wrong*, as it identifies gaps in our knowledge and sends us back to the lab. Thus, models are meant to be wrong.

> "*All models are wrong, but some are useful.*"
> — George P. Box

[1] For this, you can follow one of the advanced Theoretical Biology courses at Utrecht University like Computational Biology

Chapter 2

Population dynamics

Exponential growth, equilibria and stability

In this chapter, I will start illustrating models that describe how population sizes change over time. I will start with the simplest possible model of exponential growth, show how even the simplest model can yield very complex behaviour, and explain the basics of working with Ordinary Differential Equations (ODEs).

2.1 Learning objectives

After studying this chapter you should be able to do all the exercises as well as be able to explain the following:

- What the intrinsic rate of growth (r) represents.
- What a steady state (equilibrium) is.
- Why random fluctuations in population size may not be due to external factors
- How the steady state of an ODE is calculated
- When a steady state is stable or unstable
- When a steady state is trivial or non-trivial
- How the half-life, doubling time, expected life span of a population are calculated
- What the reproduction number (R_0) represents, and why it is so important in epidemiology.

Exponential growth, as we all know from the COVID-19 pandemic, is a very rapid process. If you think you have a good intuition for exponential growth, let's calculate how thick a piece of paper would be if you could fold it 100 times. When asked, most people intuit that this is probably very

thick, perhaps as big as a house or even an entire city! The actual answer is however much, much bigger. Paper is approximately 0.1 mm thick, and every time we fold it this number doubles (0.1, 0.2, 0.4, 0.8, ...). After 100 folds, the thickness would be $0.1 \cdot 2^{100}$ mm. Converted to kilometres, this piece of paper would be $1.27 \cdot 10^{23}$ km thick, which is not much smaller than the observable universe. In other words: the answer is in the order of billions of lightyears. Clearly, our brain is not very good at guessing how even this simple process plays out, and it is fundamental to so many processes in biology! So instead of guessing, let's model this process instead by looking at a story about rabbits that is both funny and tragic.

2.2 Rabbits in Australia

In 1859, Thomas Austin introduced 13 rabbits into Australia, so that he and his friends could hunt them. While rabbits are not native in Australia, the population grew rapidly (see Figure Fig. 2.1). Less than a decade later, Thomas and his friends could no longer keep up, and they were gonna need a lot more help to control the rabbit population! While millions of rabbits were caught or shot in the decades that followed, this did not even leave a dent in the rabbit population. There are now hundreds of millions of rabbits in Australia.

Figure 2.1: Rabbits in Australia

Suppose that we would like to model this exponential growth of rabbits. Where would we start? Which things should we include? As described in Chapter 1, we have to start thinking about what we model (the variable), and what assumptions we are comfortable making. Our variable of interest is the rabbit population size (let's call it R for short), which relies on the independent variable time (let's call this t for short). More formally, we assume R is a function of time, which we can write as R(t). Let's describe the rabbit population's growth by using a simple difference equation (see Chapter 1). For example, if we assume every rabbit gets two offspring and then dies, the population simply doubles every time step. So the equation then becomes:

$$R(t+1) = 2 \cdot R(t) \tag{2.1}$$

Now, we have a simple mathematical function that translates how many rabbits we have now (R(t), the current state) into how many rabbits we have one time step later (R(t+1), the next state). Such a function is aptly called a **next-state function**. If we start with the 13 rabbits released by Thomas

Austin, we can simply apply Equation 2.2 multiple times, e.g. until we have hundreds of millions of rabbits:

$$\begin{aligned} R(0) &= 13 \\ R(1) &= 26 \\ R(2) &= 52 \\ R(3) &= 104 \\ R(4) &= 208 \\ \vdots & \quad \vdots \\ R(24) &= > 100 \text{ million} \end{aligned}$$

After 24 time steps, we see the rabbit population size exceeds 200 million. However, what does this time step even mean? Weeks? Months? Hours? And what if want to take a bigger time step? The latter can simply be done by modifying the number 2 in Equation 2.2 with the number 4, meaning the population size now quadruples every time step (13, 52, 208, *etc.*). Instead of filling in these numbers, we can also replace them with a parameter called r, which stands for the **intrinsic growth rate**:

$$R(t+1) = r \cdot R(t) \tag{2.2}$$

Now that we have this simple model with a simple parameter like r, we could ask ourselves: which value or r would best fit the first wave of the COVID-19 pandemic? Questions like this, and the predictions you can make with this knowledge, will return throughout this course. But for now, let us continue thinking about the rabbit population. While the rabbit population in Australia eventually stabilised, our model does not do that. It would simply continue to yield billions of rabbits, trillions of rabbits, and rapidly the weight of these rabbits would equal the mass of the Earth. Of course, that makes no sense. In reality, the population should at some point be at *carrying capacity*, because the rabbits run out of food or nesting spaces. More formally, we expect the rabbit population to eventually reach a **steady state** or **equilibrium**, where the population size no longer changes. In the next chapter, you will learn how to introduce carrying capacities into simple models, and how to analyse the resulting steady state by using ODEs. For now, however, we will look at a very famous extension of Equation 2.2 that has a built-in carrying capacity:

$$R(t+1) = rR(1-R) \tag{2.3}$$

There are a few things to notice about Equation 2.3. Firstly, notice that I removed the $\cdot$ symbol (the multiplication of r and R is now implicit in rR), and replaced R(t) with R (simply to improve readability, the meaning did not change). Second, notice that when we now calculate the growth rate of 13 rabbits assuming $r = 2$, the equation becomes $2 \cdot 13(1-13) = 26 \cdot -12 = -312$. Obviously, there is no such thing as negative population sizes! Instead, this new model assumes the number of rabbits is a number between 0 and 1. That may appear strange to you, but this is simply a matter of **scaling**. For example, we could define R as "millions of rabbits", meaning that 1 R would be one million rabbits, and 0.3 would be 300.000 rabbits, *etc.*

To get an intuition on how Equation 2.3 will behave, let's look at extreme values of R. If R is really small (close to 0), the term between brackets (1-R) will be equal to 1. This makes the whole equation identical to Equation 2.2, since it would just be $rR \cdot 1$. In other words, small rabbit populations grow

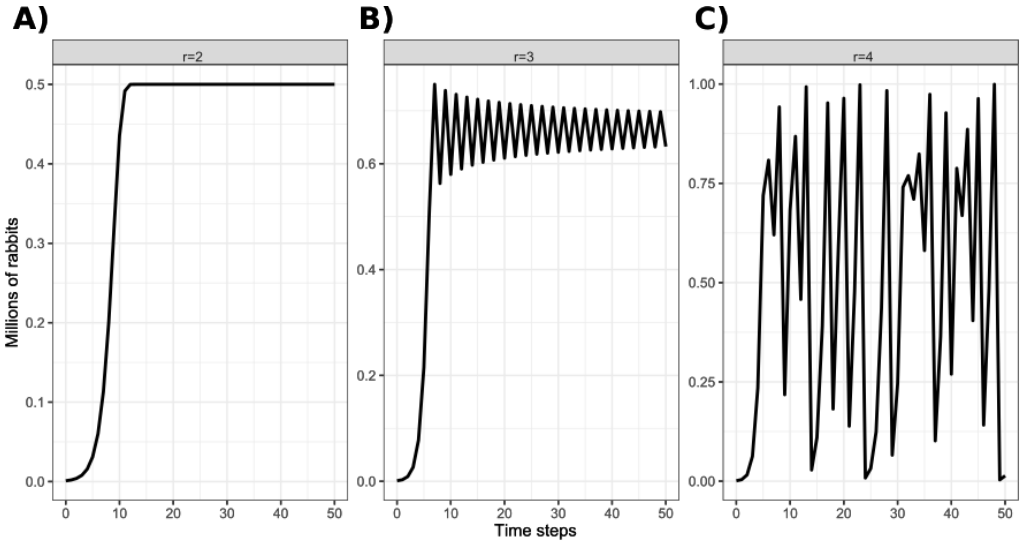


Figure 2.2: Equation 2.3 has very different behaviours depending on r.

exponentially. When R is close to 1, the (1-R) term becomes very small and the population size in the next timestep actually dramatically decreases! Somewhere in between those two scenarios, we would expect the rabbit population to reach a *steady state*. Using a simple computer program, we can calculate how Equation 2.3 behaves for various values of r. Indeed, starting from very small population sizes of rabbits (0.001), the population reaches a stable equilibrium when $r = 2$ (Fig. 2.2A). Indeed, when $R(t) = 0.5$, $R(t + 1)$ equals $0.5 \cdot 2 \cdot (1 - 0.5) = 0.5$. In other words $R(t) = R(t+1)$, so there is a stable equilibrium. However, the population size keeps over- and undershooting when $r = 3$ (Fig. 2.2B). What's more, the dynamics look extremely random (stochastic) when $r = 4$ (Fig. 2.2C), while we did not introduce any randomness in our model! Instead, the behaviour shown here is known as **deterministic chaos**, which almost looks random and is really sensitive to the initial conditions (like the weather in the Netherlands ;D). The deterministic chaos found in this simple model illustrates an important function of models: to reshape our intuition. While we initially concluded in Chapter 1 that the fluctuations in the butterfly population size had to be due to extreme winters or other external factors, analysing 2.3 has revealed that external factors are not the only explanation for this phenomenon.

Although the chaos shown from Equation 2.3 is interesting, it is an extremely simple model of butterfly population sizes, as it ignores all the subtleties of the caterpillar stage, the competition during the season, the laying of eggs, *etc.* In other words, although mapping the total population size from one season to the next could be described in discrete time steps, a lot of important processes play out more continuously *within* a single season. Interestingly, when these additional processes are introduced into this very simple model, chaos is typically not observed. In other words: perhaps the observed noise in Fig. 1.2B *is* caused by extremely bad winters after all! The truth is, whether or not (some) biological populations are inherently chaotic is not known, and research is still being done to unpack this (Rogers *et al.*, 2022). For the majority of this course, we will work with Ordinary Differential Equations (ODEs) instead of maps, which for simple butterfly populations like the one discussed does not show chaos. This allows us to choose for ourselves whether we include extreme winters, other noisy processes, or ignore these altogether. But perhaps the most important argument for learning to work with ODEs is this: the large majority of models in biology are done with ODEs because they are fairly intuitive and easy to work with. Although the last decade has seen an increase in computational power (which makes all kinds of cool simulations possible, some of which you will see during this course), ODEs remain the bread and butter of Theoretical Biology. Even if you are not a math hero, this course will teach you how to critically evaluate ODEs, find steady states, and

investigate the resulting dynamics.

2.3 Learning the basics of ODEs

In the previous section we have discussed why we (and many other biologists) often work with ODEs to make simple models. This section introduces some basic concepts underlying modelling with differential equations (ODEs). You will become familiar with the notion of a "solution", "steady state", "half-life", "fitness" R_0, and the "expected life span". Concepts like solution and steady state are important because a differential equation describes the **change** of the population size, rather than its **actual size**. We will start with simple models that are convenient for introducing these concepts. The models used later on in the course are more challenging and more interesting from a biological perspective.

The simplest possible model for a huge problem

Consider the amount of plastic, P, floating in the oceans. Since plastic decays very slowly, P increases more or less proportionally with the daily amount of plastic that is dumped into the oceans (let set this parameter to k). Based on this we can write the following simple **differential equation**,

$$\frac{\mathrm{d}P}{\mathrm{d}t} = k \ . \tag{2.4}$$

Formally one should write $\mathrm{d}P(t)/\mathrm{d}t = k$, because P is a function of t, but similar to what we did for maps, we can write P for simplicity. In this ODE, P is the variable that is changing over time, and it is expressed in terms of tons of plastic. Formally, one can say that the **dimension** of P is tons of plastic. The parameter k is a *constant* describing the rate of change of P and has the dimension "tons of plastic per day". A current estimate for the world-wide dumping rate (k) is 8 million tons of plastic per year, i.e., $k = 2.17 \cdot 4$ ton per day. Rather than being constant k has actually been increasing over time, as we have been dumping more and more plastics, but for simplicity we here consider a time period over which k is relatively constant (see question 1.6).

Equation Eq. (2.4) describes that P's derivative with respect to time (*i.e.* its rate of change) is equal to k. You may remember from highschool algebra that the solution of equations is often a value, *e.g.* $x = 5$ or $y = 2x$. The solution to an ODE is not like this, because as discussed above, P is actually $P(t)$: a function of time. So instead, the solution for an ODE is a function (or a set of functions) that satisfies the given ODE. The above equation is simple enough to find a **general solution**:

$$P(t) = P(0) + kt \tag{2.5}$$

Here, $P(0)$ is the amount of plastic that was already in the ocean at the time we started dumping k tons per day. Plotting $P(t)$ over time therefore gives a straight line, intersecting the vertical axis at $P(0)$. The slope of this line is k, which is indeed the derivative defined by Eq. (2.4). Thus, the differential equation Eq. (2.4) describes the *rate of change of the variable*, and the solution of Eq. (2.5) gives the *population size at time* t. Note that even if we specify the value of k without knowing the value of $P(0)$, the population size at a specific time point can not be computed but only be

described as a function $(P(0) + kt)$. Only when we also define the *initial value*, i.e. we specify the value of $P(0) = P_0$, we obtain a **specific solution** to an *initial value problem* allowing us to compute the actual value of P at a timepoint as $P_0 + kt$.

Typically, differential equations are too complicated to find general solutions, and the resulting math can be messy and uninsightful. Moreover, initial values and parameters are not necessarily known, meaning we cannot find a specific solution even if we get a general solution. In this course, we will therefore not focus on integration methods required for obtaining solutions of ODEs. However, having a solution one can easily check it by taking the derivative with respect to time. So let's at least do that for this simple example. The derivative of Eq. (2.5) with respect to time is $\partial_t[P(0)+kt] = k$, which is indeed the right-hand side of Eq. (2.4). Note that if we were to take measures to reduce the amount of plastic that streams into the ocean, we would only need to change the value of the parameter k. The model remains the same.

Decay and half-life

We can increase the realism of the model by incorporating the fact that plastic in the ocean is decaying slowly, *i.e.*, with a very long half-life. While the dumping rate k is independent on the amount of plastic already in the oceans, the total rate of decay should of course depend on the amount of plastic already in the ocean. Defining a rate of decay, d, the model then becomes

$$\frac{\mathrm{d}P}{\mathrm{d}t} = k - dP \tag{2.6}$$

Here, the parameter d defines the rate at which individual plastic molecules decay. Because the equation describes the rate at which P changes, each individual term in the ODE should do the same (we cannot add apples and oranges!). This is why, as above-mentioned, k has dimensions "tons of plastic per day" $(\frac{P}{t})$, such that the first term fits the rates we are trying to describe. However, if the parameter d would also be "tons of plastic per day", the total second term would become $\frac{P}{t} \cdot P = \frac{P^2}{t}$. To correctly transform the second term into "tons of plastic per day", the parameter d has to be "per day", which when multiplied with P becomes "tons of plastic per day". Now both the first and second terms are indeed expressions that describe the rate of change for the amount of plastic.

Notice that Eq. (2.6) does not necessarily have to be about plastic. Biological examples that also fit Eq. (2.6) would be red blood cells produced by the bone marrow, shrimps being washed onto a beach, daily intake of vitamins, and so on. The k parameter then defines the inflow or production, and the d parameter is a death or decay rate.

Although introducing a decay term seems a very simple extension of Eq. (2.4), it is much more difficult to obtain the general solution. Without showing you how to derive it, the solution for Eq. (2.4) is:

$$P(t) = \frac{k}{d}\left(1 - \mathrm{e}^{-dt}\right) + P(0)\mathrm{e}^{-dt} \tag{2.7}$$

We can use this solution to sketch how the amount of plastic (or any biological population) changes over time (Fig. 2.3a). The term on the right corresponds to the exponential loss of the initial value,

$P(0)$. As time progresses, this initial value becomes less and less important, and more important is the combination of influx and decay that is part of the left-hand term. When evaluating the first term at long time scales, *i.e.* if we take time to infinity ($t \to \infty$), the term between brackets $(1 - \mathrm{e}^{-dt})$ will approach one. Then, all that is left is k/d. In other words, if we wait long enough, the two terms approach k/d and 0 respectively. Thus, we can conclude the population eventually approaches a *steady state* or *equilibrium value* k/d. To write this down, we draw a bar above P to express we found the steady state: $\bar{P} = k/d$.

We can conclude from Eq. (2.7) that eventually the amount of plastic in the ocean will stabilise. However, if the decay is very slow, the equilibrium value $\bar{P} = k/d$ will be very high! Furthermore, we ignored the fact that humans dump more and more plastic in the ocean over time, so perhaps it is not safe to assume k is constant! So also *after* you have studied a model it is always important to go back and reconsider if the assumptions you made are actually reasonable.

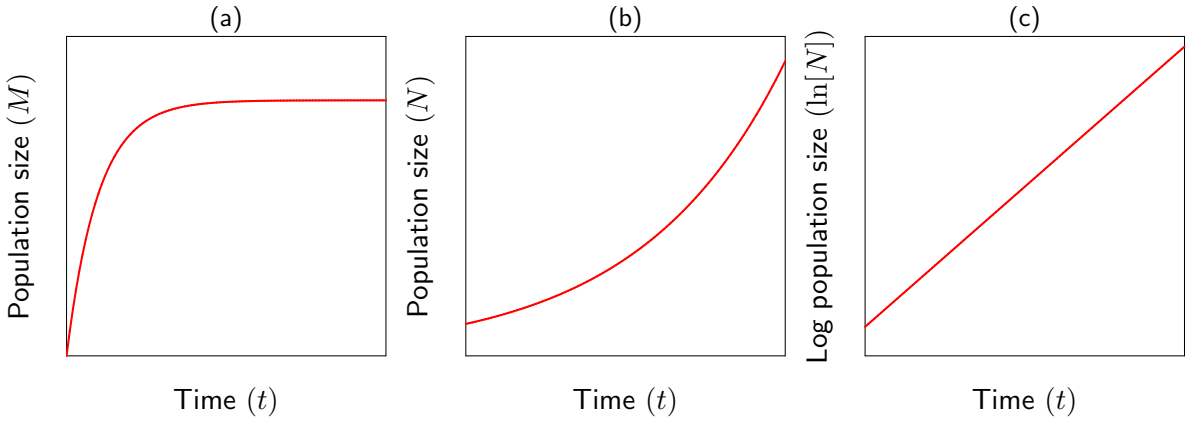


Figure 2.3: Population growth. Panel (a) depicts the solution of Eq. (2.7). Panels (b) and (c) depict exponential growth on a linear and a logarithmic vertical axis, respectively. A differential equation describes the slope of the solution for each value of the variable(s): $\mathrm{d}N/\mathrm{d}t$ is the slope of the $N(t) = N(0)\mathrm{e}^{rt}$ curve for each value of $N(t)$.

The above example of plastic in the ocean illustrates how easy it is to write down an ODE $\mathrm{d}P/\mathrm{d}t = ...$, and how complex the general solution $P(t)$ can nevertheless be. On top of this, there are many ODEs for which the general solution can not be obtained, not even in principle. So, while we often have a pretty good idea of the processes causing an increase or decrease in the variable of interest, *e.g.* dumping and decay affecting the amount of plastic in the oceans, trying to find the solution (functions for which the derivative is equal to the original ODE), is not a good attainable.

Fortunately, we do not always need a solution to understand the behavior of a model. For example, let's remind ourselves what a steady state is: a state where no change occurs. Since an ODE is a description of the rate of change, it is actually pretty easy to find the steady state: it is when this ODE is equal to zero! When we set

$$\frac{\mathrm{d}P}{\mathrm{d}t} = k - dP = 0 \quad \text{and solve this for P, we obtain} \quad \bar{P} = \frac{k}{d}\,. \tag{2.8}$$

Note that this is indeed the same value as obtained above from the general solution when taking $t \to \infty$. In other words: we do not need to solution to know where our system will eventually go!

Note that a steady state also provides some insight in the behaviour of the model. For instance, the steady state $\bar{P} = k/d$ predicts that if we were to half the amount of plastic that we dump in the oceans the world-wide burden of plastic would also half. If we could double the decay rate by using plastics with a shorter half-life, the steady state would also be halved. You may also intuit

that increasing d will shorten the half-life of plastic in the ocean, meaning that $\bar{P}$ will be approached faster.

2.4 Exponential growth and decay

Above we have already used the term half-life, and having the model of Eq. (2.6) we can precisely define what we mean by this. Consider the situation that we completely abandon the usage of plastic, meaning that all that is left to happen is for the current amount of plastic to slowly decay. To study this we do not need to change the model, we just set $k = 0$, to be left with $\mathrm{d}P/\mathrm{d}t = -dP$. This is the famous equation for the exponential decay of radioactive particles, with the almost equally famous solution $P(t) = P(0)\mathrm{e}^{-dt}$, saying that ultimately, *i.e.*, for $t \to \infty$, the amount of plastic, $P(t)$, will approach zero. Plotting the natural logarithm of $P(t)$ as a function of time would give a straight line with slope $-d$ per day (because $\ln[P(0)\mathrm{e}^{-dt}] = \ln[P(0)] + \ln[\mathrm{e}^{-dt}] = \ln[P(0)] - dt$). This exponential decay equation allows us to introduce two important concepts: the half-life and the expected life span.

The **half-life** is defined as *the time it takes to lose half of the initial population*, and can be obtained from the solution of the ODE:

$$\frac{P(0)}{2} = P(0)\mathrm{e}^{-dt} \quad \text{which simplifies into} \quad \frac{1}{2} = \mathrm{e}^{-dt}$$

$$\text{hence,} \quad \ln\frac{1}{2} = -dt \quad \text{so,} \quad \ln(1) - \ln(2) = -dt \quad \text{so,} \quad t = \frac{\ln 2}{d} \tag{2.9}$$

Since $\ln 2 \simeq 0.69$ the half-life is approximately $0.69/d$ days. Note that the dimension is correct: a half-life indeed has dimension time because d is a rate with dimension day^{-1}. The other concept is the **expected life span** which is defined as *the average time it takes before a particle/individual disappears due to turnover/death* and is equal to the inverse of the decay rate. This is like throwing a dice. If the probability to throw a four is $1/6$, the expected waiting time to get a four is six trials. Finally, note that this exponential decay model has only a single steady state, $\bar{P} = 0$: the only way for $\mathrm{d}P/\mathrm{d}t = -dP$ to be zero while $k \neq 0$, is for P itself to be zero. Because this state is approached over the course of time we call this a **stable steady state** or stable equilibrium. A steady state with a population size of zero is often called a **trivial steady state**, because it is not biologically interesting.

The opposite of exponential decay is exponential growth

$$\frac{\mathrm{d}N}{\mathrm{d}t} = rN \quad \text{with the solution} \quad N(t) = N(0)\mathrm{e}^{rt}\,, \tag{2.10}$$

which we have already seen in Chapter 1 for the rabbit example. Once again, r is known as the "intrinsic growth rate", or in non-biological scenarios "the natural rate of increase". The solution can once again be checked: the derivative of $N(0)\mathrm{e}^{rt}$ with respect to t is $rN(0)\mathrm{e}^{rt} = rN(t)$. Biological examples of this equation are the exponential growth of a pathogen in a host, the exponential growth of algae in a lake, the growth of a tumor, and so on. Similar to the half-life defined above, one can define a **doubling time** for populations that are growing exponentially:

$$2N(0) = N(0)\mathrm{e}^{rt} \quad \text{gives} \quad \ln 2 = rt \quad \text{or} \quad t = \ln[2]/r\,. \tag{2.11}$$

Similar to the exponential decay model, we once again only have a single steady state, $\bar{N} = 0$. However, since any small perturbation above $N = 0$ will initiate unlimited growth of the population, we call this an **unstable steady state** or unstable equilibrium.

Above, we have seen examples of unstable steady states, and stable yet trivial steady states. In the next chapter we will see that in populations with density-dependent birth or death rates, where competition effects result in a reduction of population growth at high population levels, stable and non-trivial (non-zero) steady states can emerge.

In replicating biological populations, the intrinsic rate of growth (r) should obviously be a composite of birth and death rates. A more natural way of writing a model for a biological population that grows exponentially therefore is

$$\frac{\mathrm{d}N}{\mathrm{d}t} = (b-d)N \quad \text{with solution} \quad N(t) = N(0)\mathrm{e}^{(b-d)t} \,, \tag{2.12}$$

where b is a birth rate with dimension t^{-1} (meaning per day, per year, or any other unit of time), and d is the death rate with the same dimension. Writing the model with explicit birth and death rates has the advantage that the parameters of the model are strictly positive (i.e. if the death rate exceeds the birth rate r will become negative, but b or d will be positive numbers). Since every individual has a birth rate of b new individuals per unit of time, and has an expected life span of $1/d$ time units, the expected number of offspring of an individual over its entire life span is $R_0 = b/d$. We will use this R_0 as the maximum "fitness" of an individual, i.e., the life-time number of offspring expected under the best possible circumstances. As you have probably noticed in the last years, in epidemiology the R_0 is used for monitoring and predicting the spread of an infectious disease: whenever $R_0 < 1$ a disease will not be able to spread (r is negative) in a population because a single infected host is expected to be replaced by less than one newly infected host (Anderson & May, 1991). Likewise, an infection with $R_0 > 1$ will grow exponentially ((r is positive), since each infected individual generates more then one individual to be infected.

In this book, we will sometimes give solutions of differential equations whenever they are known, but we do not expect you to find these yourselves. If you *do* enjoy integral calculus, you can use textbooks like the one by Adler (1997) for an overview of methods of integration, or use symbolic software like Mathematica to find the explicit solution of some of the differential equations used here. However, I repeat that for most interesting models the solution is not known. We will therefore focus on how to analyse ODEs with simple algebraic steps that any biologist can do!

2.5 Summary

Simple growth models can be written with difference equations (maps) and Ordinary Differential Equations (ODEs). While these models can both describe population dynamics, the results are not necessarily identical. Already when choosing *how* to model biology, we are implicitely making assumptions that determine the dynamics, for example resulting in chaotic behaviour (or not). In this course we will work primarily with ODEs, the bread and butter of Theoretical Biology. ODEs describes the rate of change of a variable, like population size. The *actual* population size is given by the solution of the ODE, which is generally not available. To find the population size one can compute the steady state(s), and/or solve the ODEs numerically on a computer, which gives the model's behavior. Especially when one works with more complex ODEs than the ones shown in this chapter, people typically use a computer. However, some pencil-and-paper tricks are also useful. For example, steady states are found by setting the rate of change to zero, and solving for the actual

population size. Doubling times and half-lives are solved from the solution of the exponential growth (or decay) equation $N(t) = N(0)\mathrm{e}^{rt}$. The fitness, R_0, of a population is the expected number of offspring of one individual over one generation under the best possible circumstances.

2.6 Exercises

Question 2.1. Population doubling
Assume that a population grows according to the following equation:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = 1.5n \ .$$

a. What is the population size at $t = 4$ when the initial size was $n(0) = 30$?
b. How much time does it take for the population to double its size?

Question 2.2. Finding the growth rate
A bacterial population grows exponentially, i.e. the growth of this population N satisfies the differential equation $\frac{dN}{dt} = kN$. The population doubles its size every 20 min. Find the value of k in sec^{-1}.

Question 2.3. Red blood cells
Red blood cells are produced in the bone marrow at a rate of m cells per day. They have a density independent death rate of d per day.
a. Which differential equation from this chapter would be a correct model for the population dynamics of red blood cells?
b. Suppose you donate blood. Sketch your red blood cell count predicted by this model in a time plot.
c. Suppose a sportsman increases his red blood cell count by receiving blood. Sketch a time plot of his red blood cell count.
d. Human red blood cells have an expected life span of $1/d = 120$ days, and per kg of body weight we make about $3 \cdot 10^9$ red blood cells per day. Knowing these parameters , and solving $\mathrm{d}B/\mathrm{d}t = m - dB = 0$, we can compute the normal steady state $\bar{B} = m/d = 3.6 \cdot 10^{11}$ cells per kg. To illustrate that one can numerically solve differential equations once all parameters and the initial condition are known, we provide the following function in the R-script `rbc.R`:

```
change <- function(B, m, d){
  dB <- m- d*B
  return(dB)
}
```

Download this R-script, store it in a folder on your laptop, and open `rbc.R` in RStudio. **Evaluate the script line by line!** Indeed, after setting `m <-3e9;d <-1/120`, calling

```
change(B=m/d, m=m, d=d)
```

returns a zero, because $\mathrm{d}B/\mathrm{d}t = 0$ at this steady state. Next one can perform a very crude form[1]) of numerical integration by calling this function once per day, and adding the change to the current state of $B(t)$. For instance, to study the blood donation of question **b** in a quantitative manner, we define a vector of future B values, `B <-c()`, and set `B[1] <-0.9*m/d` to define a blood donation of 10% of the blood (hence the 0.9 times the steady state value). The number of red blood cells one day later is then calculated as

```
B[2] <- B[1] + change(B=B[1], m=m, d=d)
```

[1]To do this properly numerical integrators for ODEs take small time steps to correctly solve ODEs. Some even compute the best time step to be taken given the rate at which variables change. Later in the course, you will work with the R-script `grind.R` that calls excellent integrators for you.

and so on. Having this function `change()`, one also can perform this integration over a period of 30 days, e.g., **`for`** `(i in 2:31)`, and subsequently, plot the outcome

```
plot(seq(0,30),B, xlab="Time in days", ylab="Number cells")
```

How long does it take to normalize the red blood cell counts after a blood donation? Since the recovery of blood cell numbers is asymptotic, have a look at the time it takes for blood cell numbers to reach $3.5 \cdot 10^{11}$

e. What does it mean for your number of blood cells if you donate blood 4 times a year?

f. In reality you typically donate 500ml of blood rather than a certain percentage of your blood volume. Why do you think women are allowed to donate blood less frequently then men?

Question 2.4. Bacterial growth

Every time you brush your teeth, bacteria enter your blood circulation. Since this a nutritious environment for them they immediately start to grow exponentially. Fortunately, we have neutrophils in our blood that readily kill bacteria upon encountering them. A simple model for what happens to bacteria *after* they enter the bloow, would be:

$$\frac{\mathrm{d}B}{\mathrm{d}t} = rB - kNB \ ,$$

where B and N are the number of bacteria and neutrophils per ml of blood, r is the growth rate of the bacteria (per hour), and k is the rate at which bacteria are killed by neutrophils.

a. What is the doubling time of the bacteria in the absence of neutrophils?

b. Neutrophils are short-lived cells produced in the bone marrow, and chemotherapy can markedly reduce the neutrophil counts in the peripheral blood. What is the critical number of neutrophils that is required to prevent rampant bacterial infections after chemotherapy?

c. What is the dimension of the parameters r and k?

d. The kBN term is called a mass-action term because it is proportional to both the bacterial and the neutrophil densities. A disadvantage of such a term is that each neutrophil is assumed to kill an unrealistically large number of bacteria per hour if the bacterial density becomes very large (do you see this?). Later in the course we will use saturation functions to allow for maximum killing rates per killer cell. An example of such a model would be

$$\frac{\mathrm{d}B}{\mathrm{d}t} = rB - \frac{kNB}{h+B} \ ,$$

where the total number of bacteria killed per hour approaches kN when $B \to \infty$ (do you see this?). What is now the dimension of k? What is the dimenion of h, and how would you interpret this parameter?

e. What is now the critical number of neutrophils that is required to prevent bacterial infections after chemotherapy? Can you sketch this?

Question 2.5. Corona

The figure copied from a Dutch newspaper (NRC Handelsblad 6 February 2021) nicely illustrates the two first peaks of the COVID-19 pandemic in the Netherlands. The daily number of positive corona tests is plotted as a function of time. Although the number of positive tests is coming down in December 2020, due to the Dutch corona measures, epidemiologists predicted a new peak. This was due to the British variant of the coronavirus SARS-CoV-2, which appeared to take over from the 'wild-type' virus, e.g., on 25 January 2021 this British variant was responsible for approximately half of the positive tests.

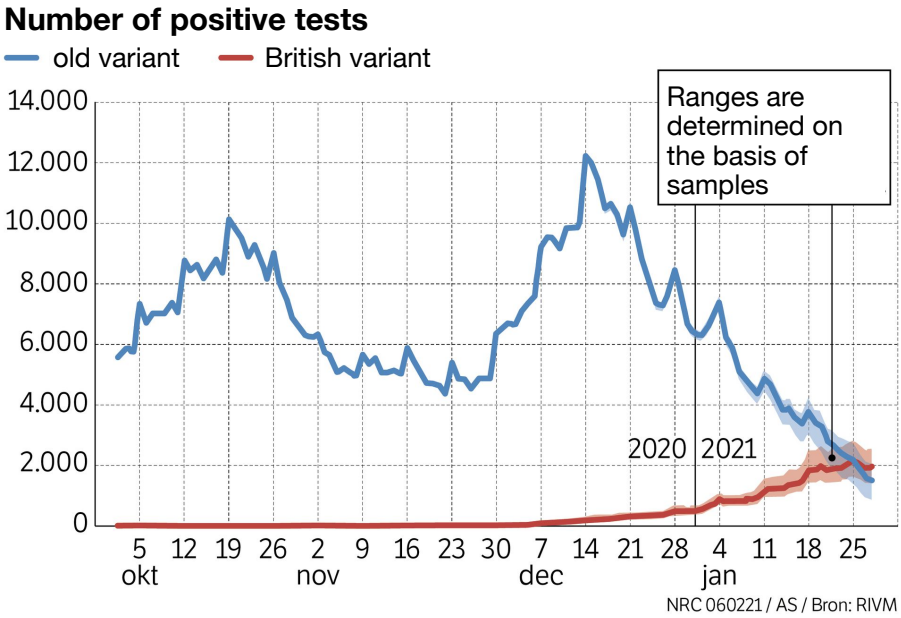


Figure taken from NRC Handelsblad 6 February 2021.

To allow you to study this predicted new peak, we have digitized the data of the mutant starting at 15 December 2020 until 25 January 2021 (6 weeks) and provide these in the file `british.txt` on the website. Download this data file and the R-script `corona.R`, store both in the same folder on your laptop, and open `corona.R` in RStudio. Evaluate the script line by line while going through the following questions.

a. Read the data using **`read.table()`** and inspect the data to see if they match the above figure taken from the NRC.

b. The data is now in the form of a `data.frame` called `data`, with a column `time` for the week number since 15 December 2020, and a column `cases` for the number of positive tests. These columns can be accessed by using **`data$`**`week` and **`data$`**`cases`, respectively. To test whether or not this new variant was growing exponentially, plot the data with a logarithmic y-axis using

```
plot(data$week,data$cases,log="y")
```

Would you qualify this as exponential growth?

c. Estimate the growth rate of the new virus by fitting the log of the data by linear regression, e.g.,

```
lm(log(cases) ~ week, data=data)
```

What is the growth rate, r, of the new mutant? What was the estimated number of cases at December 15 2020? What is the doubling time, and does that match the above figure?

d. At December 15 2020 there was a peak of about 12000 cases of the wild-type virus, and on 25 January 2021 there are about 2000 cases of the new variant. After how many more weeks would you expect the mutant to breach the original peak incidence of 12000 cases? How long would it take to reach the whole Dutch population of 17 million individuals? Hint: you can use R to compute the logarithms.

e. A simple model for the epidemic can be written as $\mathrm{d}I/\mathrm{d}t = (\beta - \delta)I$, where I is the number of infectious individuals, β is the number of new cases each infected individual causes per day, and $1/\delta$ is the number of days an individual remains infectious. Since an infected individual is expected to infect susceptible individuals over a period of $1/\delta$ days, and is expected to cause β new cases per day, the R_0 of this disease is β/δ. Estimates of the R_0 of the British variant at the time varied around 1.3, and the growth rate, $r = \beta - \delta$ per week, has just been estimated as

0.41 per week. Can you now estimate the length of the infectious period? Does this match what is known about the Corona virus?

2.7 Extra Practice Exercises

Question 2.6. Plastic

The linear ODEs used for the plastic model should be familiar to those of you who studied the famous equations for velocity and acceleration:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = v \quad \text{and} \quad \frac{\mathrm{d}v}{\mathrm{d}t} = a \ ,$$

where x is the total distance covered, v is the velocity, and a is the time derivative of the velocity, which is defined as the "acceleration". Integrating $\mathrm{d}v/\mathrm{d}t$ gives $v(t) = at + v(0)$, where the integration constant $v(0)$ is the velocity at time zero, and integrating $\mathrm{d}x/\mathrm{d}t = at + v(0)$ gives $x(t) = \frac{1}{2}at^2 + v(0)t$.

a. Check the dimensions of the velocity, v, and the acceleration, a.

b. In Eq. (2.4) we considered the case where we dump a fixed amount, k, of plastic in the oceans on a daily basis. Now consider the more realistic case where $k(t)$ becomes a variable that increases linearly over time, i.e., write that $\mathrm{d}k/\mathrm{d}t = a$, where a is the slope with which $k(t)$ increases. Starting at a time when $k(0)$ tons of plastic was dumped per day, we write the solution $k(t) = at + k(0)$. What is the new ODE for the total amount of plastic in the oceans, and what is its solution?

c. Do you expect the amount of plastic in the oceans to approach a (new) steady state?

Question 2.7. Pesticide on apples

During their growth season apples are frequently sprayed with pesticide to prevent damage by insects. By eating apples you accumulate this pesticide in your body. An important factor determining the concentration of pesticide is their half life in the human body. An appropriate mathematical model is

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \sigma - \delta P \ ,$$

where σ is the daily intake of pesticide, i.e., $\sigma = \alpha A$ where A is the number of apples that you eat per day and α is the amount of pesticide per apple, and δ is the daily rate at which the pesticide decays in human tissues.

a. Sketch the amount of pesticide in your body, $P(t)$, as a function of your age, assuming you eat the same number of apples throughout your life.

b. How much pesticide do you ultimately accumulate after eating apples for decades?

c. Suppose you have been eating apples for decades and stop because you are concerned about the unhealthy effects of the pesticide. How long does it take to reduce your pesticide level by 50%?

d. Suppose you start eating two apples per day instead of just one. How will that change the model, and what is the new steady state? How long will it now take to reduce pesticide levels by 50% if you stop eating apples?

e. What is the decay rate if the half-life is 50 days?

Question 2.8. Injecting anesthesia

Before you undergo a minor operation a certain amount of anesthesia is injected in the muscle of your upper arm. From there it slowly flows into the blood where it exerts its sedating effect. From the blood it is taken up by the liver, where it is ultimately degraded. We write the following model

for the amount of anesthesia in the muscle M, blood B and liver L:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = -eM \ , \quad \frac{\mathrm{d}B}{\mathrm{d}t} = eM - cB \quad \text{and} \quad \frac{\mathrm{d}L}{\mathrm{d}t} = cB - \delta L \ ,$$

where the parameter e is the efflux from the muscle, c is the clearance from the blood, and δ is the degradation in the liver. All parameters are rates per hour. We assume that the degradation in the muscle and blood is negligible. The initial amount of anesthesia injected is $M(0)$: the amount in the muscle at time zero.

a. Sketch the amounts of anesthesia in the muscle, $M(t)$, in the blood, $B(t)$, and in the liver, $L(t)$, as a function of time.

b. How long does it take before half of the injected amount has flown from the muscle to the blood?

c. Reason whether this the right time to do the operation?

d. Suppose the degradation rate is slow, i.e., let $\delta \to 0$, how much anesthesia will ultimately end up in the liver?

Chapter 3

Competition within populations

Density dependent growth

3.1 Introduction

In Chapter 1 we made a start with illustrating models that describe how a single population changes in size over time. In this chapter we will stick with single populations, but introduce competition *within* that population. We do so by assuming density dependence: the rate of growth of the population depends on the current size of the population.

3.2 Learning objectives

By the end of this chapter, you should be able to explain the following:

What are density-dependent birth and death rates?
What is a carrying capacity?
Why do replicating populations need density dependence to ensure a carrying capacity?
What is a phase portrait, and how can you tell from this which steady states are stable/unstable?
What is the basin of attraction of a stable steady state?

Before we get into density dependence, let us remember that ordinary differential equations (ODE) models *implicitly* make a number of (unrealistic) assumptions:

1. All individuals are equal, and hence can be described by a single variable.
2. The population is well mixed, and hence the spatial location of where interactions occur is not considered.

3. The population size N is large, so we need not to worry about population sizes smaller than one individual.
4. The parameters are constant, e.g. there is no seasonal variation in reproduction and birth rates.

Even though for many situations these assumptions are invalid, differential equation models are surprisingly successful in helping us understand complex biological processes. As the famous Robert May stated it, they help us "to think clearly" by forcing us to mathematically formalize our ideas about the process of interest, and subsequently observe the consequences of these ideas (May, 2004). In later chapters we will study how using alternative model formalisms often give alternative insights.

In Chapter 2 you were introduced to basic mathematical models. We considered models with intrinsic growth rates without any density dependence, leading to exponential growth or decay. The only equilibrium of Eq. (2.12) is $N = 0$. If $b > d$, i.e., if the fitness $R_0 > 1$, this equilibrium is unstable because introducing the smallest number of individuals into the $N = 0$ state leads to exponential growth. If instead $R_0 < 1$ the equilibrium is stable because every population will ultimately go extinct (i.e., for $t \to \infty$ the solution $N(0)\mathrm{e}^{(b-d)t} \to 0$ when $d > b$). Note that one could argue that Eq. (2.12) also has a steady state when $b = d$. However, this is a rare and strange condition because the birth rate and the death rate would have to be exactly the same over long time scales.

We also considered non-replicating populations (like dumped plastic or beached shrimps), which are maintained by an external influx, and have a constant, density-independent death rate, e.g., Eq. (2.6). Other than the exponential growth/decay model, these populations were shown to ultimately approach a steady state where the influx balances the death/decay. However, most biologically interesting populations *do* replicate without growing exponentially until the end of time, and also do not need to be maintained by an external influx of individuals. How then do we get a stable equilibrium?

In most real biological systems birth and death rates are typically not constant, but rather depend on the population size. Due to competition, *e.g.* for nesting sites or food, birth rates may decrease and death rates may increase when the population size increases (see Fig. 3.1). This is called density dependence. In this chapter we will develop models explicitly incorporating such density dependent birth or death rates. We will demonstrate how incorporating density dependence leads to the introduction of a stable non-zero equilibrium in birth-death models.

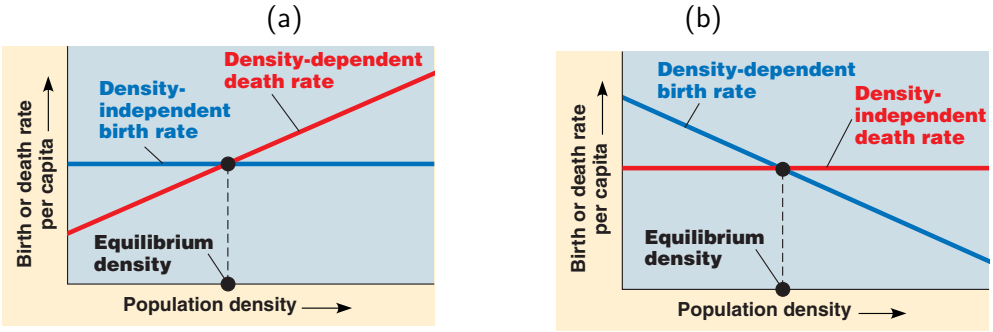


Figure 3.1: Graphs of the *per capita* birth and death rates. Equilibrium points correspond to the intersection points where the birth rate equals the death rate. From: Campbell & Reece (2008).

3.3 Density dependent death

Let us first reconsider our original population growth model with local, non-density dependent birth and death processes:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = rN = (b-d)N = bN - dN \tag{3.1}$$

Here, bN and dN represent the overall number of births and deaths, whereas b and d represent the *per capita*, i.e. per individual, birth and death rates. Now let us first consider a situation where the death rate depends strongly on density, and density dependence of the birth rate can be ignored. If the death rate increases with the population size one could, for example, propose a simple linear increase of the *per capita* death rate with the population size (see Fig. 3.1a). This linear increase need not be realistic (e.g. one may expect a maximum death rate), but would be a logical first extension of Eq. (3.1). A simple mathematical function for the graph in Fig. 3.1a is $f(N) = d + cN$, where d is the density-independent, baseline death rate that is approached when the population size is small, and where c is the slope with which the death rate increases with N. A function like $f(N)$ is formally referred to as a **functional response**: it determines how the population functionally responds to changes in density.

Although the biological interpretation of the parameter c is clear (how much extra death occurs because of density), we can also rewrite $f(N)$ to simplify its interpretation some more:

$$f(N) = d(1 + \frac{c}{d}N) = d(1 + \frac{N}{k})$$

with $k = \frac{d}{c}$. Note that the dimension of the parameter k is biomass or individuals, and its exact interpretation is that the death rate has doubled when $N = k$ because $1 + \frac{k}{k} = 2$. We can now incorporate this function $f(N)$ describing the density-dependent death in our original birth-death model:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \Big(b - f(N)\Big)N = \Big(b - d(1 + N/k)\Big)N \tag{3.2}$$

Note that when N is very small ($N \to 0$), the minimum *per capita* death rate remains d, and maximum generation time or life span remains $1/d$ time units. The birth rate is b per time unit, independent of the population size N. Since the R_0 is defined as a *maximum* fitness, it is computed for an individual under optimal conditions, which in this scenario means minimal death rate (so $N \to 0$). The fitness (R_0) of individuals obeying Eq. (3.2) therefore equals $R_0 = b/d$.

To search for steady states of Eq. (3.2) one sets $\mathrm{d}N/\mathrm{d}t = 0$, so $(b - d(1 + N/k))N = 0$. From this one obtains that either $N = 0$ or $b - d(1 + N/k) = 0$. The former once again corresponds to a trivial (zero state) equilibrium, which is not very interesting biologically. To determine the other, non-trivial, equilibrium we rewrite $b - d(1 + N/k) = 0$ as $b - d = dN/k$ and obtain

$$\bar{N} = k\left(\frac{b-d}{d}\right) = k\left(\frac{b}{d} - 1\right) = k(R_0 - 1) \tag{3.3}$$

In ecology, such a steady state is called the *carrying capacity*, the maximum population size that can occur for the population in a particular ecosystem. Note that whatever the fitness R_0 is, equation

Eq. (3.3) is a finite number. Thus, a simple linear density-dependent death rate is sufficient to result in a finite carrying capacity, preventing the population from exponentially growing out of control.

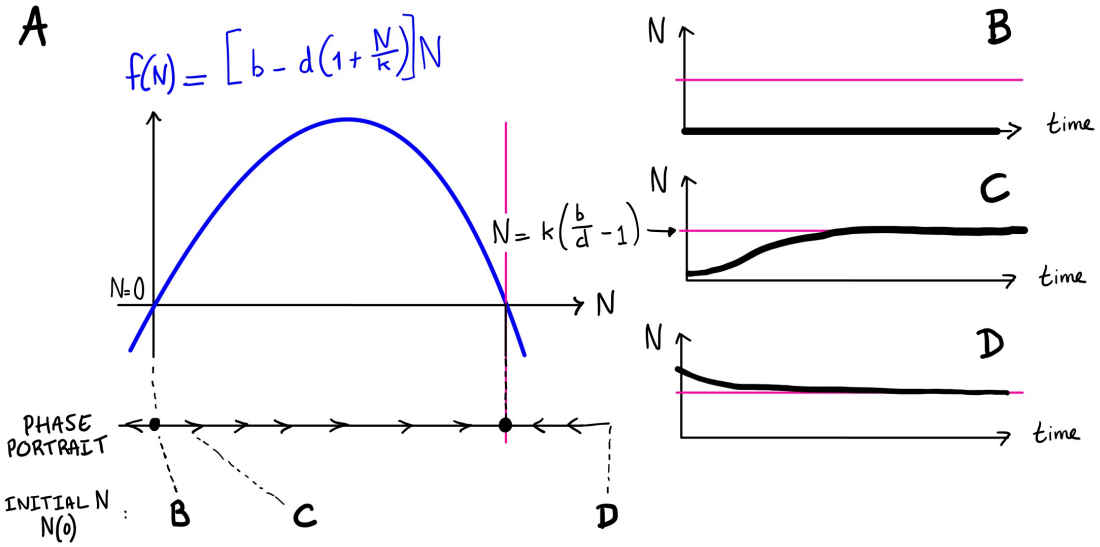


Figure 3.2: (A) Graph of $f(N) = (b - d(1 + N/k)N$ with a 1D phase portrait corresponding to this graph drawn under it. (B) Trajectory starting from initial conditions N=0. (B) Trajectory starting from small N($N < k(\frac{b}{d} - 1)$). (C) Trajectory starting from large N ($N > k(\frac{b}{d} - 1)$). The phase portrait for density-dependent birth looks identical, except then the carrying capacity in that case is equal to K.

As discussed in the previous chapters, the solution of Eq. (3.2) would enable us to see what happens when we wait sufficiently long ($t \to \infty$), allowing us to determine if the equilibrium we found is stable. However, solutions are not always available, and they are hard or impossible to derive. Therefore we will use a graphical method called **phase portrait** analysis, for which no solution is needed. For this, let us first draw $\mathrm{d}N/\mathrm{d}t$ as a function of N, *i.e.* define

$$f(N) = [b - d(1 + N/k)]N, \tag{3.4}$$

and sketch this function. Perhaps you already note that $f(N)$ is a second-order equation in N, corresponding to a downward-oriented parabola. If you don't immediately see this, multiply out the N to get $f(N) = bN - dN - \frac{dN^2}{k}$. The last term contains N^2, meaning that at small N this is even smaller that the other terms. At large N, this squared term is instead dominating, so its negative effect becomes huge. In other words, we expect $f(N)$ to first increase, and then decrease again: a downward-oriented parabola.

The parabola of $f(N)$ intersects the x-axis at two points, namely $f(N) = 0$ when for $N = 0$, and when $N = k(\frac{b}{d} - 1)$. Notice that this second intersect corresponds to the equilibrium we identified previously. If we draw this parabola on a 2D graph ($f(N)$ on the y-axis, N on the x-axis, we can sketch a 1D phase portrait below it (Fig. 3.2A). First, draw a line below the x-axis. Then, draw circles for values of N for which $f(N) = 0$ to indicate the location of both equilibria. If $f(N) > 0$ draw a $\to$ on the line to indicate that in this region, the value of N will increase. If $f(N) < 0$ draw a $\leftarrow$ to indicate that the value of N will decrease.

Now consider the trivial equilibrium $N = 0$. Right of the equilibrium, so for $N > 0$, we see $\rightarrow$ (indeed $f(N) > 0$) indicating N will increase, causing it to further deviate from the equilibrium. We can also draw a $\leftarrow$ on the left of this equilibrium where $f(N) < 0$, keeping in mind of course that negative population sizes are biologically nonsensical (so we won't draw any conclusions from this part). Either way, the equilibrium at $N = 0$ is surrounded by arrows pointing away from it, so we now know it is an *unstable equilibrium* from which the system diverges after any small perturbation. However, as the rate of change is 0 at this point, initial condition N=0 will result in no population growth. Thus, over time the population will not grow (Fig. 3.2B). If we instead start with a little bit of N, the population will grow towards the carrying capacity $N = k(\frac{b}{d} - 1)$ (Fig. 3.2C). Similarly, if we start with N greater than this carrying capacity, the population will decline until it once again reaches the carrying capacity (Fig. 3.2D). Thus, the carrying capacity is an equilibrium surrounded by arrows pointing toward it, making it a *stable equilibrium* or *attractor* of the system.

For unstable equilibria $f'(N) > 0$, whereas for stable equilibria $f'(N) < 0$. Note that more complex differential equations can have multiple stable equilibria (attractors) too (see Box 2.1)

Box 2.1 Systems with multiple equilibria; Basins of Attraction

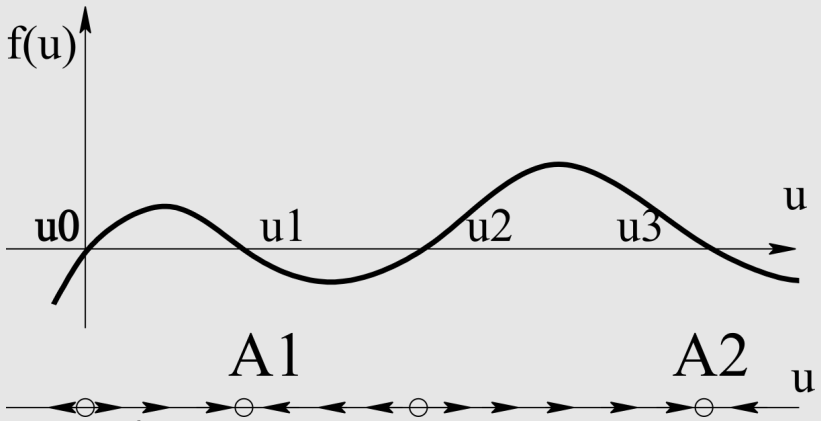


Figure 3.3: Top: graph of $\frac{du}{dt} = f(u)$, bottom: corresponding phase portrait. Figure adapted from Panfilov (2010)

Consider Fig. 3.3, which shows the graph of an unspecified population growth model

$$\frac{du}{dt} = f(u) \ ,$$

and the corresponding phase portrait.

If we sketch a phase portrait of this growth model, we see two attractors: u_1 and u_3. If the initial population size is $u_0 < u < u_2$, the population size eventually reaches u_1; if instead, the initial population size is $u_2 < u < \infty$, the population reaches u_3.

The intervals $[u_0, u_2]$ and $[u_2, \infty]$ describe the **basin of attraction** of the stable u_1 and u_3 equilibria, respectively. The boundary separating these two basins is formed by the unstable equilibrium u_2. In other words, to predict the final behavior of this system, one needs to know whether the initial population size falls inside the basin of attraction of u_1 or u_3.

3.4 Density dependent birth

As an alternative, we now consider the situation where the birth process depends more on the population density than the death rate. Hence our model should incorporate that the *per capita* birth rate b decreases with the population size. Experimental evidence supporting a decreasing birth rate in two natural populations is shown in Fig. 3.4. The simplest functional relationship between the *per capita* birth rate and the population size is again a linear one (see Fig. 3.1b), and a simple mathematical description is $f(N) = b - cN$, where b is the maximum birth rate that occurs at low population densities. We can once again rewrite this functional response into $f(N) = b(1 - \frac{c}{b}N) = b(1 - \frac{N}{k})$, with $k = \frac{b}{c}$ and use this to write the following model with density-dependent birth:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \Big(f(N) - d\Big)N = \Big(b(1 - N/k) - d\Big)N \tag{3.5}$$

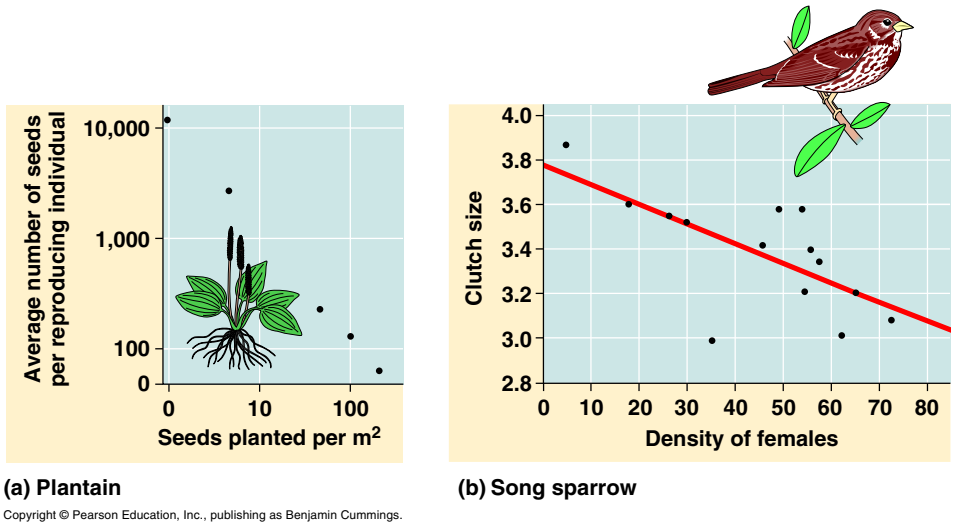


Figure 3.4: Panels (a) and (b) show for a plant species and a bird species that the *per capita* reproduction rate depends on the population size. From: Campbell & Reece (2002).

The dimension of the parameter k is again biomass, or individuals, and its exact interpretation is that the birth rate becomes zero when $N = k$. Note that at the best possible circumstances (low population size), individuals have a birth rate of b. So, the fitness (maximal birth divided by minimal death) of individuals obeying Eq. (3.5) therefore remains $R_0 = b/d$, which is natural because at a sufficiently low population size there should be no difference between the density-independent and density-dependent models. Note however that R_0 is not always simply b/d, as some models have different consequences for "the best possible circumstances".

From $(b(1 - N/k) - d)N = 0$ it follows that the steady states are now given by the trivial $N = 0$ and $b(1 - \frac{N}{k}) - d = 0$ so $b - d = b\frac{N}{k}$ which yields

$$\bar{N} = k(1 - d/b) = k(1 - 1/R_0) \ . \tag{3.6}$$

Once again, we see that there is a finite carrying capacity. Because this model also has a quadratic $f(N)$, it has a similar phase portrait as the one shown in Fig. 3.2a. Thus, for both density-dependent birth and death, the carrying capacity represents a stable equilibrium, and $N = 0$ is an unstable equilibrium.

3.5 Logistic growth

Since the model with density dependent death and the one with density dependent birth are both of the form $\mathrm{d}N/\mathrm{d}t = \alpha N - \beta N^2$, one can rewrite both models into the classical "logistic equation":

$$\frac{\mathrm{d}N}{\mathrm{d}t} = rN(1 - N/K) \ , \quad \text{with solution} \quad N(t) = \frac{KN(0)}{N(0) + \mathrm{e}^{-rt}(K - N(0))} \tag{3.7}$$

The logistic equation is one of the most famous models in biology[1]. This model once again uses the intrinsic growth rate (r), and has a second constant (K) that represents the carrying capacity. Note

[1] Although the solution for this particular model is known (and therefore given), it is also a perfect illustration of how fast these solutions increase in complexity

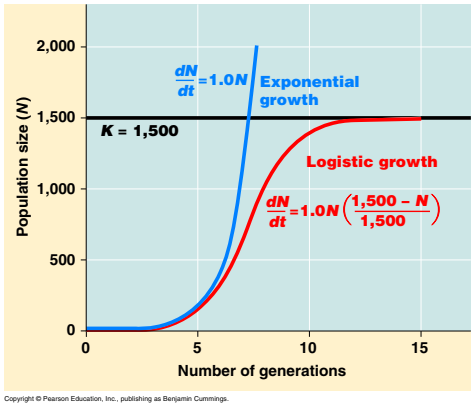


Figure 3.5: Logistic growth. From: Campbell & Reece (2008).

that because Eq. (3.7) has no explicit death rate (i.e. it is combined with the birth rate into a net growth rate), the R_0 can not be defined in this model.

Note that if we assume $K = 1$, the right-hand side of this equation is identical to the map introduced in Chapter 2. However, even at very high values of r, this model does not show the same deterministic chaos as we observed previously. While the chaos from the logistic *map* is caused by repeatedly under- and overshooting the equilibrium value (caused by taking large steps in time), ODEs take infinitely small time steps as it assumes time is continuous. Thus, this particular effect of under- and overshooting is not possible in ODEs! More complex ODE systems can however also show deterministic chaos, but that is beyond the scope of this course. For now, it is important that you remember that, even when we look at one and the same equation, its behaviour may be very different depending on the *implicit assumptions* that come with certain modelling formalisms!

3.6 Summary

A stable non-trivial population size of a replicating population is called a carrying capacity. Replicating populations will only have such a carrying capacity when the *per capita* birth and/or death rate depends on the population density, such that net population growth rate decreases with increasing population size. Non-replicating populations (i.e. populations sustained by immigration rather than birth) approach a stable steady state without any population regulation being required (i.e., without density dependence). A steady state is stable if values higher than this steady state decrease growth, and values lower than this steady state increase growth. This occurs if the local derivative of the growth function in the steady state is negative.

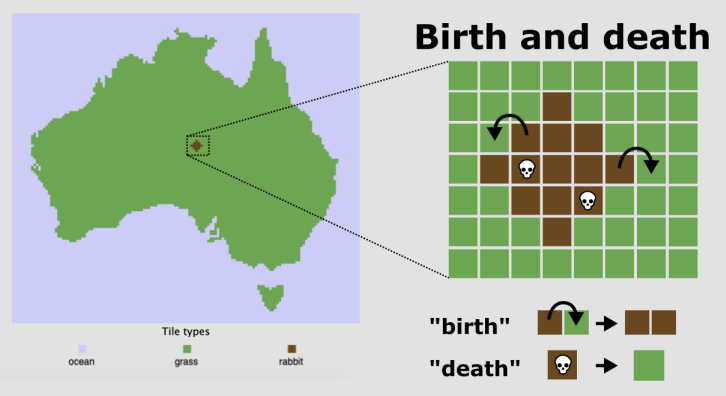
3.7 Exercises

Question 3.1. Density dependent death
Consider a replicating population where most of the death is due to competition with other individuals, i.e., let $f(N) = cN$ in a model where $\mathrm{d}N/\mathrm{d}t = (b - f(N))N$.
a. Sketch the *per capita* death rate as a function of N.

b. Sketch the *per capita* net growth rate as a function of N
c. Compute the steady states.
d. Why is the R_0 not defined?

Question 3.2. Rabbits in Australia... in space!
In Chapter 2, we have looked at a population of 13 rabbits growing exponentially in Australia. Let us extend this simulation by letting 13 individual rabbits live in a miniature "Australia" (see figure below). Let's imagine Australia is made up of tiles, where there are grassy tiles (green) on which rabbits can grow, rabbit tiles (brown), and ocean tiles (blue). For simplicity, we assume there are no desert tiles, meaning that rabbits can grow everywhere in our miniature Australia. As an initial condition for this model, 13 rabbit tiles are placed in the middle of the continent.

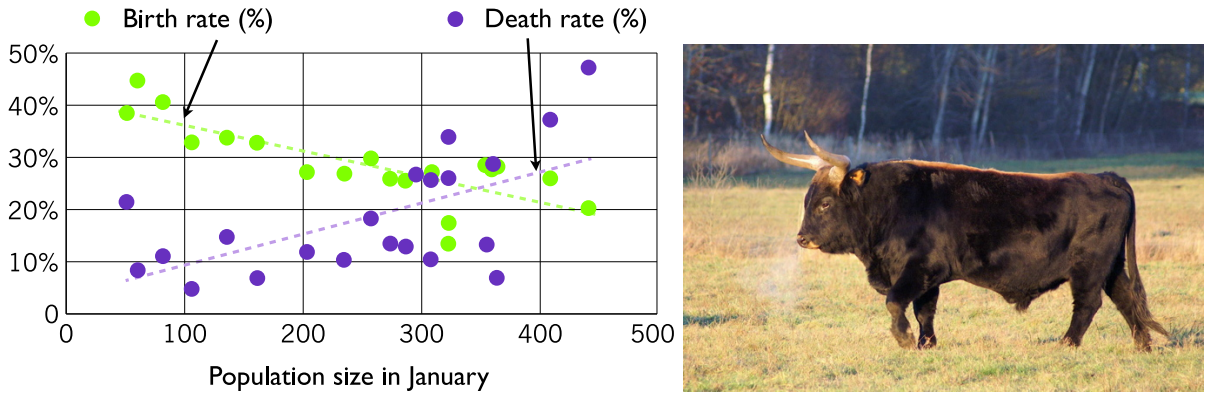
To simulate the increase in the rabbit population, we update all the tiles in discreet time steps. Every time step, every rabbit tile (brown) has a random chance to replicate into grassy tiles (which then also become brown). This "birth rate" is set to 80%, and does not decrease when there are more rabbit tiles nearby. Rabbit tiles can also change into a green tile again, which represents the death of a rabbit. Similar to the birth process, this happens at a fixed chance and does not scale with local rabbit density. For illustrative purposes, we assume rabbits do not move around.



a. Since the implemented birth and death rates are not density-dependent, how would you mathematically describe the growth of our rabbit population?
b. Given your answer to the previous question, should we expect the population to have a carrying capacity?
c. The simulation can be found online: `tbb.bio.uu.nl/bvd/simulations/australia/` Simulate by clicking the 'Start/pause' button. Look at the graphs at the bottom of the page. Does the population have a carrying capacity?
d. Reconsider whether the birth and death rates are truly density-independent. What resource are the rabbits competing over?
e. The population size early in the simulation grows rapidly: 13, 100, 292, 619, 1081, 1695, 2458, 3291. At this point, Australia is still far from fully invaded by rabbits. Plot the values in R. Is this exponential growth?
f. The rabbit population living in our miniature Australia stabilises at $\sim$ 8000 individuals, which is far fewer than hundreds of millions. We could of course make our simulation a lot bigger, but that would slow down the simulation. Instead, discuss how *scaling* could be applied and how that would change what "birth", "death", and brown tiles represent.

Question 3.3. Heck cattle
Heck cattle have been introduced to the 'Oostvaardersplassen' in the Netherlands as a semi-natural

population of grazers. They prevent the outgrowth of trees and shrubs in this open wet landscape harboring many different bird species. The population was started with a small group of animals in 1983, and after approximately 20 years the density approached a carrying capacity of 300–400 cattle. People have measured birth and death rates over the years (see the Figure taken from an article in NRC Handelsblad on 11 December 2010):



Figures taken from NRC Handelsblad 11 Dec 2010 (left) and Wikipedia (right).

Because so many animals are dying from starvation every year, there have been vigorous debates in the public arguing that these animals are suffering too much. One solution would be to shoot animals to lower the population size, and hence the death by competition for resources. Please read the NRC article. You can find it on Blackboard under Course Content.

a. How would you estimate the carrying capacity from the Figure, and what would it be?

b. Since the birth and death rates obey the simple linear functions we defined in this chapter, the data in the Figure can be defined as

$$\beta(N) = b(1 - N/k_1) \quad \text{and} \quad \delta(N) = d(1 + N/k_2) \ ,$$

for the birth and death rate, respectively. From the Figure we can see that the maximum birth rate is approximately 0.4 per year, and is half maximal at $N = 400$, and that the minimum death rate is 0.03 per year, and is 11-fold larger, i.e., 0.33 when $N = 500$. Use this information to determine b, d, k_1 and k_2.

c. Incorporate these functions into a mathematical model, and compute the carrying capacity from your model.

d. What fraction (or percentage) of the animals is dying every year when the population is at carrying capacity? How many dead animals is that?

e. What is the R_0 of this population? Would you call this a logistic growth model?

f. To reduce the number of animals dying from starvation it has been proposed to shoot a fraction of the animals per year. Calling this yearly rate of animals being killed, k, the new model would become

$$\frac{\mathrm{d}N}{\mathrm{d}t} = [\beta(N) - \delta(N)]N - kN \ .$$

Find the new steady state of the model. Use this to compute how many animals are expected to die every year.

g. At what value of k will the population go extinct? Use the R-script `heck.R` (which you can find on Blackboard under Course Content, Mathematische en Theoretische Biology) to plot how the steady state population size depends on k.

h. Use the script to plot the *number* of animals dying as a function of k. Can one reduce the number of dead animals per year by shooting them?

i. Use the script to plot the *fraction* of animals dying as a function of k. Do you increase or decrease the expected death rate of an individual by shooting them?

j. Use the script to plot the life expectancy as a function of k. Do you increase or decrease the life expectancy of an individual by shooting them?

k. The original plan was to only shoot the weaker individuals. One can explicitly model the weakened individuals by arguing that the additional density dependent death term in the model actually takes healthy individuals from the healthy population N into a subpopulation of weakened individuals, W, and that these die at a much faster rate, $d_W \gg d$. Killing only a fraction k of these weakened individuals per year would correspond to

$$\frac{\mathrm{d}W}{\mathrm{d}t} = \frac{d}{k_2}N^2 - d_W W - kW \ ,$$

where $\mathrm{d}N/\mathrm{d}t$ would remain as defined as above in (c). What is the steady state of the weakened individuals, and how many weakened individuals die per year? Hint: what would $\bar{N}$ be in this case?

3.8 Extra Practice Exercises

Question 3.4. Density dependent growth

A density dependent birth rate need not decline linearly with the population density. Consider a population with a density dependent growth term:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = (bf(N) - d)N \quad \text{with} \quad f(N) = \frac{1}{1 + N/h} \ .$$

This density dependent term $f(N)$ is called a Hill-function, for more details on Hill-functions see the appendix.

a. Sketch how the *per capita* birth rate depends on the population density N.

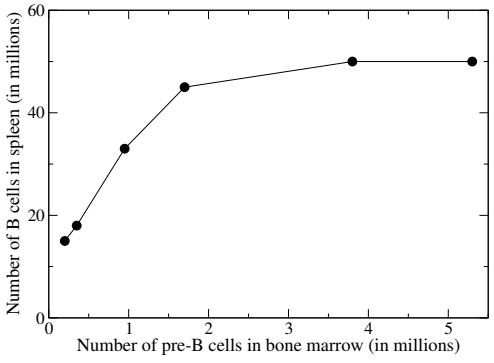
b. Sketch how the birth rate of the total population depends on the population density N.

c. Compute the steady states of the population.

d. What is the R_0 and express the steady state in terms of the R_0?

Question 3.5. Freitas

Agenes *et al.* (1997) at the Pasteur Institute manipulated the number of cells in the bone marrow (pre-B cells) producing naive B cells (e.g., in the spleen), and found the following:



The simplest model for the naive B cell population is $\mathrm{d}B/\mathrm{d}t = m - dB$ where m is the bone marrow production, and $1/d$ is the average life span of naive B cells. The rate of naive B cell production is

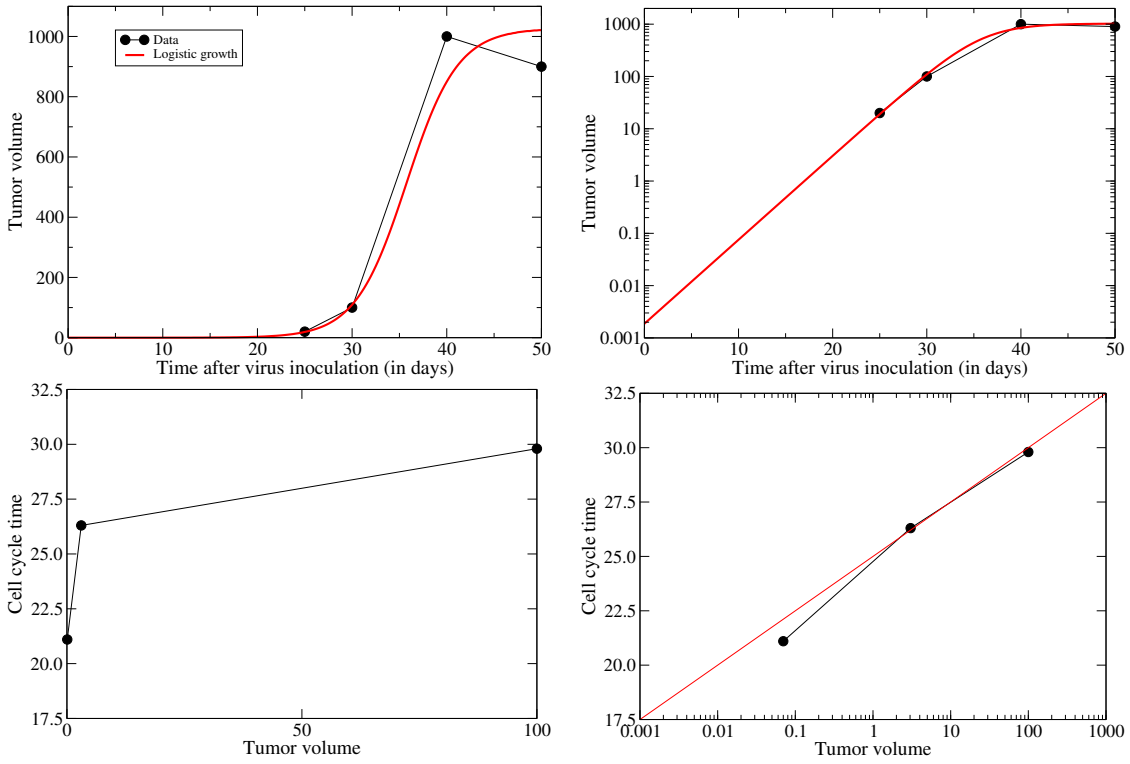


Figure 3.6: The growth of a sarcoma as measured by Zobl *et al.* (1975). The symbols denote the data and the lines our best description of this data by fitting a mathematical model.

proportional to the number of pre-B cells, i.e., $m = \alpha P$, where P is the number of pre-B cells. Note that in the graph the horizontal axis corresponds to m and that the vertical axis depicts $\bar{B}$.

a. Is this simple model compatible with the data shown?

b. Do the data require homeostasis, i.e., density dependent regulation?

c. How would you extend the model?

Question 3.6. Negative birth

The *per capita* birth rate function $f(N) = b(1 - N/k)$ of Eq. (3.5) is not completely correct because the birth rate becomes negative when $N > k$. This can be repaired by writing $f(N) = \max[0, b(1 - N/k)]$ which equals zero when $b(1 - N/k) \leq 0$ because the $\max[]$ function returns the maximum of its arguments. Will this change the steady states analyzed in this Chapter?

Question 3.7. Logistic growth of a tumor

Zobl *et al.* (1975) have studied the growth functions of tumors by inducing novel sarcomas in the kidneys of rats using Polyoma virus. These tumors initially grow exponentially and then approach a steady state volume (Fig. 3.6, upper left panel). This growth function can reasonably be described with a logistic growth function, $\mathrm{d}N/\mathrm{d}t = rN(1-N/K)$, where r defines the maximum growth rate, and K is the "carrying capacity". To visualize that the initial growth rate is truly exponential we plot their data both on a logarithmic and a linear scale in Fig. 3.6, upper left and right panels. In this figure the symbols denote the data with the volume in mm^3, and the heavy line is the best fit of the classical logistic equation to the data (with $r = 0.37$ per day or 0.015 per hour, $K = 1027$ mm^3, and $N(0) = 1.87 \times 10^{-3}$ mm^3). An R script to fit the logistic growth function to this data is available on the website as the file `tumor.R`.

a. Can you give a biological explanation for the carrying capacity observed at a tumor size of $K = 1027$ mm^3?
b. Note that we have fitted 4 data points with a function requiring at least 3 parameters (r, K, and $N(0)$). One could also try to make the model more realistic and distinguish between cell division and cell death by writing $\mathrm{d}N/\mathrm{d}t = bN(1-N/k) - dN$. What is now the biological interpretation of k? Do you think one can estimate the values of all parameters of the more realistic model with the same data?
c. In the paper Zobl *et al.* (1975) also measure the cell cycle times of the tumor cells. They find that the cell cycle time, T, is approximately 21h at day 10, 26h at day 20, and 30h at day 30. Reading the size of the tumor from the fitted curve at these time points (Fig. 3.6, lower left and right panel) we find that $T \simeq 21$h when $N \simeq 0.07$, $T \simeq 26$h when $N \simeq 3$, and $T \simeq 30$h when $N \simeq 100$. Plotting T as a function of $\log_{10} N$ reveals that the division time increases approximately linearly with the log tumor size, i.e., the diagonal line in Fig. 3.6, lower right panel obeys $T = 25 + 2.5 \log_{10}[N]$. What would be your best estimate for the cell cycle time in a tumor of 10^{-3} mm^3? What do you expect for the cell cycle time at day 50?
d. Write a simple equation for how the cell division rate depends on the tumor volume (the division rate $B(N)$ is the inverse of the cell cycle time $T(N)$).
e. Write a model implementing this division rate and compute the new steady state.
f. Estimate the death rate realizing that we should obtain the same steady state with the new model. Using this new death rate compute the net replication rate of the tumor and compare this to the net replication rate described by r in the logistic model that we started out with. What could be causing the difference?
g. Why are we now able to estimate the death rate, whereas in b we argued that we could not determine the birth and death rates but only the net replication rate?

Question 3.8. Stem cells
Stem cells are maintained by continuous division. A fraction of the daughter cells differentiates and obtains other phenotypes. A convenient model for stem cell growth is the logistic equation $\mathrm{d}S/\mathrm{d}t = rS(1 - S/k)$.
a. Expand the model with differentiation of stem cells.
b. Write a simple model for the differentiated cells.
c. Compute the steady state population sizes of this model.

Question 3.9. Bacterial growth in vitro.

Bacteria that are grown *in vitro* typically have a growth curve resembling Logistic growth. On the website we provide a (simulated) data set containing three different bacteria strains that are called Bact1, Bact2 and Bact3 in the file `growth.txt`. Download this file, and the R-script `growth.R`, into a folder on your laptop, and open the script in RStudio.
a. Read the data into a data frame (using **`read.table()`**) and check the dimensions of the data (e.g., **`dim(data)`**). What is the initial density of the three strains? Hint: click your data in the environment window.
b. Plot the data of three strains using different colors and provide a legend using:

```
plot(data$time, data$Bact1, xlab="Time", ylab="Density", col="black", pch=18)
points(data$time, data$Bact2, col="red", pch=18)
points(data$time, data$Bact3, col="green", pch=18)
legend("topleft", legend=c("B1","B2","B3"), col=c("black","red","green"), pch=18)
```

Interpret the data in your own words.

Chapter 4

Lotka Volterra model

Systems of 2 differential equations

4.1 Learning objectives

After studying this chapter you should be able to do all excersises as well as be able to explain the following:

What is the difference between **two separate** ODEs and **a system of two** ODEs? Why does the latter allow us to model interacting populations?

What is a **phase space**, what are **nullclines** and what is a **vectorfield**? How can the nullclines and vectorfield be determined? How is a **trajectory** in the phase space related to a solution of the system? How can you determine **equilibria from nullclines**? Why is that the case?

How many **steady states** are there in the **Lotka Volterra** model, and what is their **biological interpretation**? Which of these steady states are **non-trivial** and which are **stable**?

What is the **expected population size** of a prey population with carrying capacity K, and which is controlled by a predator with a fitness R_0?

4.2 Introduction into Two dimensional Systems

In the next three chapters we will develop a number of classical ecological models. Of course, biology entails much more than populations and ecology, but these models are well-studied and intuitive, and a good way to get introduced to modelling interactions. The famous Lotka-Volterra model that we will analyze in this chapter was developed around 1925 by Vito Volterra and Alfred Lotka. In 1934 Gause formulated the competitive exclusion principle (see Chapter 5). Theoretical models are common in ecology, and several ecological concepts, like "niche" and the relationship between "stability and complexity" originate from theoretical work (May, 1974). We will start with the Lotka-Volterra model that was originally developed for modeling predator-prey and host-parasite interactions, and has since been used in many situations where some expanding population is

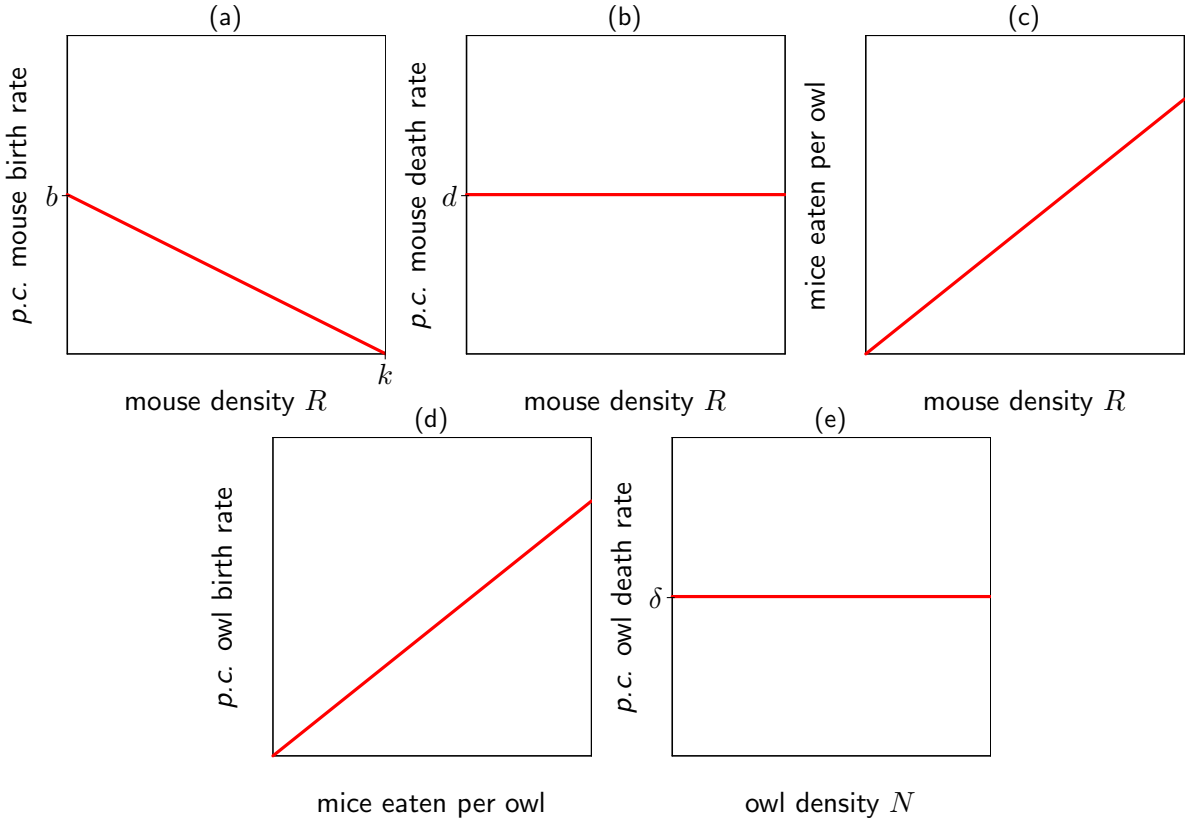


Figure 4.1: Population dynamical characteristics of a mouse and owl population. The *p.c.* in the figure means *per capita*.

controlled by another population (e.g. growing tumors, or infections controlled by immune responses).

Thus far we considered systems of a single differential equation, describing the dynamics of a single, supposedly independent, variable. However, when we consider e.g. a predator-prey system, we need to consider that the predators will affect prey dynamics and vice versa. In other words, we not only need two differential equations to describe the dynamics of two populations, but we also need to take into account that these two equations are interdependent. The general form to describe a system of two interdependent differential equations is:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x,y) \quad , \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = g(x,y) \tag{4.1}$$

where f and g are functions of both x and y. To put this in terms of studying biological populations: changes in one population will not only feed back on itself (*e.g.* through density dependence), but also feed back on other populations. If there are more predators, more preys will be eaten. If there are more immune cells, more pathogens can be neutralised, *etc.*

4.3 Lotka Volterra model; Finding equilibria

Suppose one has measurements for the interaction between a certain prey species and a certain predator, e.g., mice and owls. These measurements are summarized in Fig. 4.1, and suggest that the mice have a linear density dependent birth rate (a) and a density independent death rate (b). This can be modeled with Eq. (3.5). Panel (c) suggests that the rate at which owls catch mice is proportional

to the mouse density, i.e., if the mouse population size were to double, the owls would consume twice as many mice. For this linear density dependence and linear predation term, one obtains the prey equation of the famous Lotka-Volterra predator-prey model (where prey is represented by the letter R):

$$\frac{\mathrm{d}R}{\mathrm{d}t} = [bf(R) - d]R - aNR \quad \text{where} \quad f(R) = 1 - R/k \ , \tag{4.2}$$

with maximum birth rate b, death rate d, and a predation term aNR. In this predation term, N represents the number of predators, and a represents a predation rate. In the absence of predators the steady state of the prey population is

$$\bar{R} = k(1 - d/b) = k(1 - 1/R_0) = K \ , \tag{4.3}$$

where K defines the "carrying capacity" (see Chapter 2). Note that in the prey equation, we used explicit birth and death rates, allowing us to define an $R_0 = b/d$. In contrast, theoretical ecologists typically prefer to write the prey equation using the logistic growth term $\mathrm{d}R/\mathrm{d}t = rR(1 - R/K)$, from which the non-trivial steady state $\bar{R} = K$ (see Fig. 3.5) is immediately clear, but in that case R_0 would not be defined.

The owl "measurements" in Fig. 4.1 suggest the *per capita* birth rate of the owls is proportional to the number of mice eaten per owl, i.e., to aR. Since the owl death rate is density-independent, one would write for the predator equation:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = [caR - \delta]N \ , \tag{4.4}$$

where $1/\delta$ is the expected life-span of the predators. The parameter c converts "eaten prey biomass" into "predators born".

Box 3.1 Equilibria in 2D systems

For a 1D system

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x) \ ,$$

x^* is a steady state if $f(x^*) = 0$ as then no further change in the value of x will occur.

So, when does an equilibrium occur for a 2D system?

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x, y) \qquad , \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = g(x, y)$$

Consider a point (x^*, y^*) for which $f(x^*, y^*) = 0$ but $g(x^*, y^*) \neq 0$. At a next infinitesimal small timestep, since $\frac{dx}{dt}$ but not $\frac{dy}{dt}$ equals zero, x will have remained at the value x^*, while y will have changed to y^{**}. In this new point (x^*, y^{**}), $f(x^*, y^{**})$ may no longer equal zero, as the changes in the y population may steer $\frac{dx}{dt}$ away from 0. This will then also change x to another point, *e.g.* x^{**}. Of course, the opposite is also true for a point (x^*, y^*) $g(x^*, y^*) = 0$ but $f(x^*, y^*) \neq 0$.

Thus, a point (x^*, y^*) is a steady state only if both $\frac{dx}{dt} = f(x^*, y^*) = 0$ and $\frac{dy}{dt} = g(x^*, y^*) = 0$. Therefore, to find equilibria we need to *simultaneously* solve $f(x, y) = 0$ and $g(x, y) = 0$.

Let us do this for the system:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -2x + y \qquad , \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = x - 2y$$

Solving $\mathrm{d}x/\mathrm{d}t = 0$ one obtains $y = 2x$. Substituting this into $\mathrm{d}y/\mathrm{d}t = x - 2y = 0$ results in $x - 4x = 0$, and hence $x = 0$. Substituting this back into $y = 2x$ then generates $y = 0$. Thus, the equilibrium is $(0, 0)$.

As a first step to obtain insight into the dynamics dictated by these equations, we will compute the steady states of the Lotka-Volterra model derived above:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = [bf(R) - d]R - aNR$$
$$\frac{\mathrm{d}N}{\mathrm{d}t} = [caR - \delta]N$$

In 2D systems, an equilibrium requires that *both variables do not change* (see Box 3.1). Hence, to find equilibria we need to *simultaneously solve* $\mathrm{d}N/\mathrm{d}t = 0$ *and* $\mathrm{d}P/\mathrm{d}t = 0$. We start by solving the simplest equation, $\mathrm{d}N/\mathrm{d}t = 0$. This yields

$$\bar{N} = 0 \quad \text{and} \quad \bar{R} = \frac{\delta}{ca} \,. \tag{4.5}$$

Next, in order to simultaneously fulfill $\mathrm{d}R/\mathrm{d}t = 0$ and $\mathrm{d}N/\mathrm{d}t = 0$, we substitute these solutions *one by one* into $\mathrm{d}R/\mathrm{d}t = 0$. Substituting the first solution $\bar{N} = 0$ yields $\mathrm{d}R/\mathrm{d}t = [b(1 - R/k) - d]\, R = 0$ and hence

$$\bar{R} = 0 \quad \text{and} \quad \bar{R} = k(1 - d/b) = K, \tag{4.6}$$

with K the carrying capacity of the ecosystem for the prey in absence of predators. So, using only the first solution from $\mathrm{d}N/\mathrm{d}t = 0$ we already obtained two steady states, the trivial steady state $(0, 0)$ in which both prey and predators are absent, and $(k(1 - d/b) = K, 0)$ in which prey are at their maximum carrying capacity and predators are absent.

Next we solve $\mathrm{d}R/\mathrm{d}t = 0$. First, we divide all terms by R, therewith obtaining $b(1-R/k)-d-aN = 0$ and substitute the non-trivial solution $\bar{R} = \frac{\delta}{ca}$ obtaining

$$b\left(1 - \frac{\delta}{cak}\right) - d - aN = 0 \quad \text{and hence} \quad \bar{N} = \frac{1}{a}\left[b\left(1 - \frac{\delta}{cak}\right) - d\right] \tag{4.7}$$

While above we found two solutions when setting $\mathrm{d}N/\mathrm{d}t = 0$, we now only found one solution more. Thus, the model has three steady states in total. The third steady state we obtained last $(\frac{\delta}{ca}, \frac{1}{a}\left[b\left(1 - \frac{\delta}{cak}\right) - d\right])$ is called non-trivial because both populations are present (> 0). Note from the above that the non-trivial solution for prey R is obtained from $\mathrm{d}N/\mathrm{d}t = 0$, whereas the non-trivial solution for predators N is obtained from setting $\mathrm{d}R/\mathrm{d}t = 0$. In other words, sometimes you can (or have to!) find the steady state of a population by looking at the equation of the *other* population.

Finally, let's define the R_0 of the predator to simplify the expression for the non-trivial steady state. This will tell us something about the effect the predator has on the prey density. Since the birth of the predators depends on the number of prey eaten, the maximum fitness R_0 should be computed for the maximum prey density $\bar{R} = K$, resulting in the maximum birth rate of the predator caK. With an expected life span of $1/\delta$ one can then define the R_0 of the predator as $R_0 = \frac{caK}{\delta}$. This allows us to rewrite the equilibrium prey density defined in Eq. (4.9) as $\bar{R} = K/R_0$. Interestingly, this tells us that the prey population size, relative to its maximum value of K, is only proportional to the fitness of the predator, and does not depend on prey parameters at all!

4.4 Lotka-Volterra; Phase plane analysis

In the previous chapter, we analysed 1D systems (systems with a single population) by using a phase portrait. By drawing a horizontal line from 0 to ∞, drawing arrows to the right when the population is expected to grow, and drawing arrows to the left when the population is expected to decline, we could analyse the behaviour of our system. A steady state is stable when nearby arrows point towards it, and is unstable when nearby arrows point away from it. Moreover, we could define basins of attraction: all values that are attracted to a particular steady state.

The strategy described above does not work for 2D systems (with 2 populations, like the Lotka-Volterra system), as we cannot draw a single line. Instead, *both* populations can have values from 0 to ∞, so we would have to draw two axes where *e.g.* the x-axis represents how many prey we have, and the y-axis how many predators we have. The same is true for the arrows we draw to indicate direction: they cannot only go left or right, but also up and down! Otherwise, the idea is the same, we draw a simple sketch from which we can observe how the system will behave. This strategy is called *phase plane* analysis.

Box 3.2 Nullclines and vectorfield

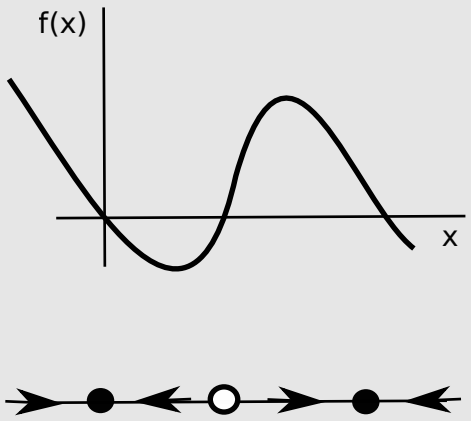


Figure 4.2: Top: graph of $\mathrm{d}x/\mathrm{d}t = f(x)$, bottom: corresponding phase portrait.

Remember that for the phase portrait of a 1D system $\frac{dx}{dt} = f(x)$, we first draw circles for the equilibrium points ($f(x) = 0$). Since at equilibrium points $\mathrm{d}x/\mathrm{d}t$ changes sign, they subdivide the system into different *domains* with different dynamics (Fig. 4.2). Subsequently one determines the dynamics in these domains, drawing $\leftarrow$ or $\rightarrow$ depending on whether $f(x) < 0$ or $f(x) > 0$. From the direction of the arrows around an equilibrium one can then tell its stability.

The single line above is sufficient to cover all possible states of a 1D system, but you cannot represent all possible states of a 2D system on a single line! To analyze a 2D system, one has to represent the system's dynamics on a 2D (x, y) plane. On this plane, one can use $\leftarrow$ and $\rightarrow$ to indicate areas where $\mathrm{d}x/\mathrm{d}t < 0$ and $\mathrm{d}x/\mathrm{d}t > 0$, respectively and $\downarrow$ and $\uparrow$ to represent areas where $\mathrm{d}y/\mathrm{d}t < 0$ and $\mathrm{d}y/\mathrm{d}t > 0$, respectively. We will refer to the combination of a horizontal and vertical arrow as a *vector*. To determine where to draw what vector, we first need to subdivide the 2D *phase plane* into domains with distinct dynamics, and thus find the boundaries separating these domains. While in the 1D phase portrait the arrows changed direction when you pass a distinct point (a stable state), you cannot "pass a point" in a 2D space. Instead, changes occur when you pass a certain line where either $\mathrm{d}x/\mathrm{d}t$ or $\mathrm{d}y/\mathrm{d}t$ changing sign. Such a line is called the *nullcline* of that equation, meaning that there is an x-nullcline and a y-nullcline. When you pass the x-nullcline, the horizontal arrow flips, and when you pass the y-nullcline, the vertical arrow flips.

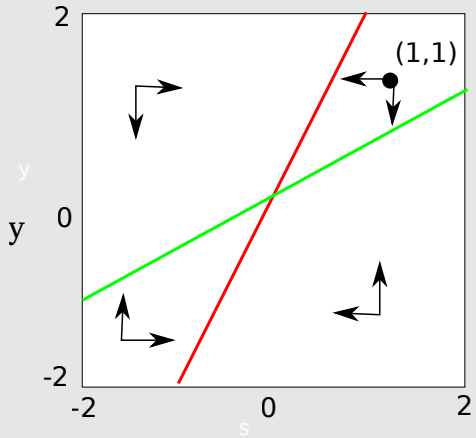


Figure 4.3: Phase plane analysis of the 2D system defined below

As an example, let us draw a phase plane for the following (non-biological) system of equations:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -2x + y \qquad , \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = x - 2y$$

From $\mathrm{d}x/\mathrm{d}t = 0$ we obtain $y = 2x$, the red line in Fig. 4.3. As long as you are *on* this line, the x-nullcline, x does not change. This is because the line was found by analysing $\mathrm{d}x/\mathrm{d}t = 0$. This x-nullcline is shown as a red line in Fig. 4.3. From $\mathrm{d}y/\mathrm{d}t = 0$ we obtain $y = 0.5x$, the y-nullcline, which is the green line in Fig. 4.3.

Note that since for equilibria of 2D systems both $\mathrm{d}x/\mathrm{d}t = 0$ and $\mathrm{d}y/\mathrm{d}t = 0$, equilibria correspond to the intersection points of x an y nullcline. Equilibria are therefore surrounded by 4 distinct domains, which dynamics determine equilibrium stability.

To determine the *vectorfield*, one first determines the vector in one domain. Consider the point $(1, 1)$. For this point $\mathrm{d}x/\mathrm{d}t = -2+1 = -1 < 0$ which is depicted as $\leftarrow$, while $\mathrm{d}y/\mathrm{d}t = 1-2 = -1 < 0$ which is depicted as $\downarrow$.

Since one knows that at the x-nullcline, dx/dt changes sign and at the y-nullcline dy/dt changes sign, one can then move from this region to a new region determining the direction vector thereby *flipping the direction of the x vector when passing the x-nullcline, while flipping the direction of the y-vector when passing the y nullcline*.

We proceed by sketching the phase space with the nullclines and vector field of the Lotka-Volterra model (see Box 3.2). The prey nullclines are obtained by solving $\mathrm{d}R/\mathrm{d}t = 0$, while the predator nullclines are obtained by solving $\mathrm{d}N/\mathrm{d}t = 0$. Thus, for nullclines, the two equations need to be solved *independently*, and you do not have to substitute them into one another. Setting $\mathrm{d}R/\mathrm{d}t = 0$ will yield the prey-nullclines:

$$\bar{R} = 0 \quad \text{and} \quad \bar{N} = \frac{1}{a}\left[b(1 - R/k) - d\right] \ . \tag{4.8}$$

The first solution ($\bar{R} = 0$) corresponds to the vertical axis in Fig. 4.4, as these are all the values where R equals zero. The second solution ($\bar{N} = \frac{1}{a}\left[b(1 - R/k) - d\right]$) is more not a straight line, as there is a negative R term in there. This term is linear, so we expect a linearly decreasing line for the second prey-nullcline. We can also determine the points where this line will intersect with the

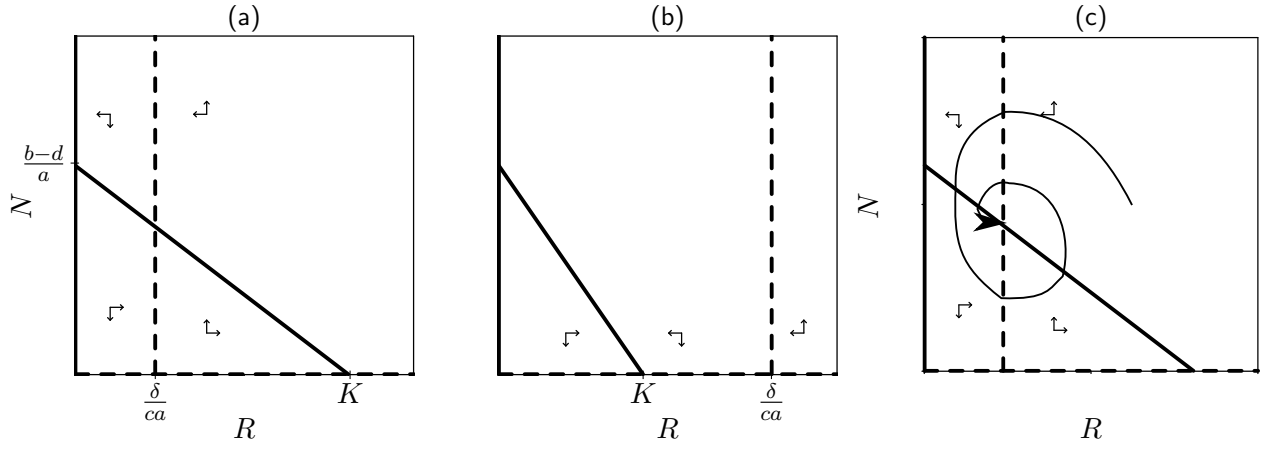


Figure 4.4: The Lotka-Volterra model. The heavy lines are the nullclines of the prey; the dashed lines those of the predator.

x- and y-axes by setting it to 0, or by filling in $R = 0$. The former is equivalent to finding the prey carrying capacity, so we can simply write K (which we already determined previously) at the x-axis.

Now for the predator-nullclines. Solving $\mathrm{d}N/\mathrm{d}t = 0$ gives

$$\bar{N} = 0 \quad \text{and} \quad \bar{R} = \frac{\delta}{ca} \ . \tag{4.9}$$

In Fig. 4.4, $\bar{N} = 0$ corresponds to the horizontal axis, whereas $\bar{R} = \frac{\delta}{ca}$ is a vertical line.

Note that we didn't specify the values for the parameters, so the precise configuration of the nullclines is not yet known. There are two qualitatively different possibilities for the phase space: when $\delta/(ca) < K$, the predator- and the prey-nullcline intersect at a point where neither is zero: we have a non-trivial steady state where the two populations coexist. If $\delta/(ca) > K$ the maximum prey density K is insufficient for predator growth (Fig. 4.4b), and this non-trivial steady state is "absent" (i.e. it lies at negative predator values, which is biologically impossible).

Next, we need to determine the vector field, so that we can learn how the populations change if we start with a given number of predators/prey. The example of Box 3.2 has no free parameters so we could simply calculate in which directions the arrows would point. However, since we have not specified values for the model parameters for the Lotka-Volterra model, we can not simply fill in e.g. a point $(1, 1)$ to determine the vector field. Instead, we can determine the direction of the vector field for the different domains (the four domains of Fig. 4.4a and the three domains of Fig. 4.4b) by looking at extremely large, or extremely small values for R and N. The equations of the ODE can then tell us whether the populations are expected to grow even further (arrows to the right/up) or decline (arrows to the left/down).

Let us determine the vector field in the top right-hand side region of the phase space of Fig. 4.4a. In this domain, both prey and predators have large population sizes. Rewriting Eq. 3.1 we obtain $\mathrm{d}R/\mathrm{d}t = (b-d)R - \frac{bR^2}{k} - aNR$, which contains three terms. The first term is positive and linearly depends on R. The second and third terms are negative and are quadratic ($R \cdot R$ and $R \cdot N$). So when both predators and prey are highly abundant (large N and R), the linear term will be small compared to the quadrativ (non-linear) negative terms, meaning $\mathrm{d}R/\mathrm{d}t$ will be negative. Thus we draw a $\leftarrow$ to indicate a decrease of R in this region of the phase plane. Similarly, rewriting Eq. 3.3 yields $\mathrm{d}N/\mathrm{d}t = caRN - dN$, and here for large N and R the positive non-linear term dominates, allowing us to draw a vertical upward-oriented arrow indicating increase of N. From this, we can then derive the remainder of the vector-field in both situations, as the prey-nullcline flips the horizontal arrow, and the predator-nullcline flips the vertical arrow.

Now that we have a vector field, let us study what we can conclude from it. The first equilibrium (steady state) is at the origin ($(0, 0)$). For small population sizes (close to the origin), the vertical arrows point towards $(0, 0)$ and the horizontal arrows point away from it. Since equilibria are only stable if the system converges to it from all directions, the equilibrium $(0, 0)$ is unstable (both in Fig. 4.4a and Fig. 4.4b). Note that this makes sense biologically, as a population of 0 predators and 0 prey cannot grow (and is therefore is a steady state by definition), but small populations of prey should be able to grow (especially with few predators!). This biologically reasonable fact can be inferred from our phase plane. There is another equilibrium at $(K, 0)$, but the arrows around this point differ in Fig. 4.4a and Fig. 4.4b. In Fig. 4.4a, this equilibrium is unstable, as the vertical arrows point away from it. In contrast, in Fig. 4.4b both horizontal and vertical arrows converge to $(K, 0)$, rendering the equilibrium stable.

What about the stability of the most interesting, non-trivial, steady state in Fig. 4.4a? At first glance, it appears unstable, as some arrows are pointing away from the equilibrium. However, the

vector field indicates a rotating type of dynamics, which suggests the system will spiral around this equilibrium point. If it goes around this point but gets closer and closer, it would be called a **stable spiral**, as is shown in the **trajectory** drawn in Fig. 4.4c. However, how can we tell that the trajectory does not keep oscillating around the point? This is what would happen if the equilibrium point is an **unstable spiral**. Whether the equilibrium is stable or unstable, we may at preliminarily conclude that the predators and prey will both persist, because neither of the other equilibria is stable, and there is no region where both predators and prey grow exponentially. How exactly the dynamics around this interesting equilibrium play out, will be discussed in the next chapter.

4.5 Summary

Systems of ODEs are distinct from separate ODEs because the variable of one equation may appear in another. This enables us to describe interacting populations, but also other biological phenomena, like protein expression, the growth of a tumour, or whatever else you can think of. The most famous biological model of interacting populations is the Lotka-Volterra model for predator-prey dynamics, which is a 2D system of equations. Even this simple model delivers surprising results, like how the prey population size does not depend on its own birth or death rates when it is controlled by a predator. Sketching the nullclines and the vector field of a 2D system helps one to find the different steady states of the model, and is often enough to determine their stability. For the Lotka-Volterra model, however, we were not yet able to determine whether the observed spiral was a stable spiral or an unstable spiral.

4.6 Exercises

Question 4.1. Seals
Assume that seals in the Waddenzee have a density-dependent birth rate and a density-independent death. Healthy seals S live on average $1/d$ days, and can become infected with a virus carried by infected seals I. Infected seals die after a short period averaging about $1/\delta$ days. We write the following model:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = bS(1 - S/k) - dS - \beta SI \quad \text{and} \quad \frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - \delta I \quad \text{where} \quad \delta \gg d\ .$$

a. What are the steady states of the seal population in the absence of the infection?
b. What is the R_0 of the seals? What is the R_0 of the infection?
c. Express the steady state from **a.** in terms of the R_0 of the seals.
d. Suppose that pollution with chemicals (like PCBs) halves the birth rate of the seals. What is the steady state of the seal population under polluted circumstances?
e. Now let us consider that an infection is present. How many healthy seals S do you expect in a population chronically infected with this deadly virus, but in absence of PCBs?
f. How is this healthy seal population size in the infected steady state changing by water pollution with PCBs?
g. Sketch the nullclines of the model and identify all steady states. Assume the non-trivial steady state is a stable spiral (in the next chapter you will learn how to determine this), and loosely sketch a trajectory in your phase plane.

h. Sketch the nullclines of the model in the presence and the absence of PCBs in one picture (for the case where the virus is present).

Question 4.2. Solving the steady state
Find the non-trivial steady state value of the population B in the following food chain assuming that all species are present:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = rA(1 - A/K) - cAB \ , \quad \frac{\mathrm{d}B}{\mathrm{d}t} = cAB - dB - eBC \ , \quad \frac{\mathrm{d}C}{\mathrm{d}t} = eBC - fC \ .$$

Hint: this should not be a lot of work.

Question 4.3. Density dependent birth
In the Lotka-Volterra model (i.e., Eqs. 4.2 & 4.4) we assumed a linear decrease in the prey birth rate with the prey density, i.e., $f(R) = 1 - R/k$. Now consider the curved function $f(R) = 1/(1 + R/k)$. This type of functions are called Hill functions and are commonly used to describe non-linear dependencies. Make sure you know how to sketch this function (for details on Hill functions see the appendix).
a. Sketch the nullclines for the case with a non-trivial steady state (compute the intersects with the axis and asymptotes of the new nullcline).
b. Write an expression for the new carrying capacity K of the prey.
c. What is the R_0 of the predator?
d. Note the similarity in the expressions for the non-trivial steady state of the prey, $\bar{R}$, and the R_0 of the predator. Can you simplify the expression for $\bar{R}$ using the R_0 of the predator?
e. Identify all steady states. The non-trivial steady state is stable (in the next chapter you will learn how to determine this). However, assuming it is an unstable spiral, what would a trajectory look like?
f. Do you find this model very different from the Lotka-Volterra model?

Question 4.4. Lotka-Volterra in space

In the previous chapter, we looked at the population growth of rabbits in space. Let us also put the Lotka-Volterra system in space (see Fig. 4.5), assuming the following rules:

- Prey (yellow tiles) can only grow in "empty sites" (black tiles)
- Predators (red tiles) can only grow by replacing nearby prey tiles
- Predators die with a fixed probability

Similar to the rabbits in miniature Australia, we do not need to explicitly add a carrying capacity for prey reproduction, as the carrying capacity is set by the limited amount of space. The simulation can be found here: `https://tbb.bio.uu.nl/bvd/simulations/lotkavolterra`
a. Run the simulation. Look at the graphs at the bottom. Is this equivalent to a stable or an unstable spiral?
b. Using the buttons, enable mixing and restart the simulation. Did the number of predators/prey change? Did the *type* of equilibrium change?
c. Verbalise why mixing has a positive impact on the predator population size.

d. The "kill prey" button removes 90% of the prey individuals. By clicking this button repeatedly, you can kill all the prey (you may have to click really fast, or pause the simulation). The prey population will never recover once it is dead, and hence the predators also die. In terms of the ODE model, we are now in the trivial steady state $(0, 0)$. Would you be able to "kill all the prey" in the ODE model in the same way? Why/why not?

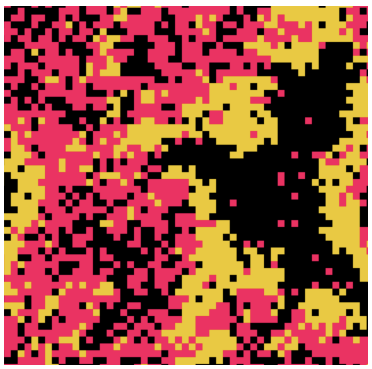


Figure 4.5: The Lotka-Volterra system in space has empty tiles (black), prey tiles (yellow) and predator tiles (red).

4.7 Extra Practice Exercises

Question 4.5. Malaria
Consider an infection of red blood cells that are produced at a fixed rate by the bone marrow.

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \sigma - dB - aBI \quad \text{and} \quad \frac{\mathrm{d}I}{\mathrm{d}t} = aBI - \delta I$$

where B are uninfected red blood cells and I are infected cells.
a. Sketch the nullclines for the case where the infection can maintain itself (do compute the asymptotes).
b. Write an expression for the "carrying capacity" K of the red blood cells.
c. What is the steady state $\bar{B}$ during a chronic infection?
d. Express this steady state $\bar{B}$ in terms of the carrying capacity K and the R_0 of the infection.
e. Determine the stability of the steady states.
f. What are the major differences between this model and the Lotka-Volterra model?

Question 4.6. Algae and zooplankton
In fresh water lakes green algae are eaten by several zooplankton species. Let us model this with the simple Lotka-Volterra model

$$\frac{\mathrm{d}A}{\mathrm{d}t} = rA(1 - A/K) - bAZ \quad \text{and} \quad \frac{\mathrm{d}Z}{\mathrm{d}t} = cbAZ - dZ \ ,$$

where we have collapsed the birth and death processes of the algae into a net growth term known as logistic growth.
a. Sketch the nullclines and determine the stability of all the steady states for the case with a non-trivial steady state.
b. Consider a lake with algae and zooplankton coexisting at steady state. Eutrophication of the lake with nitrogen and phosphate increases the availability of food for the algae. In this model this means

that the carrying capacity parameter K increases by eutrophication. Sketch in the same phase space the nullclines of a lake with and without eutrophication.

c. Which of the two populations increases most by the eutrophication?

d. Which model in the exercises of Chapter 3 closely resembles this model?

Question 4.7. Growth of insects

Consider an insect population consisting of larvae L and adults A:

$$\frac{\mathrm{d}L}{\mathrm{d}t} = aA - dL(1+eL) - cL \quad \text{and} \quad \frac{\mathrm{d}A}{\mathrm{d}t} = cL - \delta A \ .$$

a. Interpret all terms of the model.

b. Sketch the nullclines and the vector field.

c. Determine the stability of the steady state(s).

Question 4.8. Eider down

Eider ducks make their nest on the ground with a very rich down that on Iceland is being harvested for the highest quality sleeping bags and coats. Some populations of the Common Eider, *Somateria mollissima*, are infected with parasitic worms that are transmitted directly between healthy and infected eiders. Thus, the most important enemies of the eiders are (1) people ruining their nests for collecting eider down, and (2) this lethal worm. Consider the following model for healthy eiders, E, and dying infected eiders, D, where we assume that healthy eiders suffer from a density dependent death (the infected eiders die rapidly anyway):

$$\frac{\mathrm{d}E}{\mathrm{d}t} = E(fb - d(1+cE) - \beta D) \quad \text{and} \quad \frac{\mathrm{d}D}{\mathrm{d}t} = D(\beta E - \delta) \ ,$$

where b is the normal birth rate, β is an infection rate, and f is the fraction of nests that is not harvested for eider down. The d and δ parameters are death rates.

a. What is the carrying capacity of the eiders in the absence of harvesting and worms (i.e., for $f = 1$ and $D = 0$)?

b. What is the R_0 of the ducks, and what is the R_0 of the infection?

c. Express the steady state from **a** in terms of the R_0 of the ducks.

d. What would be the steady state of the ducks if half of the nests were destructed ($f = 1/2$) in the absence of the infection ($D = 0$)?

e. What is the steady state of the healthy ducks, $\bar{E}$, in the presence of the infection?

f. What would be the effect on the steady state number of healthy ducks, $\bar{E}$, if one would forbid the harvesting of down in infected eider populations?

g. Sketch the nullclines for $f = 1$ and $f = 1/2$ for an area with infected ducks.

Chapter 5

Interactions beyond predator-prey

Equilibrium stability, self-feedback and bifurcations

5.1 Learning objectives

After studying this chapter you should be able to do all exercises as well as be able to explain the following:

How different types of interactions lead to different types of system dynamics, such as co-existence and competitive exclusion.

How equilibrium stability and basins of attraction can be determined from the phase plane.

How self-feedback can be applied to derive equilibrium stability from a vector field with rotating dynamics.

What bifurcations are and how they may be related to the extinction of a species.

5.2 Introduction: Equilibrium Types

In the previous chapter we described the interactions between predators and prey with a system of two ODEs. We can also use ODEs to describe how other types of populations interact. For example, let us consider how the competition between two very similar species. These two species have very similar growth rates, and experience competition from eachother (*interspecific competition*) and from themselves (*intraspecific competition*). Let us describe these two populations with the following equation of N_1 and N_2:

$$\begin{aligned}\frac{\mathrm{d}N_1}{\mathrm{d}t} &= rN_1(1 - aN_1 - bN_2)\\ \frac{\mathrm{d}N_2}{\mathrm{d}t} &= rN_2(1 - aN_2 - bN_1)\end{aligned}$$

Here, r is the maximum net growth rate, a the intraspecific and b the interspecific competition.

Let us begin with the assumption that there is more competition *within* species than there is *between* species. I.o.w., let us assume $a > b$. To investigate whether these species can co-exist, we will perform a phase plane analysis. By setting $\mathrm{d}N_1/\mathrm{d}t = 0$, we get the N_1 nullclines which are $N_1 = 0$ and $r(1 - aN_1 - bN_2) = 0$ from which we obtain $N_2 = \frac{1}{b} - \frac{a}{b}N_1$. Similarly, from $\mathrm{d}N_2/\mathrm{d}t = 0$ we obtain the N_2 nullcline $N_2 = 0$ and $r(1 - aN_2 - bN_1) = 0$, from which follows $N_2 = \frac{1}{a} - \frac{b}{a}N_1$. Ignoring the two trivial nullclines, we now have two equations for N2 as a function of N1:

$$\begin{aligned}\mathrm{N}_1 - \text{nullcine}: &\qquad f(N1) = \tfrac{1}{b} - \tfrac{a}{b}N_1\\ \mathrm{N}_2 - \text{nullcine}: &\qquad f(N1) = \tfrac{1}{a} - \tfrac{b}{a}N_1\end{aligned}$$

What do these functions look like? Remember, by putting N_1 to zero we can get the intercept with the y-axis. For this intercept, only the first terms of the equations matter. Since we assume that $a > b$ we know that the N_1 nullcline $N_2 = \frac{1}{b} - \frac{a}{b}N_1$ has a higher intercept, because dividing by a smaller number (b) gives a larger value. We can also conclude that N_1 has a steeper (negative) slope than the N_2 nullcline, because $\frac{a}{b} > \frac{b}{a}$. To determine the directions in the vectorfield, we consider the upper right corner where both N_1 and N_2 are large, meaning that $\mathrm{d}N_1/\mathrm{d}t < 0$ and $\mathrm{d}N_2/\mathrm{d}t < 0$. Together this results in the phase plane shown in Fig. 5.1a.

We see four points for which the N_1 and N_2 nullclines intersect, the equilibria $(0, 0)$ (both species absent), $(\frac{1}{a}$,0) (only N_1 present), $(0, \frac{1}{a})$ (only N_2 present) and $(\frac{b-a}{b^2-a^2}, \frac{1}{b} - \frac{a}{b}\frac{b-a}{b^2-a^2})$ (both species present). We see that for the last, non-trivial equilibrium the vectors of all 4 neighboring domains point towards the equilibrium. If we numerically simulate solutions of this model (Fig. 5.1a, bottom) for various initial population sizes, we indeed see all solutions converging to the non-trivial equilibrium. Thus, this is a stable equilibrium or attractor. So, when $a > b$ in this system, species N_1 and N_2 can co-exist. A biological interpretation of this situation is two species that consume different resources. If the population consists of N_1, there is very high competition for the resource preferred by N_1 and this population will decrease. If instead the whole population consists of N_2 (the other species), N_1 experiences very little competition and will grow. *Vice versa* for $N2$. Somewhere in between these

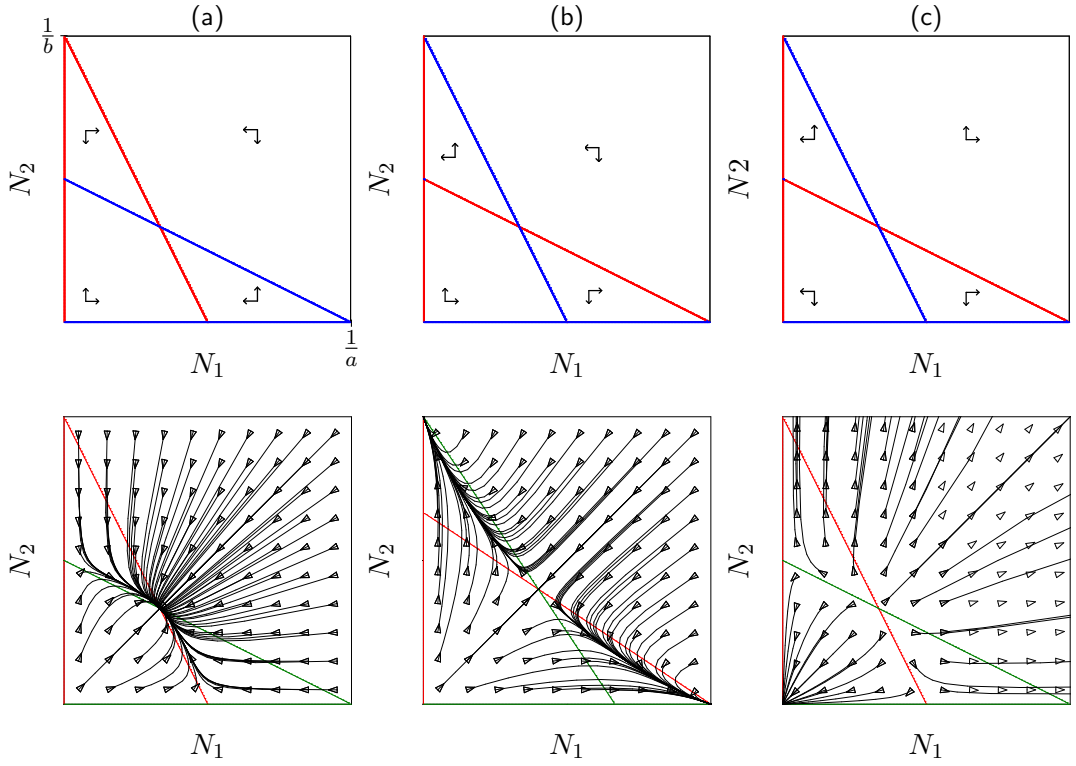


Figure 5.1: Phase plane with null clines and vector field (top row) and with nullclines and trajectories (bottom row) for stable node, unstable saddle point and unstable node equilibria. Red nullclines are for N_1, blue nullclines are for N_2.

two extremes must be the point where neither $N1$ or $N2$ will grow in size, hence our tiny ecosystem (consiting of only two species) is stable.

Now let us assume instead that $a < b$. This is a situation where the species experience much more competition from the other species, than they do from themselves. Under these conditions the N_1 nullcline has a lower intercept and shallower slope than the N_2 nullcline, causing the two nullclines to swap positions (Fig. 5.1b). Note that the vectorfield in the upper right corner remains the same (we did not change the equations!), yet due to crossing the nullclines in a different order in other regions the vectorfield changes. One can see now that while the vector field in the upper right and lower left corners point towards the non-trivial equilibrium, the vectorfield in the two other domains point away from the equilibrium. Thus, while this equilibrium was stable before, it is now unstable. In contrast, the two equilibria with only one species present only have vectors poointing towards them. From the numerical solutions (Fig. 5.1b, bottom) we observe that while solutions initially approach the non-trivial equilibrium they subsequently diverge away from it, approaching one of the two equilibria in which only one of the two species are present. You can also see that whoever is more abundant at the beginning, will end up winning the competition.[1] A biological interpretation of this scenario is *interference competition*, for example the production of toxins by bacteria to kill other species of bacteria, lions and hyenas fighting over resources, and plants producing compounds that inhibit the growth of other plant species.

In summary, if individuals compete more with individuals of their own species than of the other

[1]Except when you start with exactly the same number of N_1 and N_2, as you will then move along the diagonal and stay in the non-trivial equilibrium. Note however that this is unrealistic, as any small amount of noise will push the system out of this state.

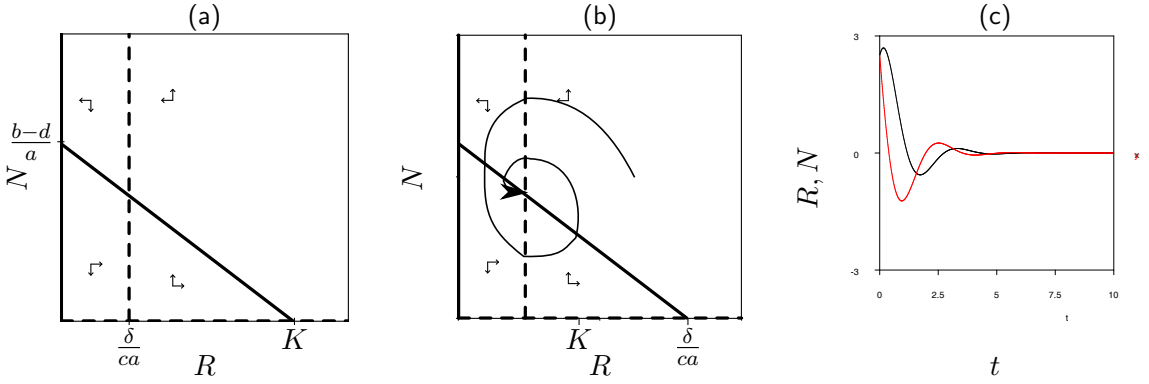


Figure 5.2: a) The phase plane of the Lotka-Volterra model for $\delta/(ca) < K$. The heavy lines are the nullclines of the prey; the dashed lines those of the predator. b) Phase plane with trajectory. c) Dynamics of R and N over time for the trajectory shown in b.

species ($a > b$) co-existence occurs, while if they compete more with individuals of the other species ($a < b$) the exclude one another.

Next we consider another type of ecological interaction. Here, species N_1 and N_2 have both intraspecific *cooperation* that improves their birth rates, and interspecific competition that increases the death rate, described by the following equations:

$$\begin{aligned} \frac{\mathrm{d}N_1}{\mathrm{d}t} &= aN_1^2 - dN_1(1 - N_2) \\ \frac{\mathrm{d}N_2}{\mathrm{d}t} &= aN_2^2 - dN_2(1 - N_1) \end{aligned}$$

with $a > d$

From $\mathrm{d}N_1/\mathrm{d}t = 0$ we obtain for the N_1 nullcline $N_1 = 0$ and $N_2 = 1 - \frac{a}{d}N_1$. Similarly, from $\mathrm{d}N_2/\mathrm{d}t = 0$ we obtain for the N_2 nullcline $N_2 = 0$ and $N_2 = \frac{d}{a} - \frac{d}{a}N_1$. From $a > d$ it follows that $\frac{d}{a} < 1$, causing the N_2 nullcline to have a lower intercept and shallower slope than the N_1 nullcline. Filling in large values for N_1 and N_2, we obtain that $\mathrm{d}N_1/\mathrm{d}t > 0$ and $\mathrm{d}N_2/\mathrm{d}t > 0$ in the upper right hand corner of the vectorfield. Together this results in the phase plane shown in Fig. 5.1c. For this model, in all abutting domains of the non-trivial equilibrium vectors point away from it. In agreement with this, all numerical solutions diverge away from this point, converging either to the equilibrium $(0, 0)$ or with N_1 and N_2 increasing indefinitely (Fig. 5.1c, bottom). Of course, the unlimited growth implied by this model is completely unrealistic.

5.3 Lotka-Volterra : Self-feedback

Now let us reconsider the Lotka-Volterra model of the previous chapter:

$$\begin{aligned} \frac{\mathrm{d}R}{\mathrm{d}t} &= \left(b\left(1 - \tfrac{R}{K}\right) - d\right)R - aNR \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= caNR - \delta N \quad , \end{aligned}$$

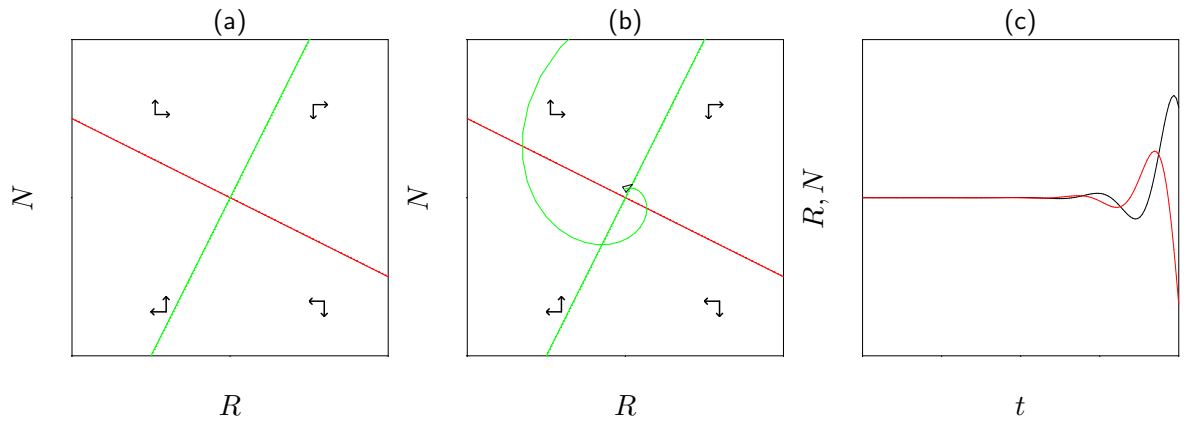


Figure 5.3: a) Phase plane with nullclines and vector field. b)Phase plane with nullclines and trajectory. c) Temporal dynamics of a single trajectory.

for which we derived the R nullcline $R = 0$ and $N = \frac{1}{a}(b(1 - \frac{R}{K}) - d)$ and the N nullcline $N = 0$ and $R = \frac{\delta}{ca}$. For the situation where $\delta/(ca) < K$ we obtained the phase plane shown in Fig. 5.2 in the previous chapter. The vectorfield, displaying a rotating type of dynamics, does not immediately tell us whether the equilibrium is stable.

We can determine equilibrium stability by examining the local feedback of the variables onto themselves. For the prey, starting from the equilibrium position, we add a little prey (i.e. we move a bit to the right in the phase plane) and examine what the local vectorfield tells us about the dynamics of the prey (i.e., considering the horizontal part of the vectorfield at that location). One sees that upon adding a little prey, $\mathrm{d}R/\mathrm{d}t$ becomes smaller than 0, so the number of prey decreases. Similarly, by removing a little prey we end up on the other side of the R-nullcline, so the prey population will increase. Thus, a destabilization of the number of prey from the number in the equilibrium will be restored. For the predators, we can do the same thing. Starting from the equilibrium point we add a little predators (i.e., moving a bit upward on the phase plane), we examine the effect on the predator growth (i.e., the vertical part of the local vectorfield). However, we see that we are exactly at the nullcline and hence the vertical arrow of the vectorfield is zero. In other words, an increase or decrease in predators will not become automatically restored, but it will also not amplify leading to a further increase/decrease! So overall, we can conclude that the self-feedback around this equilibrium is negative: deviations from the equilibrium will bring you back to it. This information suggests that the nontrivial equilibrium point is a *stable* spiral, which is further confirmed by the solution (the trajectory) depicted in Fig. 5.2b showing inward spiraling dynamics towards the non-trivial equilibrium. Fig. 5.2c shows the temporal dynamics of N and R corresponding to this trajectory, displaying oscillations that decrease their amplitude until the stable equilibrium is reached.

Fig. 5.3a shows a non-specified model also displaying rotating dynamics in the vectorfield. Studying the selffeedback for this system we see that for an increase in the R variable on the x-axis, a further increase in that variable will result. Similarly, an increase in the N variable on the y-axis will result in a further increase in that variable. So overall, self-feedback is positive, leading to divergence from the equilibrium. This can be seen in the numerical solution in Fig. 5.3b, and in the time plot in Fig. 5.3c showing oscillations with increasing amplitude. In summary, simply by reading the vector field, we can determine the stability of equilibria with rotating dynamics. So once you have the vector field, you can often learn a lot about your system without doing any further math!

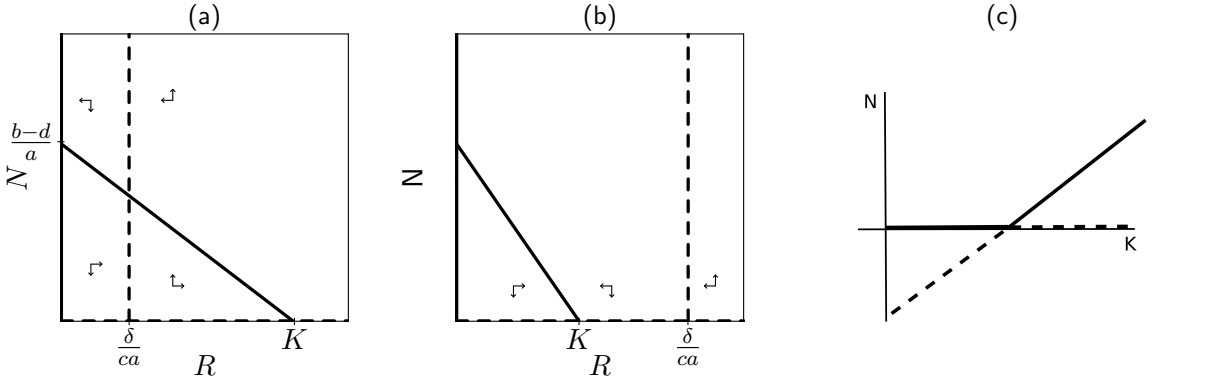


Figure 5.4: a, b) Two distinct phase plane situations for the Lotka-Volterra model. The heavy lines are the nullclines of the prey; the dashed lines those of the predator. c) Bifurcation diagram displaying changes in equilibrium location and stability for N as a function of K, with heavy lines for stable and dashed lines for unstable equilibria.

5.4 Lotka-Volterra; Bifurcations

In the previous chapter we already observed that two distinct phase plane possibilities exist for the Lotka-Volterra model, shown again in Fig. 5.4. While for $\frac{\delta}{ca} < K$ a non-trivial steady state exists, for $\frac{\delta}{ca} > K$ this equilibrium is absent (nullcline intersection point occurs for negative predator numbers which is biologically irrelevant). Additionally, while in the first scenario (Figure Fig. 5.4a) the equilibrium $(K, 0)$ is unstable, in the second scenario (Figure Fig. 5.4b) this equilibrium has become stable. The equilibrium $(0, 0)$ is unstable in both scenarios.

Let us now consider what happens when due to e.g. climate change the carrying capacity K for the prey species gradually decreases. Starting from a situation like the one depicted in Figure Fig. 5.4a the equilibrium point $(0, K)$ will shift leftward. At first, this will only result in *quantitative* changes: decreasing the carrying capacity of prey decreases the number of predators in the system, but they are still converging on the same non-trivial equilibrium point where there is coexistence. However, at a certain point K will be lower than $K = \frac{\delta}{ca}$, yielding a situation like that shown in Figure Fig. 5.4b. Now, we observe a *qualitative* change in the system: there are no longer enough prey species for the predators to grow, not even in the best possible circumstances! The only stable point in the system corresponds to the carrying capacity of the prey, and there will be no coexistence. Such a qualitative change in system behavior in response to changes in parameter values is called a **bifurcation** (Fig. 5.4c).

5.5 Exercises

Question 5.1. Saturated proliferation
Consider two type of immune cells (type 1 and type 2) that both response to the antigen of the same pathogen. Both types of immune cells will undergo clonal expansion and reduce the pathogen concentration. By reducing the pathogen concentration, they also reduce the antigen concentration and hence also their own activation. Assume that the amount of the pathogen's antigen level, A, equals

$$A = 1 - kE_1 - kE_2 \ ,$$

where E_1 and E_2 are the number of cells of each immune response. Note that a higher E_1 and/or E_2 indeed decreases the antigen levels.

The maximum proliferation rate of the immune responses is a saturation function (i.e., a Hill function) of the amount of antigen A. Thus, let the immune responses be described by

$$\frac{\mathrm{d}E_1}{\mathrm{d}t} = \frac{pE_1A}{h_1 + A} - dE_1 \quad \text{and} \quad \frac{\mathrm{d}E_2}{\mathrm{d}t} = \frac{pE_2A}{h_2 + A} - dE_2 \ ,$$

where $h_2 > h_1$ means that the second response requires a higher amount of antigen for obtaining the same proliferation rate. Because the proliferation is saturated it seems that exclusion would be less likely.

a. Sketch the *per capita* proliferation rates of as a function of the concentration of antigen.

b. Draw the nullclines in a phase space of E_1 and E_2. Hint: To get the non-trivial nullclines, you will have to substite $A = 1 - kE_1 - kE_2$ back into the equation. However, try to postpone this as long as possible, as that makes the math easier.

c. Can the two responses coexist?

Question 5.2. Competitive proliferation

Again consider two immune responses to the same pathogen, and again assume that the immune responses reduce the pathogen's antigen concentration to

$$A = 1 - kE_1 - kE_2.$$

Now, let the immune responses be described by

$$\frac{\mathrm{d}E_1}{\mathrm{d}t} = \frac{pE_1A}{1 + c_1E_1} - dE_1 \quad \text{and} \quad \frac{\mathrm{d}E_2}{\mathrm{d}t} = \frac{pE_2A}{1 + c_2E_2} - dE_2 \ ,$$

where $c_2 > c_1$ means that the second response has a stronger intra-specific competition.

a. Sketch for a fixed antigen concentration the *per capita* proliferation rates as a function of the clone size.

b. Draw the nullclines in a phase space of E_1 and E_2. Hint: Postpone substituting $A = 1-kE_1-kE_2$ as long as possible.

c. Can the two responses coexist?

d. What is the difference with the previous question?

Question 5.3. Larvae and adults

Consider an insect population where there is competition between the larvae and the adults. The larvae L therefore suffer from density dependent death imposed by the adults A:

$$\frac{\mathrm{d}L}{\mathrm{d}t} = aA - bL(1 + A/k) - cL \quad \text{and} \quad \frac{\mathrm{d}A}{\mathrm{d}t} = cL - dA \ .$$

a. Sketch (!) the nullclines for the two qualitatively different possibilities.

b. Determine the vector field in both scenarios, and determine the stability of any non-trivial steady states

c. Explain in biological terms how the parameters d and c determine whether the insect population survives.

5.6 Extra Practice Exercises

Question 5.4. Virus competition experiments

To determine the relative fitness of two variants of a virus one typically grows them together in conditions under which they grow exponentially. Thus, consider two variants of a virus that grow exponentially according to

$$\frac{\mathrm{d}V_1}{\mathrm{d}t} = rV_1 \quad \text{and} \quad \frac{\mathrm{d}V_2}{\mathrm{d}t} = r(1+s)V_2 \ ,$$

where s is the conventional selection coefficient. One way to represent the data is to plot how the fraction $f \equiv V_2/(V_1+V_2)$ evolves in time. To compute how the fraction $f(t)$ changes one needs to employ the quotient rule of differentiation: $[f(x)/g(x)]' = (f(x)'g(x) - f(x)g(x)')/g(x)^2$. Thus, using $'$ to denote the time derivative, one obtains for $\mathrm{d}f/\mathrm{d}t$:

$$\begin{aligned}
\frac{\mathrm{d}f}{\mathrm{d}t} &= \frac{V_2'(V_1+V_2) - (V_1'+V_2')V_2}{(V_1+V_2)^2} \ , \\
&= \frac{V_2'V_1 - V_1'V_2}{(V_1+V_2)^2} \ , \\
&= \frac{r(1+s)V_2V_1 - rV_1V_2}{(V_1+V_2)^2} \ , \\
&= r(1+s)(1-f)f - rf(1-f) \ , \\
&= rsf(1-f) \ ,
\end{aligned}$$

which is the logistic equation with growth rate rs and steady states $f=0$ and $f=1$. Thus one expects a sigmoidal replacement curve of the two variants.

a. Now write a differential equation of the ratio $\rho = V_2/V_1$ of the two populations.

b. Virologists plot the logarithm of the ratio in time to determine the relative fitness (Holland *et al.*, 1991). What is the slope of $\ln[\rho]$ plotted in time?

Chapter 6

The predator functional response

Limit cycles and oscillations

6.1 Learning objectives

After studying this chapter you should be able to do all exercises as well as be able to explain the following:

The function $y = ax$ is a **linear function** and the function $y = ax/(h + x)$ is a **saturation function**. What is their fundamental difference? Why is it **more realistic** to use a saturation function for the consumption of prey by predators? What is the meaning of the **parameters** a and h in $y = ax/(h + x)$?

What causes a system to oscillate? What is a **Hopf bifurcation** and when does it arise? What is a **limit cycle**?

What is the difference between **global** and **local** dynamics?

Why can a limit cycle be a stable **attractor** but not a steady state?

Which population increases most in a predator prey model when one feeds the prey?

6.2 Introduction

In the previous chapter we derived the Lotka-Volterra model for a predator-prey interaction. That model assumed that the number of prey caught per predator is proportional to the prey density, using a linear relationship. The more prey there is, the more prey gets eaten per individual predator *per capita*. Realistically, predators would get satiated at high prey densities, and/or would become limited by the time needed to handle the prey it has caught.

Let us define the concept of a **functional response**, which describes the expected number of prey eaten per predator as a function of the prey density. Ad abovementioned, the classical Lotka-Volterra

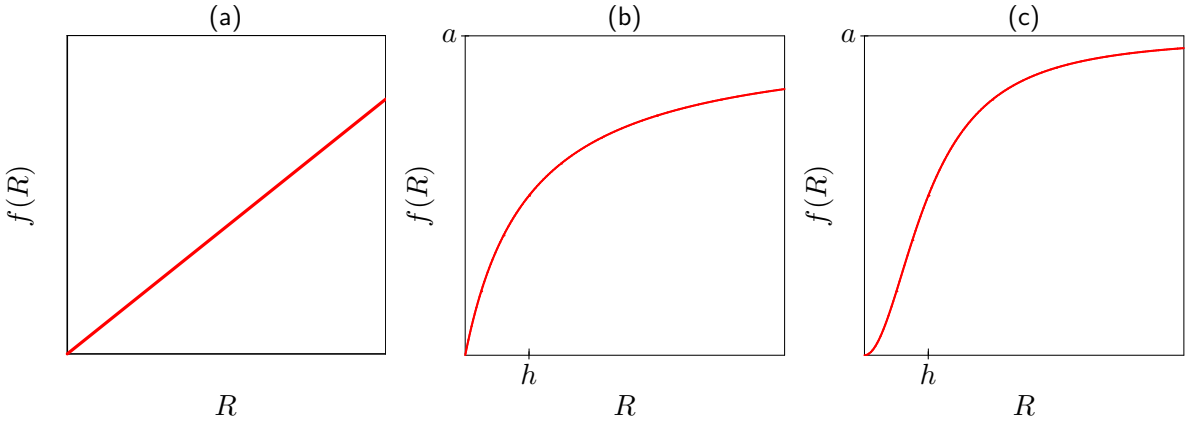


Figure 6.1: Plotting the number of prey eaten per predator as a function of the prey density R. A linear (a), a Monod saturated (b), and a sigmoid (c) functional response.

model has a linear functional response (see Fig. 6.1a).

Let us rewrite the Lotka-Volterra model to include a general function, called $f(R)$, for the per capita consumption per predator:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = rR(1-R/K) - Nf(R) \quad \text{and} \quad \frac{\mathrm{d}N}{\mathrm{d}t} = cNf(R) - dN \ , \tag{6.1}$$

where $f(R)$ is the functional response, i.e. the amount of prey biomass eaten by one predator per unit of time. For simplicity we have collapsed the prey birth and death processes into a net growth term (i.e. the intrinsic growth parameter). The parameter c is again a conversion factor, meaning that whatever function we plug into this set of equations, predation will always be scaled with c. The three functional responses depicted in Fig. 6.1 can be defined by the following three equations:

$$f(R) = aR \ , \quad f(R) = \frac{aR}{h+R} \quad \text{and} \quad f(R) = \frac{aR^2}{h^2+R^2} \ , \tag{6.2}$$

which define the classical linear response, a "Monod saturation" response, and a sigmoid ("s-shaped") functional response. Ecologists also call these the Holling type I, type II and type III functional responses, respectively (Holling, 1959). More generally speaking, the latter two functions are a specific type of saturation functions called "Hill functions"(for details see the appendix). The Hill-functions in Eq. (6.2) have the pleasant property that $f(R) \to a$ when $R \to \infty$, and that $f(R) = \frac{1}{2}a$ when $R = h$. These two simple parameters are very useful, because these can be emperically determined not only for predators eating prey, but also bacteria consuming glucose or enzymes converting substrates. For the Lotka-Volterra model, a is the maximum prey biomass that a predator can consume per unit of time. The saturation constant h is the prey density at which predator consumption is half of this maximum. The h-parameter of the Lotka-Volterra model is partly determined by the "handling time" (see our Biological Modelling course (De Boer, 2016)).

To move beyond the overly simplistic linear relationship, we will now study the model with a Monod functional response. We take the general equation from Eq. (6.1) and plug in the second functional response of Eq. (6.2), yielding:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = rR(1-R/K) - \frac{aNR}{h+R} \quad \text{and} \quad \frac{\mathrm{d}N}{\mathrm{d}t} = \frac{caNR}{h+R} - dN \ . \tag{6.3}$$

To sketch the nullclines we write $\mathrm{d}R/\mathrm{d}t = 0$ to find

$$R = 0 \quad \text{and} \quad N = (r/a)(h+R)(1-R/K) \ , \tag{6.4}$$

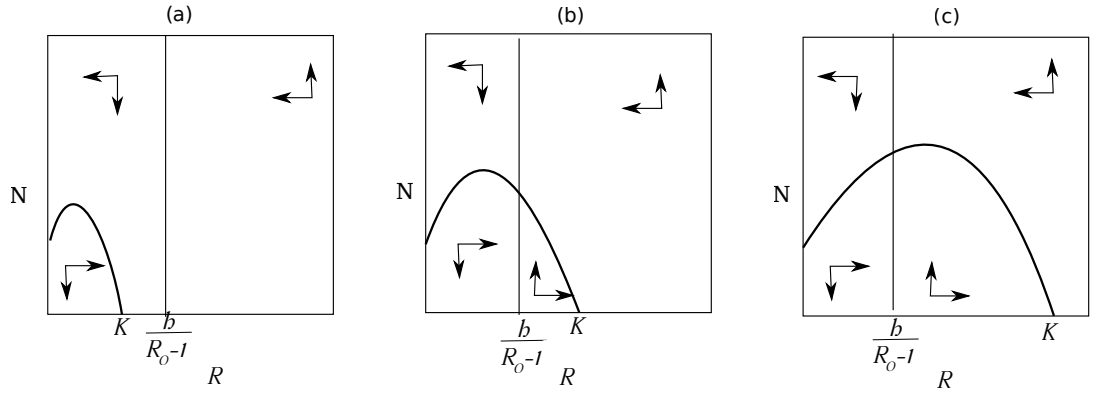


Figure 6.2: The nullclines and vector field of a predator prey model with a Monod functional response (Eq. (6.3)). Situations are shown for increasing carrying capacity K not supporting (a) or supporting (b,c) predator survival. For K supporting predator survival the non-trivial equilibrium may occur right (b) or left (c) of the top of the parabola depicting the prey nullcline.

where the latter describes a parabola that equals zero when $R = -h$ and $R = K$ (i.e., the latter is of the form $y = \alpha(h + x)(1 - x/K)$). For the predator nullcline we write $\mathrm{d}N/\mathrm{d}t = 0$ to find

$$N = 0 \quad \text{or} \quad R = \frac{h}{ac/d - 1} \,, \tag{6.5}$$

which are horizontal and vertical lines in the phase space.

To simplify we again define an R_0. Because we have collapsed birth and death into a logistic equation, the R_0 of the prey is not defined. To define an R_0 of the predator we can now employ the fact that predator consumption is saturated. Indeed for an infinite prey population the *per capita* predator birth rate approaches ac, and over an expected life span of $1/d$ time units, we obtain a maximum fitness of $R_0 = ac/d$. The location of the predator nullcline in Eq. (6.5) can now be written as $R = h/(R_0 - 1)$.

The prey nullcline is the parabola depicted in Fig. 6.2. The point where the parabola intersects the horizontal axis is the carrying capacity of the prey ($R = K$). Rather than deriving the vector-field from the equations, it is sometimes also possible to determine the vector-field from biological reasoning. For this it is important to consider that there are only two possibilities, a variable will either increase or decrease. Thus, for a particular nullcline relevant for that variable, one only needs to determine at which side of the nullcline the increase and at which side the decrease will occur. In this particular example it is natural that the prey population increases below the parabola (e.g., below its carrying capacity when $N = 0$) and decreases above it. The predator nullcline is a vertical line at $R = h/(R_0 - 1)$, see Fig. 6.2. Here we can apply a similar approach: left of the nullcline prey numbers are low and the predators that depend on these prey will decrease, right of the nullcline prey numbers are high enough for the predator to increase.

If $h/(R_0 - 1) > K$ the maximum prey density, K, is insufficient for predator growth. Hence predators can not survive and a prey population at carrying capacity is the only attractor of the system. If $h/(R_0 - 1) < K$ the two nullclines intersect in a non-trivial steady state, and we once again observe a type of rotation in the vector field. Importantly, there are two qualitatively different possibilities. The situation where the predator nullcline intersects at the right side of the top of the parabola (i.e., if $h/(R_0 - 1) > (K - h)/2$) differs from that where it intersects at the left side of the top in an important way. When you are in situation Fig. 6.2b, adding a little prey takes you above the parabola, hence prey decreases. When you are in sutation Fig. 6.2c, adding a little prey actually takes you *under* the parabola. You may remember from the last chapter that this may change the

stability of the equilibrium.

In Fig. 6.4a, where $h/(R_0-1) > (K-h)/2$, there is a negative feedback of the prey on itself, and a zero feedback of the predators on itself. This is similar to the situation in the Lotka-Volterra model, and hence we expect a stable (spiraling) equilibrium. In Fig. 6.2c, the prey have a positive feedback on themselves, while the predators still have zero feedback on themselves. Thus the equilibrium is now *unstable*, such that the populations will spiral away from this point. The question still remaind exactly what type of dynamics will occur. For this, we have to learn about other types of attractors (Box 6.1).

Box 6.1 Limit cycles

Thusfar, we have mostly encountered equilibria where attractors take the system to a single point in the phase space. However, systems of two or more differential equations can also have attractors consisting of a series of multiple connected points. The trajectory of a limit cycle looks like a closed (circular-ish) shaped in the phase space (Fig. 6.3). If a limit cycle is stable (i.e. an attractor), the system will converge to the limit cycle and subsequently perpetually walk along its curve in the direction prescribed by the vector field. This causes the variables of the system to continuously oscillate with a constant amplitude.

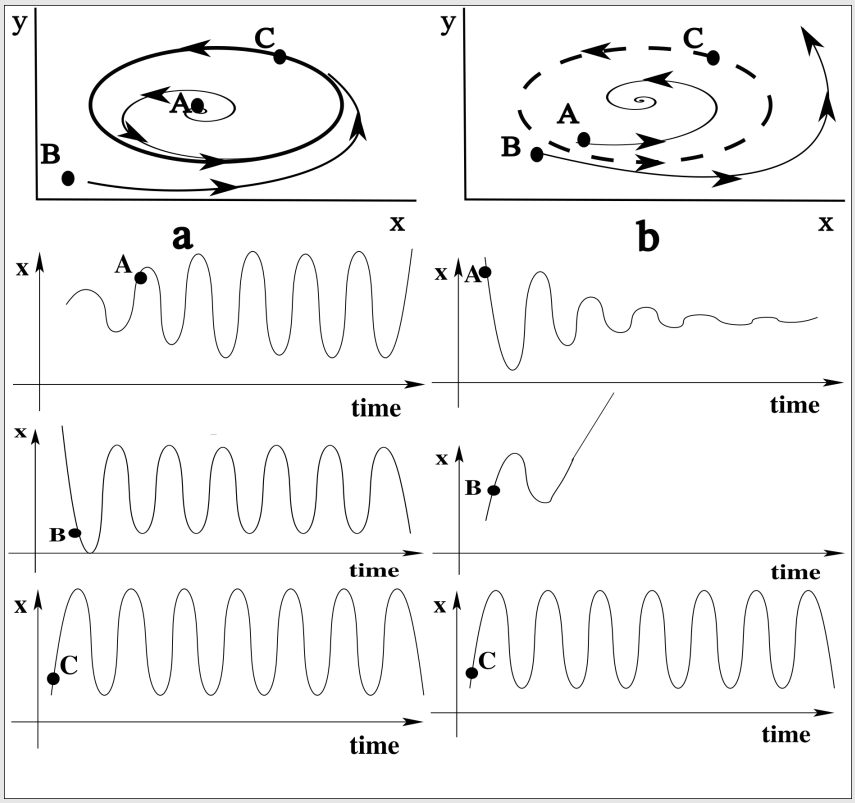


Figure 6.3: Top: phase plane with limit cycle, second row: temporal dynamics for point starting inside limit cycle, third row: temporal dynamics for point starting outside limit cycle, fourth row: temporal dynamics for point starting on limit cycle for situation with stable (a) and unstable (b) limit cycle. Figure adapted from Panfilov (2010)

Fig. 6.3a shows a stable limit cycle (bold ellipse), as well as three trajectories, one starting inside (A), one outside (B) and one exactly on (C) the limit cycle. As the limit cycle is an attractor the inside trajectory will spiral outward towards it, the outside trajectory will rotate inward towards

it, and the trajectory starting on the limit cycle will stay there, resulting in oscillations with decreasing, increasing or constant amplitude, respectively (Fig. 6.3a). The dynamics inside the stable limit cycle show that there is an unstable equilibrium inside the limit cycle.
Fig. 6.3b shows an unstable limit cycle (dashed ellipse), again with three trajectories with different starting points. As the limit cycle is a repellor, trajectories starting inside or outside of the limit cycle diverge away from it. The inside trajectory spirals further inward, indicating the presence of a stable equilibrium. This results in oscillations that decrease in amplitude until a constant value is reached (Fig. 6.3b, second row). Trajectories starting outside the limit cycle may converge to an alternative attractor outside the limit cycle, or, if such an attractor is absent, go to plus or minus infinity (Fig. 6.3b, third row). The trajectory starting exactly on the unstable limit cycle will remain there, resulting in constant amplitude oscillations (Fig. 6.3b, bottom row) until a perturbation occurs causing it to fall either inside or outside the limit cycle. The unstable limit cycle acts as a *separatrix* or boundary for the basin of attraction of the stable equilibrium inside the limit cycle.

6.3 Monod limit cycle

Let us further consider the phase portraits shown in Fig. 6.2b and Fig. 6.2c. For Fig. 6.2b we concluded that the non-trivial point was a stable equilibrium, thus, based on the rotating vector field, we expect trajectories to rotate towards this equilibrium point. Indeed, the trajectory for this situation is shown in Fig. 6.4a, making a neat inwards spiral. For Fig. 6.2c we concluded that the non-trivial equilibrium point has become unstable. However, in both Fig. 6.2b and Fig. 6.2c, we see that equilibrium point $(0, 0)$ and equilibrium point $(K, 0)$ are unstable equilibria. Thus, with the non-trivial equilibrium becoming unstable, no other point attractor arose. So we have a system that is pushed away from this point at a *local* scale (closeby the point), and pushed toward it at a *global* scale (far from the point). So, where will the system go?

The only manner in which this paradox of conflicting inward (stable) global dynamics and outward (unstable) local dynamics can be resolved is through the presence of a stable limit cycle to which the global dynamics can spiral inwards and the local dynamics around the unstable equilibrium can spiral outwards (see Box 6.1). (To further practice this challenging concept of conflicting global and local dynamics we made a DWO Lotka-Volterra exercise.)

Let us imagine we are moving increasing the carrying capacity of the prey (the K-parameter). At low K, there is no intersection between the vertical line and the parabols: predators cannot survive and only the prey remains. When we start feeding the prey, and K is increased, the vertical line will start intersecting the parabola on the *right* side of the top. This gives a stable spiral, causing the system to spiral inwards no matter where one starts. When pushing K further (feeding the prey even more), the stable spiral turns into an unstable spiral, meaning that the system will spiral away from this point, even though the *global dynamics* are still describing an *inward* rotating motion. This transition from a stable spiral to an unstable spiral (resulting in periodic behaviour), is called a **Hopf bifurcation**. An example of real life oscillatory predator prey dynamics is given in Fig. 6.5.

Importantly, the Hopf bifurcation in our extended Lotka-Volterra model goes from a stable spiral to a stable limit cycle, meaning that it is not the end of the world: both predators and prey still survive, although they now oscillate. If a bifurcation instead involves a very large, abrupt system change, it is called a catastrophic bifurcation. As one increases K further and further (or moves the predator nullcline to the left), the oscillations will become bigger and bigger (*e.g.* compare Fig. 6.4b/e and Fig. 6.4c/f). Note that during part of the oscillations predator and prey numbers become

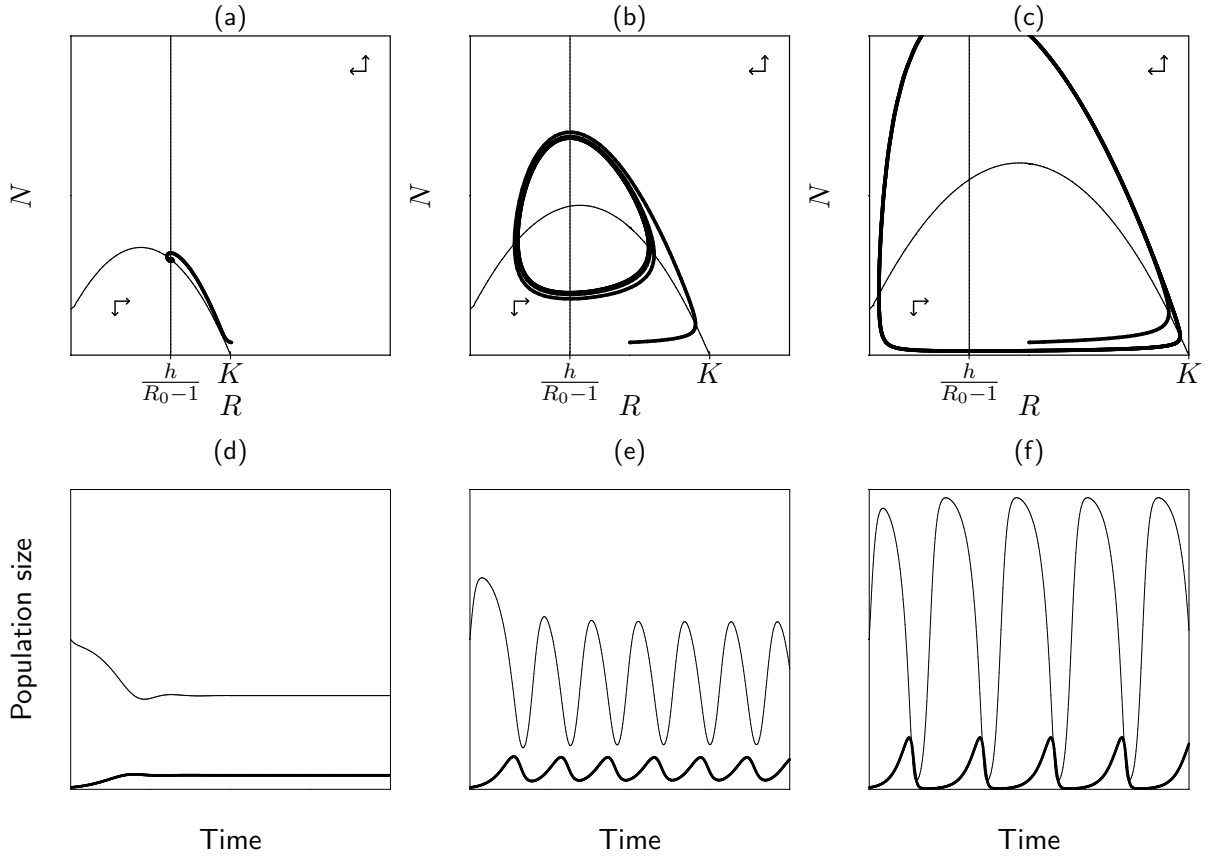


Figure 6.4: The nullclines and trajectories of a predator prey model with a Monod functional response, see Eq. (6.3). The carrying capacity K is indicated. The predator nullcline is the vertical line located at $R = h/(R_0 - 1)$. From left to right the carrying capacity increases. In the two panels on the right the model behavior approaches a stable limit cycle. The heavy line in the time plots is the predator.

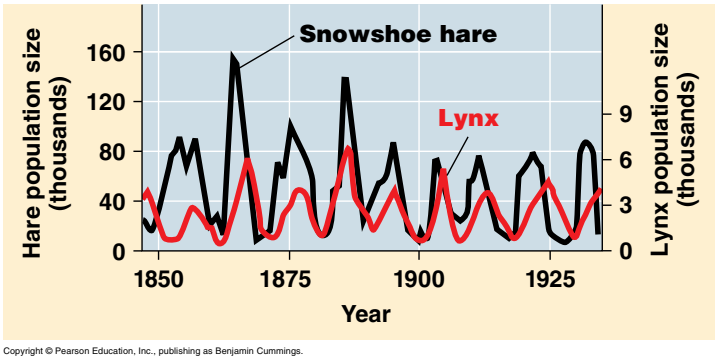


Figure 6.5: Population cycles in the snowshoe hare and lynx. From: Campbell & Reece (2008).

very close to zero, but still recover. Because real biological individuals are discrete entities (and not concentrations), and because of stochastic effects in nature, such small population numbers can be argued to represent a situation that can easily lead to the extinction of the predators or both the predators and prey. Thus, if you're an ecologist that cares about biodiversity, you still want to make sure the oscillations are not too extreme!

A non-intuitive result from the predator prey models described thus far is that the prey population does not increase when its food availability is increased. This interesting phenomenon is known as

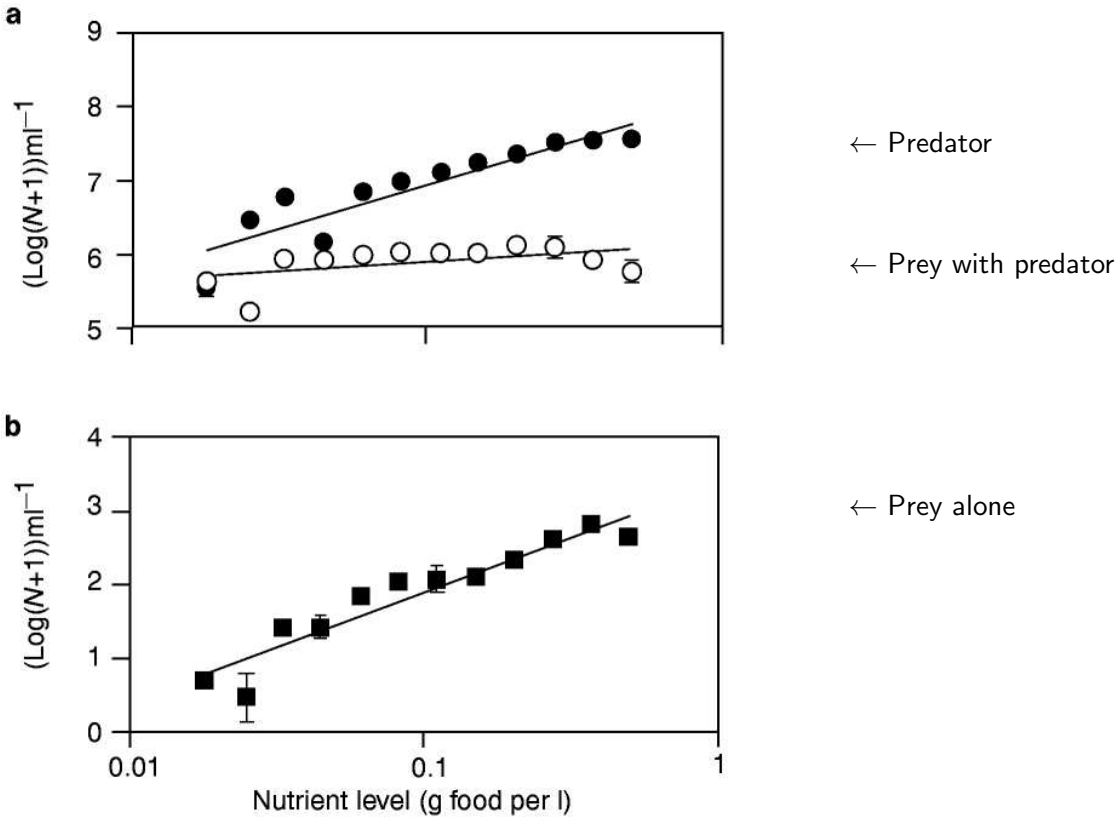


Figure 6.6: The effect of nutrients on the density of the prey *Serratia marcescens* growing on its own (b: filled squares); and on that of the prey *Serratia* (a: open circles) growing with a predator *Colpidium striatium* (a: closed circles). From: Kaunzinger & Morin (1998).

the "Paradox of Enrichment" (Rosenzweig, 1971), and has been studied intensively. Fig. 6.6 shows an example of a bacterial food chain providing strong support for the existence of this paradox in real life (Kaunzinger & Morin, 1998). If the prey *Serratia marcescens* grows on its own, the steady state density increases with nutrient availability. (Fig. 6.6b). However, if the prey *Serratia* grows together with the bacterivorous ciliate *Colpidium striatium*, it is largely the predator density that increases with nutrient availability (Fig. 6.6a).

6.4 Summary

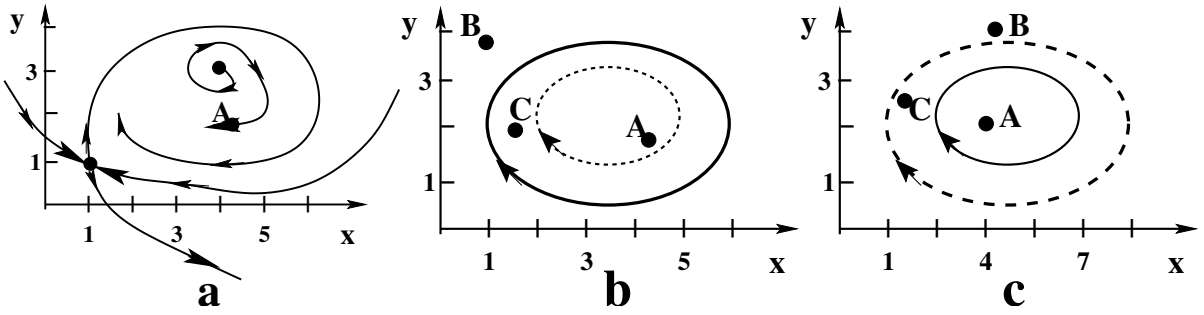
Simple saturation effects extend the Lotka-Volterra model into a system where the non-trivial steady state need not be stable. Oscillatory behavior therefore seems a very natural behavior of a biological system, and is here brought about by a local positive feedback of the prey onto itself that destabilizes the non-trivial equilibrium. Note that while this positive feedback is clear from the vectorfield around the non-trivial equilibrium it is not at all obvious from the systems equations. Indeed, whether or not this feedback is positive or negative turned out to depend on the location of the non-trivial equilibrium. In this model one can compute an R_0 of the predator for an infinite prey density. Like in the simpler Lotka Volterra model, feeding the prey is still not increasing the prey density as long as the predator is also present.

There are many textbooks on Theoretical Ecology. If you're an ecologist thinking about questions

of biodiversity, the books of Yodzis (1989), Case (2000), and Hastings (1997) are a good addition to the material covered here.

6.5 Exercises

Question 6.1. Completing phase planes
Complete the phase portrait and qualitatively sketch the temporal dynamics of the variable x (change of the variable x over time t) for the indicated points (**A**, or **A,B,C**).



- For Figure a
- For Figure b
- For Figure c

Question 6.2. Paradox of enrichment
Rosenzweig (1971) analyzed eutrophication of lakes with algae and zooplankton. Water pollution was at that time an even larger problem than it is now, with large lakes like lake Erie in Canada being nearly dead. It was well known at that time that the pollution was largely due to excess nutrients (nitrogen and phosphate), but it was unclear how this drove ecosystems to extinction. As always in biology, one can argue for several factors contributing to the negative effects of pollution:

- eutrophication leads to growth of the algae which leads to high concentrations of oxygen during the day, but to low concentrations at night due to oxygen consumption;
- water pollution also involves toxic waste that kills fish, zooplankton and/or algae;
- eutrophication leads to a shift from edible green algae to toxic blue algae; etcetera.

The contribution of Rosenzweig was to develop a model allowing us to "think clearly" (May, 2004). Rosenzweig argued that due to saturation effects, ie the amount of prey eaten per predator saturating with prey number, the algae nullcline should typically have a maximum. Furthermore he argued that the zooplankton nullcline should typically be vertical (like the ones in Fig. 6.4). He showed that the state and stability of the system depends on the location of the zooplankton nullcline, and argued that increasing the carrying capacity of the algae by eutrophication was **expected** to destabilize the system (Rosenzweig, 1971).

a. Rosenzweig was criticized by McAllister *et al.* (1972) who was growing salmon in ponds. To increase the salmon production he added nutrients to the ponds to feed the algae. His criticism was that the system remained healthy. The water remained clear, i.e., the density of algae was not increasing, while the salmon density increased markedly (8-fold). Does this criticism invalidate Rosenzweig's analysis?

b. Large studies comparing various lakes show that the density of the algae is increasing with eutrophication. While this increase is much larger when there are no zooplankton (Persson *et al.*, 2001), a modest increase is still observed in their presence that can not be explained by the

original vertical zooplankton nullcline. Extend Eq. (6.3) with a small density dependent death for the zooplankton, and sketch the nullclines.

c. What do you now expect for the algal density after eutrophication in the presence and in the absence of zooplankton?

Question 6.3. Enriching oligotrophic lakes

Consider a oligotrophic lake (i.e., a lake with very low concentrations of nutrients). The lake has a low stable density of algae. Invasion of zooplankton is never successful because an algal population at carrying capacity is insufficient for the survival of the zooplankton.

a. Model this lake with Eq. (6.3) and sketch the nullclines for this situation.

b. What is the parameter condition for this situation?

c. What happens if one adds nutrients to such a lake?

d. Does eutrophication of lakes always lead to a decrease of ecosystem diversity?

Question 6.4. Bacterial oscillations

The bacterium *Streptococcus pneumonia* can be grown in a chemostat with a constant supply of resources and a constant environment. The bacteria replicate very fast, and –despite the constant environment– their densities oscillate over several orders of magnitude (Cornejo *et al.*, 2009). It can be shown that the bacteria produce a toxin, and that the toxin concentration also oscillates with the same period. Peaks in the toxin concentration more-or-less coincide with peaks in the bacterial population size. It has been established decades ago by Monod that the replication rate of bacteria follows a simple saturation function of the resource densities. A natural model would therefore be

$$\frac{\mathrm{d}R}{\mathrm{d}t} = s - wR - \frac{aNR}{h+R}\ , \quad \frac{\mathrm{d}N}{\mathrm{d}t} = \frac{bNR}{h+R} - wN - xNT \quad \text{and} \quad \frac{\mathrm{d}T}{\mathrm{d}t} = pN - wT\ ,$$

where w is the "wash out" rate of the chemostat, R is the resource concentration, N is the bacterial density, and T is the concentration of the toxin. We here assume that toxin is produced at a rate p per bacterium per hour.

a. Why do all populations have the same "death rate" w?

b. What is the interpretation of the xNT term?

c. Simplify the model by applying a quasi steady state assumption for the toxin (explained in more detail in Chapter 6). For this we set $\mathrm{d}T/\mathrm{d}t = pN - wT = 0$ which gives us the equation $T = (p/w)N$. Next, we substitute this equation for T into the equations $\mathrm{d}R/\mathrm{d}t$ and $\mathrm{d}N/\mathrm{d}t$ and obtain a simplified 2-dimensional model. (Note that since we now have an algebraic equation for T we no longer use $\mathrm{d}T/\mathrm{d}t$).

d. Sketch the nullclines of the simplified model (assuming that bacteria survive).

e. Do you indeed expect oscillations?

f. Consider the model in the absence of the toxin, i.e., set $p = x = 0$, and compare it to the predator-prey model of Eq. (6.3) on Page 58. Do you expect oscillations in predator-prey systems if the resource is maintained by a constant source rather than by logistic growth?

6.6 Extra Practice Exercises

Question 6.5. Ditch

A local ditch is polluted with chemicals that are toxic for zooplankton, but have little effect on the algae.

a. What parameter(s) of Eq. (6.3) change due to this form of water pollution?

b. Sketch the nullclines with and without pollution in one diagram and predict the effect of pollution

on the algae and the zooplankton.

Question 6.6. Pump

A small lake with algae and zooplankton is dirty and green of the high algal densities. Biologists attempt to clean up the water by putting in a water pump that selectively filters the algae out of the water, and leaves the zooplankton in. The pump has been in place for months and the lake has approached a new steady state.

a. Extend Eq. (6.3) with this device.

b. Sketch the nullclines before and after the installation of the pump in one diagram, and predict the effect of the pump on the algae and the zooplankton. Remember that there are three different possibilities for the initial state of your lake.

Chapter 7

Gene regulation

Bistability and hysteresis

7.1 Learning objectives

After studying this chapter you should be able to do all exercises as well as be able to explain the following:

What do we mean with the **time scale** at which a variable changes?

How can we simplify our models if the time scales of variables are very different?

How does a quasi steady state assumption differ from an actual steady state?

What is bi-stability, and why can it only occurr in non-linear systems?

What does it mean when a bi-stable system shows *hysteresis*?

7.2 Introduction

In all organisms, transcription of DNA leads to the production of mRNA, which is then translated into proteins. In text books, this is often called the central dogma of biology[1]: "DNA makes RNA and RNA makes protein". Species like *Homo sapiens* have more than twenty thousand genes. However, not all these genes are active in all cells at all times. Instead, different cell types express different subsets of genes, thus allowing multicellular organisms in which all cells have the same genotype nevertheless have distinct types of cells. In addition, physiological state and diseases influence the set of genes active within a cell.

Understanding the processes that determine which genes are expressed is of crucial importance in many areas of biology. The expression of genes is, among other things, regulated by so-called

[1] Not to say we ought to be dogmatic about this, perhaps we'll find exceptions to this rule in the future!

transcription factors that bind to special sites on the DNA in the neighborhood of the gene and that influence that gene's transcription. Transcription factors are proteins that are encoded by a special class of so-called regulatory genes.

With techniques like RNA-chips and high throughput RNA sequencing, the regulatory networks of biological systems appears increasingly complex. Mathematical models play an important role in understanding basic regulatory mechanisms of the cell, like genes expression switching on or off, or how signal transduction changes a protein from inactive to active. With more an more players becoming known, these mathematical models become too difficult and laboursome to solve by hand. Instead, for such complex systems, nummerical approximations are used. This means that, instead of doing algebra with "free parameters", one defines the parameters numerically (*i.e.* we set all the rates to some numeric values), as well as the initial states of the variables. Then, we let a computer calculate the "next state" of all the variables again and again, so we can study the trajectory. Although we won't work with such complex systems in this course, it is generally good to know that when the algebra gets too hard, we can still study mathematical models with the help of our *silicon friends*.

7.3 Models

One can write simple models for the intracellular concentration of the mRNA that is produced by transcribing DNA, and the corresponding protein concentration resulting from the translation of the mRNA:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = c - dM \quad \text{and} \quad \frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P \ , \tag{7.1}$$

where c is the transcription rate, in say molecules per hour, and l is the translation rate (per hour). The d and δ parameters are the decay rates, or turnover rates, of mRNA and protein, respectively. The mRNA equation is an example of a non-replicating population that we have studied in earlier chapters, and has the stable steady state $\bar{M} = c/d$ molecules. Solving $\mathrm{d}P/\mathrm{d}t = 0$ nullcline yields the straight line $M = (\delta/l)P$ (see Fig. 7.1a). The nullclines intersect in one unique steady state, which can be solved from $c/d = (\delta/l)P$, giving $(\bar{P}, \bar{M}) = (\frac{cl}{d\delta}, \frac{c}{d})$ molecules.

Let us determine the vector-field in the rightmost lowest part of the phase plane, i.e. below the line $M = \frac{c}{d}$ and right of the line $M = \frac{\delta}{l}P$. In this region P is large, while M is small. It follows from Eq. 7.1 that in this region M will increase, while P will decrease. From this, we can determine the rest of the vector-field. The vector field around the steady state shows that the point is stable. The system will thus always approach this stable steady state.

Transcription factors can inhibit the transcription of their own mRNA. Let us model this by a declining Hill function $1/(1+x)$ (Note that $1 - x/(1+x) = (1+x)/(1+x) - x/(1+x) = 1/(1+x)$) (see Chapter 11):

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{c}{1+P/h} - dM \quad \text{and} \quad \frac{\mathrm{d}P}{\mathrm{d}t} = lM - \delta P \ , \tag{7.2}$$

where c now is the maximum transcription rate (molecules per hour), and l remains the translation rate. When $P = 0$ the gene is "on", and the transcription rate is maximal (c). When $P \to \infty$ the gene is "off" and the transcription rate approaches zero. When $P = h$ molecules, the transcription rate is $c/2$ molecules per hour, which is half-maximal. To analyze this slightly more complicated model we again draw nullclines. Setting $\mathrm{d}M/\mathrm{d}t = 0$, it is easiest to solve for M. We obtain $M = \frac{c/d}{1+P/h}$, which is an inverse Hill function with maximum c/d when $P = 0$ (see Fig. 7.1b). Solving $\mathrm{d}P/\mathrm{d}t = 0$ for M yields the same straight line $M = (\delta/l)P$ as above (see Fig. 7.1b). The

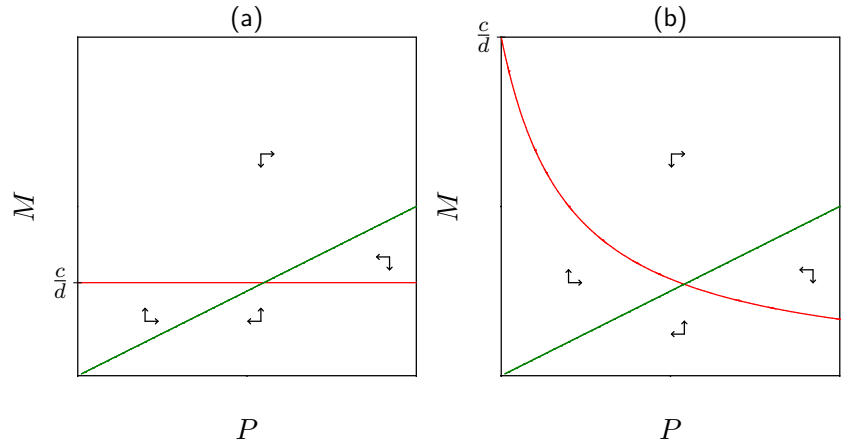


Figure 7.1: The nullclines of Eq. (7.1) in Panel (a) and Eq. (7.2) in Panel (b). In both cases there is only one possible phase space with one stable steady state.

nullclines again intersect in only one steady state. The vector field is similar to before. Thus, the steady state remains stable in the presence of this negative feedback on the transcription rate.

7.4 Separation of time scales

Often the expression of two or more genes will be relevant for a biological process of interest. Modeling for each gene both the mRNA and protein dynamics than quickly results in a complex model with many equations. To reduce this complexity we can make use of a method called separation of timescales that reduces the number of equations in a model.

Let us assume that proteins are degraded rapidly, i.e., that the turnover of proteins is much faster than the turnover of mRNA molecules. This implies that proteins vary over a much more rapid timescale than the mRNAs, and that therefore the protein concentration at any one moment will typically be close to the steady state value corresponding to the current concentration of its mRNA. Therefore we can approximate the level of the protein with its steady state value, which is called a "quasi steady state approximation".

The quasi steady state of Eq. (7.2)b is obtained by solving P from $\mathrm{d}P/\mathrm{d}t = 0$, resulting in $P = (l/\delta)M$. In this simple case, the QSS assumption boils down to assuming that the protein concentration is proportional to the concentration of its mRNA (Golding *et al.*, 2005). Substituting $P = (l/\delta)M$ into $\mathrm{d}M/\mathrm{d}t$ yields the simplified quasi steady state model

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{c}{1 + (l/\delta)M/h} - dM = \frac{c}{1 + M/h'} - dM \ , \tag{7.3}$$

where $h' = h\delta/l$ is the new saturation constant. We have thus reduced a two dimensional to a one dimensional model. If this quasi steady state is a fair assumption, the behavior of the simplified model should be very similar to that of the full model. We will apply this simplification in the next paragraph.

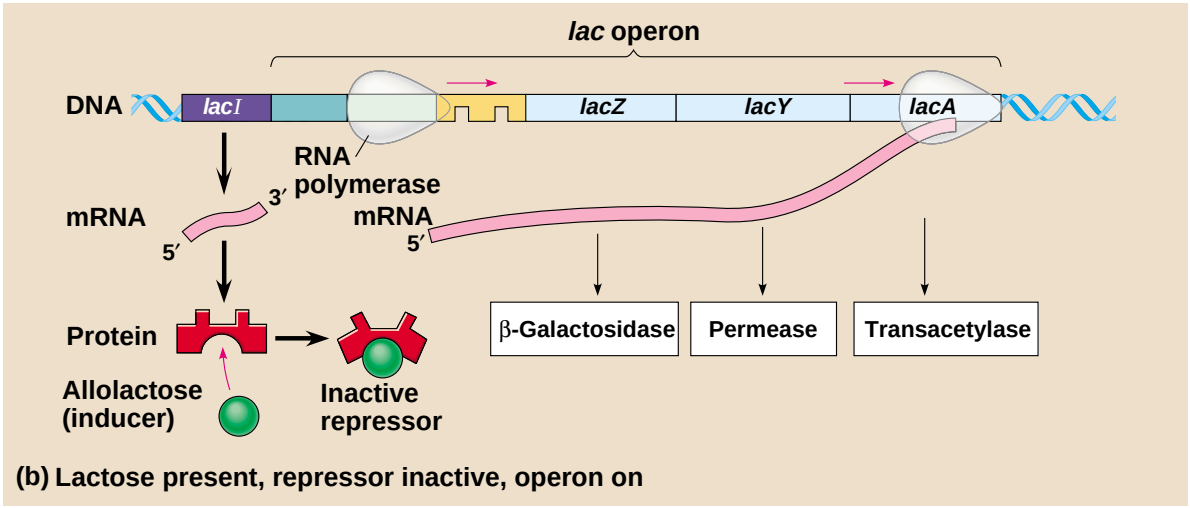


Figure 7.2: The *lac* operon: regulated synthesis of inducible enzymes. From: Campbell & Reece (2008).

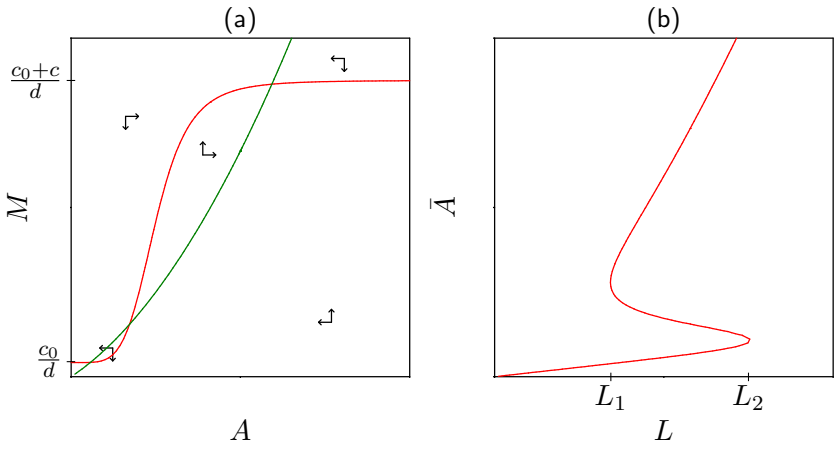


Figure 7.3: Nullclines of Eq. (7.4). Parameters: $L = c = d = 1$, $c_0 = 0.05$, $v = 0.25$, $n = 5$, and $\delta = 0.2$.

7.5 Lac-operon

Bacteria can use several external substrates (food sources) for cellular growth and switch the corresponding intracellular pathways on and off depending on the available resources. One of the possible substrates is the sugar lactose, and the regulation of the "Lac-operon" was one of the first unraveled gene regulation circuits (Jacob & Monod, 1961).

In bacterial operons the expression of a series of consecutive genes is determined by a single, shared regulatory region (Fig. 7.2). The lac operon consists of three genes, of which only the first two appear to be involved in lactose metabolism. The second gene of the operon, permease, imports extracellular lactose into the cell. The disaccharide allolactose, an isomer of lactose, is formed in small amounts from intracellular lactose. The first gene of the operon, β-galactosidase hydrolyzes allolactose into glucose and galactose. Regulation of the lac-operon involves positive feedback: Upon limited expression of the genes in the operon, the permease imports lactose into the cells thus leading to the formation of some allolactose. Allolactose subsequently deactivates a repressive transcription factor thereby increasing the expression of the genes in the operon. The degradation of allolactose

by β-galactosidase puts a limit on this positive feedback.

To determine the dynamic behavior of the lac-operon we develop a model, making use of the quasi steady state assumption we applied above in Eq. (7.3), i.e., assuming that the protein concentrations of permease and β-galactosidase remain proportional to the concentration of their mRNA. Because we know so little about the formation, degradation and deactivation of the repressor we model the activity of the repressor phenomenologically using the Hill-function $R = \frac{1}{1+A^n}$. This leads to the following model:

$$\begin{aligned} R &= \frac{1}{1+A^n} \ , \\ \frac{\mathrm{d}M}{\mathrm{d}t} &= c_0 + c(1-R) - dM \quad = \quad c_0 + \frac{cA^n}{1+A^n} - dM \ , \\ \frac{\mathrm{d}A}{\mathrm{d}t} &= ML - \delta A - vMA \ , \end{aligned} \tag{7.4}$$

where c_0 is the baseline transcription rate and c the repressor dependent transcription rate. Setting $n = 5$ causes the operon to steeply switch between on (high A and hence low R) and off (low A and hence high R). M is the mRNA concentration for both permease and β-galactosidase, L is a parameter representing the extracellular lactose concentration, and A is the concentration allolactose inside the cell. The allolactose concentration increases when the gene complex is active, i.e., when permease is present, and extracellular lactose L is transported from the extracellular to the intracellular environment. This is formulated as a simple "mass action term" of the external lactose concentration, L, and the permease concentration that is assumed to be proportional to the amount of mRNA M. Allolactose is hydrolyzed according to another mass action term depending on the enzyme β-galactosidase (the concentration of which is again assumed to be proportional to the amount of mRNA M). In addition, there is a small β-galactosidase independent degradation rate δ. Overall there is a positive feedback because increasing M increases A, which increases M (Griffith, 1968).

To analyze the model we draw nullclines. Setting $\mathrm{d}M/\mathrm{d}t = 0$ and solving for M yields

$$M = \frac{c_0}{d} + \frac{(c/d)A^n}{1+A^n} \ , \tag{7.5}$$

which is a sigmoid Hill function with an offset $M = c_0/d$ when $A = 0$ (see Fig. 7.3a). One obtains the vector field for M by noting that $\mathrm{d}M/\mathrm{d}t > 0$ when A is large and M is small. The $\mathrm{d}A/\mathrm{d}t = 0$ nullcline is solved from

$$M\,(L - vA) = \delta A \quad \text{or} \quad M = \frac{\delta A}{L - vA} \ , \tag{7.6}$$

which is of the form $y = ax/(1-bx)$. The nullcline goes through the origin, and has a horizontal asymptote $M = -\delta/v$ (approached for A going to $-\infty$), and a vertical asymptote $A = L/v$. Around the origin A is small, so $M \simeq (\delta/L)A$, which is a straight line with slope δ/L. Increasing the external lactose concentration, L, therefore shifts the vertical asymptote to the right and decreases the slope in the origin. Fig. 7.3a depicts the nullclines for the situation where the hyperbolic $\mathrm{d}A/\mathrm{d}t = 0$ nullcline intersects the sigmoid $\mathrm{d}M/\mathrm{d}t = 0$ nullcline three times. To determine the vector field for A note that when the concentration of mRNA is high, and that of allolactose A is low, the allolactose concentration increases ($\mathrm{d}A/\mathrm{d}t > 0$). The overall vector field shows that the steady state in the middle is a saddle point, and that the two at the boundaries are stable nodes.

The vector field we have sketched in Fig. 7.2a offers an intriguing biological insight. Lactose (L) is the regulator of the operon expression, so our basic intuition says that, depending on L, the operon will either be "off" (little to no expression) or "on" (high expression). Perhaps we expect the operon

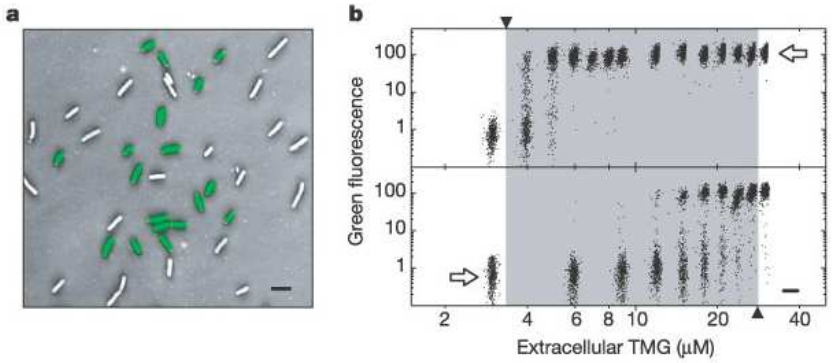


Figure 7.4: Figure 2 in Ozbudak *et al.* (2004): Hysteresis and bistability in single cells. **a**, Overlayed green fluorescence and inverted phase-contrast images of cells that are initially uninduced for lac expression, then grown for 20 h in 18μM TMG (which is an analogue of lactose). The cell population shows a bimodal distribution of lac expression levels, with induced cells having over one hundred times the green fluorescence of uninduced cells. Scale bar, 2μmm. **b**, Behavior of a series of cell populations, each initially uninduced (lower panel) or fully induced (upper panel) for lac expression, then grown in media containing various amounts of TMG. Scatter plots show log[green fluorescence] versus log[red fluorescence] for about 1,000 cells in each population. Each scatter plot is centered at a position that indicates the underlying TMG concentration. White arrows indicate the initial states of the cell populations in each panel. The TMG concentration must increase above 30μM to turn on initially uninduced cells (up arrow), whereas it must decrease below 3μM to turn off initially induced cells (down arrow). The gray region shows the range of TMG concentrations over which the system is hysteretic.

to be half-way in-between "on" and "off" when L is intermediate. However, Fig. 7.3a shows that, at intermediate L, two non-trivial attractors exist simultaneously, so the operon can both be "on" and "off" under exactly the same conditions! So what then determines which state the operon is in?

The effect of the lactose concentration on the operon can be better visualized by making a quasi steady state assumption for the mRNA equation, i.e., by assuming that the transportation and degradation of allolactose has a slow time scale, such that all the other variables are approximately always in their current steady state. Substituting Eq. (7.5) into $\mathrm{d}A/\mathrm{d}t$ in Eq. (7.4) yields the one-dimensional quasi steady model:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = -\delta A + (L - vA)\left(\frac{c_0}{d} + \frac{(c/d)A^n}{1 + A^n}\right) \ . \tag{7.7}$$

From this point, there are two ways to get insight into this system. First, we could draw a simple phase portrait for this 1-D system, as we did for growth models in an earlier chapter. You will practice with this during the exercises. Alternatively, we can solve $\mathrm{d}A/\mathrm{d}t = 0$, which would then describe how $\bar{A}$, the equilibrium value of A, changes as a function of the parameters. Then we could try and sketch $\bar{A}$ as a function of L, and see if we indeed get multiple steady states at a single value of L. Unfortunately, this can no longer be done by hand, but using the computer program Grind (see Chapter 10) we can easily depic $\bar{A}$ as a function of the lactose concentration in Fig. 7.3b. The curve in Fig. 7.3b is indeed a strange one: at intermediate lactose concentrations, $\bar{A}$ can has three steady states! Two of these states (the upper and lower one) correspond the the stable equilibria and Fig. 7.3a, while the line in the middle corresponds to the saddle node.

We can read Fig. 7.3b as a bifurcation diagram. Let us go back to the biology. Bacteria growing in an environment that is extremely poor in lactose are in a state with low intracellular levels of allolactose, thus the Lac-operon is off. This is the part left of L_1. Bacteria grown in high lactose conditions

have high expression of the operon, corersponding to the part right of L_2. Bacteria growing in an environment with an intermediate lactose concentration (greater than L_1 and smaller than L_2) can be in either of these two states (Novick & Weiner, 1957; Ozbudak *et al.*, 2004; Van Hoek & Hogeweg, 2006), which is indeed confirmed experimentally (see Fig. 7.4).

At intermediate lactose concentrations, the bacteria have what is known as "alternative stable states" (May, 1977; Scheffer *et al.*, 2001; Ozbudak *et al.*, 2004). Which stable state the bacteria are in, depends on the state they are currently in. When starting at high concentrations of lactose, slowly decreasing the concentration maintains a high expression of the operon (the upper line). Only when the concentration drops below L_1, will the bacteria switch to the low-expression state. Interestingly, slowly increasing the lactose concentration from this point onwards, does *not* result in a switch back. Instead, the concentration of lactose has to increase all the way to L_2 to switch back to high expression! In other words: for the intermediate values of L, the history of the bacteria determines in which state they will be. This is called "hysteresis": the system has a form of memory and tends to remain in the state where it was.

The bifurcations in Fig. 7.3b are called "saddle-node" bifurcations. Since the system shows a sudden discontinuity as it jumps to an alternative attractor, these transitions are so-called catastrophic bifurcations. They are import to understand, as irreverisable "tipping points" in ecosystems and the Earth's climate are, of course, undesirable.

7.6 Gene networks

Models of gene regulation have recently attracted much more attention because one can nowadays read the mRNA expression of thousands of genes in a single RNA-chip experiment. To understand the properties of complicated networks of genes influencing each other, people are studying models composed of many equations, one for each of the genes in the network. As an example, consider the equation for a gene producing protein "one", P_1, that is down-regulating its own transcription, but is up-regulated by another gene product, P_2:

$$\frac{\mathrm{d}P_1}{\mathrm{d}t} = c\,\frac{h_1}{h_1+P_1}\,\frac{P_2}{h_2+P_2} - dP_1\ , \tag{7.8}$$

where one uses simple Hill functions for the stimulatory and inhibitory effects the proteins P_1 and P_2 have on the production of protein one. Instead of using Hill functions one can also use "logical" functions switching genes "on" or "off" depending on their input signals (Alon, 2007). Models like this can obviously be extended to study the influence of many different proteins on the transcription of one of them. Writing ODEs or logical functions for all of the proteins, one obtains a model of a large gene network. As mentioned, at this point it is not productive to try and analyse the steady states by hand. Instead, we can use computers to numerically calculate how the system unfolds.

7.7 Summary

Models for mRNA and protein synthesis have a very simple general form. Positive feedback loops, as discussed for the lactose operon, can cause alternative stable steady states and hysteresis. Simple models for gene activity can be extended into models for complicated networks of regulatory interactions. If you are interested to dive deeper into this (this is not part of the course), the excellent book by Alon (2007) gives an exciting introduction into the structure of gene networks regulated by

transcription factors, and uses simple mathematical models to illustrate the functioning of various interaction schemes.

7.8 Exercises

Question 7.1. Gene network
Consider a protein, P_1, that is down-regulated by a transcription factor, P_2. The transcription factor itself is up-regulated by P_1:

$$\frac{\mathrm{d}P_1}{\mathrm{d}t} = \frac{c_1}{1 + P_2/h_2} - d_1 P_1 \quad \text{and} \quad \frac{\mathrm{d}P_2}{\mathrm{d}t} = \frac{c_2 P_1}{h_1 + P_1} - d_2 P_2$$

a. What is the biological interpretation of h_1?
b. What is the steady state of P_1 in the absence of its transcription factor?
c. What is the steady state of P_2 in the absence of P_1?
d. Sketch the nullclines, and determine the stability of all steady states.
e. What is the expected behavior of this network?

Question 7.2. Lac-operon
The model for the Lac-operon has a positive feedback loop because an increased concentration of allolactose increases the expression of permease, which further increases the allolactose concentration. There is also a negative feedback loop because increasing allolactose levels increases the expression of β-galactosidase, which decreases the allolactose concentration by the hydrolysis of allolactose. To test which of these feedback loops is required for the hysteresis we remove the negative feedback loop by setting $v = 0$ in Eq. (7.4).
a. Sketch the nullclines, assuming $n > 1$. Consider different values of L.
b. Determine the stability of the steady state(s)
c. Assume that the mRNA kinetics is much faster than that of the allolactose, and write a model for $\mathrm{d}A/\mathrm{d}t$. Analyze equilibria and their stability for this simplified 1D model and compare it to the full 2D model. Hint: draw the function described by $\mathrm{d}A/\mathrm{d}t$ for different values of L.
d. What is the role of β-galactosidase in the hysteresis of the lac operon? Hint: Go back to your answers to questions a and c.

Question 7.3. Michaelis-Menten
The famous Michaelis-Menten term comes from a quasi steady state assumption in enzymatic reactions. Consider the following reaction for the formation of some product P from a substrate S. The enzyme E catalyzes the reaction, i.e.,

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

Because the enzyme is released when the complex dissociates one writes a conservation equation

$$E + C = E_0 \ .$$

.
a. Write the differential equations for the product P, the substrate S, and the complex C. Use the conservation equation to express E as a combination of E_0 and C.
b. Assume that the formation of the complex is much faster than that of the product, i.e., make the quasi steady state assumption $\mathrm{d}C/\mathrm{d}t = 0$.
c. Write the new model for the rate of product formation. Simplify your final answer by combining all the rate constants (all the k's) into a new parameter called K_m.
d. Sketch the rate at which the product is formed ($\mathrm{d}P/\mathrm{d}t$) as a function of the substrate concentration S.
e. Under our quasi-steady state assumption for C, the equation for the $\mathrm{d}C/\mathrm{d}t$ will always be zero. We can add the equation for $\mathrm{d}C/\mathrm{d}t$ to our equation for $\mathrm{d}S/\mathrm{d}t$, without it effecting the rate. How does this effect our final equation for $\mathrm{d}S/\mathrm{d}t$?

Question 7.4. Self-study exercise: Catastrophic shifts in ecosystems
Read the paper by Scheffer *et al.* (2001) which gives a biological overview of catastrophic shifts between alternative stable states.
a. Check that Eq. (1) in Box 1 of the paper indeed gives the hysteresis picture of Fig. 1c in the paper. Hint: use a so-called graphical construction method and split Eq. (1) into its positive part $\mathrm{d}x/\mathrm{d}t = a + f(x)$ and negative part $\mathrm{d}x/\mathrm{d}t = -bx$ and determine from their intersection points the shape of the nullcline.

b. What data in the paper unequivocally support the conjecture of hysteresis? Hint: what data truly require Fig. 1c, and cannot be explained with Fig. 1b.
c. For interested students: compare this paper with that of May (1977) on the same topic.

7.9 Extra Practice Exercises

Question 7.5. Positive feedback
Rewrite the mRNA protein model of Eq. (7.2) assuming that the protein is a transcription factor increasing its own transcription.
a. Sketch the nullclines
b. Determine the stability of the steady state(s). Can such a system with positive feedback be stable?
c. Assume that the mRNA kinetics are much faster than those of the protein molecules, and write a model for $\mathrm{d}P/\mathrm{d}t$.

Chapter 8

Biological Pattern Formation

PDE's, CAs and IBMs

8.1 Learning Objectives

After studying this chapter you should be able to do all excersises as well as be able to explain the following:

What are the **implicit assumptions** regarding spatial patterns and variable values when using ODEs?

What are the differences between homogeneous and heterogeneous spatial patterns and under which conditions can heterogeneous spatial patterns be expected to arise?

What is a **partial differential equation (PDE)**? Which assumptions are different and which assumptions are similar compared to an ordinary differential equation?

What are the properties of **Cellular Automatas (CAs)** models and **Individual Based Models (IBMs)** When is it more appropriate to use a CA or IBM instead of a differential equations model? What are the similarities and differences between CA and IBM models?

8.2 Introduction

Up until now, we have mostly worked with ODE models: simple mathematical models of how variables change over time. However, biology is about a lot more than just "amounts" of things. Instead biological organisms are individuals with a position (somewhere in space), with resources nearby (or not) and other individuals nearby (or not). Moreover, each individual could potentially carry a unique combination of properties like age, sex, energy, food preferences, and so on. For example, foliage at the edge of a forest will catch more light. Dessert plants may hold more water when close together than alone. Bacteria in the center of a colony will have fewer resources (already consumed by prior generations). Because of this, a unique mutant at the edge of the colony may spread more easily (Fusco *et al.*, 2016). Such an effect would never be covered by an ODE model,

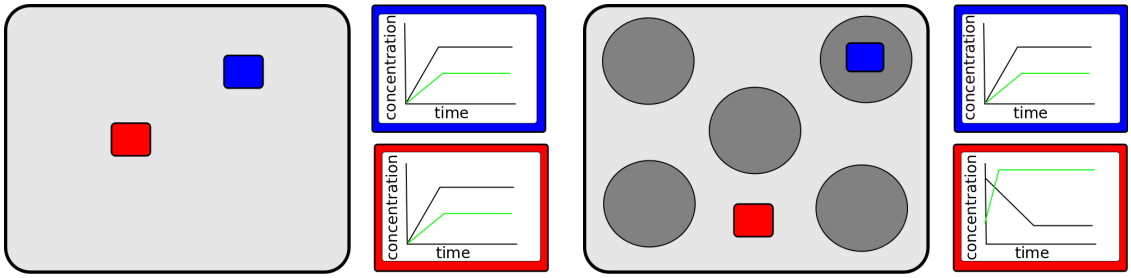


Figure 8.1: A) On the left, a field with homogeneous conditions (light grey): at different places (red and blue) the same things happen at the same time. **B)** On the right, a field with heterogeneous conditions (light grey versus dark grey): at different places, different things happen at the same time.

which assumed everything is "well-mixed" at all times.

Also at the molecular scale, proteins and metabolites can form patterns, driving the developmental programmes of plants and animals, and making sure a cell can differentiate left from right. These molecular details can lead to beautiful patterns on the macroscale, such as the beautiful patterns on zebras, snakes, giraffes, and many other creatures. To study these processes, we need to design models where space is explicitely taken into account.

Simply giving our ODEs a position in space is not enough. This is depicted in Fig. 8.1A), where the same things occur at the same time and in the same way. Although we can imagine the blue and the red system to have a "position", it clearly has no impact. That is to say, our space is **homogeneous**. Studying both systems is no different from studying only one of the systems, as they both behave in an identical way.

In Fig. 8.1B we see a different situation. Here the behaviour of the blue and the red system is different, as they both are in a different environment (light- and darkgray). We call such a system **heterogeneous** with regard to space: there are **spatial patterns**. As a consequence, we cannot undertand such a system by just observing the dynamics in a single point.

Given that there are only light- and darkgray areas in Fig. 8.1B, we can describe the dynamics of the variables in this field by writing down independent ODEs for these two external conditions. However, what if the gray areas represent concentrations of a diffusing resource? What if the populations living in each point in space can migrate? When this happens, the formerly "independent" systems have become coupled, and influence one another locally[1]. For instance, the number of animals in a location can change due to local birth and death, as we have seen before, but it can also change due to immigration from and emigration to other locations. If we want to model this, we need a model that describes the change of variables not just as a function of time, but also *as a function of space*. We will discuss these types of models in this last part of the course.

As a modelling biologist, it is not always easy to know whether we can expect a (more or less) homogeneous situation, and when we ought to expect spatial patterns. However, we can take an educated guess. If the "coupling" between points in space (diffusion, migration, *etc.*) is *strong and fast*, differences between different points in space will tend to even out rather quickly. In this case, the system will be (approximately) homogeneous or "well-mixed", and a simple ODE may be sufficient. If, in contrast, the coupling between points in space is *weak and slow*, differences between different points in space may persist for a long time, and spatial patterns will form. Note however, that there

[1] Note that this is very similar to how coupled ODEs work, except now the systems are coupled to local neighbouring systems

are exceptions to this rule. In fact, the most famous pattern-generating algorithm in biology, *Turing systems*, deviates from this expectation Fig. 8.2. One of the fathers of the modern computer, Alan Turing, discovered a way to make patterns that do not only form when diffusion is high, it *requires* strong diffusion. While this particular system is outside the scope of this course, I highly recommend spending a night on Youtube for some great explainer videos and beautiful examples.

Figure 8.2: While patterns generally form when diffusion (or other types of mixing) is restricted, Turing patterns actually *require* high diffusion. Play with these patterns yourself at `https://pmneila.github.io/jsexp/grayscott/`.

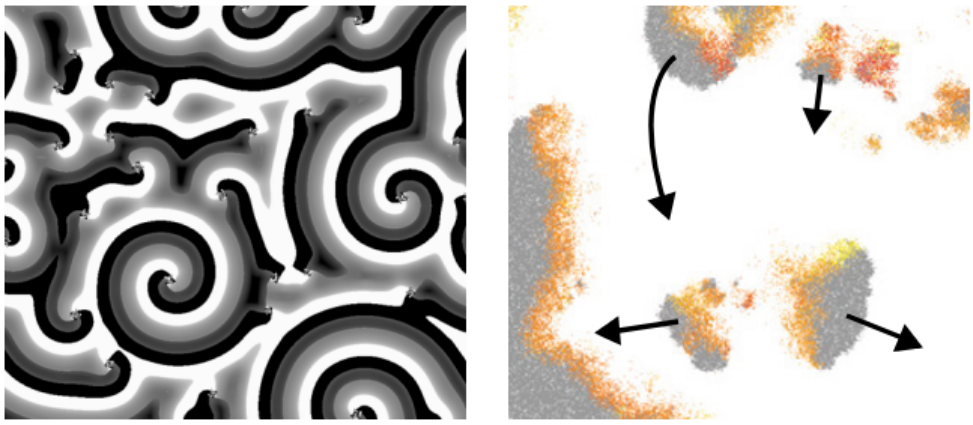


Figure 8.3: Dynamical patterns in biological models often come in the forms of spirals (left) and waves (right).

The patterns discovered by Alan Turing are **stationary patterns**, meaning that after some time they will attain a state and no longer change. It is important to know that Turing patterns and other stationary patterns are common in models of developmental biology. While these models of development are not a part of this course, you will learn the basic principles of models with diffusion.

Many systems also show **dynamical patterns**: spatial patterns that keep changing over time. In biological models, dynamic patterns often occur in the form of traveling waves and rotating spirals Fig. 8.3. We will discuss some examples of this in Chapter 9.

8.3 Including space in models: PDEs and Diffusion

How can we make models in which variables vary both over time and space? To achieve this, our models need to do two things: **1.** they need to describe the dynamics of variables *in each individual*

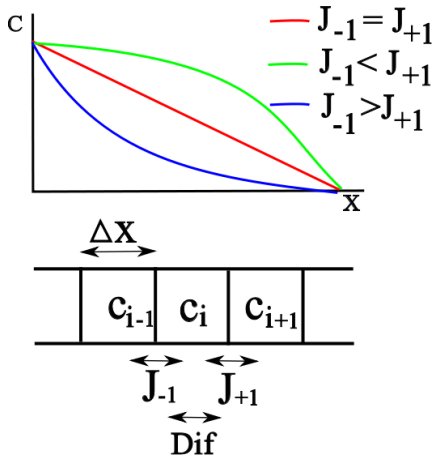


Figure 8.4: Top: Different spatial concentration profiles. **Bottom:** Fluxes arising from concentration differences between nearby cells.

point in space, and **2.** they need to include the *coupling with variables in nearby points* in space. The simplest process by which variables in different positions can influence each other is by diffusion. In its literal sense, diffusion means the net transport of particles from a region of high concentration to a region of low concentration. However, we can also approximate the migration of animals or the dispersal of seeds as a diffusion-like process.

How can we model a diffusion process? For simplicity, let us study diffusion in a one-dimensional cylinder or cable. In Fig. 8.4 we zoom in on three points somewhere on this cable, $i-1$, i and $i+1$, each having a concentration c of some particle. We know that the magnitude of the net flux J between two neighbouring locations increases with the *concentration difference* between the two points, decreases with the *distance* Δx between the points, and depends on the *diffusion constant* D, which describes how easily this type of particle diffuses. Thus for the flux between points $i-1$ and i we can write:

$$J_{-1} = D\frac{c_{i-1} - c_i}{\Delta x} = D\frac{\Delta c}{\Delta x} \quad , \tag{8.1}$$

where Δc is the concentration difference and Δx is a distance. While for the flux in point $i+1$ we can write:

$$J_{+1} = D\frac{c_i - c_{i+1}}{\Delta x} = D\frac{\Delta c}{\Delta x} \tag{8.2}$$

Note from the above equations that it is conventional to first write the concentration in the leftmost point and then substract the concentration in the rightmost point. As a consequence, net flux from left to right has a positive sign, net flux from right to left a negative sign.

If we want to know the net change in concentration in the middle point i that arise due to fluxes with its two neighbouring points $i-1$ and $i+1$, we can write:

$$F = \frac{J_{-1} - J_{+1}}{\Delta x} = \frac{\Delta J}{\Delta x} = \frac{\Delta \frac{D\Delta c}{\Delta x}}{\Delta x} = D\frac{\Delta^2 c}{\Delta x^2} \tag{8.3}$$

Note that we take $+J_{-1}$, since a positive J_{-1} flux implies net flux from $i-1$ to i and hence an increase in concentration in point i. In contrast we take $-J_{+1}$, since a positive J_{+1} flux implies net flux from i to $i+1$ and hence a decrease in concentration in point i.

If we now consider a situation where the points are infinitely close together we can write the above as:

$$F = D\frac{\partial^2 c}{\partial x^2} \tag{8.4}$$

So, apparently, we can model the change in concentration due to diffusion as a second order derivative to x (the variable that describes space). Can we somehow understand this somewhat more intuitively? Let us take a look at the three different spatial concentration profiles shown in Fig. 8.4. First consider the straight (red) line. As the slope of this line (and the other two) is negative, the derivative is negative. The slope itself, however, does not change, meaning that the second order derivative is 0. The concentration differences between cells $i-1$ and i and between cells i and $i+1$ are equal. As a consequence the influx from cell $i-1$ (J_{-1}) on the left and the efflux to cell $i+1$ ($-J_1$) on the right are equal, and hence there is *no net change* in the concentration of cell i! So indeed, the second derivative of 0 matches the rate of change in this point.

Next, let us look at the lower, convex (blue) line that first declines steeply and then less steeply. Mathematically, this means the second order derivative is positive. In this case the concentration difference between $i-1$ and i on the left is larger than between i and $i+1$ on the right. So, the influx from $i-1$ is larger than the efflux to $i+1$, and hence the concentration in cell i will *increase* due to diffusion. The positive second order derivative indeed has the same sign as the rate of change in this point.

Finally, look at the upper, concave line. The line first declines slowly, but then steeply (which means the second derivative is negative). Here, the concentration difference between $i-1$ and i on the left is smaller than between i and $i+1$ on the right. So, the influx form $i-1$ is smaller than the efflux to $i+1$, and hence the concentration in cell i will *decrease* due to diffusion. Once again, the second order derivative has the same sign as the rate of change.

To summarise, diffusion only causes concentration changes if the concentration profile is non-linear: if the profile has a non-zero second order derivative. Diffusion will cause an increase in concentration if the second order derivative is positive, and a decrease if it is negative. Thus, as we have derived mathematically above, we can now intuit why the second order derivative gives us the net concentration change due to diffusion. Where the ODEs we worked with so far only included derivative with respect to time, we will now briefly discuss a model that includes derivatives to both space and time.

8.4 Partial differential equations

Up until now we have worked with equations that are known as **ordinary differential equations** (ODEs). These equations only contain the derivative of N to time:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = f(N) \tag{8.5}$$

If we now want to write a spatial model, where N depends on both time and space, we write:

$$\frac{\partial N}{\partial t} = f(N) + D\frac{\partial^2 N}{\partial x^2} \tag{8.6}$$

We call this a **partial differential equation** (PDE), as it contains partial derivatives of N with respect to both time t (the $f(N)$ part) and N with respect to space (x) in the second term. Note

that we need to apply this equation at each point x in space, and that the coupling between the variable N at different locations here is through a local diffusion process.

Using the same logic, we could make a PDE of the Lotka-Volterra models we studied before, using diffusion to model the movement of prey- and predators:

$$\begin{aligned}\frac{\partial R}{\partial t} &= rR(1-\tfrac{R}{K}) - bRP + D_R\frac{\partial^2 R}{\partial x^2}\\ \frac{\partial N}{\partial t} &= cbRN - dP + D_N\frac{\partial^2 N}{\partial x^2}\end{aligned}$$

You may remember that in ODEs, variables like R and N were shortcuts for $R(t)$ and $N(t)$, as these were (unknown) functions of time. The same is true for the PDEs above, where we should formally write $R(x,t)$ and $N(x,t)$ to indicate that R and N are functions of both space an time. Using this model we could investigate the influence of prey diffusion (D_R) and predator diffusion (D_P) on ecosystem dynamics. As you can imagine, however, the math can grow to be quite complex to solve analytically. Once again, such systems are often simply numerically solved on a computer. For example, by defining a large grid of X×Y points in which ODE systems are solved in small steps, while the variables diffuse between the grid points, a PDE can be approximated (see Fig. 8.6). Modelling systems on a grid is very common in both biology, physics, and mathematics in general. It is conceptually easy to grasp (we have rows and columns), and computationally efficient (interactions only need to be calculated with the neighbouring grid points). Alternative topologies can of course also be implemented, for example to study how plant hormones flow through the plant root (see Fig. 8.5)

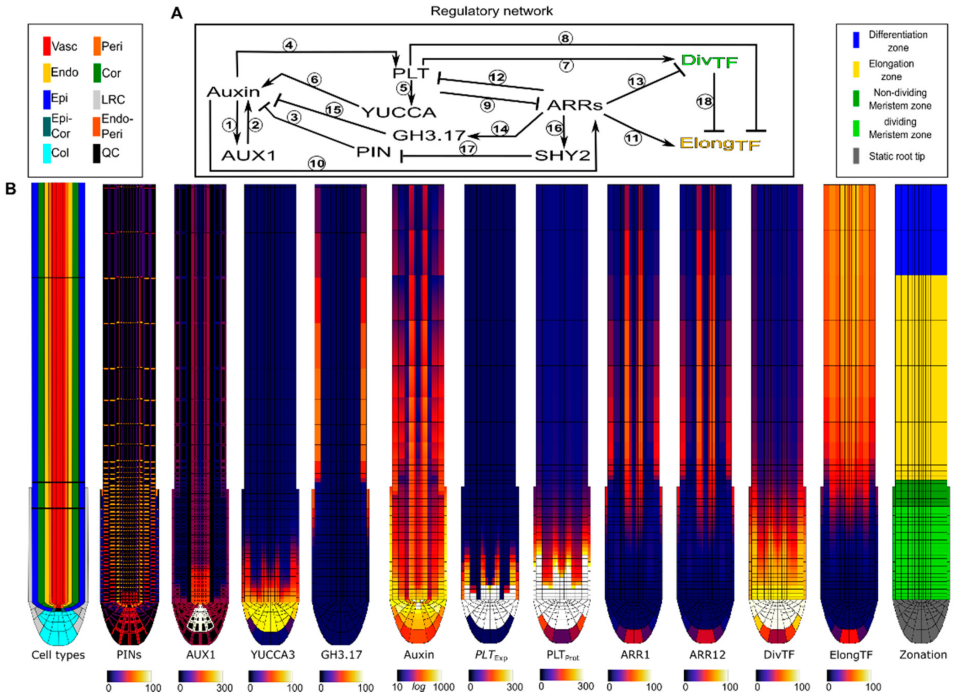


Figure 8.5: A computational model of how a plant hormone (Auxin) produces different protein expression patterns in the plant root (Rutten *et al.*, 2021)

Whereas above we have briefly discussed continuous variables (population sizes) in grid points, we

could also put discreet entities like individual animals in the grid points, which can be either "dead" or "alive", and may have properties like "2 years old" or "hungry".

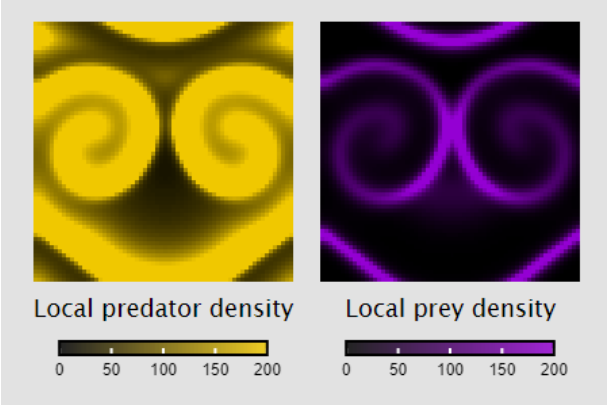


Figure 8.6: Lotka-Volterra numerically integrated on a grid. See https://jsfiddle.net/bramvandijk88/fLu018cm/show

8.5 Modelling discrete entities with CAs and IBMs

Inherent to both ODE and PDE models is that variables take on continuous values, that is to say, they can not only take on integer values like 0, 1, 2, 3, ..., 1000, ..., n, but also values like 0.1, 1.3, 2.74, 3000.2 etc. Such continuous values are not problematic if they describe a concentration or biomass. They are also a reasonable approximation when used to describe the number of molecules, cells or individuals provided that these are present at high numbers. For example 1000.3 is a reasonably good approximation for 1000 individuals. However, is 1.4 a good approximation of one rabbit? What about 0.2 rabbits? Of course, this is biologically non-sensical, and in effect we should consider this population of rabbits extinct. In these types of situations different model formalisms in which individual entities are represented by discrete values are more appropriate. In this chapter we will discuss so called Cellular Automata (CAs) and Individual Based Models (IBMs). Besides their suitability for studying processes in terms of discrete entities, CAs and IBMs are also highly suited for studying spatial patterning processes.

8.6 Cellular Automata (CAs)

In Cellular Automata, we once again use a grid. In this grid, both time, space and entities are discrete. There is no such thing as 0.2 rabbits, and time progresses in incrementing steps: 0, 1, 2, ..., *etc.* Each grid point has a **state** (e.g. alive or dead, hungry or satiated, present or absent), and a local **neighbourhood** of nearby grid points. The future state of a point depends on its own state and the states of neighbouring points (see Fig. 8.7). The simplest CA has only two possible states for each grid point, 0 (white) and 1 (black). We could say that the point is either "dead" or "alive", or "empty" versus "occupied" (by an organism or molecule). In more complex CAs, a larger number of integer states can be used. Classical CAs however, usually have just these two states.

Each time step, a new state is determined for each grid point, based on its own current state and on the current state of neighbouring gridpoints. In classical CAs, the "update rules" determining

the next state of a grid point are often given as a table (see Fig. 8.7), and is called the **next-state function**.

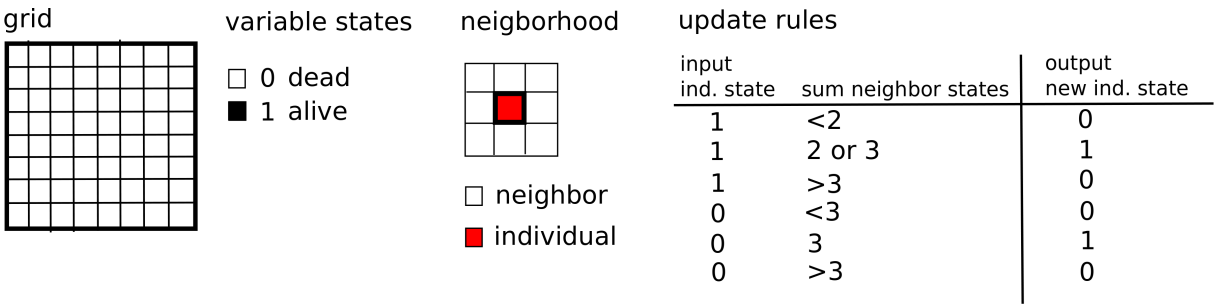


Figure 8.7: Overview of the ingredients of a CA model. The model contains a grid of discrete points that can be in different states (left). Each point has a local neighborhood consisting of itself and its neighboring points, which will determine the state of the point at the next time step (middle). A set of update rules takes the state of the point itself and that of its neighbours, and gives the state of the point at the next time step (right).

In some of the exercises, you have already seen some CAs. For example, the Lotka-Volterra system in space was a simple CA, where each grid point is in either one of three states 0: empty, 1: prey, 2: predator. Updating in this model occurs according to the following rules:

1. if the state is 0 (empty)
   - **a**. if there are one or more prey in neighboring points the next state is 1 (reproduction of the prey) with a probability $p = \alpha$
   - **b**. else the next state is 0 (nothing happens)
2. if the state is 1 (prey)
   - **a**. if one or more neighboring states are 2 the next state is 2 (prey is eaten and hence disappears, and the predator reproduces into this point) with a probability $p = \gamma$
   - **b**. else with a probability $p = \beta$ the next state is 0 (standard death of the prey)
   - **c**. else the next state is 1 (nothing happens)
3. if the state is 2 (predator)
   - **a**. with a probability $p = \delta$ the next state is 0 (standard death of the predator)
   - **b**. else next state is 2 (nothing happens)

where α, β, γ and δ are the probabilities for the different events. The cover of this reader shows that, already, these simple rules give very interesting patterns, with traveling waves accross the grid. While you can easily dissect the basic rules (predators follow prey), individual events of new waves forming can be hard to foresee. Is this unpredictability because of the stochastic nature of this simulation, or can fully deterministic systems be equally surprising? As it turns out, yes it can.

A very famous example of a deterministic CA model generating spatial patterns that are almost "life-like" is called "Game of Life", invented in 1970 by John Conway. In this model each grid point is either "dead" (state zero) or "alive" (state one). Each time step, all the automata (grid points) count their eight immediate neighbors. A cell dies if it has too many or too few neighbors. The simple rule of the "game" is that a cell can only stay alive when it has two or three neighbors. In addition, a dead cell can become alive when it has exactly three neighbors (see Fig. 8.8). This extremely simple CA can be easily studied with a computer, and has become famous for its very complex behavior, despite its simple rules. Although the Game of Life is completely deterministic, its long term behavior has been proven to be wholy unpredictable. It can have replicating structures and "gliders", which are structures that propagate through space (see Fig. 8.8). Complex behaviour occurs everywhere in biology, and although Game of Life does not represent anything biological per se, it is a good reminder of the fact that complexity can arise even from very simple rules.

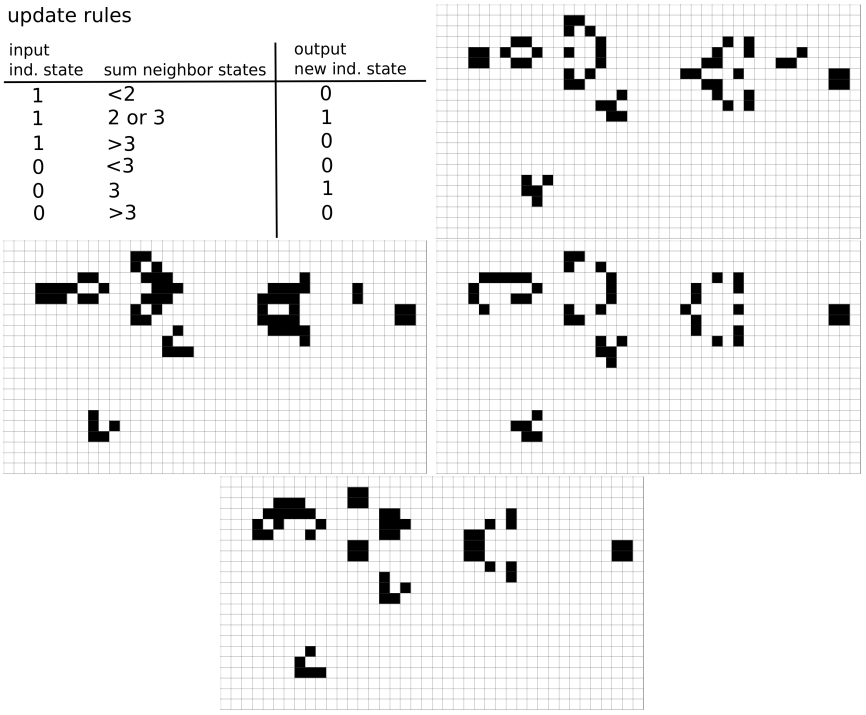


Figure 8.8: A Glider gun in the Game of Life. Four consecutive time steps are shown in a, b, c and d. To better see the dynamical patterns in action, see `https://jsfiddle.net/bramvandijk88/n73jvtbh/260/show`

Another example of a deterministic CA with only two states that produces nice spatial patterns, is the "Majority Voting" CA (see Fig. 8.9). In this CA the grid cells count the states in their 3×3 immediate neighborhood (including their own state), and simply adopt the state of the majority in their neighborhood. Thus if more than four cells are alive, a cell becomes alive. The cell dies if less than five cells in the immediate neighborhood are alive. It turns out that this "doing what the majority around you does" produces a patchy spatial pattern, which resembles certain vegetation patterns in which plants need each other to more effectively store and harness water from the soil.

Yet another example is the so-called "Diffusion Limited Aggregation" (DLA). This CA is a model for water molecules that are diffusing in space, and that will freeze whenever they touch another frozen water particle. The CA thus has three possible states for each grid point: empty, moving water and frozen water. One rule of the DLA model is that the water molecules follow a Brownian motion (random movement). The second rule is that a moving particle becomes a frozen particle, whenever there is a frozen particle in their immediate 3×3 neighborhood. The simulation depicted in Fig. 8.10 started with a random distribution of water molecules and one frozen particle in the middle. This simple rule generates branching structures that are known as **fractals**, and that are pleasingly similar to ice crystals, branching trees, or branching structures in small arteries.

8.7 Individual Based Models (IBMs)

In this section we give a simplified introduction to Individual-based Models (sometimes called Agent-based models). IBMs share certain characteristics with CA models. Like CAs, IBMs describe entities in a discrete manner. An individual creature may have a size, an age, can be hungry or satiated, *etc.*. While IBMs can be "well-mixed", most IBMs are modelled in space. This can once again be a

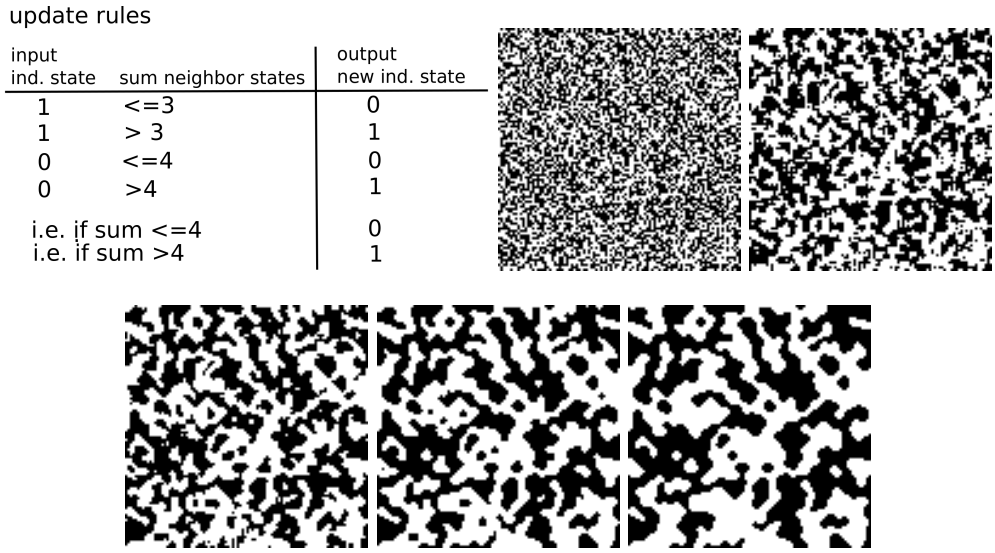


Figure 8.9: Majority voting: from an initial random distribution a stable pattern is attained. First the update rules are shown. Then from left to right and top to bottom time steps 0, 1, 2, 4 and 8 are depicted. Note how a patchy spatial pattern arises. See `https://jsfiddle.net/bramvandijk88/9hojbegw/show`

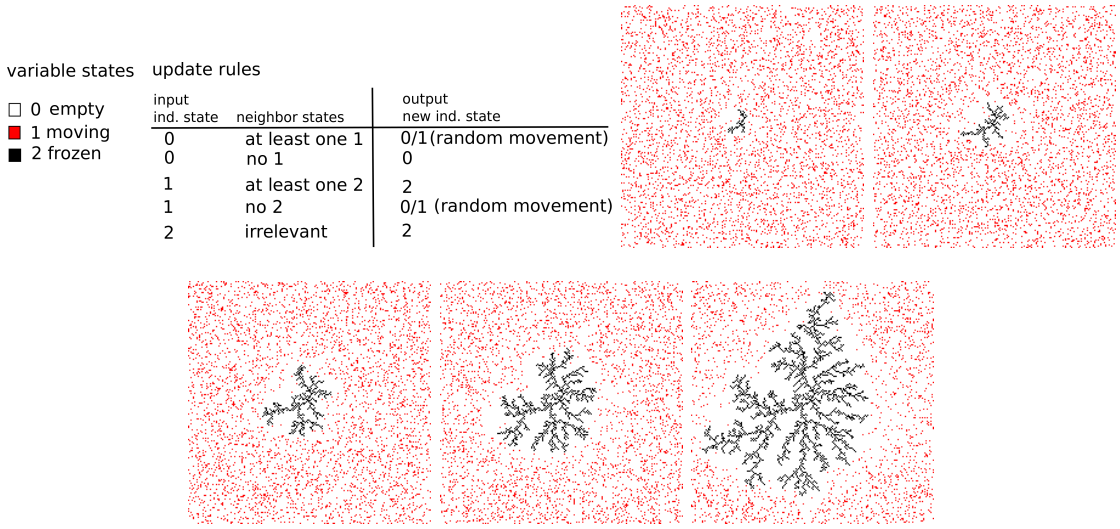


Figure 8.10: Diffusion limited aggregation. From left to right, time steps 100, 200, 400, 800, and 1600 are depicted. Note the growth of a finely structured, fractal-like structure, which resembles a frozen water crystal. `https://jsfiddle.net/bramvandijk88/0mu9ah5p/show`

grid (as this is very efficient), but also continuous space (this is more realistic but computationally expensive). Finally, similar to CAs, IBMs are governed by a set of stochastic or deterministic rules that drive the dynamics of the agents.

There are also some differences between IBMs and CAs. An important difference was already mentioned above, as IBMs can both have discrete space and continuous space. Moreover, an IBM may not necessarily limit the number of individuals at a certain site to one, as multiple entities may live in a certain area. Furthermore, in CAs the rules are applied on a per-gridpoint basis, while in IBMs the rules are applied on a per individual basis. Let us explain this in more detail for an example case: determining whether reproduction will take place. In the case of a CA, we start out by determining for each grid point whether it is empty, as it is only in empty sites that newborn

individuals can be placed. Next, we count the number of non-empty neighboring grid points, thus assuming that the number of individuals next to the empty grid point influences the chances that a local reproduction event will occur. The discrete grid space and the need for empty space to create new entities necessarily leads to an implicit competition for space between entities in CA models. In an IBM we start from the perspective of the individual, determining for each individual its current chances of reproduction, which may or may not depend on the emptiness of the space around it[2]. If reproduction occurs, other things may then determine whether the offspring lives or dies. In the presence of a continuous space, and in the absence of maximum densities, no implicit competition for space will occur om these IBMs.

Like CAs, Individual Based Models can be used to test the effect of discrete population numbers on population dynamics, as well as to investigate spatial patterning processes. A very nice example is the application of IBMs to study bird flock dynamics (Hemelrijk & Hildenbrandt, 2011). At dusk, before settling down for the night, groups of starlings fly in intricate patterns above their nesting site. The model was developed to describe and understand these flight patterns.

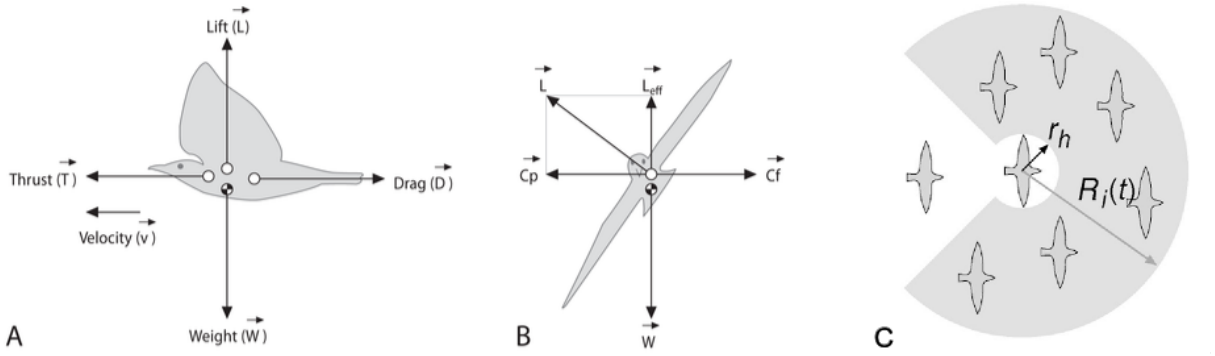


Figure 8.11: Building blocks of the starling flocking model. **A** Forces involved in simulating aerodynamically realistic flight. **B** As the bird reorients, for example during banking (see text) the forces are also reoriented. **C** Birds perceive the neighbors in front and to their sides but not behind them. Based on the perceived neighbors direction and speed of movement and orientation are adjusted. Figure adjusted from (Hemelrijk & Hildenbrandt, 2011)

The model of starling flocking dynamics consists of a three dimensional space representing the neighborhood of the nesting site in which a number of *in silico* starlings are flying around. Each individual bird has the following properties (see also Fig. 8.11):

1. current location
2. speed and direction of movement
3. set of visible neighbors

In addition, realistic aerodynamic properties of bird flight such as lift, drag and banking are included in the model (see below). For each individual simulated starling the following rules are applied:

1. if neighbors are too close, move further away (repulsion)
2. if neighbors are too far, move closer (attraction)
3. align your direction towards direction of neighbors (alignment)

Moving further away or closer by can be achieved by adjusting speed and direction of movement. As one might expect, these rules cause the *in silico* birds to maintain an approximately constant distance, resulting in an alignment of their flight direction. However, these rules also cause the abrupt turnings of the entire flock that give rise to the spectacular shapes and moves typical of starling flocks, something that can not easily be deduced from the rules. Indeed, it turns out that this dynamical behavior is the result of the movement rules combined with the incorporation of

[2] I mean, how often has a giraffe not given birth because there was literally no space for the baby giraffe?

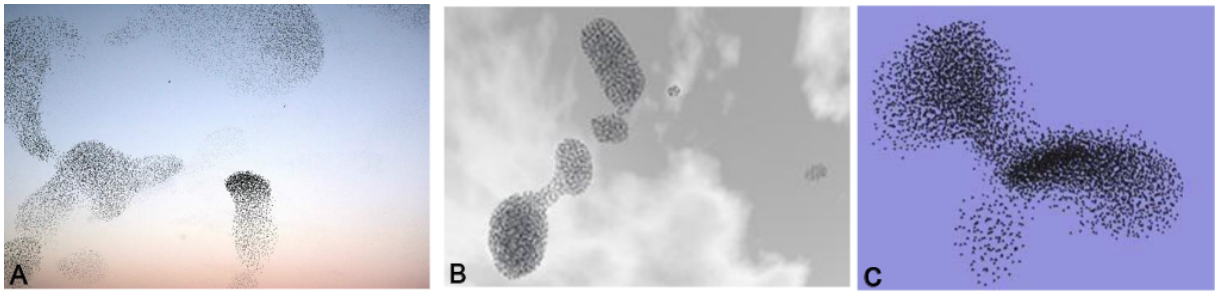


Figure 8.12: Comparison of actual (**A**) and simulated (**B,C**) starling flocking dynamics. Figure **A** was taken from Ballerini et al, PNAS, 2008. Figures **B, C** were taken from the website of Prof. Hemelrijk and Dr. Hemelbrand, respectively.

realistic aerodynamic flight behavior, particularly the so-called banking: when birds (and planes as well) make a turn to the left or right they also rotate in the third dimension, positioning their inside wing lower than the outside wing (Hemelrijk & Hildenbrandt, 2011) (Fig. 8.12).

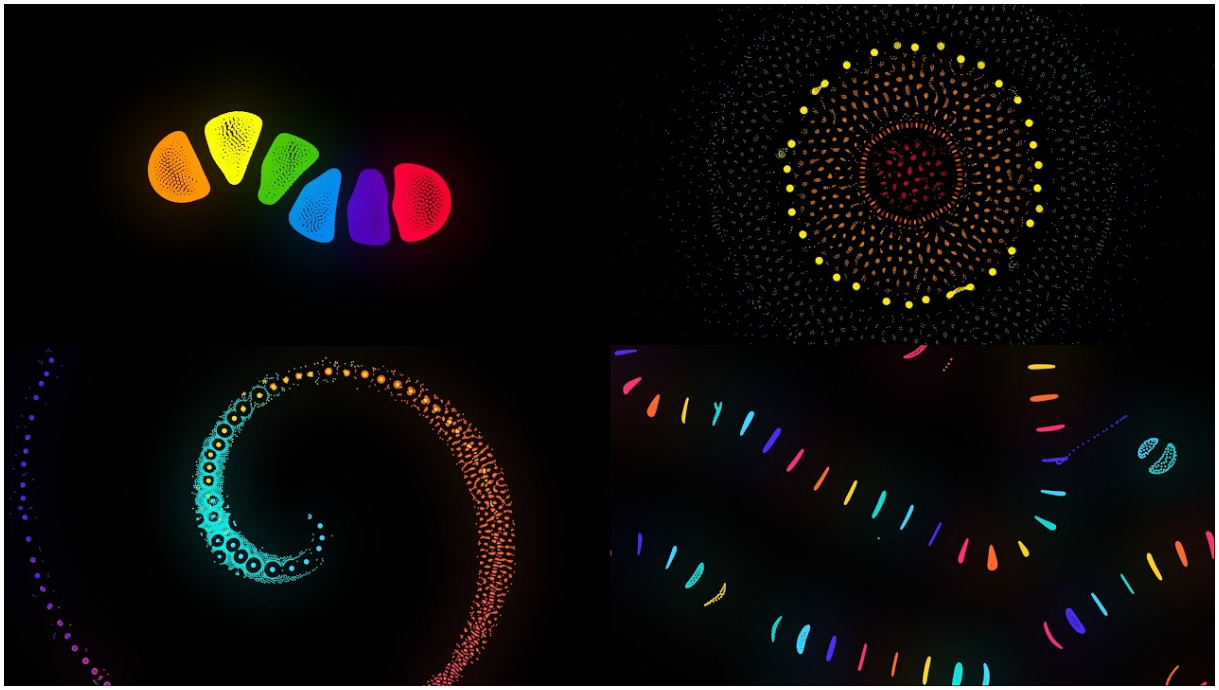


Figure 8.13: A few astonishing patterns generated by Particle life, see `https://youtu.be/p4YirERTVF0`.

Even when not considering biological organisms like birds, simple points repelling and attracting one another can already give beautiful "life-like" patterns. An example of this is the spiritual successor of the aforementioned Game of Life: "Particle Life". In Particle Life, differently coloured dots are attracted and repelled by one another, leading to the most astonishing patterns based on this rule alone (see Fig. 8.13).

These models model are once again an illustration of how simple rules applied to simple and identical individuals can give rise to complex dynamics and emergent patterns. Indeed, CAs and IBMs play an important role in understanding complex processes with emergent properties, not only in biology but also in fields such as economy and social sciences. Next time you see a very interesting pattern, for example a colourful lichen on a tree, ask yourself: does this mean it is created by a complex process?

8.8 Summary

Partial differential equations are an extension of ordinary differential equations in which variables depend not only on time but also on space. PDEs thus enable the modeling of spatial patterns.

While many models in biology are ODEs, Cellular Automata and Individual Based Models are popular alternative model formalisms. While ODEs describe variables as having continuous values, CAs and IBMs allow us to describe entities such as molecules, cells or individuals using discrete values. In situations in which entities are present at low numbers, models allowing for discrete values are more appropriate. Apart from their usefulness for investigating the effect of discrete valued variables, CAs and IBMs are like PDEs of great use for studying spatial patterning processes.

Importantly, the fact that space is incorporated in a model, be it a PDE, CA, or IBM does not mean that spatial patterns necessarily will arise. Whether or not a spatial pattern arises depends on the rules of the model. As mentioned before, if individuals or molecules move around fast and random this will cause a mixing over space and spatial patterns will be prevented, whereas if movement is more local and/or more directed spatial patterns are expected to arise. Interestingly, under particular conditions diffusion may play a critical role in generating rather than dissipating spatial patterns, a mechanism called Turing pattern formation (Turing, 1952).

8.9 Exercises

Question 8.1. Diffusion
In the chapter we derived the diffusion equation as

$$\partial c/\partial t = D\partial^2 c/\partial x^2,$$

which states that the rate of change of a concentration c at a specific time and location can be found from the product of the diffusion rate and the second order space derivative of the concentration c. We also saw that for a discrete space and timestep (as opposed to $\Delta t \to 0$ and $\Delta x \to 0$) this can be written as

$$\Delta c/\Delta t = D\frac{\frac{c_{i-1}-c_i}{\Delta x} - \frac{c_i - c_{i+1}}{\Delta x}}{\Delta x}$$

Give an intuitive explanation for why we need the second order derivative to space to describe diffusion using the terms concentration gradient, fluxes and net change of concentration.

Question 8.2. Rabbit populations
Below we list a number of different situations, in which two rabbit populations can occur. Explain what type of modeling formalism (ODE, PDE, CA) you would use to describe these situations, and why.
a. Two large rabbit populations living on grasslands separated by a mountain range
b. Two large rabbit populations living on grasslands separated by a forest. What parameter would change depending on the size of the forest?
c. Two tiny rabbit populations living in a grassland with in between them a forest

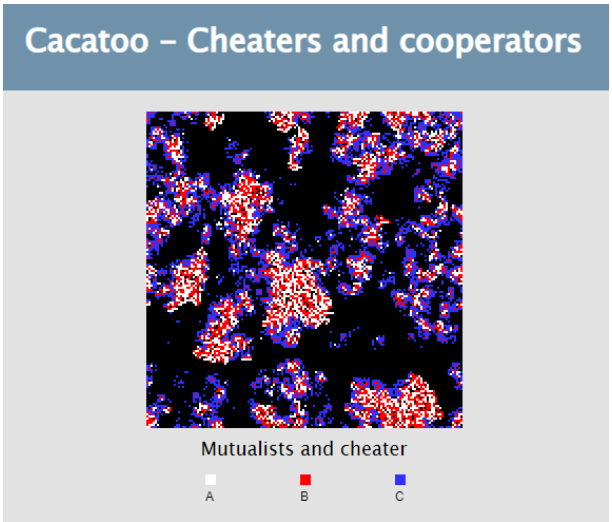


Figure 8.14: Cheaters and cooperators in a stochastic CA

Question 8.3. Cooperators and cheaters
Cooperation is common in nature. A famous example is how meerkats ("stokstaartjes") warn others when predators are nearby. Sometimes, individuals also directly help eachother reproduce. Examples of such cooperative reproduction are parental care in animals, pollination of flowering plants by insects, or cross-feeding of nutrients in bacterial communities. However, such systems are sensitive to so-called "cheaters", who will not reciprocate: they are getting help in their reproduction but

give no help back. ODE models often predict cheaters to die out (when they are too weak) or for the entire system to collapse (when the cheaters are strong), which is generally referred to as "the cheater problem". Let us now study the cheater-cooperator problem (or cheater-mutualist) in a CA (see Fig. 8.14).

a. Visit `https://tbb.bio.uu.nl/bvd/simulations/cheaters/`. Which colours represent the two cooperating species, and which colour represents the cheater?

b. Click the "well-mix" button, explain what happens.

c. At the bottom there are sliders with which you can tune four parameters: "A2B", "B2A", "B2C", and "death". Using the sliders, explain what the first three parameters mean biologically.

d. Use the sliders at the bottom to see if you can cause the spatial system to collapse due to cheaters. Similarly, see if you can cause the "well-mixed" system to coexist (all three colours have to persist). Does spatial structure help or hinder coexistence?

e. What is your conclusion regarding the "cheater problem", and the impact of the type of model that is used to generate conclusions?

Question 8.4. Exponential Population Growth

Assume we wish to model exponential growth (i.e. absence of density dependence). Of the two model formalisms discussed in this chapter, Cellular Automata and Individual Based Models, which do you think is more suited for modeling exponential growth and why?

Question 8.5. Majority Voting and plants in the desert

Explain why majority voting gives patterns similar to those of vegetation patterns in arid (desert-like) areas. (Hint: the major problem to survive for plants in such areas is to hold on to water in the soil.)

Question 8.6. Two populations

Assume there are two populations, living, reproducing and dying in the same environment. They do not eat the same food, they do not eat or kill each other. We model these populations as discrete individuals in a stochastic CA model.

a. Are these two populations truly independent?

b. What do you expect if at the start of the simulation one population is 10 times bigger than the other population? (Assume the individuals of the two populations are randomly distributed over the simulation grid)

Chapter 9

Neurons, action potentials, and excitability

Waves and timescales

9.1 Learning objectives

After studying this chapter you should be able to do all exercises as well as be able to explain the following:

What are the characteristic properties of **excitable systems** such as nerve and cardiac tissue? What distinguishes a stimulus that generates an action potential from one failing to do so? Why does an excitation wave propagate in only one direction?

The Hodgkin-Huxley model was simplified using a **conservation equation**. What is a conservation equation and how does it differ from the constancy assumption discussed in the previous chapter? How come you can determine the stability of the equilibrium despite having both positive and negative self-feedback in the simplified Hodgkin-Huxley model and the Fitzhugh-Nagumo model (in case of a non-zero input current)?

In space, excitable systems display wave patterns. Why do convex and concave waves **straighten out** (loose curvature)? Why does an obstacle lead to the formation of a **free wave end**? Why does a free wave end lead to **spiral formation**, thereby increasing rather than decreasing curvature?

How does defibrillation work? How does ablation (burning scars on the heart) work in preventing renewed arrhythmias? Why is there a critical threshold level for vaccination? Why are there in Dutch forests alleys made without trees?

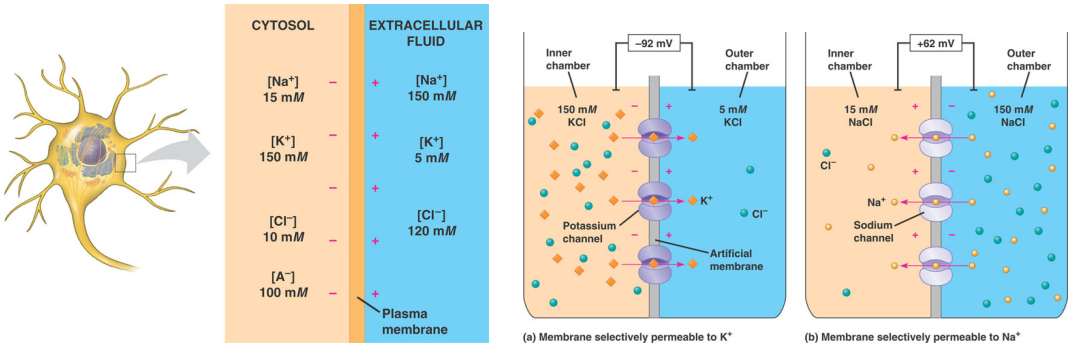


Figure 9.1: The resting membrane potential. Taken from Campbell and Reece.

9.2 Introduction

The term Systems Biology has only come into fashion in the last two decades. However, it stands for a much older approach in which models are applied to understand biological phenomena. This approach has a long tradition, especially in ecology and physiology. We have discussed several examples of models developed in ecology and in this last chapter we turn to an application of modeling in physiology. We will start with a discussion of the famous Hodgkin-Huxley model (1952) that describes the dynamics of action potentials in nerve cells. After this, we will move on to simpler, phenomenological models that can be used both for nerve cells but also more generally for excitable systems. We end this chapter by studying how propagation of excitations over tissue may lead to different types of spatiotemporal wave patterns and how this relates to cardiac disease, forest fires and epidemics.

9.3 Action potentials

To understand action potentials, a little background knowledge is required. Cell membranes are semi-permeable, meaning that some substances can easily pass through them, yet others require transport by specialized protein channels. This non-permeability enables cells to maintain concentration gradients between their inside and the outside world. Ions are among the substances that can not pass unless transported through protein channels. In resting conditions, when the major ion transporting protein channels are closed, Na^+ concentrations are higher outside cells and K^+ concentrations are higher inside cells. In addition, cells contain many negatively charged large molecules. As a net result, there is more negative charge inside cells than outside cells, causing a charge difference that is called the **transmembrane potential** (Fig. 9.1).

When protein channels open, ions will passively flow through them according to the **electro-chemical gradient** for that ion. That is, ion flux is not only driven by concentration differences (a chemical gradient) but also charge differences (an electrical gradient). For Na^+ both the concentration and charge gradient are inwardly oriented (positive charge is drawn towards the negatively charged cell interior). In contrast, for K^+ the concentration gradient is outward and the charge gradient inward oriented resulting in a net weaker outward driving force. It is these fluxes of ions that lead to changes in charge and hence transmembrane potential that give rise to the action potentials generated in neurons and cardiac muscle cells.

Figure Fig. 9.2 depicts the different, nowadays well known phases of an action potential. We see that

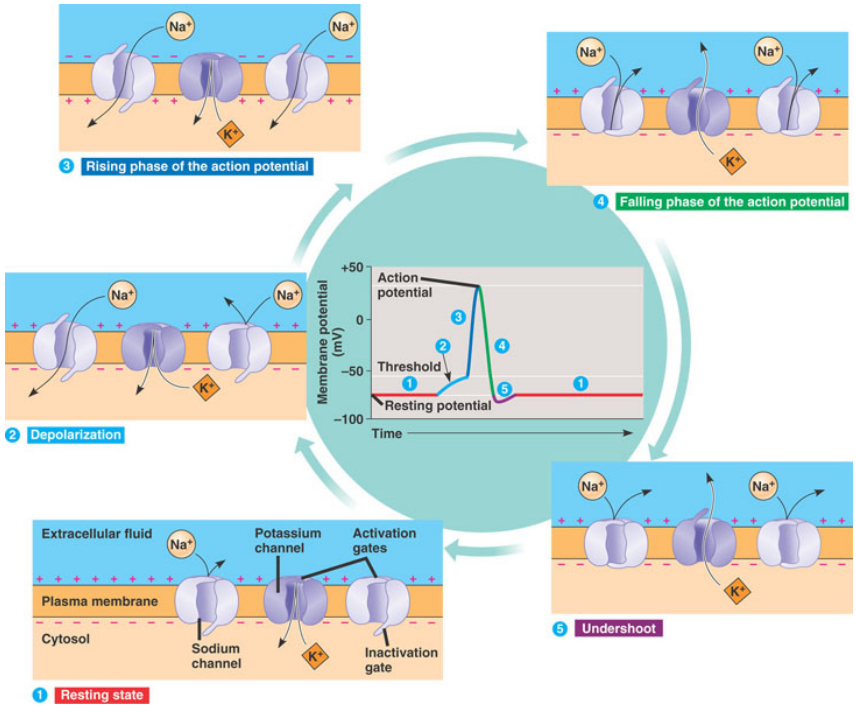


Figure 9.2: Textbook illustration of the events during an action potential. Taken from Campbell and Reece.

an action potential starts with a depolarization that triggers a conformational change in the Na^+ channel proteins, causing them to open up, thereby generating an inward flow of Na^+ ions. This leads to a further depolarization of the membrane potential, resulting in the opening of more Na^+ channels, etcetera, thereby generating the rising phase of the action potential. Next, the voltage increase also triggers a slower conformational change in the Na^+ channel proteins, closing up the channel and hence stopping the inflow of Na^+ ions. At the same time, an equally slow conformational change in the K^+ channel protein causes this channel to open up, resulting in the efflux of K^+ out of the cells. Together now a net efflux of positive charge occurs, leading to the falling phase and undershoot of the action potential. Once membrane voltage recovers, all conformational changes reverse and the membrane returns to the resting state.

9.4 The Hodgkin-Huxley model

Before we get into the Hodgkin-Huxley model, please know you that the point is not to know it by heart. Instead, you should be able to read the model and evaluate it critically. How many variables ("dimensions") does the model have? What could all the seperate terms mean? Which **biological processes** do they represent? With that out of the way, let us dive into the deep end together.

The model Hodgkin and Huxley formulated for these processes is written as:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{1}{C}(I_{Na} + I_K + I_R)) \tag{9.1}$$
$$I_{Na} = G_{Na} m^2 h(\overline{E_{Na}} - V) \tag{9.2}$$
$$I_K = G_K n^2(\overline{E_K} - V) \tag{9.3}$$
$$I_R = g_R(\overline{E_R} - V) \tag{9.4}$$
$$\frac{\mathrm{d}m}{\mathrm{d}t} = 0.1(1-m)\frac{V+25}{\mathrm{e}^{(V+25)/10}-1} - 4m\mathrm{e}^{V/18} \tag{9.5}$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = 0.07(1-h)\mathrm{e}^{V/20} - \frac{h}{\mathrm{e}^{(V+30)/10}+1} \tag{9.6}$$
$$\frac{\mathrm{d}n}{\mathrm{d}t} = 0.01(1-n)\frac{V+10}{\mathrm{e}^{(V+10)/10}-1} - 0.125n\mathrm{e}^{V/80} \tag{9.7}$$

with $G_{Na} = 120$, $G_K = 36$, $G_R = 0.3$, $\overline{E_{Na}} = -115$, $\overline{E_K} = 12$, and $\overline{E_R} = -10.5989$.

While we see seven equations, we only see four ODE equations (starting with $\mathrm{d}/\mathrm{d}t$). The model is thus 4-dimensional. The other equations (I_{Na}, I_K, I_R) appear in the $\mathrm{d}V/\mathrm{d}t$ equation, making it easier to read [1]. The first ODE equation (V) describes the dynamics of the transmembrane voltage, while m, h, and n are "gating" variables between 0 and 1 describing if a channel is closed (0) or open (1). m and h describe the opening and subsequent closing of Na channels during depolarisation, whereas n describes the opening of the K channels during repolarisation.

$\mathrm{d}V/\mathrm{d}t$ depends on the three other equations that have a few constants (*e.g.* G_{Na}, G_K, and E_{Na}). The G's are the maximal channel conductances, and the E's are the so-called **Nernst potentials**. The Nernst potential describes the relation between transmembrane voltage, and inside and outside concentrations for which zero net transport of that ion species occurs. Since $E_x - V$ describes the distance of the current potential from this Nernst equilibrium potential it determines the driving force behind this current, G_{Na}. Finally, we see that these three non-differential equations depend non-linearly on the gating variables m, h, and n, as they are raised to the power two. As m, h, and n are also complex non-linear functions, we can already guess that this model will be very hard to analyse with pen-and-paper alone. However, if we have reasonable estimates (*e.g.* from experiments) of the parameters (the G's and E's, given below the equations), we can study how these equations behave with the computer.

We will see in the next section that, apart from the somewhat complex looking functions for the gating variable dynamics, the model nicely matches what we saw in Fig. 9.2. To understand why this model earned Hodgkin and Huxley the Nobel prize, it is important to realize that in those days voltage gated ion channels were not yet discovered. Hodgkin and Huxley predicted their existence up to the level of the types of opening and closing gates they should have. Additionally, back then, so-called voltage clamp techniques to measure ionic currents were very coarse grained and had to be applied to giant axons of squids rather than small cells or even membrane patches. Finally, computers did not yet exist and the computations to verify their model had to be run on slow, mechanical computing devices.

[1] Note that writing these three equations seperately rather than putting them in $\mathrm{d}V/\mathrm{d}t$ directly, has *no* effect on the model, and is only for readability

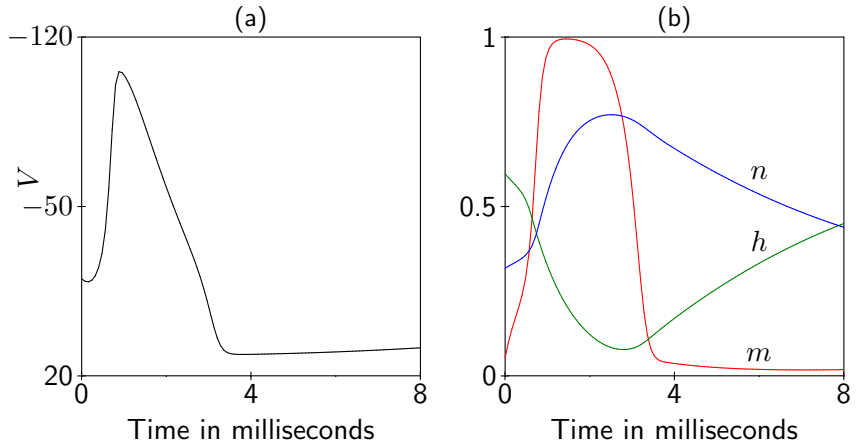


Figure 9.3: An action potential in the Hodgkin-Huxley model. **a.** Voltage dynamics. **b.** Gating dynamics. Note that the vertical axis in panel (a) runs from positive to negative, in order to get the picture of an action potential that we are now used to.

9.5 Analyzing the Hodgkin-Huxley model

Before starting our discussion of the Hodgkin-Huxley model, one more thing needs to be said. Nowadays, it is conventional to depict a resting membrane potential as being negative (-80 to -90 mV), with an action potential causing the membrane potential to become positive (+20 mV). However, in the days of Hodgkin and Huxley's research these conventions did not yet exist, and they used a different, opposite normalisation. They normalised the rest potential at 0 mV, with an action potential producing a strong negative polarisation to -100 mV. Keep this in mind to avoid confusion!

Fig. 9.3 shows an action potential simulated with the Hodgkin-Huxley model. We see that a sufficiently large decrease of the resting potential (note the y-axis, and remember that their voltage runs in the opposite direction to what is now conventional) results in a very realistically looking action potential. We also see that after the action potential, the model returns to a stable steady state at $V \simeq 0$, $m \simeq 0.05$, $h \simeq 0.6$ and $n \simeq 0.3$.

Looking at the dynamics of voltage and m, h and n gates we can now see how the model indeed predicted the dynamics shown in Fig. 9.2:

1. Due to the decrease in voltage, the m gate of the sodium channels open (see Fig. 9.3) and a small current of Na^+ ions starts leaking inwards. This causes the membrane potential to further decrease, and Na^+ current to further increase (positive feedback). As the conductance for Na^+ is now much larger than that for other ions, the voltage approaches the Nernst equilibrium potential for sodium, $\overline{V_{Na}} = -115$.
2. The continued decrease in voltage triggers the closing of the h gate of the sodium channels (see Fig. 9.3), causing the sodium channels to become closed again and stopping Na^+ influx.
3. In addition, the voltage decrease triggers the opening of the n gate of the potassium channel, allowing K^+ to leave the cell (see Fig. 9.3). As now positive charge is leaving rather than entering the cell, the membrane voltage starts to recover. Because now the membrane is almost exclusively permeable to K^+ ions, the membrane potential approaches the Nernst equilibrium potential for potassium, $\overline{V_K} = 12$, producing an "undershoot" of the voltage to well below the resting potential.
4. Finally, due to the decrease in voltage the m and n gates close, the h gates open and the voltage reverts to the resting potential.

With this new knowledge in mind we can now also understand what happens in figure Fig. 9.4. Only if a sufficiently large change in membrane potential in the right direction occurs will the I_{Na} current

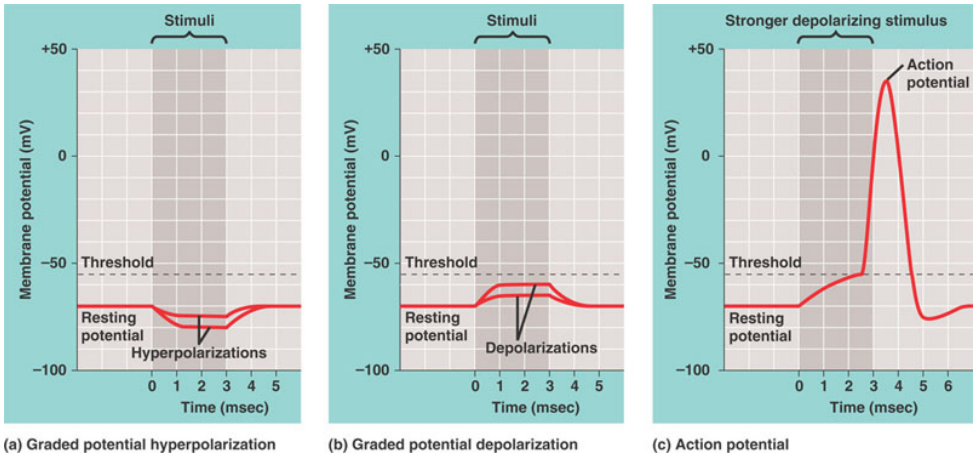


Figure 9.4: Membrane dynamics in response to perturbation. Only if a stimulus drives the membrane potential above a certain threshold, an active action potential is generated (right figure). Otherwise a passive return to the resting potential occurs (left and middle figures). Taken from Campbell and Reece.

activate and the resulting positive feedback lead to an all-or-none action potential. For smaller changes or changes in the wrong direction, the membrane potential will simply passively return to its equilibrium value. Simplifying the model further will help us understand what determines the threshold value beyond which action potentials can be generated.

9.6 Simplifying the Hodgkin-Huxley model

Because of its 4 equations and the complex functions in the gate equations, the Hodgkin-Huxley model is unpleasantly complex. As a consequence, even professional theoretical biologists can do little more than simulate the model on a computer to see its behavior in time. Several researchers have tried to simplify the model to obtain better insight into its behavior (and thus into the behavior of neurons). Citing Fitzhugh (1960): "The usefulness of an equation to an experimental physiologist (...) depends on his understanding how it works." Fitzhugh (1960) first analyzed the Hodgkin-Huxley model to simplify it, and subsequently derived a much simpler phenomenological model (see next section and exercises).

One of the things Fitzhugh observed is that the variables have quite different time scales: the V and m variables change much more rapidly than h and n. For instance, during the first milli-second in Fig. 9.3, h and n have hardly changed. Because $\mathrm{d}m/\mathrm{d}t$ is so much faster than the h and n variables, we apply a **quasi steady state** (QSS) approximation: $\mathrm{d}m/\mathrm{d}t = 0$, which gives us $\bar{m}$, which in case of the Hodgkin-Huxley model is often referred to as m_∞ (the steady state value is the value you reach when $t \to \infty$). This equation gives us a value for m for any value of V. By removing the equation $\frac{dm}{dt}$ from the model and replacing all occurrences of m with the algebraic expression for m_∞, we simplify the Hodgkin-Huxley model from a full four-dimensional model to a three-dimensional QSS model.

There is another reasonable simplification that can be made. One can see in Fig. 9.3 that the behavior of the h and n variables is approximately complementary, i.e., $n + h \simeq 0.91$. This is called a **conservation equation**. One can therefore eliminate the $\mathrm{d}n/\mathrm{d}t$ differential equation by substituting $n = 0.91 - h$ in Eq. 9.3. This then delivers a two-dimensional model, which has the $\mathrm{d}V/\mathrm{d}t = 0$ and $\mathrm{d}h/\mathrm{d}t = 0$ nullclines as depicted in Fig. 9.5. Fig. 9.5b depicts a trajectory of the

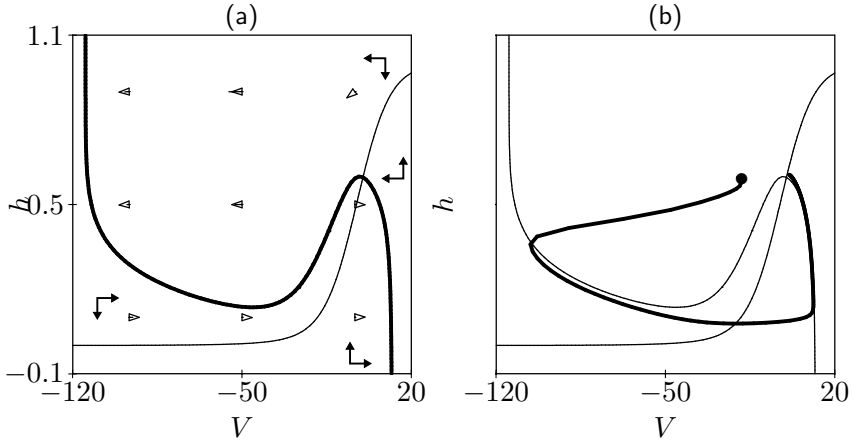


Figure 9.5: The nullclines of the Hodgkin-Huxley model for the QSS assumption $\mathrm{d}m/\mathrm{d}t = 0$ and the approximation $n = 0.91 - h$. The heavy line in (a) is the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline and the heavy line in (b) is a trajectory of the complete 4-dimensional model. The trajectory of the full model appears to obey the nullclines of the simplified model.

full four-dimensional model projected onto the two-dimensional phase space of the simplified model. This figure demonstrates that the trajectory obeys the vector field and nullclines reasonably well, indicating that our simplified model is a reasonable approximation of the full model.

Now that we have arrived at a 2-dimensional model, we can use our earlier techniques of phase plane analysis to get an understanding of the behavior of the model. From the vectorfield we can determine that both V and h have a negative feedback on themselves, which implies that the equilibrium – which corresponds to the resting state of a neuron – is stable.

Next we analyze what happens if we perturb the system from the stable equilibrium, by considering possible trajectories in the phase plane. To be able to do so, we take one more look at Fig. 9.3. This depicts the dynamics of V, m, h and n, of which only V and h are relevant for the simplified model that we are now working with. If we compare the dynamics of V and h, we see that h changes much slower than V. Thus, in the phase space of Fig. 9.5, if we would draw the vector field in a more *quantitative way*, arrows in the horizontal direction would be much longer than those in the vertical direction. This means that changes in the horizontal direction are very fast, and changes in the vertical directions are very slow.

If we decrease the voltage beyond the rising part of the V-nullcline, one enters an area where $\mathrm{d}V/\mathrm{d}t < 0$ and $\mathrm{d}h/\mathrm{d}t < 0$. As we discussed above, V dynamics are much faster than h dynamics, so the trajectory goes mostly to the left and only somewhat downward, until it approaches the downward oriented part of the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline. After passing this nullcline, the vector field now dictates the trajectory to move to the right and further downward. However, now the trajectory can not go mostly to the right and only a little downward: it would immediately cross the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline again, and there the vector field would force it back in the opposite direction again. Indeed, the dominant horizontal direction of the vector field forces the trajectory to stay on the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline as it moves to the right and slowly downward. (Put differently, V is much faster than h. But as h now has to change, V is in steady state with it, so $\mathrm{d}V/\mathrm{d}t = 0$.) This continues until we meet the upward part of the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline. The trajectory can no longer follow it, as this would conflict with what the vector field dictates. Thus now, due to the horizontal dynamics being dominant, the trajectory moves mostly to the right and slightly downward, until we meet the second downward oriented part of the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline. Here again a mostly horizontal trajectory is not possible, h has to change and the fast V dynamics cause the trajectory to follow the nullcline until

finally the intersection point of the V and h nullclines is reached and the system returns to its stable equilibrium.

According to this description an action potential is a large excursion through phase space, that was triggered by a sufficiently large perturbation of the steady state. This particular nullcline configuration defines an "excitable" system. A small disturbance (excitation) is blown up into a large signal, that ultimately reverts back to its resting state. The shape of the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline creates a threshold around the steady state that has to be breached to initiate the action potential. If a smaller stimulus is applied and the threshold is not passed, a direct return to the equilibrium occurs, as dictated by the vector field (see also Fig. 9.4).

During the final part of the action potential, i.e. when the trajectory moves upwards along the rightmost branch of the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline, the system is refractory to new excitations. To excite the neuron within that time window, one has to give a much larger stimulus. This can be easily understood from the picture: because the distance to the threshold (i.e. to the the upward part of the V-nullcline) is much larger, a larger decrease in the voltage is required for excitation.

9.7 The Fitzhugh-Nagumo model and Wave Propagation

An alternative approach to simplifying the original Hodgkin-Huxley model would be to devise a simple, phenomenological model that rather than describing in detail all involved currents and gates, merely describes the essential parts of the behavior of an action potential:

- a stable resting potential
- an excitation threshold
- refractoriness

This approach was independently followed by both FitzHugh and Nagumo. They both proposed a simple two variable model with equations for voltage and recovery, which led to the famous FitzHugh-Nagumo model that you will work with in the exercises:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -V(V-a)(V-1) - W \quad \text{and} \quad \frac{\mathrm{d}W}{\mathrm{d}t} = \epsilon(V - bW) \ ,$$

where V is a variable representing the voltage, which depends on itself non-linearly, and is also suppressed by a second variable W. $\mathrm{d}W/\mathrm{d}t$, the other equation, goes up whenever V goes up. This "refractionary" state decays with a rate b. The ϵ parameter can be used to change the *timescale* of $\mathrm{d}W/\mathrm{d}t$ compared to $\mathrm{d}V/\mathrm{d}t$. By setting ϵ to a very low value, the dynamics of W become slow.

Above we discussed the typical behavior of neuron cells. Characteristic properties of this system are that, in response to a below-threshold stimulus, only a passive return to the equilibrium occurs: the neuron doesn't fire. An above-threshold stimulus on the other hand, produces a large excursion through phase space, i.e. an action potential. This type of behavior is called an *all-or-none response*. Furthermore, after such a response, a so-called refractory period occurs, during which the system is recovering, and it is not (or less) sensitive to subsequent stimulation.

Another characteristic property of neurons is that action potentials propagate over the neuron cell body and along the axon. If at a certain location an action potential is generated, passive diffusion of ions causes an elevation of membrane potential in nearby locations, causing them to exceed their threshold and generate their own action potential. As a consequence, a propagating action potential wave arises. Due to refractoriness there is a minimal time interval between subsequent activation waves, and waves can not travel in the backward direction.

The general properties of activity-waves followed by a refractory period are in fact not unique to nerve cells, but also hold for a number of other biological, chemical and physical systems. Such systems are generally referred to as **excitable media**.

The easiest way to model a spatial excitable medium with wave propagation, is to add diffusion of voltage to the FitzHugh-Nagumo (FHN) model:

$$\frac{\partial V}{\partial t} = -V(V-a)(V-1) - W + D(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}) \tag{9.8}$$

$$\frac{\partial W}{\partial t} = c(V - bW) \tag{9.9}$$

Note that this describes a two-dimensional spatial system: equation Eq. (9.8) has two diffusion terms, denoting diffusion of voltage in two spatial directions (x and y). Note also that the recovery variable W does not diffuse, it is a locally fixed property that does not displace.

9.8 Wave patterns

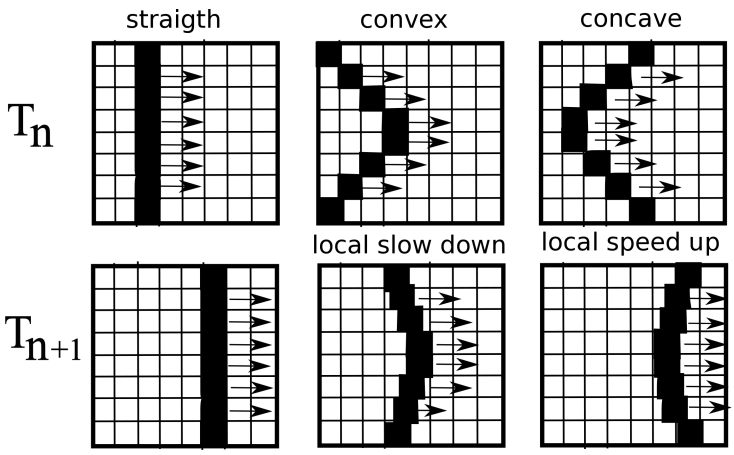


Figure 9.6: Top: Straight, convex and concave waves at time T_n. **Bottom:** The same waves at the next time step T_{n+1}. All waves propagate from the left to the right across the tissue. The straight wave maintains the same shape. The convex and concave waves become less convex and concave. Over time they will straighten out.

Now let us consider two-dimensional (2D) excitable media. In 2D, a wave takes the shape of a line on a surface. It turns out that curvature (non-straightness) of this line affects its local propagation speed. To see why this is the case, consider Fig. 9.6.

First consider the convex wave, and look at the part of the wave furthest to the right. At this point the curvature of the wave is largest, and this point of the wave is furthest ahead of the rest. Because the rest of the wave is lagging behind, the excitation (voltage) in this point not only diffuses to points right in front of it, but also to points to the side and back. The flow of excitation to neighboring

points is thus divided over more points, causing it to be less per point. Therefore it will take longer for these neighboring points to reach the threshold level for which they generate their own excitation response, causing a delay in the propagation of the wave. The more curved the wavefront locally is, the more points will need to be excited by the local point, and the larger the delay is. As a consequence, the points in the wave that are furthest ahead get the largest delay, causing the curved wavefront to straighten out over time.

For a concave wavefront, exactly the opposite applies. Here, consider the most leftward part of the wave, that is most curved and lags behind the most. Because the rest of the wave is ahead of it, not only does this part of the wave only have to excite the points to the right (directly in front of it), but also part of its job has already been done by other parts of the wave. As a consequence, this part of the wave can excite its neighbors faster than normal, causing a speedup in wave propagation. The more curved the wave is (the further it is lagging behind), the more of its job has already been done, and hence the larger the speedup is. So, also in this case the curved wave will tend to straighten out.

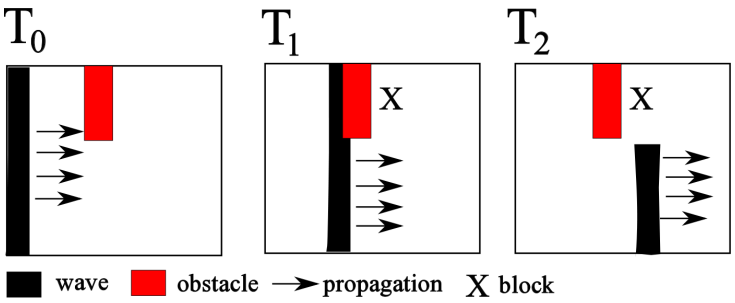


Figure 9.7: Left: A wave is initiated on the left side of the 2D tissue (black). In the middle of the tissue is an obstacle (red), that does not conduct the wave. **Middle:** As the wave propagates to the right, its upper half runs into the obstacle, whereas its lower half does not. **Right:** As the wave propagates further to the right, the upper half of the wave that was blocked by the obstacle has disappeared and only the lower half remains.

In Fig. 9.7 we show what happens when a wave meets an obstacle. An obstacle is a part of the field that can not be excited, that is, it does not conduct the wave. In nerve or cardiac tissue it can be formed by scar tissue. It can also be formed by a part of the tissue that has different properties due to disease, and is still refractory.

If a wave runs into an obstacle, it locally becomes blocked (at the site of the obstacle), and subsequently disappears. The reason for this is simple. First, because the obstacle does not conduct the wave, the wave can not proceed into and through the obstacle. Second, because there is also no diffusion of the excitation signal through the obstacle, the wave can also not jump across it to excite the normal tissue on the other side. So, at the site of the obstacle, the wave simply comes to a halt and dies out once locally the end of the excitation duration is reached. In Fig. 9.7 we see that if the size of the wave is larger than the size of the obstacle, only part of the wave is blocked and disappears. The other part of the wave can still propagate. As a consequence, the remaining wave will no longer span the entire tissue height, and a free wave end or wave-break is formed.

What happens if, due to an obstacle, a wave with a free wave end is formed? Due to the curvature of such a free wave end, propagation will locally slow down. As a consequence, the wave end will lag behind, curvature will increase, causing even more lagging behind, etcetera. The end-result is that the free wave end will curl back on itself, leading to the formation of a **spiral wave** (Fig. 9.8). (Note that in the case of a free end, curvature of the wave front increases, whereas in the absence of a free end the opposite occurs: curvature decreases.)

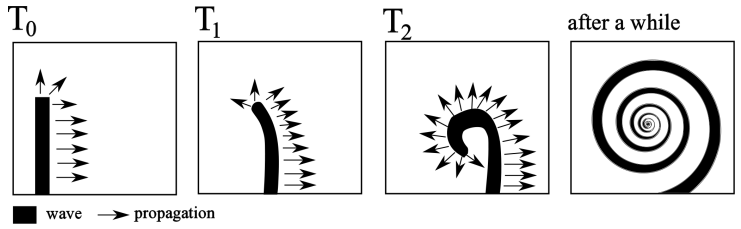


Figure 9.8: From left to right we display how the presence of a wave with a free wave end (far left) over time transforms into a spiral shaped wave (far right).

Spiral waves are a special type of waves. Because they rotate, they come back to tissue that has already been excited (i.e. has produced an action potential) and has recovered again (i.e. is no longer refractory), to re-excite it. Spiral waves are thus self-perpetuating. This is in contrast to a wave that is initiated by stimulating the tissue once. Such a wave will simply propagate over the tissue, until it reaches the tissues borders, and then disappear, leaving the tissue behind in its resting state.

Figure 9.9: Left: Target wave pattern **Middle:** Spiral wave pattern **Right:** Turbulent multi-spiral pattern.

It turns out that we can have three different types of patterns in 2D tissue. First, **target wave patterns** arise if the tissue is stimulated normally: a single stimulus produces a single wave (Fig. 9.9, left). Second, we saw that a **spiral wave pattern** can be produced from a target wave pattern if a wave break occurs (Fig. 9.9, middle). Furthermore, it turns out that some spiral waves are unstable, and fragment into a pattern of multiple spiral waves, a self-maintaining **turbulent wave pattern** (Fig. 9.9, right).

9.9 Cardiac tissue and Arrhythmias

The cells in the heart behave both like nerve cells (they generate and conduct action potentials), and like muscle cells (they contract to produce force). These two properties are connected, the action potential signals the cardiac cells when to contract. Under normal conditions, the natural pacemaker of the heart (the sinus node) produces action potentials at a regular frequency. These action potentials then quickly spread over the heart, causing the coordinated contraction of first the atria, and then the ventricles. This regular electrical activity is reflected in a regular ECG pattern (Fig. 9.10).

During cardiac arrhythmias, the normal rhythm and coordination of contraction is disturbed. Cardiac arrhythmias are usually caused by abnormalities in action potential generation and propagation, and are reflected by abnormal ECG patterns. In Fig. 9.11 we show ECG patterns of the normal sinus rhythm, tachycardia and fibrillation. During tachycardia, the heart rate is increased, but contraction

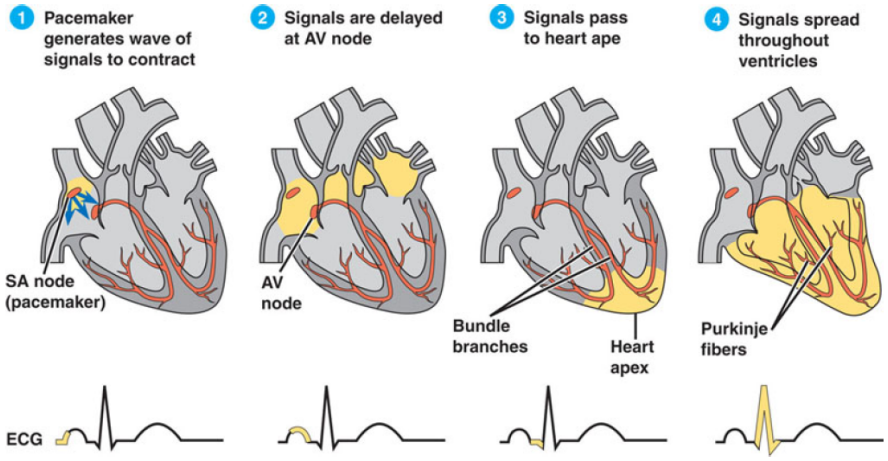


Figure 9.10: Sequence of events during a single normal heart beat, and the corresponding ECG (electrocardiagram) phase. **1.** The heart's pacemaker, the sinus node, generates an electrical signal. **2.** The electrical wave spreads fast across the atria, but can only cross from the atria to the ventricles via the atrioventricular node, where it is delayed. This delay is needed to allow contraction of the atria to occur before contraction of the ventricles. **3.** The His-Purkinje system first conducts the electrical signal from the AV node to the apex of the heart. **4.** From the apex, the electrical wave spreads over the ventricles in a bottom-to-top direction. This direction of wave-spread and contraction is needed, as the arteries through which the blood is pushed out of the heart, are located at the top of the ventricles.

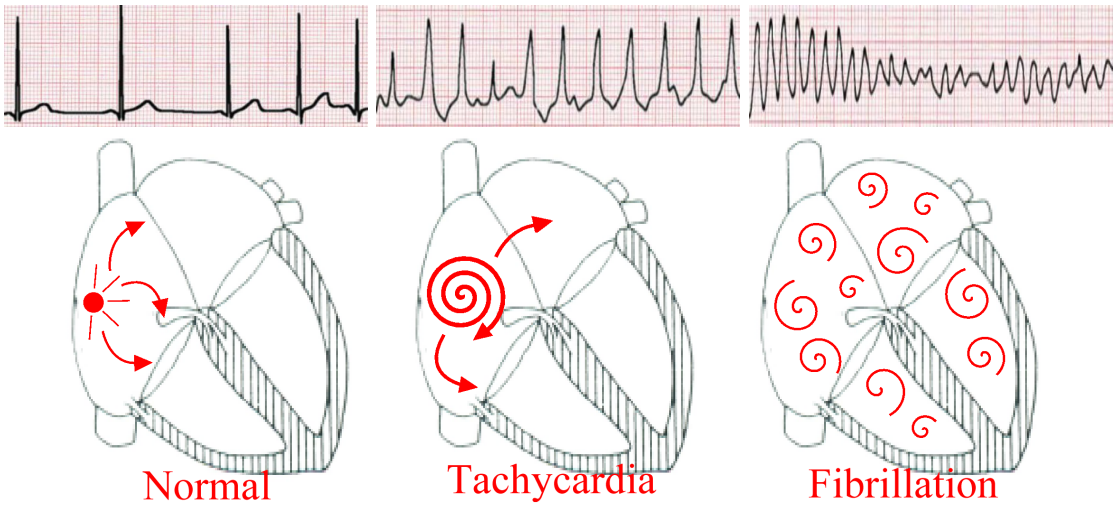


Figure 9.11: Left: ECG and excitation pattern during normal heart beats. **Middle:** ECG and hypothesized excitation pattern during tachycardia. **Right:** ECG and hypothesized excitation pattern during fibrillation.

is still quite coordinated. As a consequence, the pumping of blood is less efficient, but still more or less sufficient. During fibrillation, the heart rate is even further increased, and in addition the coordination of contraction is lost. As a consequence, no effective pumping of blood occurs, so this is lethal within a few minutes. Theoreticians hypothesized that while normal sinus rhythm would correspond to a target wave pattern, tachycardia would correspond to a single spiral wave, and fibrillation would correspond to a multi-spiral turbulent wave pattern (Fig. 9.11).

The idea behind this hypothesis is that for example an infarction scar can act as an obstacle that generates a spiral wave in the heart. Spiral waves typically maximize their rotation frequency: they return to a patch as soon as the action potential and refractory period are over. In contrast, the sinus node will typically operate at a safe frequency, lower than the maximally possible one. Thus the spiral wave emits waves faster than the sinus node. As a consequence, cells will receive an excitation signal from the spiral wave earlier than from the sinus node and hence will respond to the spiral wave signal, and be refractory to the sinus node signal. Therefore the spiral wave takes over control, and it will produce a higher heart rate. If instead of a single spiral, multiple spirals are present, each of these spirals will be in control of its own piece of heart tissue, and these different pieces of tissue will become uncoordinated, causing fibrillation.

Experimental studies in both animal and human hearts have confirmed that the presence of single spiral waves in the heart lead to tachycardia, whereas the presence of multi-spiral turbulence gives rise to fibrillation. Therapies are aimed at preventing spiral waves from occurring, or preventing their fragmentation, or, if they do occur, eliminating them as fast as possible. We will discuss some possible interventions in the exercises.

9.10 Other excitable media

Thus far we have discussed nerve cells and cardiac muscle cells as examples of biological excitable media. However, there are many more types of excitable media in biology.

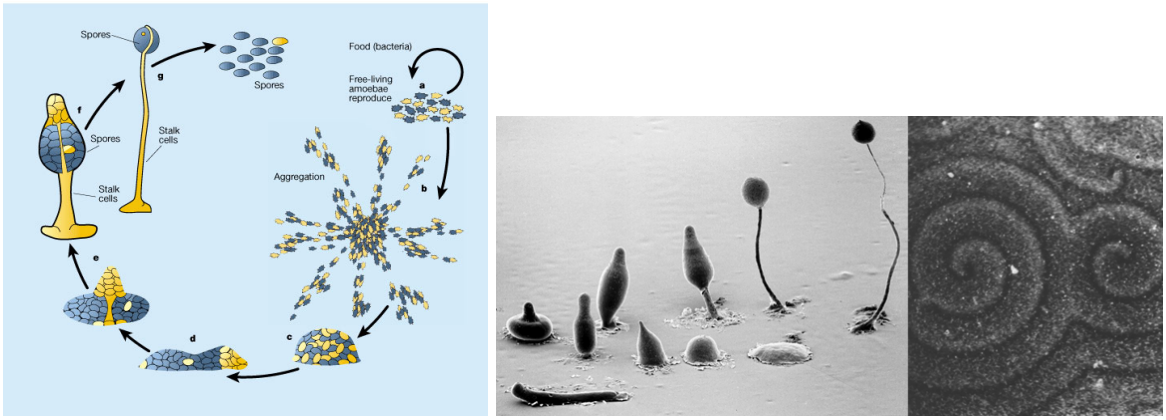


Figure 9.12: Life cycle of the slime mold *Dictyostelium discoidum*. If food and light are sufficiently available, these slime molds live and reproduce as single celled amoebae. However, if food and light become scarce, the single amoebae aggregate into a pile, and this pile changes into a kind of slug. This multi-cellular slug moves in a coordinated manner toward light and heat. If a suitable location is reached, the slug halts and transforms into a stalk with a fruiting body on top. From the fruiting body, spores are released. Upon germination, the spores become single celled amoebae again. (photo on the right from https://www.wired.com/2010/02/slime-molds/)

One interesting example is the slime mold *Dictyostelium discoidum* (Fig. 9.12). Slime molds normally

occur as single celled amoeba, living in soil. However, when food or light become scarce, these single cells aggregate into a multicellular slug that crawls through the soil to the surface, where it forms a fruiting body. This fruiting body emits single-celled spores, which hopefully spread to locations with better conditions. In order for the cells to aggregate and to coordinately move once they form a multicellular "super-organism", they communicate with each other through the signaling molecule c-AMP. c-AMP is produced by the cells under stress (too little light or food), and acts as a chemo-attractant to other cells. In addition, these other cells will respond by producing more c-AMP. Finally, after having produced c-AMP the cells become refractory: for a while they can not produce c-AMP or respond to it. Another interesting example was discovered more recently, which was published with beautiful videos. Researchers at MIT identified spiral waves on the surface of an egg cell during fertilisation (see Fig. 9.13), showing how these patterns are not just pretty, but a key element in life!

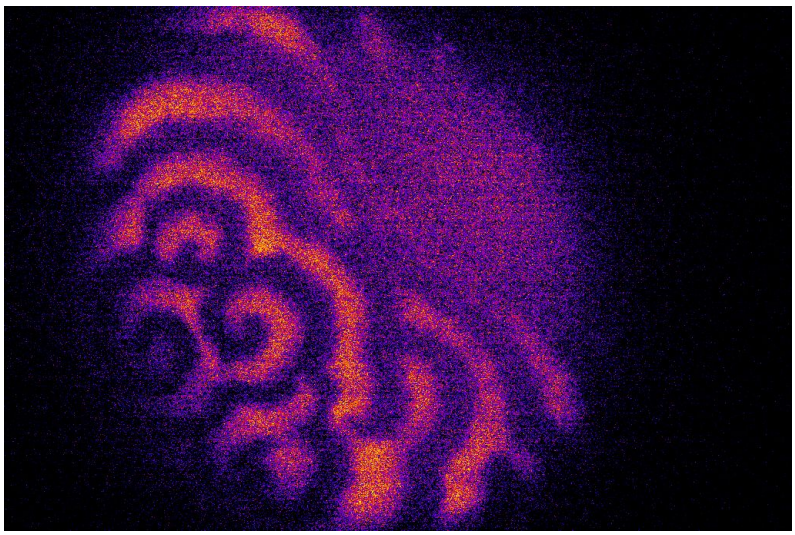
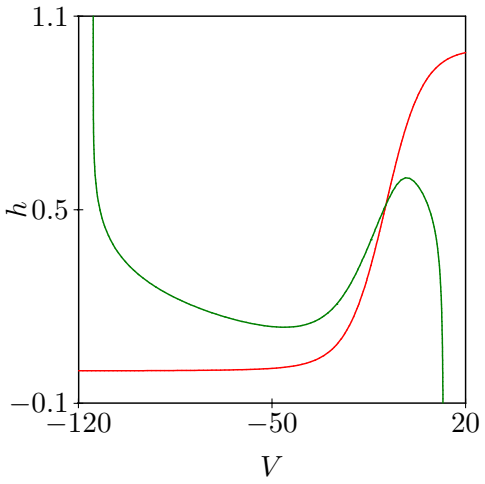


Figure 9.13: Waves formed on the surface of a fertilised egg. Images available under Creative Commons Attribution Non-Commercial license (courtesy of the researchers).

9.11 Exercises

Question 9.1. Hodgkin Huxley
We have simplified the Hodgkin-Huxley model and found the nullclines depicted in Fig. 9.5. Changing the parameters of the model, one can also obtain the following nullclines:



After this (minor) change of the parameters the h variable has remained much slower than the V variable (like it is in Fig. 9.5).

a. Determine the stability of the steady state (you can "borrow" the vectorfield from Fig. 9.5).
b. Sketch a trajectory and let it approach the final behavior of the system.
c. Sketch the behavior in time.
d. Give a biological interpretation of a neuron with these parameters.

Question 9.2. FitzHugh-Nagumo model

Instead of deriving a reasonable simplification of the Hodgkin-Huxley model, one can also define a "phenomenological" model that has essentially the same behavior. A famous phenomenological model is the FitzHugh-Nagumo model,

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -V(V-a)(V-1) - W \quad \text{and} \quad \frac{\mathrm{d}W}{\mathrm{d}t} = \epsilon(V - bW) \ ,$$

where V is some arbitrary variable representing the voltage, and W is a slow variable basically following V. The steady state of W is $W = V/b$ and the small ϵ parameter makes $\mathrm{d}W/\mathrm{d}t$ a slow equation. Note that one can easily express the $\mathrm{d}V/\mathrm{d}t = 0$ nullcline as $W = -V(V-a)(V-1)$, which is zero at three values of V. Because the model should resemble the Hodgkin-Huxley model, make sure that the nullclines intersect in only one steady state.

a. Sketch the nullclines of the model assuming that $a < 1$.
b. Determine the stability of the steady state.
c. Sketch a trajectory corresponding to an excitatory perturbance of this steady state.
d. Does this resemble the action potential of the Hodgkin-Huxley model?
e. Is this a good model for the action potential?
f. Now add an external input, e.g., from a dendrite, $\mathrm{d}V/\mathrm{d}t = i - V(V-a)(V-1) - W$ and sketch the nullclines for all qualitatively different possibilities.
g. Determine the stability of all steady states.
h. Sketch for each situation a representative trajectory.

Question 9.3. Epidemic

The population of a large island has been suffering from an unpleasant infectious disease for decades. The disease tends to spread over the island from village to village, returning each year. The main reason for the persistence of the epidemic is that the immunity to this disease only lasts for a few months. These observations suggest that the epidemic is a wave traveling through an excitable medium.

a. What happens when a wave rolls over a village that was recently infected by another wave? Someone suggests to eradicate the disease from the island by bringing all susceptible individuals together to infect them all at the same time.
b. Would this work?
c. A small number of susceptible defects (does not show up for their shot) and stays at home. How would that affect this idea?
d. What happens if tourists from non-vaccinated countries visit?

Question 9.4. Arrhythmias

Go to `https://tbb.bio.uu.nl/bvd/simulations/spiral/`, showing an interactive simulation of the FitzHugh-Nagumo model (Fig. 9.14).

Figure 9.14: Spatial model of action potentials according to the FitzHugh-Nagumo model

a. Wait for the simulation to run for a while, and notice how often do the newly formed action potentials (blue) reach the right-hand side of the field (shown in the graph). What does this remind you of?
b. Click the "disrupt" button to create some disturbance in the action potential. How do minor disturbances (no more than 0.3, meaning 30%) influence the waves?
c. Create a major disturbance (*e.g.* more than 0.6). What happens to the wave? Reading the graph, and describe what happened.
d. Why can the newly formed action potentials (starting at the left) not break through? Click the "CLEAR!" button, and describe how that fixes the problem.

Question 9.5. Fire spread

Go to `https://tbb.bio.uu.nl/bvd/simulations/forestfire/`, showing an interactive simulation of the forest fires (Fig. 9.15). The CA model now contains tree tiles (green), ground tiles (brown), and burning/burned tiles (black). Burning tiles cause nearby trees to catch fire. Ground tiles can however not catch fire. The fire is started in the middle of the forest.
a. Start the simulation a couple of times with tree density 0.4. Roughly speaking, what fraction of the forest burns? Is there much variation between repeated experiments?
b. Repeat this experiment with tree density 0.2, 0.3, 0.5, and 0.6. Draw the fraction of burned trees as a function of tree density. Explain the shape of this function.
c. If you would want to prevent devastating forest fires, what would you recommend?

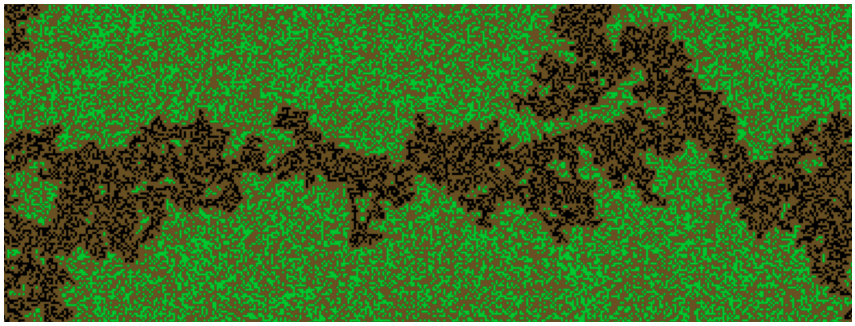


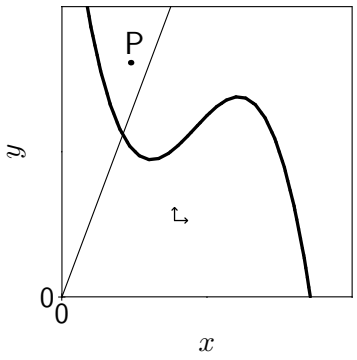
Figure 9.15: Spatial model that simulates the spread of forest fires

9.12 Extra Practice Exercises

Question 9.6. Time scales
Consider the following biochemical system

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x,y) \quad \text{and} \quad \frac{\mathrm{d}y}{\mathrm{d}t} = \epsilon(ax - by) \ ,$$

where $a, b > 0$ and $\epsilon \ll 1$ such that **the kinetics of y is much slower than that of x.** The phase space is:



where the heavy line represents the $\mathrm{d}x/\mathrm{d}t = 0$ nullcline, and the straight line is the $\mathrm{d}y/\mathrm{d}t = 0$ nullcline.

a. Sketch a trajectory from the point P.

Now consider a case where y is actively produced from a substrate S by a reaction that is catalyzed by x:

$$S + x \xrightarrow{k} y + x \ .$$

b. Which parameter of the model above should be changed if S is decreased?
c. How will the nullclines change?
d. Sketch two qualitatively different nullcline configurations.
e. Sketch trajectories for both of them.

Question 9.7. Evolution of Virulence and Contagiousness
A host and its virus pathogen co-evolve. The host tries to prevent infection, the virus tries to optimize infection. For most viruses, this evolution does not lead to maximum virulence (pathogenicity, how sick you get of a given pathogen) and contagiousness ("besmettelijkheid"), as one at first sight may naively expect. Explain why, keeping the knowledge you gained in this chapter in mind.

Chapter 10

Phase plane analysis in R

Most phase portraits in this book were made with a computer program called Grind, for Great integrator differential equations. The current version of Grind is an R-script called `grind.R` (previous versions were coded in C or Fortran: Grind has a very long history that started in 1983!). Grind is based upon the R-packages `deSolve`, `FME`, and `rootSolve` developed by Karline Soetaert and colleagues (Soetaert & Herman, 2009; Soetaert *et al.*, 2010; Soetaert, 2009; Soetaert & Petzoldt, 2010), and uses a function in R for plotting contour lines to make phase planes. Grind simplifies the interface to these libraries by defining five easy-to-use functions:

- `run()` integrates a model numerically and provides a time plot or a trajectory in the phase plane,
- `plane()` draws nullclines and can provide a vector field or phase portrait,
- `newton()` finds steady states (using the Newton-Raphson method) and can provide the Jacobian with its eigenvalues and eigenvectors.
- `continue()` performs parameter continuation of a steady state, providing a bifurcation diagram,
- `fit()` fits a model to data by estimating its parameters, and depicts the result in a timeplot.

The best way to get started is to download our example analyzing the Lotka Volterra model. We will work in the RStudio environment, which has a window for the code, a console window, a window defining the environment, and a window for asking help or viewing graphics. Download the `grind.R` and the `lotka.R` files from the `http://tbb.bio.uu.nl/rdb/grindR/` webpage, store them in a local directory, and open both of them via the `File` menu. Both will be tabs in the code window. It may anyway be useful to set the working directory to the folder where your R-codes are stored (`Set working directory` in the `Session` menu of RStudio). Files will then be opened and saved in that directory.

First "source" the `grind.R` file (button in right hand top corner) to define the five functions. (In case you get an error message like "Error in library(deSolve): there is no package called deSolve", the Soetaert libraries have to be installed by using `Install Packages` in the `Tools` menu of RStudio). When `grind.R` is successfully "sourced", it is time to "run" the model with its parameter and state definitions from the `lotka.R` script. In the R-console below the `lotka.R` panel, one can then type the function calls given in the example session below. Once you have a picture that you like, you may copy the lines creating that figure into the `lotka.R` window for later usage. (Use "Run" or "Control Enter" to execute lines from the `lotka.R` panel into the console).

10.1 Tutorial 1: Lotka Volterra model

The ODEs of the model are defined in the simple notation defined for the `deSolve` package. The following is an example of the Lotka Volterra model, here defined by the function `model()`:

```
model <- function(t, state, parms) {
  with(as.list(c(state,parms)), {
    dR <- r*R*(1 - R/K) - a*R*N
    dN <- c*a*R*N - delta*N
    return(list(c(dR, dN)))
  })
}

p <- c(r=1,K=1,a=1,c=1,delta=0.5) # p is a named vector of parameters
s <- c(R=1,N=0.01) # s is the initial state
```

where the two lines below the function define the parameter values in the vector `p`, and the initial state of the variables in the vector `s`. Note that the function returns a list of derivatives `(dR,dN)`. The names `model`, `s`, and `p` are the default designations for the model, state, and parameter values in all `grind.R` functions. This example should be self explanatory as it just defines the Lotka Volterra model $\mathrm{d}R/\mathrm{d}t = rR(1 - R/K) - aRN$, and $\mathrm{d}N/\mathrm{d}t = caRN - \delta N$, with its parameter values and initial state as R-vectors, `p <- c(r=1,K=1,a=1,c=1,d=1,delta=0.5)`, and `s <- c(R=1,N=0.01)`, respectively. Note that the order of the variables in the state vector should be the same as the order of their derivatives in the model. The following tutorial is an example session illustrating the usage of the four `grind.R` functions analyzing this Lotka Volterra model (see Fig. 10.1 for its graphical output):

```
run() # run the model and make a timeplot (Fig. 10.1a)
plane() # make a phase plane with nullclines
plane(xmin=-0.001,ymin=-0.001) # include the full axis in the phase plane (Fig. 10.1b)
plane(tstep=0.5,portrait=TRUE) # make a phase portrait (Fig. 10.1c)
plane() # make a clean phase plane again (Fig. 10.1d)
p["K"] <- 0.75 # change the parameter K from 1 to 0.75
plane(add=TRUE) # add the new nullclines
s["R"] <- 0.1 # change the initial state to (R=0.1,N=0.01)
run(traject=T) # run the model and plot a trajectory
newton(c(R=0.5,N=0.5),plot=T) # find a steady state around (R=0.5,N=0.5) (Fig. 10.1d)
f <- newton(c(R=0.5,N=0.5)) # store this steady state in f
continue(f,x="K",xmax=2,y="N") # continue this steady state while varying K (Fig. 10.1e)
continue(f,x="K",xmax=2,y="N",step=0.001) # get better values with a smaller step size
p["K"] <- 0.5 # set K to the value at which N goes extinct
plane(vector=T) # make a phase plane for this value of K (Fig. 10.1f)
```

10.2 Tutorial 2: the Lac-operon

This slightly more sophisticated example on the operon model shows how one can continue steady states to make a bifurcation diagram with a saddle-node bifurcation. We use the operon model as defined in Chapter 7, while choosing arbitrary parameter values. The graphical output of the example session in R is shown in Fig. 10.2. In the session we find the exact same phase plane as shown in Chapter 7, by calling `plane(xmax=4)`. Note that bullets indicate stable steady states and circles depict unstable equilibria. Then we start close to the three steady state with a call to the Newton-Raphson algorithm, and store these states in the variables `low`, `mid`, and `hig`, respectively.

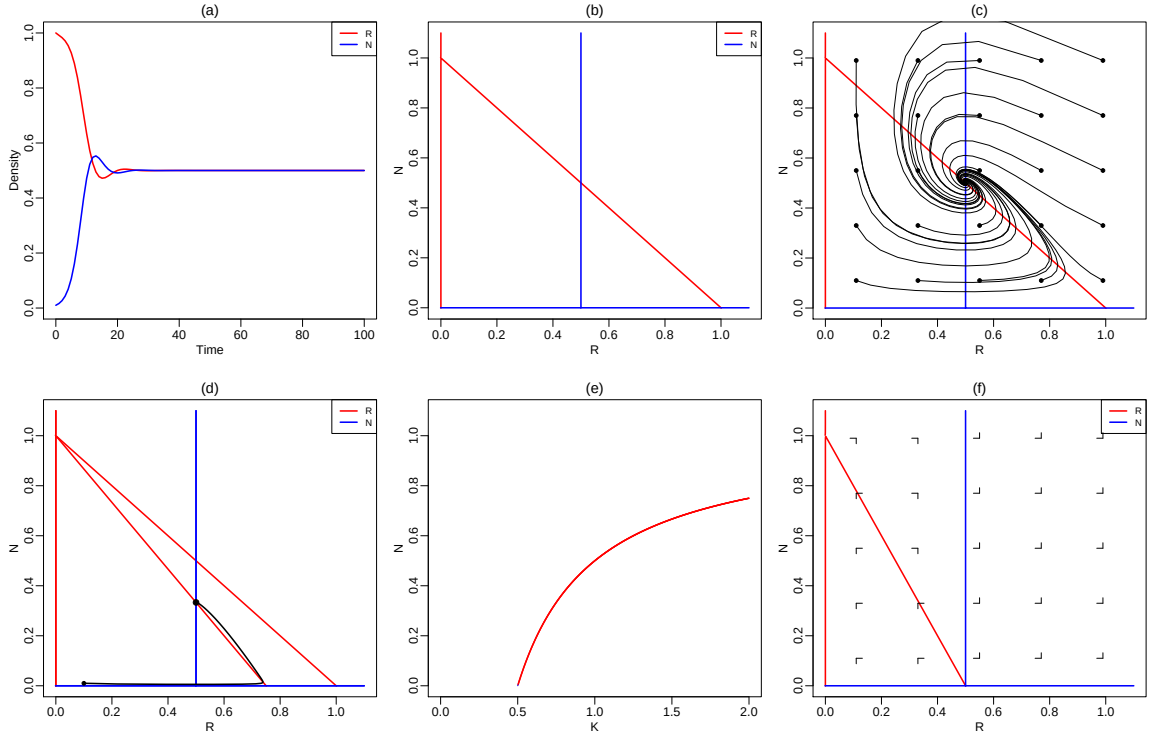


Figure 10.1: Numerical integration, phase plane analysis, and a bifurcation diagram of the Lotka Volterra model. The six panels collect the graphical output of the example session listed above.

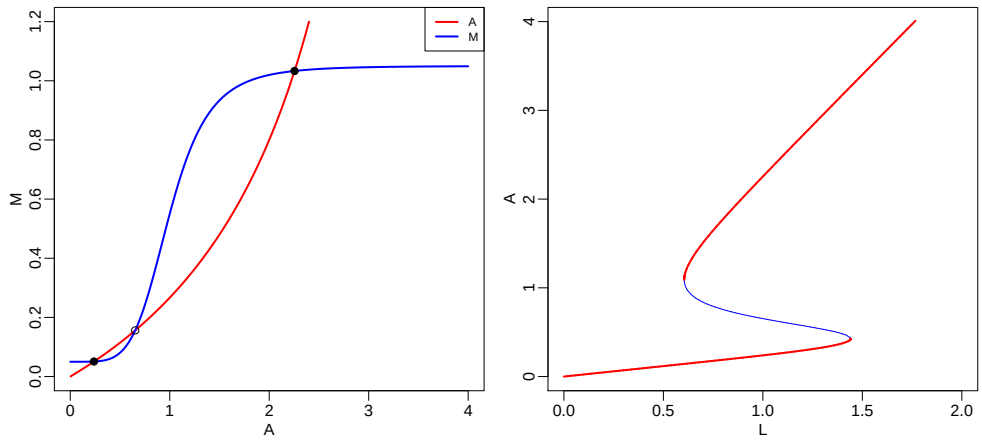
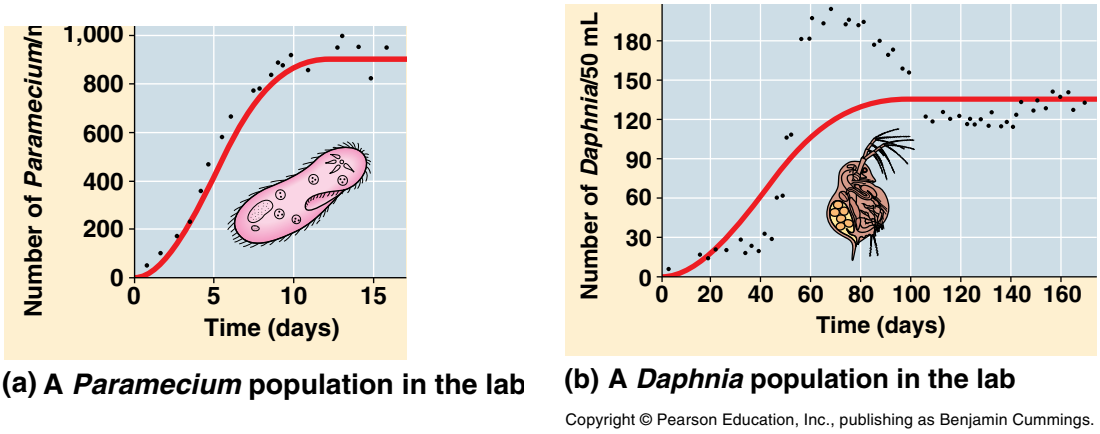


Figure 10.2: Nullclines and a bifurcation diagram of the Lac-operon model.

Using parameter continuation we make a bifurcation diagram in which we follow the middle steady state as a function of the external lactose concentration, L, by a call to `continue(mid,...)`:

```
model <- function(t, state, parms) {
  with(as.list(c(state,parms)), {
  R = 1/(1+A^n)
  dA = M*L - delta*A - v*M*A
  dM = c0 + c*(1-R) - d*M
  return(list(c(dA, dM)))
  })
}
```



(a) A *Paramecium* population in the lab

(b) A *Daphnia* population in the lab

Figure 10.3: Logistic growth of *Paramecium* and non-logistic growth of *Daphnia*. From: Campbell & Reece (2008).

```
p <- c(L=1,c=1,c0=0.05,d=1,delta=0.2,n=5,v=0.25)
s <- c(A=0,M=0)
plane(xmax=4)
low <- newton(s,plot=T)
mid <- newton(c(A=0.8,M=0.2),plot=T)
hig <- newton(c(A=2,M=1),plot=T)
continue(mid,x="L",y="A",xmax=2,ymax=4,add=T)
```

These tutorials should be a sufficient introduction for the standard phase plane analyses we perform in this course. `grind.R` can do much more for you, and this is described in the tutorial available on the `grind.R` website `tbb.bio.uu.nl/rdb/grindR/`.

10.3 Exercises

Question 10.1. Tutorial

Here is a set of questions to test if you understood the tutorial you just did:

a. When you called `run()` you got a nice graph with red and blue lines on your screen (see Fig. 10.1a). Explain in intuitive terms what these lines mean.

b. How is the system of ODEs exactly defining these lines?

c. When you called `plane()` you also got a graph with red and blue lines on your screen (see Fig. 10.1b). Explain in intuitive terms what these lines mean.

d. What happens when $K = 0.5$ (see Fig. 10.1e & f)?

Question 10.2. The Monod functional response

In Chapter 6 we analyzed the following predator prey model with a saturated functional response:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = rR(1 - R/K) - \frac{aRN}{h + R} \quad \text{and} \quad \frac{\mathrm{d}N}{\mathrm{d}t} = \frac{caRN}{h + R} - \delta N$$

which is available as the file `monod.R` on `http://tbb.bio.uu.nl/sb/models/`.

a. Open the Monod model in RStudio and check the equations and its parameter values.

b. Make a time plot showing the logistic growth of the prey by starting with zero predators and few

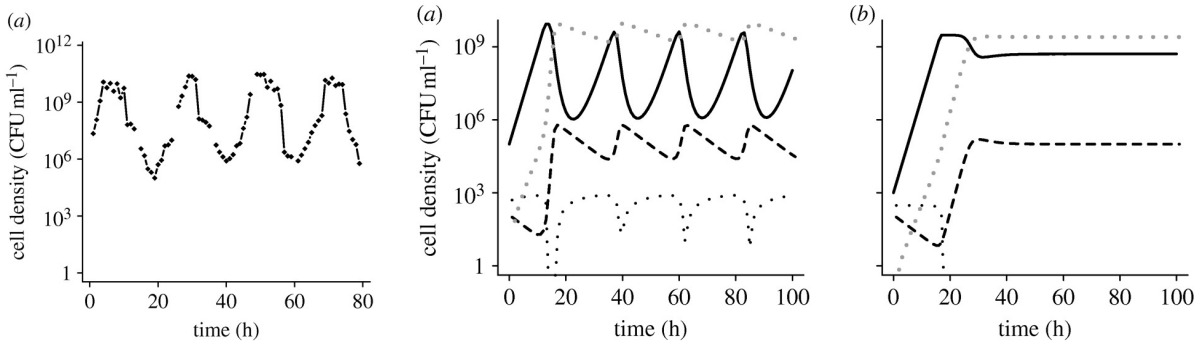


Figure 10.4: Figures taken from Cornejo *et al.* (2009). Left data: *Streptococcus pneumoniae* R6 in chemostat culture. (a) Cell density estimated from colony-forming units (CFU ml^{-1}). Right: simulation results. Changes in the densities of bacteria N (black solid line); killed bacteria (gray dotted line); and the concentration of the resource R (black dotted line) and toxin T (black dashed line). Parameters in Panel (a): $s = 100$, $a = 10^{-7}$, $b = 1$, $h = 25$, $w = 0.1$, $x = 5 \times 10^{-6}$, $p = 4 \times 10^{-10}$, $d = 0.1$. In Panel (b) the density of bacteria is reduced by changing a parameter.

prey (`s <- c(R=0.01,N=0)` and `run()`). Explain in words what this curve represents.
c. Now study the 2-dimensional system by making a phase space (using `plane()`). Change parameter values to make qualitatively different phase spaces. Sketch trajectories for each of these systems (using `plane(...,traject=T)`). What is the behavior when the steady state is unstable?
d. When is the non-trivial steady state stable and when is it unstable? Hint: the best way to study this is to make a bifurcation diagram varying the parameter that you changed continuously. For instance, after running into a stable steady state, you can follow that state by a call to `continue`: `f<-run();f<-newton(f);continue(f,x="name",xmin=..,xmax=..)`, where "name" is the name of the parameter you changed to make qualitatively different phase spaces.
e. Draw nullclines for the bifurcation points that you found and interpret what they mean.
f. What is the effect of changing the carrying capacity of the prey? Can you repeat Rosenzweig's paradox of enrichment?
g. Which population increases most when you increase the carrying capacity of the prey?
h. In Fig. 10.3 the growth of *Daphnia* is compared with logistic growth of *Paramecium* (see Fig. 10.3). A striking difference is that *Paramecium* asymptotically approaches its carrying capacity, whereas *Daphnia* has an oscillatory approach to its steady state. As *Daphnia* feeds on algae you can use this Monod saturated predator prey model, with R denoting the algae and N representing *Daphnia*, to see if you can understand *Daphnia*'s growth curve depicted in Fig. 10.3b. Simulate the experimental curves in Fig. 10.3 by adding a few predators to a prey population at carrying capacity. Can you obtain the oscillatory approach of *Daphnia*?
i. Can you also obtain the asymptotic approach of *Paramecium* with the same model for other parameter values? What does this tell you?

Question 10.3. Bacteria and toxin

In Chapter 6 we studied the following system:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = s - wR - \frac{aNR}{h+R}\,, \quad \frac{\mathrm{d}N}{\mathrm{d}t} = \frac{bNR}{h+R} - wN - xNT \quad \text{and} \quad \frac{\mathrm{d}T}{\mathrm{d}t} = pN - wT\,,$$

describing a population of bacteria (N) living in a chemostat (with washout rate w) from a resource (R) and producing a toxin (T) that increases their own death rate. In Chapter 6 we simplified this model by making a quasi steady state assumption for the toxin. Actually, Cornejo *et al.* (2009) used a model with an autocatalytic production of the toxin, thus making the production of the toxin proportional to both the bacteria and the toxin concentration, and added a decay rate of the toxin, i.e., $\mathrm{d}T/\mathrm{d}t = pNT - dT - wT$. Their model does not allow for a quasi steady state assumption

for the toxin, and needs to be studied numerically in its full 3-dimensional form. On the website we provide the model in the file `toxin.R` with the parameters defined by Cornejo *et al.* (2009) (see Fig. 10.4). Note that T is renamed into `Q` because `T` means "true" in R. Because no toxin will be produced if one starts without toxin, one can perform phase plane analysis for a situation lacking toxin (which corresponds to the nullclines you sketched during the practical).

a. Repeat the nullclines you sketched in the practical by calling `plane(xmax=6, ymax=4e10, portrait=T)`. Is that indeed the same? Is the steady state stable? Which variable has the fastest time scale, and is that reasonable?

b. Call `f <- newton(c(R=3, N=1e10, Q=0), plot=T)` to test the stability of the steady state. Why is the steady state unstable now?

c. Run the full model with toxin to obtain the oscillations shown in Fig. 10.4. Is this truly a limit cycle? Is the steady state unstable?

d. The authors are concerned that the high densities reached by the bacteria in the chemostat are much higher than those in their natural habitat, the human nasopharynx. They indeed adapt one parameter of their model that reduces the bacterial densities, and find that the oscillations disappear because they are strongly dampened (see Fig. 10.4b). If you were to do the chemostat experiment, which parameter would you change to have lower bacterial densities? What happens when you change that parameter?

e. Is there a "sharp transition in the dynamical behavior", as claimed by Cornejo *et al.* (2009)? Is this parameter undergoing a bifurcation?

f. It seems somewhat strange that the bacteria need toxin to start the production of toxin. One could merge both models by writing $\mathrm{d}T/\mathrm{d}t = p_0 N + pNT - dT - wT$. Add this $p_0 N$ to the model, try to define what a small p_0 value would be, and test if this qualitatively changes the interpretation of the model.

10.4 Projects

Below you find three projects. Per group of 2 or maximum 3 students you can choose on of these projects to work on. Each group should hand in a report on their project.

Question 10.1. Cattle in the Sahel

In Chapter 7 we discussed catastrophic tipping points (saddle-node bifurcations). We here ask you to study a model for catastrophic changes in vegetation densities, which is based on the dynamics of water uptake in arid zones (Rietkerk & Van de Koppel, 1997; HilleRisLambers *et al.*, 2001).

Their main idea is that in arid areas without any vegetation coverage, most of the water that falls on the soil by the sometimes heavy rainfall fails to penetrate the soil. Instead, the water is rapidly washed off into rivers and disappears. Thus, the vegetation cover increases the penetration of water into the soil. Models for vegetation growth in arid areas can remain simple because the availability of water in the soil is typically the major limiting factor for vegetation growth. This main idea is translated into the following model:

$$\frac{\mathrm{d}W}{\mathrm{d}t} = P\Big(w_0 + \frac{V}{h_2 + V}\Big) - e_W W - \frac{uVW}{h_1 + W} \ ,$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = s + \frac{cuVW}{h_1 + W} - dV \ ,$$

where P is the precipitation (rainfall) (in mm d^{-1}), V is the vegetation biomass (in g m^{-2}), and W is the amount of water in the soil (mm). The model has two saturation constants, h_1 (mm) defines the amount of water at which the vegetation grows at half its maximal rate, and h_2 (g m^{-2}) is the vegetation cover at which the penetration of water into the soil is $R(w_0 + 1/2) = 1.4$ mm d^{-1}. Parameters of this model have been estimated by Rietkerk & Van de Koppel (1997) and HilleRisLambers *et al.* (2001) and are:

Name	interpretation	value	dimension
P	precipitation (rainfall)	2	mm d^{-1}
c	conversion of water to plant biomass	10	g $mm^{-1}m^{-2}$
d	death rate of vegetation	0.25	d^{-1}
u	maximum water uptake	0.05	mm g^{-1} m^2 d^{-1}
h_1	half saturation constant	5	mm
h_2	half saturation constant	5	g m^{-2}
e_W	soil water loss due to evaporation	0.2	d^{-1}
w_0	water infiltration in absence of vegetation	0.2	—
s	seed/plant influx	0.01	g m^{-2} d^{-1}

The death rate of the vegetation is partly due to normal turnover and partly due to grazing by cattle. In the absence of cattle the vegetation turnover is about $d = 0.05$ d^{-1}, and the vegetation reaches a carrying capacity of approximately 450 g m^{-2}. A single cow per farm corresponds to a grazing rate of 0.025 d^{-1}. In the absence of vegetation, there is about 2 mm of water in the soil. The model and its parameters are available on the website under the name `sahel.R`. Buying cows in the model should increase d, e.g., `p["d"]<-0.075`, and selling cows is the reverse. The `cattle_in_the_sahel.R` file defines a logarithmic axis for the vegetation because the vegetation grows exponentially and covers a wide range of densities.

a. Check the dimensions of all terms. Why is there 2 mm of water in the soil if there is no vegetation?

b. Compute the approximate location of the $dV/dt = 0$ nullcline by ignoring the immigration term i. How much water do you expect in the soil if there is a rich vegetation?

c. Draw nullclines for a herd size of 8 cows per farm, i.e., set $d = 0.05 + 8 \times 0.025 = 0.25$ d^{-1}.

d. Identify the stability of all steady states and give each of them a biological interpretation.

e. Make a phase portrait by the `plane(...,portrait=TRUE)` command. Which of the two variables has the fastest time scale, and is that reasonable?

f. Study the effect of increasing and decreasing the herd size by buying and selling cows. Make a sketch of the expected vegetation cover as a function of the death and grazing rate d.

g. Make a bifurcation diagram by finding the three steady states (using `newton()`) and following each of them using d as a bifurcation parameter (using `continue()`). Make sure you understand what this bifurcation diagram means! For instance:

```
fhig <- newton(c(W=5,V=50),plot=T)
fmid <- newton(c(W=5,V=2),plot=T)
flow <- newton(c(W=2,V=0.1),plot=T)
continue(flow,x="d",xmax=0.5,y="V",ymin=0.01,ymax=1000,log="y")
```

h. Perform a similar analysis for the effect of the rainfall (parameter P). What is the effect on the vegetation of a few years of low, or high, rainfall, and how does this depend on the herd size?

Question 10.2. Differentiation of cell types

Our understanding of how during development cells with the same genetic content can differentiate into different cell types was pioneered by Lewis Wolpert (Wolpert, 1969). He introduced the concept

of so-called morphogen gradients, graded distributions of instructive signalling molecules that range from a high concentration at one side of the tissue to a low concentration at the other end of the tissue. Wolpert subsequently postulated that if different genes respond to morphogens differently –e.g. one gene is being activated by morphogen M_1 while the other is being activated by morphogen M_2 which gradient runs in the opposite direction as M_1 – this will result in different sets of gene activation in cells at different positions in the tissue. Cell differentiation then corresponds to the activation of a different subset of genes. Here we will analyze a simple, two-morphogen two-gene model for cell differentiation:

$$\begin{aligned}
\frac{\mathrm{d}A}{\mathrm{d}t} &= e + r_A \frac{(A+cM_1)^q}{(A+cM_1)^q + h_A^q} \frac{k_A^m}{B^p + k_A^p} - d_A A \\
\frac{\mathrm{d}B}{\mathrm{d}t} &= e + r_B \frac{(B+cM_2)^q}{(B+cM_2)^q + h_B^q} \frac{k_B^m}{A^p + k_B^p} - d_B B \\
\frac{\mathrm{d}M_1}{\mathrm{d}t} &= -d_M M_1 \\
\frac{\mathrm{d}M_2}{\mathrm{d}t} &= -d_M M_2
\end{aligned}$$

where M_1 is a morphogen that at the start of development forms a gradient with its maximum at the anterior ($x = 0$) end of the body axis: $M_1(t = 0) = e^{-x/30}$, and M_2 is a morphogen that at the start of development forms a gradient with its maximum at the posterior ($x = 100$) end of the body axis: $M_2(t = 0) = e^{(x-100)/30}$, A is the expression level of the first transcription factor gene, and B is the expression level of the second transcription factor gene.

- e is the baseline expression of proteins A and B
- r_A, r_B are the regulation dependent translation rates of proteins A and B, respectively;
- d_A, d_B are the degradation rates of A and B, respectively;
- h_A, h_B are the concentrations at which A and B respond half-maximal to the morphogens and themselves;
- k_A, k_B are the concentrations at which A and B respond half-maximal to each other
- q is the Hill-coefficient for the effect of the morphogens and transcription factors
- p is the Hill-coefficient for the effect of A on B, and vice versa;
- We set $e = 0.001$, $r_A = r_B = 1$, $c = 0.1$, $d_A = d_B = 1$, $h_A = h_B = 0.1$, $k_A = k_B = 0.6$, $q = 3$ and $p = 5$.

For more background on gene expression regulation modeling we refer to Chapter 7. This model is available on the website as the file `differentation_of_cells.R`. Note that in the R model, there are no differential equations for M_1 and M_2. Instead they are treated as parameters. By putting them to different values you can investigate the impact of different spatial positions and different time points (the morphogens degrade over time) on the dynamics of genes A and B.

a. Plot the dependence of A on A and M, and the dependence of A on B. Sketch a network of interactions for A, B and M.

b. First consider the case where the morphogens have disappeared, i.e., set $M_1 = 0$ and $M_2 = 0$. Analyze the system in terms of nullclines, vector field, and equilibria. Is it possible to obtain cellular differentiation in this setting? What do different cell types correspond to?

c. Next consider the case where morphogens are present (i.e. at the start of development), and study a cell in the anterior part of the embryo (i.e. $M_1 > M_2$). Choose values for M_1 and M_2 and study what happens for the nullclines and the long term dynamics of the system. Why does B first increase and then decrease?

d. Now study a cell in the posterior part of the embryo, and perform the same analysis as above.

e. What thus is the function of the morphogen gradients?

f. Draw the expression of genes A and B as a function of cell number (cells from left to right are $x = 0, 1, \ldots, 100$).

g. Consider $q = 1$. What has changed? What would this imply biologically?

h. Go back to $q = 3$, now consider $p = 2$. What has changed? What would this imply biologically? How many cell types exist in this system?

Question 10.3. Several immune responses to HIV

It is not well understood why some people infected with the AIDS virus survive much longer than others. One of the prevailing ideas is that individuals who survive better mount more immune responses to HIV than those with fast disease progression. You will be asked to study the effect of the diversity of the immune response during a chronic viral infection. Shortly after sexual transmission HIV migrates into lymphoid tissues where the viral particles infect activated $CD4^+$ T cells, which after about two days burst and produce tens of thousands new virions. The new virions infect new $CD4^+$ T cells in the lymphoid tissues. Over the course of a few weeks, infected individuals develop several $CD8^+$ cytotoxic T cell (CTL) immune responses. CTL kill virus-infected cells. The death rate of infected cells has been measured in hundreds of patients, and surprisingly it was found that in almost all individuals the expected life span of productively infected $CD4^+$ T cells is one to two days and that this life span hardly depends on the virus load, or the immune response in these patients (Bonhoeffer *et al.*, 2003). Thanks to collaborative work between immunologists, virologists and mathematical modelers, many parameters of this viral infection have been quantified. We know that the virus replicates at a rate of approximately $r = 1.5$ d^{-1} before the number of $CD4^+$ target cells and/or the immune responses become limiting, and we know that the maximum effective population size is about $N = 10^5$ infected cells. Activated CTL divide at a maximum rate of approximately $p = 1$ d^{-1} and have an expected life span of about ten days ($d = 0.1$ d^{-1}). Every infected individual mounts several CTL responses, that seem to co-exist despite differences in their affinity, a_i, for the epitopes expressed by infected cells. This can be summarized by the following model:

$$\kappa = k\sum_{i=1}^{n} a_i E_i \quad , \quad \frac{\mathrm{d}I}{\mathrm{d}t} = rI(1 - I/N) - \kappa I \quad , \quad \frac{\mathrm{d}E_i}{\mathrm{d}t} = \frac{pE_i a_i I}{h + E_i + a_i I} - dE_i \ ,$$

where $i = 1, 2, \ldots, n$ defines the number of immune responses. Here κ is the death (killing) rate as determined by the total cytotoxic response, I is the number of infected cells, and E_i is the number of killer cells in each immune response. The proliferation rate of the immune responses is determined by a competitive saturation function allowing a maximum division rate p d^{-1} when $a_i I \gg h + E_i$, and requiring more infected cells $a_i I$ at higher effector cell numbers (i.e., E_i in the denominator basically increases the saturation constant h). Since CTL require few infected cells to become fully stimulated, we set $h = 100$ cells. The parameter $0 \leq a_i \leq 1$ measures the affinity of each response for the epitopes expressed by infected cells. A CTL with an affinity $a_i = 1$ requires the lowest amount of infected cells to become stimulated, i.e., will divide at its half maximal rate when $I = h$ cells. This model, with $n = 3$ immune responses, and its parameters are available on the website as the file `several_immune_responses.R`. The script contains a special function to report the killing rate, κ. The affinity is set to $a_1 = 1, a_2 = 0.5$ and $a_3 = 0.1$, and the mass-action killing rate to $k = 10^{-4}$ per CTL per day, i.e., about 10^4 CTL are required to achieve a killing rate of $\kappa = 1$ d^{-1}. The parameter file defines logarithmic axes because all populations grow exponentially and cover wide ranges of densities.

a. Study a simple infection by starting with one infected cell, $I = 1$ cell, and one excellent CTL, $E_1 = 1$ cell, and simulate the model for about three months (`f <- run(ymin=1, ymax=1e5, log="y")`). Does this resemble the early phase of an HIV infection? Use the final state of this run to approach the steady state by `f <- newton(f)`. What is the set-point level of infected cells, what is the steady state immune response, and what is the killing rate at that steady state? For the latter use the function `kill(f,p)`.

b. What would the set-point be if the affinity of E_1 were 10-fold lower? What is now the size of the immune response and what is the killing rate? How does the set-point viral load and the size of the immune response depend on a_1? Hint make bifurcation diagrams with a_1 on the horizontal axis and I and E_1 on the vertical axis.

c. Note that for $h \ll E_i + a_i I$ the steady state expression of the equation for the immune response simplifies to

$$pE_i a_i I/(E_i + a_i I) - dE_i = 0 \ ,$$

which after division by E_i delivers a simple relation between the expected number of killer cells per infected cell. Derive this relation and check numerically whether it is approximately correct for $h = 100$ cells.

d. Now study a diverse immune reaction by allowing $n = 3$ CTL responses, i.e., set $a_1 = 1, a_2 = 0.5$ and $a_3 = 0.1$ and initialize I, E_1, E_2, and E_3 as one cell. Study the first three months of the infection. What is now the viral load at set point and what are the densities of the three immune responses? What is the expected killing rate of infected cells? How can it be that this does not depend on the diversity of the immune response?

e. What would this killing rate be if all three immune responses were of high affinity? Can you explain this? (Hint: check the steady state expression of $\mathrm{d}I/\mathrm{d}t = 0$ for the case that the immune responses collectively keep $I \ll N$).

f. What is you expectation for the life span of infected cells in patients with very different immune responses? What is the effect of the diversity of the immune response in the viral set point on 1) number of infected cells, 2) the size of the immune response, and 3) the killing rate.

Chapter 11

Appendix: Hill-functions

The rate at which biological processes proceed often depends in a non-linear fashion on the value of a variable. As an example, the amount of prey that a predator eats per unit of time will for low prey numbers increase with the number of prey present, while for very high prey numbers this increase is no longer possible since the predator is either satiated or can not capture, eat and digest prey any faster. Thus, the predation rate depends in a saturating manner on the number of prey present. As an alternative example, the number of individuals born per individual animal per time interval may decrease in a non-linear manner with population density.

Hill-functions are a convenient family of saturation functions that are frequently used to describe such non-linear dependencies:

$$f(x) = \frac{x^n}{h^n + x^n} \quad \text{and} \quad g(x) = 1 - f(x) = \frac{1}{1 + (x/h)^n} \ , \tag{11.1}$$

in the first of which you may recognize the classical Michaelis-Menten saturation function for $n = 1$ (see Fig. 11.1a). The "saturation constant" h is the value of x where $f(x)$ or $g(x)$ attains half of its maximal value. The exponent n determines the steepness of the function. Whenever $n > 1$ the function is sigmoid (see Fig. 11.1b), and for $n \to \infty$ both $f(x)$ and $g(x)$ become step functions

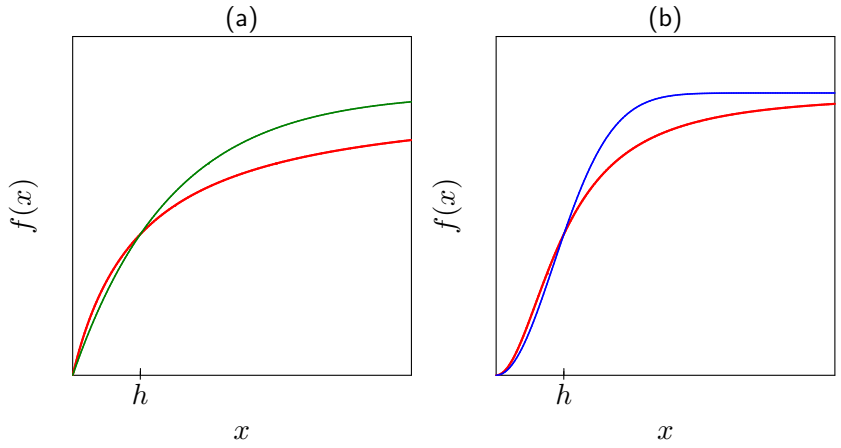


Figure 11.1: The increasing saturation functions defined by Eq. (11.1). The left panel depicts $f(x) = x/(h+x)$ and $f(x) = 1 - \mathrm{e}^{-\ln[2]x/h}$ which both have the convenient property that $0 \leq f(x) < 1$ and $f(x) = 0.5$ when $x = h$. In the panel on the right we draw their corresponding sigmoid variants $f(x) = x^2/(h^2 + x^2)$ and $f(x) = 1 - \mathrm{e}^{-ln[2](x/h)^2}$.

switching between zero and one at $x = h$. The slope of $f(x)$ in the origin is determined from its derivative, which for $n = 1$ equals

$$\partial_x f(x) = \frac{1}{h+x} - \frac{x}{(h+x)^2} \ , \tag{11.2}$$

which delivers a slope of $1/h$ for $x = 0$. For $n > 1$ the derivative is

$$\partial_x f(x) = \frac{nx^{n-1}}{h^n + x^n} - \frac{nx^{2n-1}}{(h^n + x^n)^2} \ , \tag{11.3}$$

which means that for $x = 0$ the slope is zero.

Because Hill functions are dimensionless and remain bounded between zero and one, i.e., $0 \leq f(x) \leq 1$, one can easily multiply any term in a model (corresponding to some biological process) with such a Hill function. Note that by multiplying the Hill-function with an arbitrary number a, we can easily obtain a process with a maximum rate of a. An advantage of using Hill functions in mathematical models is that solving steady states corresponds to solving polynomial functions.

The **exponential functions**

$$f(x) = 1 - \mathrm{e}^{-\ln[2]x/h} \quad \text{and} \quad g(x) = \mathrm{e}^{-\ln[2]x/h} \ . \tag{11.4}$$

are as conventional as Hill functions. Here we multiply the exponent with $ln[2]$ to obtain a parameter h corresponding to the x-value for which $f(x)$ and $g(x)$ equal $1/2$. They may be more convenient for finding solutions of equations, but they are more cumbersome when it comes to finding steady states, which is why we do not use them in this course. Like Hill functions we have $f(0) = 0$. For finding the half maximal value of $f(x)$ one solves $0.5 = \mathrm{e}^{-\ln[2]x/h}$ to find that $x = h$. The slope in the origin is determined from the derivative $\partial_x[1 - \mathrm{e}^{-\ln[2]x/h}] = (\ln[2]/h)\mathrm{e}^{-\ln[2]x/h}$ which for $x = 0$ gives a slope of $\ln[2]/h$. Like the Michaelis-Menten function this exponential function is not sigmoid (see Fig. 11.1a). The sigmoid form of the exponential function is known as the Gaussian distribution

$$f(x) = 1 - \mathrm{e}^{-\ln[2](x/h)^2} \ , \text{and} \quad g(x) = \mathrm{e}^{-\ln[2](x/h)^2} \ . \tag{11.5}$$

Thanks to our scaling with $\ln[2]$ these sigmoid functions are also half maximal when $x = h$ (and $x = -h$); see Fig. 11.1b.

Glossary

Assumptions Things that are accepted to be true, or true enough, for a given system. 2

Basin of attraction All (combinations of) initial values that end up in a specific attractor. If a model has multiple attractors, there are multiple basins of attraction. 28

Bifurcation When changes in a parameter result in a qualitative change in the systems behaviour. This can occur when changes in parameters cause nullclines to stop intersecting, when the intersection between nullclines is no longer in the positive domain (biologically no longer relevant), or when the intersection is maintained but the local vector field is different (e.g. as seen in the Hopf bifuraction).. 54

Deterministic chaos When a system shows unpredictable behavior and extreme sensitivity to initial conditions, yet there is no intrinsic driver of randomness, it is called deterministic chaos. 10

Difference equations Equations that map how a variable changes from one time step (t) to the next (t+1). Difference equations are commonly referred to as maps because they directly map how the state of a system changes using a simple "next-state" function. 4

Differential Equation A mathematical functions that describe rates of change. 11

Dimension The units in which a certain variable is expressed, for example, number of bacteria, concentration, or "per hour". 11

Doubling time The time it takes for an initial concentration/population to double in size. 14

Dynamical patterns Spatial patterns that do not converge to a stable state where the pattern no longer changes.. 79

Equilibrium When a variable, or a system of variables, has reached a state of balance so that there are no net changes occurring. 9

Expected life span The average time it takes before a particle/individual disappears due to turnover/death. 14

Functional response A function describing how a population responds to changes in density (eiter in birth, death, or other modelled processes). 25, 57

General solution The general solution of an ODE is a function (or set of functions) that satisfies the given ODE.. 11

Half-life The time it takes to lose half of the initial concentration/population. 14

Hopf bifurcation A critical point in parameter changes where a system's behaviour changes from a stable steady state to a periodic cycle. 61

Individual-based models (IBMs) A model formalism that describes unique individuals, their behavioural rules, how they interact, and in case of a spatial model, what patterns they form. 5

Intrinsic growth rate In ecology, the intrinsic growth rate describes how much a population can grow in a given time period. 9

Modelling The design and investigation of interesting simplifications of real-world systems. 1

Next-state function The function that is used to calculate the next state of a variable or system. 8

Ordinary Differential Equations (ODEs) ODEs are mathematical functions that describe the rates at which variables of interest change, typically over time. 3

Parameters Constant quantities used in models, often described with a letter such as catalysis rate (k_{cat}) growth rate (r), and carrying capacity (K). 3

Phase portrait A graphical representation of a system that can be sketched, allowing us to investigate the trajectory (direction) of the variable(s), and how/if this depends on the initial conditions.. 26, 72

Scaling When a variable does not represent the actual number, but some proportion of the actual number. Scaling can be useful to simplify the math, but one has to be careful to not jump to biological conclusions without considering the scaling (*e.g.* if your model predicts the survival of 0.0001 rabbits, is that still a "whole rabbit"?). 9

Specific solution The specific solution of an ODE can only be found when the general solution, the initial values, and all parameters are known. 12

Stable spiral A type of equilibrium around which the variables of a system keep oscillating, slowly converging closer to a stable point.. 45

Stable steady state Any state that is approached over the course of time, if one waits long enough.. 14

Stationary patterns Spatial patterns that converge to a stable state where the pattern no longer changes.. 79

Steady state When a variable, or a system of variables, has reached a state of balance so that there are no net changes occurring. 9

Trajectory Starting from an initial condition, a trajectory for an ODE describes all the points visited over time. Note that two trajectories can never cross, as that would imply that the same initial condition (that intersection point) would give two different results!. 45

Trivial steady state A stable steady state that is not interesting, *e.g.* when all variables are 0.. 14

Unstable spiral A type of equilibrium around which the variables of a system keep oscillating, slowly diverging further away from the stable point.. 45

Unstable steady state A steady state (the state remains unchanged when unperturbed), but any small perturbation leads to the system going away from this steady state. 15

Variable A quantity or element of interest that is assumed to vary over time (assuming time is the *independent variable*. 3

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