Mathematical Models in Biology

Lecture, held in the Winter-Semester 2003/2004

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Contents

1 Introduction I: General Remarks

(a) Aim of the lecture

- review of some mathematical methods frequently used in mathematical biology
- review of some standard models
- introduction into the art of modeling

(b) Biomathematics versus Bioinformatics

Bioinformatics (better: Computational Biostatistics & Data Banks)

- structuring large data sets
- Data mining / Biostatistics
- Especially: Methods independent of the mechanisms of biological systems

Best example: BLAST, search in a data bank of genes.

Aim: Description and structure of data, prediction.

Biomathematics

- Modeling Mechanisms
- Especially: Methods depend strongly on the mechanisms of biological systems

Example: Population dynamics

Aim: Understanding mechanisms, prediction.

Connection

Model comparison, prediction, structuring observations (what is relevant/irrelevant), extracting relevant questions..

(c) The Two Ways of Biomathematics

Qualitative theory

The basic mechanisms are modeled in a/the most simple way; parameter fitting and analysis of data are not very important.

We expect qualitative results. The models can be rigorously analyzed. These qualitative results (like prediction of oscillations, bistability or alike) can then compared with experimental observations. This approach does not aim to predict quantitatively experimental results.

Quantitative theory

The biological system under observation is modeled very detailed. Parameter are fitted. Analysis of the system is less important, simulations of certain trajectories are of higher interest.

We expect quantitative prediction of the experimental data. Here, an interaction between mathematician and biologist is absolutely necessary!

Quantitative versus Qualitative Methods

	Quantitative	Qualitative
Analysis	less important / not possible	possible and central
Simulation	important	less important
Aim	quantitative prediction of results	qualitative behavior
Advantage	quantitative prediction is possible ("Bioengineering")	overview over possible behavior
Disadvantage	Only special case considered	A lot of effects neglected

(d) Methods

We aim at the description of the dynamics of biological systems. There are three criteria that structure modeling approaches:

(1) One has to distinguish between small and large populations (stochastic of deterministic approach possible / necessary).
(2) Moreover, the time may be discrete (e.g. generations or state in spring) or continuous (chronological time, age etc.).
(3) The third important structure is given by the interaction: The entities may not or do strongly interact. In consequence we either get linear or nonlinear models.

We obtain the following scheme:

		Small Populations	Large Populations
independent individuals	discrete time	Galton-Watson Process	linear difference equations
	continuous time	Time continuous branching processes	linear differential equations
interacting individuals	discrete time	Cellular Automata	nonlinear difference equations
	continuous time	Interacting Particle Systems	nonlinear differential equations

Accordingly, the lecture consists of two parts: In the first part, we will look at the linear theory. Here, we keep the structure of the scheme above. The second part is concerned with nonlinear models. Rather than using the methodological approach, in this second part we focus on different fields in biology.

(e) Literature / Books

We touch a lot of issues: Modeling, stochastic processes, dynamical systems and statistics.
Modeling:
[48] Murray, J.D., *Mathematical Biology*, Springer, 1989,

[19] Edelstein-Keshet, Leah, *Mathematical models in biology*, McGraw-Hill, 1988.

Stochastic Process:

[6] Bauer, Heinz, *Wahrscheinlichkeitstheorie und die Grundzüge der Maßtheorie* Walter De Gruyter, 1978.

Dynamical Systems:

[40] Kuznetsov, Y.A.,*Elements of applied bifurcation theory*, Springer, 1995.

[2] Arrowsmith, D.K. and Place, C.M, *Ordinary Differenital Euqations*, Chapman and Hall, 1982.

Statistics:

[55] Pruscha, Helmut, *Angewandte Methoden der Mathematischen Statistik*, B.G. Teubner Verl., 1996.

[24] Gilks, W.R. and Richardson, S. and Spiegelhalter, D.J., *Markov Chain Monte Carlo in Practice*, Chapman & Hall, 1998.

2 Introduction II: Death Process

We consider a population of individuals who are alive at time zero. The only thing these individuals do is dying. We will apply a variety of methods, presenting many of the concepts and ideas of this lecture in a nutshell. Furthermore, this is one of the most fundamental processes. Though a death process sounds quite special, "death" can be interpreted in a quit general way: basically, it refers to an individual that leaves a certain state and changes to another state. For example, a ligand binds to an receptor. A susceptible that becomes infected. An infected, that recovers. You will find an unlimited number of examples. Thus, it is of interest to be clear about this process, and to spend some time on it.

2.1 Small Population

If we describe a small population, necessarily we have to take into account random fluctuations. Hence, we use a stochastic model.

2.1.1 Survival of one Individual

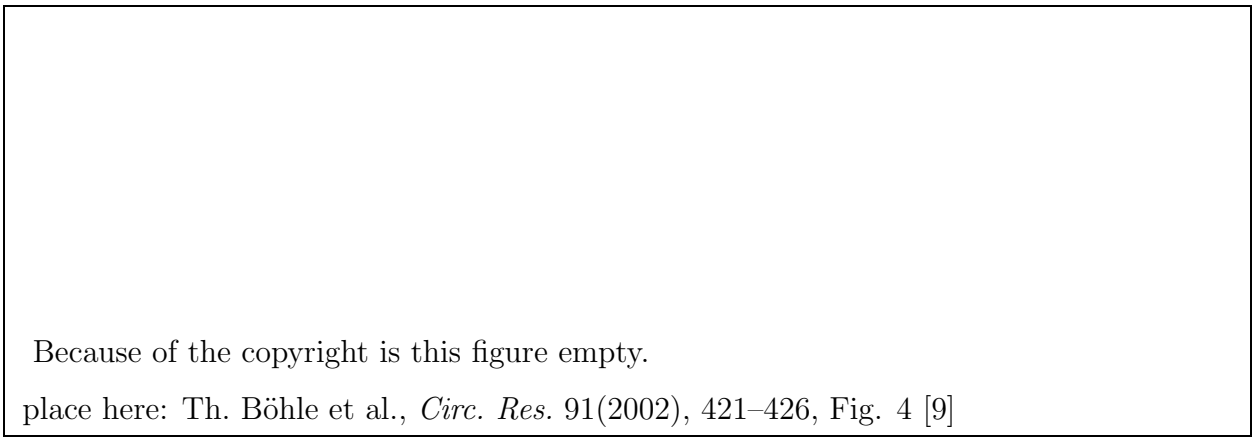

Figure 1: Histograms of the gating time of ion channels.

Individual based models (IBM) are in fashion. The reason is simply, that these models are quite straight-forward to formulate and to communicate. However, to analyze IBM's is quite difficult (and often not possible at all). The starting point for individual based models is (obviously) the behavior of *one single individual* .

An example are data about ion channels: Ion channels are channels in neurons, that allow ions to tunnel through the wall of the cell. They may be open and close. The time, that they are open depends on the voltage between the insight and the outside of the cell. However, once the voltage is fixed, it is believed that the time they stay in a certain state

does not depend on other influences. One obtains data about the gating behavior of one individual ion channel (see, e.g. [9] or [41] and Fig. 1). They show the opening time of certain ion channels that run in different modes. The details can be found in the article. The relevant questions are: (1) develop a model that describes the times a gate is open / closed, (2) estimate the parameters of this model.

One individual

State:

One individual may be dead or alive. It has a binary state description.

Dynamics / Change of state:

The only possible change of state is going from alive to dead (Fig. 2). How to formu-

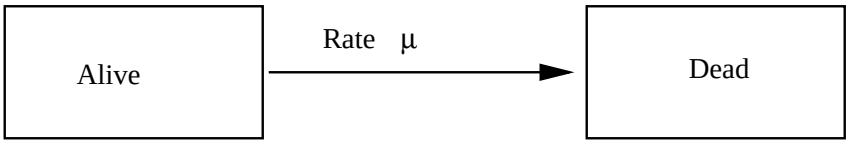

Figure 2: Change of state.

late this as a stochastic process? Obviously, we have to provide the probability for this individual to be alive at age a. *If* the Individual is alive at age a, then

$$P(\text{dead at } a + \Delta a | \text{ alive at } a) = \mu\, \Delta a + \mathfrak{o}(\Delta a)$$

Here, $\mathfrak{o}(.)$ denotes the Landau-symbol,

$$\lim_{x \to 0} \frac{\mathfrak{o}(x)}{x} = 0$$

In other words:

Let A be the random variable that gives the age of the individual at time of his/her death, then

$$P(A \in [a, a + \Delta a) \,|\, A > a) = \mu\, \Delta a + \mathfrak{o}(\Delta a).$$

This is a complete characterization of the model.

Remark: Modeling Approach

We used two steps to formulate the model. It is necessary and important to be clear about this proceeding.

First step: Characterization of the state space

Second step: Characterization of the transitions between different states, i.e. characterization of the dynamics.

Excursion: Probability and Random Variables

People from calculus love to think about functions and small perturbations. Stochastics has a completely different approach: Here, the ensemble is the basic approach. I.e., we always think about sets and subsets, respectively about the measure of sets. Also when dealing with a probability like $P(A \leq a)$, which is a function of a, it is not useful at all to think about this as a function. This expression is the measure of a set that changes in the age a.

Hence, if we define the behavior of *one* individual of age a by $P(A \leq a)$, we do not really consider *one* individual. We consider many, many individuals, all born a time units ago. Some of them will be alive at age a, others will be dead. $P(A \geq a)$ is the relative number of persons who are still alive.

One may visualize this idea (Fig. 3). Hence,

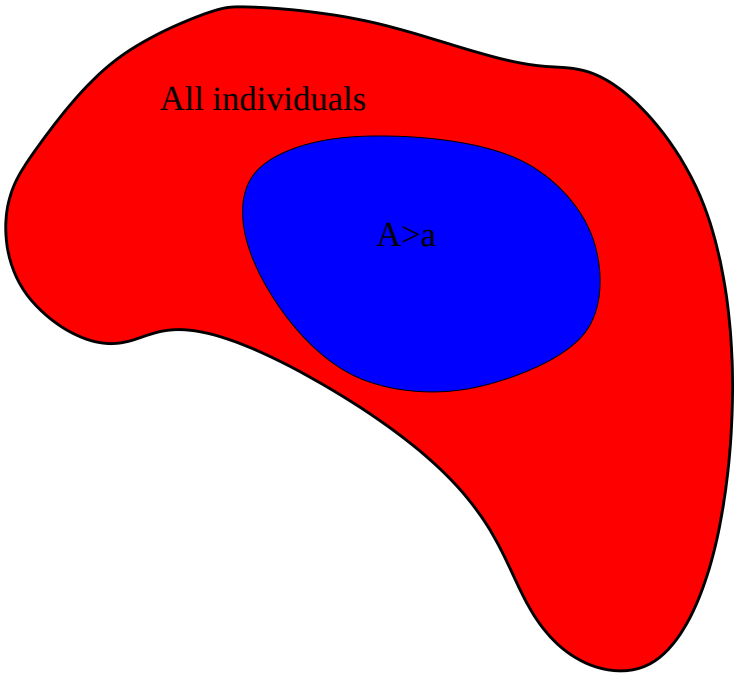

Figure 3: Probabilities as sizes of sets.

$$\begin{aligned} P(A > a) &= \text{relative area of the set } A > a \text{ in the set } A \in \mathbb{R}_+ \\ &= \frac{\text{Area of } A > a}{\text{Area of } A \in \mathbb{R}_+} \end{aligned}$$

Now we want to work with conditional probabilities. I.e., our reference set is not the set of all individuals, but a subset. What does $P(A \in [a, a + \Delta a] \,|\, A > a)$ mean (see Fig. 4)?

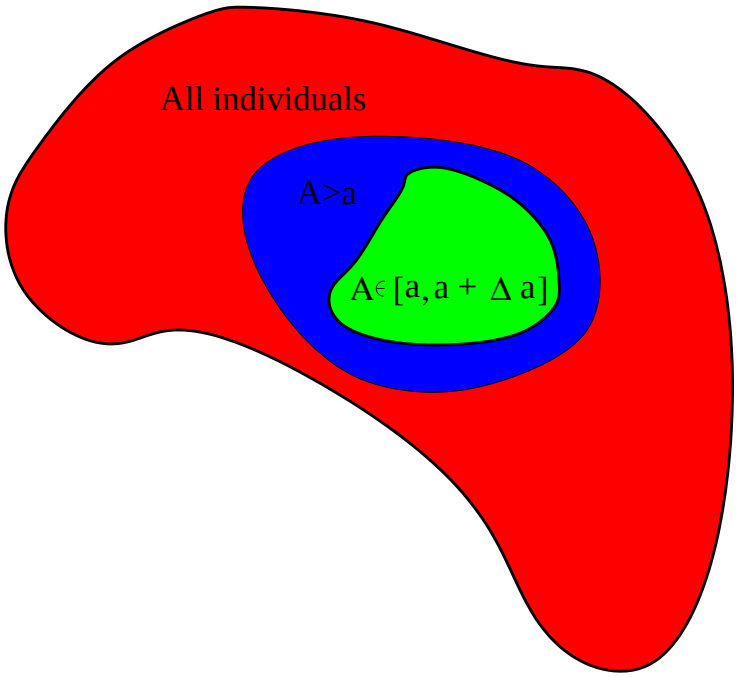

Figure 4: Conditional probabilities as sizes of sets.

$$\begin{aligned} P(A \in [a, a+\Delta a] \,|\, A > a) &= \frac{P(A \in [a, a+\Delta a] \wedge A > a)}{P(A > a)} \\ &= \frac{P(A \in [a, a+\Delta a])}{P(A > a)} \end{aligned}$$

The definition of a probability in a more formal way needs a set, the measurable subsets and a probability measure on these subsets.

Definition 2.1: **(1)** Let Ω be a non-empty set, $\mathcal{A} \subset \mathcal{P}(\Omega)$. $\mathcal{A}$ is a σ-algebra, if

- $\Omega \in \mathcal{A}$
- $a \in \mathcal{A} \quad \Rightarrow \quad \Omega \setminus a \in \mathcal{A}$
- $a_n \in \mathcal{A} \quad \Rightarrow \quad \cup_n a_n \in \mathcal{A}$.

(2) Let P a map $P : \mathcal{A} \to [0, 1]$ with

- $P(\{\}) = 0$
- $P(\Omega) = 1$
- $P(\cup_n a_n) = \sum_n P(a_n)$ if $a_i \cap a_j = \{\}$ for $i \neq j$.

Then P is a random measure.

(3) Let $A, B \in \mathcal{A}$ with $P(B) > 0$. Then,

$$P(A \,|\, B) = \frac{P(A \cap B)}{P(B)}.$$

Later on, we will use the Theorem of Bayes. Since it is quite simple to prove, we state and prove this theorem here.

Theorem 2.2: (Bayes)
Let $A, B \in \mathcal{A}$, $P(A)$, $P(B) > 0$. Then,

$$P(A|B) = \frac{P(B|A)\, P(A)}{P(B)}$$

Proof:

$$P(A|B) = \frac{P(A \cap B)}{P(B)} = \frac{P(A \cap B)\, P(A)}{P(A)\, P(B)} = \frac{P(B|A)\, P(A)}{P(B)}.$$

□

A further useful construction are random variables. The set Ω can be very general. However, it is more easy to work with numbers. Hence, one defines a random variable.

Definition 2.3: A random variable Z is a map

$$Z : \Omega \to \mathbb{R}$$

s.t. all sets $\{\omega \in \Omega \,|\, Z(\omega) \leq r\}$ for any $r \in \mathbb{R}$ is measurable. Hence, $P(Z \leq r)$ is well defined.

Survival Probability
We derived the formula for the survival probability of one individual

$$P(A \in [a, a + \Delta a] \,|\, A > a) = \mu(a)\Delta a + \mathcal{O}(\Delta a).$$

Note, that the death rate μ may depend on age a. We assume $\mu(a) \in C^0(\mathbb{R}_+)$. With our definition about conditional probabilities we find $P(A \in [a, a + \Delta a] \,|\, A > a) = P(A \in [a, a + \Delta a])/P(A > a)$ and

$$\begin{aligned} P(A \in [a, a + \Delta a]) &= P(A > a)\, \mu(a)\Delta a + \mathcal{O}(\Delta a) \\ -\frac{P(A > a + \Delta a) - P(A > a)}{\Delta a} &= P(A > a)\mu(a) + \frac{\mathcal{O}(\Delta a)}{\Delta a} \\ &\downarrow \quad \Delta a \to 0 \\ \frac{d}{da} P(A > a) &= -\mu(a) P(A > a), \qquad P(A > 0) = 1. \end{aligned}$$

For the last step, we needed that $\mu(a)$ is relatively smooth (continuous). Hence,

$$P(A > a) = e^{-\int_0^a \mu(\tau)\, d\tau}.$$

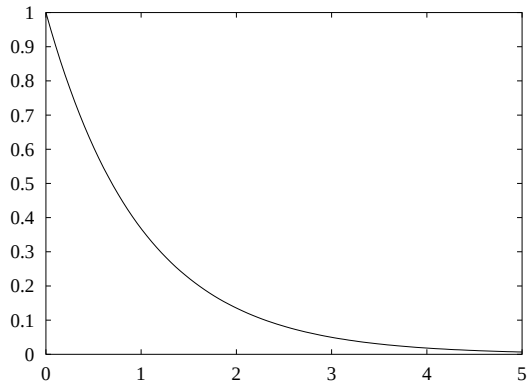

Figure 5: Exponential distribution ($\mu = 1$).

If $\mu(a) \equiv \mu$ is constant, we find the exponential distribution (Fig. 5),

$$P(A > a) = e^{-\mu a}.$$

Summary/Conclusion
What did we learn? First of all, the golden rule of modeling: We first determine the state space, and in the second step we introduce the dynamics, i.e. how the state changes in time.
Next, we developed a model for the change of the state of one individual. We obtain an exponential distribution, if the rate is constant, and a more general distribution, if the rate depends on age resp. the time, that an individual is in a certain state.

2.1.2 IBM: Level of small populations

Now we go from the individual level to the population level. We consider N individuals, numbered by $1, 2, .., N$ and define the random variables

$$X_i^{(t)} = \begin{cases} 1 & \text{if individual } i \text{ is alive at time t} \\ 0 & \text{if individual } i \text{ is dead at time t} \end{cases}$$

Random variables, that are one if an individual satisfies a certain property, and zero otherwise, are also called "random characteristics" [35]. It is possible to count all individuals with a given property at a certain time with a given property by summation over these random variables. In our case, we are able to determine the size of the (living) population. Let the age of all individuals at time zero be zero. The population size reads

$$Y_t = \sum_{i=1}^{N} X_i^{(t)}.$$

We know

$$P(X_i^{(t)} = 1) = e^{-\int_0^a \mu(\tau)\,d\tau}$$

and thus Y_t is distributed according to a binomial distribution,

$$Y_t \sim \text{Bin}(N, e^{-\int_0^a \mu(\tau)\,d\tau}.$$

Especially,

$$E(Y_t) = N\, e^{-\int_0^a \mu(\tau)\,d\tau}, \quad \text{Var}(Y_t) = N\, \left(1 - e^{-\int_0^a \mu(\tau)\,d\tau}\right)\, e^{-\int_0^a \mu(\tau)\,d\tau}.$$

Thus we are able to characterize the dynamics of the system in a similar way like tat of on individual: Choose a time interval Δa small. Assume furthermore, that we have k individuals in the population at time t. Then, the probability that two individuals die in this small time interval $[a, a + \Delta a]$ is of higher order $\mathcal{O}(\Delta a)$. The probability that at least one individual dies is

$$\begin{aligned} & 1 - (1 - P(\text{death of one specific individual}))^{k+1} \\ = \; & 1 - (1 - \mu(a)\Delta a + \mathcal{O}(\Delta a))^{k+1} \approx 1 - (1 - (k+1)\mu(a)\Delta a + \mathcal{O}(\Delta a)) + \mathcal{O}(\Delta a) \\ = \; & (k+1)\mu(a)\Delta a + \mathcal{O}(\Delta a). \end{aligned}$$

Since this is up to higher order terms also the probability that exactly one individual dies, we find

$$P(Y_{a+\Delta a} = k \,|\, Y_a = k+1) = (k+1)\,\mu(a)\,\Delta a + \mathcal{O}(\Delta a).$$

If we assume the special case $\mu(a) \equiv \mu$, then for $0 \le t_1, t_2$

$$E(Y_{t_1+t_2}) = E(Y_{t_1})\, e^{-\mu\, t_2}.$$

A similar property also holds true for each individual,

$$P(A > a + b | A > a) = e^{-\mu b}.$$

This probability does not depend on a. This distribution is "memoryless". It forgets the history. Such a process, whose fate depends only on the state is called a Markov process. We will investigate some characteristics of Markov processes later.

Again, we made two steps.
First step: State of the system defined as the number of living individuals
Second step: Dynamics of the system given by $P(Y_{t+\Delta t} = k \,|\, Y_t = k{+}1) = k\,\mu\,\Delta t{+}\mathcal{O}(\Delta t)$.

2.1.3 Simulation Techniques

In the present case, strictly spoken no simulations are necessary. We are able to obtain all information analytically. However, for more complex model it is often not possible to derive results about the behavior of the model analytically. In this case, simulation and

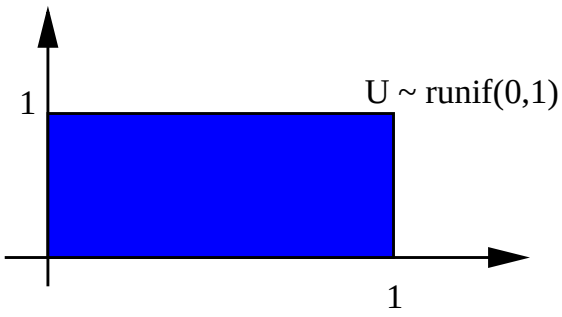

Figure 6: Density of the uniformly distributed random variable U ($\mu = 1$).

numerical analysis is required. Furthermore, simulations may be useful to visualize the behavior of he system and to communicate the ideas (especially to non-mathematicians). We present here two different approaches for simulation of this stochastic process.

Every (or at least nearly every) computer language provides a pseudo random number generator. We assume, that a function is available that returns random variables distributed uniformly between zero and one (Fig. 6).

Possibility 1: Transformation
We transform U with a function

$$f : [0, 1] \to \mathbb{R}_+,$$

s.t. $X = f(U)$ is exponentially distributed with parameter μ.

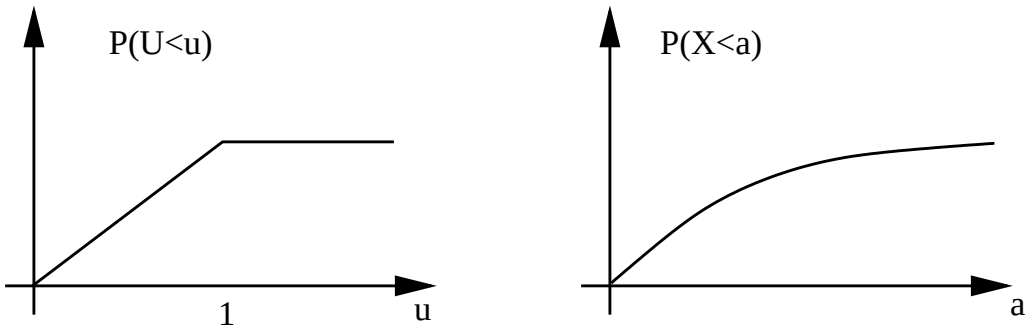

Figure 7: Transformation of the random variable U.

We have (see Fig. 7)

$$P(U < u) = \begin{cases} 0 & \text{for } u < 0 \\ u & \text{for } 0 \le u < 1 \\ 1 & \text{for } 1 < u \end{cases} \qquad P(X < a) = \begin{cases} 0 & \text{for } u < 0 \\ 1 - e^{-\mu a} & \text{for } 0 \le u \end{cases}$$

We assume, that f is monotonously, s.t. the inverse f^{-1} is well defined. Then,

$$\begin{aligned} 1 - e^{-\mu\, a} &= P(X \le a) = P(f(U) \le a) \\ &= P(U \le f^{-1}(a)) = f^{-1}(a) \end{aligned}$$

where we used $f^{-1} \in [0,1]$ in the last line. Hence,

$$f(a) = -\frac{1}{\mu} \ln(1-a)$$

and, since U as well as $1-U$ are uniformly distributed in the interval $[0,1]$, we may use the transformation

$$g(a) = -\frac{1}{\mu} \ln(a)$$

Algorithm:

Step 1:
Define N real numbers A_1,..,A_N as

$$A_i = -\frac{1}{\mu} \ln(\text{runif}(0,1)).$$

Step 2:
Determine the population size at time t by

$$Y(t) = \#\{A_i > t\}.$$

This scheme can be easily extended to death rates that depend on age, $\mu = \mu(a)$.

Possibility 2: Discretization of Time
The second approach uses the characterization of the dynamics

$$P(Y_{t+\Delta t} = k \,|\, Y_t = k+1) = k\,\mu\,\Delta t + \mathrm{o}(\Delta t).$$

We choose the time steps Δt to be small, s.t. $\mathrm{o}(\Delta t)$ can be neglected. Let

$$t_i = i\,\Delta t, \qquad Y_i \approx Y^{t_i} \qquad\qquad i \in \mathbb{N}_0$$

where we define the approximations Y_i of Y^{t_i} recursively by

$$Y_{i+1} \,|\, Y_i = \begin{cases} Y_i & \text{with probability } 1 - Y_i \mu \Delta t \\ Y_i - 1 & \text{else} \end{cases}.$$

(Here $Y_{i+1} \,|\, Y_i$ does mean the value/distribution of the random variable Y_{i+1} if we know the value of the random variable Y_i in the realization under consideration). This equation does only make sense, if

$$1 - Y_i \mu \Delta t \ge 0 \qquad \Rightarrow \qquad \Delta t \ll \frac{1}{\mu N},$$

i.e. we obtain a restriction for the step size.

Algorithm:

Step 1: initialize
$Y_0 := N; \quad i := 0; \quad t := 0$
Step 2: loop
while ($t <$ time horizon) {
    $u :=$ runif$(0, 1)$;
    If ($u < \mu Y_i \Delta t$) then {
        $Y_{i+1} := Y_i - 1$;
    } else {
        $Y_{i+1} := Y_i$;
    }
    $i := i + 1$;
    $t := t + \Delta t$;
}

This scheme corresponds to the explicit Euler scheme for ordinary differential equations. It is not possible to extend this scheme in a straight forward way to death rates that depend on age.

Comparison
The first scheme can be easily extended to situations, where the death rate depends on age, $\mu = \mu(a)$. This is not the case for the second scheme. However, the first scheme needs more computer time than the second scheme (the variables A_i have to be sorted somehow), such that large populations are faster to simulate with the second approach.

2.1.4 Parameter Identification

Until now, we considered an abstract model. Now we want to confront the model with real data. One could discuss several issues, e.g. testing the appropriateness of the model. However, we focus on the issue of parameter estimation, and sketch four methods (perhaps the four most important approaches) to obtain parameter values.

We assume that we have information about the life span of n individuals (see histogram in Fig. 8),

$$a_1, .., a_n.$$

We assume that these measurements are independent. We want to determine the parameter/rate μ.

Momentum Method

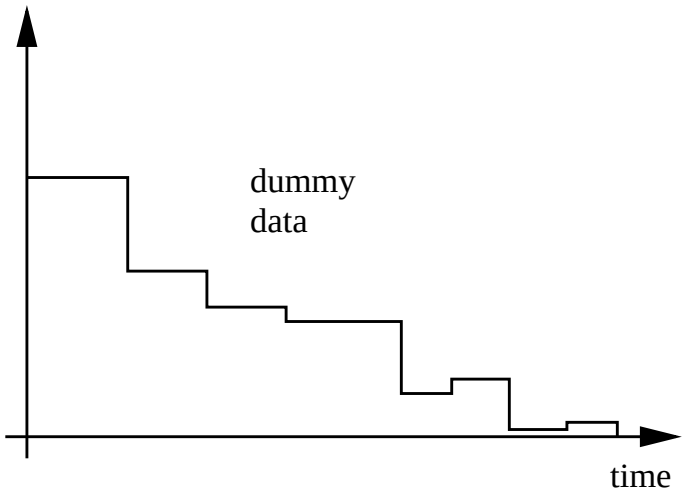

Figure 8: Histogram of the data.

The expected value of the life span A of our individuals reads

$$E(A) = \int_0^\infty a \left(-\frac{d}{da} P(A > a) \right) da = \int_0^\infty a\, \mu e^{-\mu a}\, da = -\mu \frac{d}{d\mu} \int_0^\infty e^{-\mu a}\, da = \frac{1}{\mu}.$$

Hence, $\mu = 1/E(A)$. A naive estimator will be

$$\hat{\mu} = \left(\sum_{i=1}^{n} a_i \right)^{-1}.$$

Maximum Likelihood Method
Since

$$P(A \in (a, a + \Delta a)) = \mu e^{-\mu a} \Delta a + \mathcal{O}(\Delta a)$$

the "likelihood" to find the life span a_i for the i'th individual reads $\mathcal{L}_i = \mu e^{-\mu a_i}$. Hence, the likelihood to find the n independent measured data a_1,..,a_n is

$$\mathcal{L}(\mu) = \Pi_{i=1}^{n} \mu e^{-\mu a_i} = \mu^n e^{-\mu \sum_{i=1}^{n} a_i}$$

The central idea of the maximum-likelihood method is, that the data are typical. Hence, for the true parameter, we expect the data to be where they are. Conversely, a parameter for which the likelihood is small is not very likely to be the true parameter. The best estimator $\hat{\mu}$ is the parameter that maximizes the likelihood, $\mathcal{L}(\mu)|_{\mu=\hat{\mu}} \geq \mathcal{L}(\mu)\ \forall \mu \in \mathbb{R}_+$. Since $\mathcal{L}(.)$ is smooth, and $\mu = 0$ resp. μ very large will definitely be no good choices, we find

$$\frac{d}{d\mu} \mathcal{L}(\mu)|_{\mu=\hat{\mu}} = 0.$$

It is more easy to work with $\ln(\mathcal{L}(\mu))$, the log-likelihood. Since the logarithm is monotonously, $\hat{\mu}$ will also maximize $\ln(\mathcal{L}(\mu))$. We find

$$\begin{aligned} 0 &= \frac{d}{d\mu}\ln(\mathcal{L}(\mu)) \\ &= \frac{d}{d\mu}\ln\left(\mu^n e^{-\mu\sum_{i=1}^n a_i}\right) \\ &= \frac{d}{d\mu}\left(n\ln(\mu) - \mu\sum_{i=1}^n a_i\right) \\ &= \frac{n}{\mu} - \sum_{i=1}^n a_i. \end{aligned}$$

Thus,

$$\hat{\mu} = \left(\sum_{i=1}^n a_i\right)^{-1}.$$

In this case, we obtain the same estimator like in the momentum method. In more general situations, estimators derived by these two approaches will disagree.

The present case is relatively simple: The exponential distribution belongs to the so-called exponential family, which is quite close to the normal distribution. A lot of concepts of the normal distribution ("linear models" in statistics) can be generalized to the exponential family ("generalized linear model", see [55]) If the number of data is high, it is possible (even for nonlinear models) to derive also confidence intervals.

χ^2-Value
We start with the histogram, and fit a curve in an optimal way.

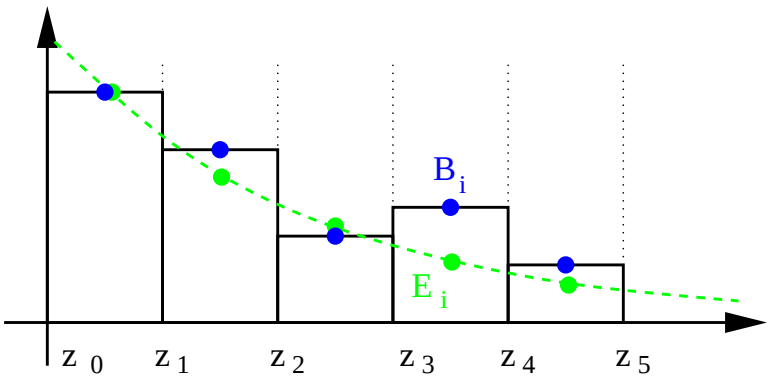

Figure 9: Histogram of the data.

Let $z_0 = 0 < z_1 < z_2 < ... < z_l = \infty$ and

$$B_i = \#\{a_j \,|\, z_{i-1} \le a_j < z_i\} \qquad i = 1, ..l.$$

Rule of thumb
The first and the last interval should contain at least five data points, all other intervals at least three data points.

For a given parameter μ, we also determine the expected number of observations within the corresponding interval,

$$E_i = E_i(\mu) = n \left(e^{-\mu a_{i-1}} - e^{-\mu a_i} \right)$$

Obviously, a good choice of μ should minimize the differences between observed and expected number of data within these intervals,

$$\Delta(\mu) = \sum_{i=1}^{l} (B_i - E_i(\mu))^2 = \text{minimum}.$$

In a slightly more sophisticated approach, one takes into account the variance structure. If the number of data n is much larger than the number of intervals l, then approximatively the variables B_i are distributed accordingly to a Poisson distribution. The variance of a Poisson distribution equals its expected value. Hence,

$$\frac{B_i - E_i}{\sqrt{E_i}}$$

has expectation zero and variance one; in this sense, minimizing

$$\chi^2(\mu) = \sum_{i=1}^{l} \frac{(B_i - E_i(\mu))^2}{E_i(\mu)} = \text{minimum}.$$

is more fair to the intervals. If only a few data are expected to be in the interval (and are observed in this interval, indeed) then the contribution of this interval to the estimation of μ will be weak, if we use $\Delta(\mu)$. Taking the variance structure into account, this interval will be weighted with a higher weight $1/E_i$, s.t. intervals with a high expected value and intervals with low expected values have equal rights.

A further justification is the fact, that $(B_i - E_i)/\sqrt{E_i}$ approximate normal distributions (from this fact, the rule of thumb above is derived, though such a low number of data points is still poor), s.t. $\chi^2(\mu)$ is approximately χ^2_p distributed, where $p = n - 1$ denotes the degree of freedom. This fact opens the opportunity to find confidence intervals and criteria for the goodness of fit, i.e. to get an idea if the model is appropriate. One may find more details in this direction in [55].

Bayesian Approach
The basic idea of the Bayesian statistics is different to the classical approach: we want to estimate the parameter μ, i.e. we aim at the probability distribution $\pi(\mu|\text{Data})$ of $\mu|\text{Data}$ (the probability distribution of μ under the condition that we observe certain data, Fig. 10).

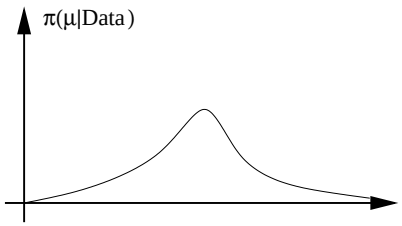

Figure 10: Probability distribution of $\mu|\text{Data}$.

The point estimator of μ will be then the expectation of $\mu|\text{Data}$,

$$\hat{\mu} := E(\mu|\text{Data}).$$

However, we do not know $\mu|\text{Data}$, but we only know the likelihood,

$$\mathcal{L}(\mu|\text{Data}) = \Pi_{i=1}^{n} \mu e^{-\mu a_i} = P(\text{Data}\,|\,\mu).$$

In order to derive $\mu|\text{Data}$ from $\text{Data}\,|\,\mu$, we use the theorem of Bayes,

$$\pi(\mu|\text{Data}) = C^{-1} P(\text{Data}\,|\,\mu)\, P(\mu) = C^{-1} \mathcal{L}(\mu|\text{Data})\, P(\mu).$$

Here, C is a constant that normalize $\int \pi(\mu|\text{Data})\, d\mu$ to one,

$$C = \int \pi(\mu|\text{Data})\, d\mu = \int_0^\infty \mathcal{L}(\mu|\text{Data})\, P(\mu)\, d\mu.$$

A further, new expression appears: $P(\mu)$. This is an *a-priori* information about μ, the so-called *prior* . Even before we perform the experiment, we are assumed to have some idea where the parameter may be (e.g., we know that that the gating times of ion channels are rather small, ranging in milli-seconds rather than in seconds). This knowledge can/has to be included here. This is the draw-back of the Bayesian approach: Two persons, who evaluate the data may use different priors, and thus derive different estimators. A non-objective element appears in Bayes-statistics. However, once the prior is chosen, the estimator is fixed. The resulting distribution of the parameter is then called *a-posteriori*-distribution.

How does an estimator looks like for our situation? We first have to choose a prior. Like noted before, we are free to think about some reasonable distribution for the prior. There is a choice, that makes life simple, because we can compute the *a-posteriori*-distribution analytically: the Γ-distribution. We choose distribution $g(\mu)$ of the prior to be

$$P(\mu) \sim \Gamma(\alpha, \beta), \qquad \text{i.e. } g(\mu) = \frac{\mu^{\alpha-1} e^{-\mu/\beta}}{\Gamma(\alpha)\beta^\alpha}.$$

The *a-posteriori* distribution follows to be

$$\pi(\mu|\text{Data}) = C^{-1} \mathcal{L}(\mu|\text{Data})\, P(\mu) = C^{-1} \left(\mu^n e^{-\mu \sum_{i=1}^n a_i}\right) \frac{\mu^{\alpha-1} e^{-\mu/\beta}}{\Gamma(\alpha)\beta^\alpha}$$

where C is determined by

$$C = \int_0^\infty \left(\mu^n e^{-\mu \sum_{i=1}^n a_i}\right) \frac{\mu^{\alpha-1} e^{-\mu/\beta}}{\Gamma(\alpha)\beta^\alpha}\, d\mu.$$

With

$$\int_0^\infty x^{a-1} e^{-b\,x}\, dx = b^{-a} \int_0^\infty y^{a-1} e^{-y}\, dy = \Gamma(a) b^{-a}$$

we find

$$C = \left(\frac{1}{\Gamma(\alpha)\beta^\alpha}\right) \int_0^\infty \mu^{\alpha+n-1} e^{-\mu(\sum_{i=1}^n a_i + 1/\beta)}\, d\mu = \frac{\Gamma(\alpha+n)(\sum_{i=1}^n a_i + 1/\beta)^{-(\alpha+n)}}{\Gamma(\alpha)\beta^\alpha}$$

and hence

$$\pi(\mu|\text{Data}) = \left(\frac{(1/\beta + \sum_{i=1}^n a_i)^{\alpha+n}}{\Gamma(\alpha+n)}\right) \left(\mu^{\alpha+n-1} e^{-\mu(1/\beta + \sum_{i=1}^n a_i)}\right)$$

The point estimator then reads

$$\hat{\mu} = E(\mu|\text{Data}) = \int_0^\infty \mu\pi(\mu|\text{Data}) = \left(\frac{(\sum_{i=1}^n a_i) + 1/\beta}{n+\alpha}\right)^{-1}.$$

Interpretation: If $\alpha = 1/\beta = 0$, then we find the classical maximum-likelihood-estimator. α can be interpreted as the number of *a-priori* observations, where $1/\beta$ is the sum of the length of the life-spans of these *a-priori*-observations. The estimator uses the experimental observations a_i and the *a-priori* observations, and constructs with all observations the classical estimator. This interpretation is quite typical for Bayes-estimators.
However, if $n \ll \alpha$ and $1/\beta$ not too large, the prior does not matter, in this case

$$\left(\frac{(\sum_{i=1}^n a_i) + 1/\beta}{n+\alpha}\right)^{-1} \approx \left(\frac{\sum_{i=1}^n a_i}{n}\right)^{-1}$$

which is the classical estimator for this experiment. Only if the number of observations is small, the prior influences the estimator.

Summary/Conclusion
What did we learn? There are two basic concepts for estimators: the classical approach and the Bayesian approach.
Perhaps the most important classical estimator is the maximum likelihood estimator. If the underlying model is nonlinear, there are in general only asymptotic results (number of data tends to infinity) available. Hence, this method works well, if enough data are available, but may have a problem for only a small amount of data.
The Bayes-estimator works (theoretically) fine, even if only a small amount of data is available. However, we need to specify a prior (which penalizes parameter ranges where we assume the data not to be). If there are many data this prior information does not

influence the result significantly. If only few data are there, this prior knowledge (or pre-justice) will have a strong influence.
All in all, the classical and the Bayes-approach work well, if we have a lot of data, but do have problems, if only few data are available. Note: Be cautious with statistics, if you do not have a lot of data!!!!!

2.2 Deterministic Models

Of course, there are also deterministic models for the death process. How to justify deterministic models? The central question of this section will be the connection between stochastic and deterministic model, respectively how to go from the stochastic model to the deterministic model. Related with this question is the problem, that differential equations do have real state variables, while our biological system has discrete entities, i.e. only assumes values in $\mathbb{N}$.

There are two major ways of reasoning: either one takes expected values, or (perhaps more important) one considers large (homogeneous) populations. In the latter case, we expect variations to play only a minor role. Hence we may use a differential equation instead of a stochastic process to describe the system.

Remark: Somewhere between small and large populations are medium sized populations. They may be better described by stochastic differential equations. However, since this type of model needs a certain technical effort, it is not very often used in mathematical biology. Also here, this type of model will not be discussed.

Small population: Expected Values
State: Let $x(t)$ be the population size at time t of a deterministic model, describing a *finite population*.
$x(t)$ will not be a natural number in a deterministic model (indeed, if we have continuous time, there is no possibility to define a model in a sensitive way that only assumes discrete states; implicitly, one has to introduce somewhere an element of discrete time). How to interprete $x(t)$?
We consider a finite population, hence there will be some (perhaps little) stochasticity in the model. It makes no sense to look at a certain realization and try to match $x(t)$ with this certain realization. We should look at a typical trajectory, i.e. at the mean value,

$$x(t) = E(Y_t).$$

The mean value, however,does not have to be / is in general not a natural number. Hence, in this interpretation we do not have a problem with the seemingly contradiction between real numbers for $x(t)$ and natural numbers for Y_t.

Dynamics: Since we know $E(Y_t)$, we find at once the equation governing the dynamics

$$\frac{d}{dt}\mu(t) = -\mu x(t), \qquad x(0) = N.$$

This interpretation seems very straight forward, but this is not the case: We average about all trajectories of the stochastic model. There are cases (especially for spatial structured models), where we average out some interesting properties. Especially, if uses corresponding methods for nonlinear models. E.g., how to keep spatial correlations in such an average process is not clear at once. We will discuss approaches later on, that try to get on with this problem (rapid stirring limit, moment equations).

Large Population: Population Densities
The second approach makes no (direct) use of expectations. The idea here is to use the fact, that we consider *large* (homogeneous) populations. I.e., we let the initial population size Y_0 go to infinity. In this case, we expect the random fluctuations (relatively to the mean value) to be small. Of course, we have to normalize the population size; otherwise the population size just tends to infinity. Let

$$u(t) = \lim_{Y_0 \to \infty} \frac{Y_t}{Y_0}.$$

More general, one may consider sone reference magnitude, define $z(t) = Y_t/\text{reference magnitude}$, and let this magnitude go to infinity, where - at the same time - also Y_t tends to infinity. A standard example is the area individuals are living. Then,

$$z(t) = \lim_{\text{area} \to \infty} \frac{\text{population in a certain area}(t)}{\text{area}}$$

i.e., $z(t)$ is the population density (number of individuals per square meter etc.).

Which equation does $u(t)$ satisfy? Define

$$U_{Y_0}(t) = \frac{Y_t}{Y_0}.$$

We may argue, that $u(t)$ is described by $e^{-\mu t}$. Therefore, we consider

$$v(t) = \sqrt{\frac{Y_0}{e^{-\mu t}\left(1 - e^{-\mu t}\right)}}\ (U_{Y_0} - e^{-\mu t}) = \left(e^{-\mu t}\left(1 - e^{-\mu t}\right) Y_0\right)^{-1/2}\ (Y_t - E(Y_t)).$$

Hence,

$$E(v(t)) = 0.$$

Recall, that $Y_t = \sum_{i=1}^{Y_0} X_i^{(t)}$ is the sum of Bernoulli-random variables, that are i.i.d. (independently and identically distributed). Then,

$$\begin{aligned}
\text{Var}(v(t)) &= \left(e^{-\mu t}\left(1 - e^{-\mu t}\right) Y_0\right) \text{Var}(Y_t - E(Y_t)) \\
&= \left(e^{-\mu t}\left(1 - e^{-\mu t}\right) Y_0\right) \text{Var}\left(Y_t\right) \\
&= \left(e^{-\mu t}\left(1 - e^{-\mu t}\right) Y_0\right) \text{Var}\left(\sum_{i=1}^{Y_0} X_i^{(t)}\right)
\end{aligned}$$

$$
\begin{aligned}
&= \left(e^{-\mu t}\left(1-e^{-\mu t}\right)Y_0\right)\left(\sum_{i=1}^{Y_0}\mathrm{Var}(X_i^{(t)})\right)\\
&= \left(e^{-\mu t}\left(1-e^{-\mu t}\right)Y_0\right)\left(Y_0\mathrm{Var}(X_1^{(t)})\right)\\
&= \left(e^{-\mu t}\left(1-e^{-\mu t}\right)Y_0\right)\left(Y_0 e^{-\mu t}\left(1-e^{-\mu t}\right)\right)\\
&= 1
\end{aligned}
$$

Since Y_t is the sum of i.i.d. Bernoulli-variables, we find by the central limit theorem, that asymptotically

$$\sqrt{\frac{Y_0}{e^{-\mu t}\left(1-e^{-\mu t}\right)}}\left(U_{Y_0}(t)-e^{-\mu t}\right) \sim_a N(0,1).$$

Hence, the difference between $e^{-\mu t}$ and $U_{Y_0}(t)$ becomes small, if (see Fig. 11)
- $1-e^{-\mu t}\approx 0$, i.e. $t\approx 0$
- $e^{-\mu t}\approx 0$, i.e. $t\approx\infty$
- $Y_t\approx\infty$.

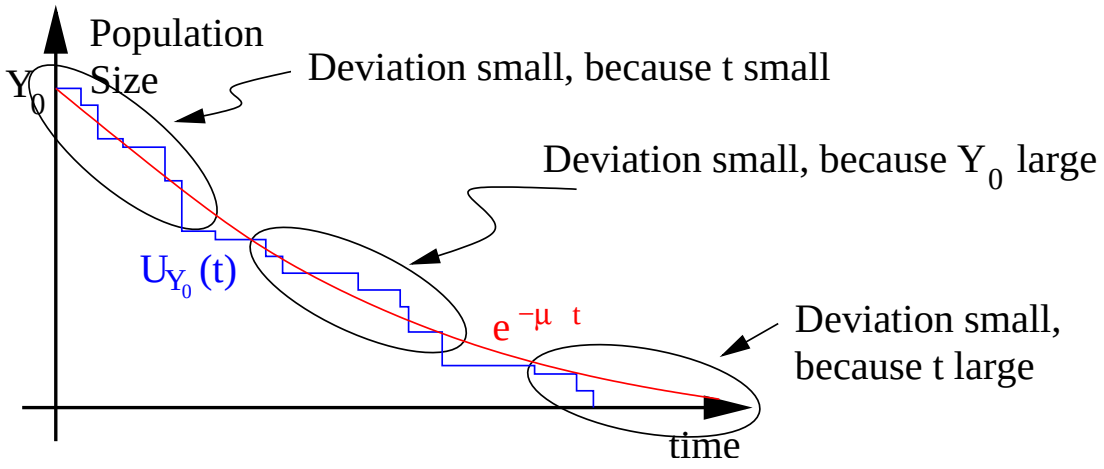

Figure 11: Deviation of stochastic ($U_{Y_0}(t)$, blue line) and deterministic ($e^{-\mu t}$, red line) model.

Especially, $u(t)=\lim_{Y_0\to\infty}U_{Y_0}(t)=e^{-\mu t}$ with respect to the probability measure P, i.e. we find

$$\frac{d}{dt}u(t)=-\mu u(t),\qquad u(0)=1.$$

The important point is, that this way of reasoning does also work out for nonlinear models. One may find examples in [39].

Remark: An open problem are hybrid systems. Consider e.g. a diseases that breaks out periodically, but for a certain time is almost eradicated in a population. During the outbreak, the description you want to chose is deterministically, since there a large number of individuals are involved (infected), and stochastic effects only play a minor role

(Fig. 12). During the silent phase, there are a few (perhaps unobserved) infecteds that keep the disease alive; here e.g. the possibility that the disease may die out is high. If we use at this point a deterministic model, we run in the problem of "attofoxes": a paper describing the spread of rabies in a fox-population used a deterministic model; they did not recognize, that the number of infected foxes came down to 10^{-9}, which made some conclusion of the model not really reliable.

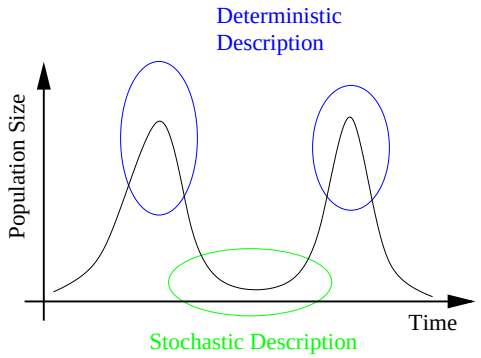

Figure 12: Switching between stochastic and deterministic model.

What one really would like, is to swith from the deterministic to the stochastic description at the appropriate time point. However, the stochastic model is formulated in terms of individuals, while the deterministic model considers densities. These two approaches do not match. This problem appears in some papers and models; a proper solution seems not to be available in general.

Summary/Conclusion
Two ways are appropriate to justify deterministic models. If the particles are independent, one may take the expected values. One then derives a well defined deterministic model. However, if we consider a small population, one may loose in this way information, since stochastic effects are expected to play a certain role.
The second approach works out for large, homogeneous populations. In this way, random fluctuations and correlations only play a minor role, and one can derive for the relative densities deterministic models. This approach also works for nonlinear models (interacting particles), but it needs a large, homogeneous population.
Note, that the latter approach is therefore useless, if we have a highly structured population, e.g. a spatially structured population. In this case, we have to think about possible generalizations of the first approach to nonlinear models. We will return to this point later.

2.3 More than one type of transition

In and out

The examples below are all deterministic models. However, to have only one transition in a model is rather boring. Therefore, we introduce multiple transitions. The most simple case is the following: we have three states X, Y and Z. At time zero, all particles are in state X. They go from state X to state Y with rate α and leave state Y with rate β. I.e., the time they stay in state X is exponentially distributed with rate α, and the time the particles stay in state Y is also exponentially distributed, this time with rate β (see Fig. 13). The aim is to derive an ODE that describes the evolution of the mean values

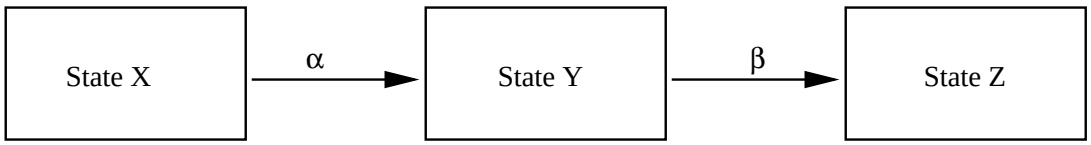

Figure 13: Model system for two transitions.

of this system. Therefore, we first define the corresponding stochastic model.

State: Let X_t, Y_t and Z_t be the number of particles at time t in state X, Y and Z, respectively.
Dynamics: We have two events, the transition from X to Y and transition von Y to Z.
Transition $X \to Y$:

$$P\left(\begin{array}{c|c} X_{t+\Delta t} = k-1 & X_t = k \\ Y_{t+\Delta t} = l+1 & Y_t = l \end{array} \right) = k\alpha\Delta t + o(\Delta t).$$

Transition $Y \to Z$:

$$P\left(\begin{array}{c|c} Y_{t+\Delta t} = l-1 & X_t = l \\ Z_{t+\Delta t} = m+1 & Y_t = m \end{array} \right) = l\beta\Delta t + o(\Delta t).$$

Let $x(t) = E(X_t)$, $y(t) = E(Y_t)$, $z(t) = E(Z_t)$. We know from the considerations about the simple death process, that

$$\dot{x} = -\alpha x, \qquad x(0) = E(X_0)) =: x_0.$$

Furthermore,

$$\begin{aligned} E(Y_{t+\Delta t}) &= E(Y_t) + P(Y_{t+\Delta t}|Y_t = Y_t + 1) - P(Y_{t+\Delta t}|Y_t = Y_t - 1) + o(\Delta t) \\ &= E(Y_t) + \alpha\, E(X_t)\, \Delta t - \beta\, E(Y_t)\, \Delta t + o(\Delta t). \end{aligned}$$

Thus $(y(t+\Delta t) - y(t))/\Delta t = \alpha\, x(t) - \beta\, y(t) + o(\Delta t)/\Delta t$, and taking the limit yields

$$\dot{y} = -\beta\, y + \alpha\, x, \qquad y(0) = E(Y_0)) =: y_0.$$

The same reasoning gives

$$\dot{z} = \beta\, z, \qquad z(0) = E(Z_0) =: z_0.$$

All in all, we find

$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} = \begin{pmatrix} -\alpha & 0 & 0 \\ \alpha & -\beta & 0 \\ 0 & \beta & 0 \end{pmatrix}\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix}, \qquad \begin{pmatrix} x(0) \\ y(0) \\ z(0) \end{pmatrix} = \begin{pmatrix} x_0 \\ y_0 \\ z_0 \end{pmatrix}.$$

We find a linear ordinary differential equation (like expected),

$$\mathcal{X} = A\mathcal{X}, \qquad \mathcal{X}(0) = \mathcal{X}_{\prime}.$$

The matrix A has two special properties:
• Multiplication with the vector $(1,1,1)$ from l.h.s. yields zero, $(1,1,1)A = 0$.
• $A_{i,j} \geq 0$ for $i \neq j$.

Reason enough, to look closer at such matrices.

M-Matrices and linear ODE's
Definition 2.4: *A Matrix A with $A_{i,j} \geq 0$ for $i \neq j$ is called M-matrix.*

You may find more theorems about M-matrices in [8]. For us, especially the following theorem is of interest. Some definitions before. Let $\mathbf{e}_i$ be the i'th unit vector, and $\mathbf{e} = (1,1,\cdots,1)^T$ the vector with all entries one.

Definition 2.5: **(1)** The positive cone of $\mathbb{R}^n$ is the set $\{x \in \mathbb{R}^n \,|\, x \geq 0\}$ where the inequality $x \geq 0$ is to interprete as $x_i \geq 0$ for each entry x_i of x.
(2) The solution-operator $S_t x_0$ of the ODE $\dot{x} = Ax, x(0) = x_0$ is called semigroup with generator A (or fundamental system for A).

Theorem 2.6: *Let $A \in \mathbb{R}^{n\times n}$ be a matrix, and $S_t = e^{At}$ the semigroup induced by A on $\mathbb{R}^n$. The semigroup S_t leaves the positive cone of $\mathbb{R}^n$ invariant, if and only if A is an M-matrix.*
Proof: $\Rightarrow$: If A is an M-matrix, then there is a $\lambda > 0$, s.t. $A + \lambda I$ is non-negative in each element. Hence, $e^{(A+\lambda I)t}$ is also non-negative. Since A and I commute, we find

$$S_t = e^{(A+\lambda I)t}e^{-\lambda t},$$

and thus S_t is a non-negative matrix (in the sense that all entries are non-negative).
$\Leftarrow$: If S_t is a semigroup with infinitesimal generator A, then

$$S_t = I + tA + \mathcal{O}(t^2).$$

Let $\mathbf{e}_i$ be the i'th unit vector. Since S_t leaves the positive cone invariant, we find $\mathbf{e}_i^t S_t \mathbf{e}_j \geq 0$, i.e.

$$0 \leq \mathbf{e}_i^T S_t \mathbf{e}_j = \mathbf{e}_i^T \mathbf{e}_j + t\mathbf{e}_i^T A\mathbf{e}_j + \mathcal{O}(t^2).$$

Thus, if $i \neq j$, we find

$$0 \leq \mathbf{e}_i^T A\mathbf{e}_j + \mathcal{O}(t).$$

and therefore $0 \leq \mathbf{e}_i^T A \mathbf{e}_j$.

□

In biology, the conservation of positivity is quite important; thus, M-matrices play a certain role. With a simple trick, it is possible to reduce the dimension of the ODE $\dot{x} = Ax$.

Proposition 2.7: *Let A be an M-matrix and $y(t)$ defined by*

$$\dot{y} = (I - y\mathbf{e}^T)\, A\, y, \qquad y(0) = y_0.$$

This ODE leaves the simplex $\mathcal{S} = \{x \in I\!R^n_+ \,|\, \mathbf{e}^T x = 1\}$ invariant. Furthermore, if $x(0) \in I\!R^n_+$, $x(0) \neq 0$ and $y(0) = x(0)/\mathbf{e}^T x(0)$, then $y(t) = x(t)/\mathbf{e}^T x(t)$.

One may interprete this proposition as the possibility to project solutions of $\dot{x} = Ax$ into the simplex $\mathcal{S}$ by the map $T; \mathbb{R}^n_+ \setminus \{0\} \to \mathcal{S}, x \mapsto x/\mathbf{e}^T x$. This projection $y(t)$ again satisfies an autonomous ODE (see Fig. 14).

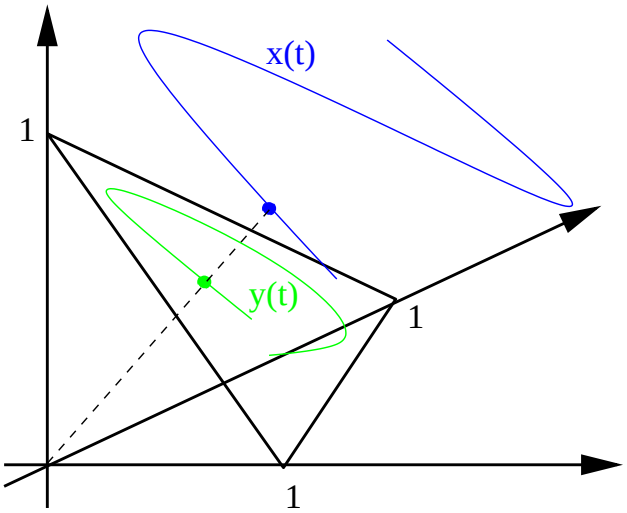

Figure 14: Projection of the linear ODE to the simplex $\mathcal{S}$.

Proof: The proposition follows by a straight-forward computation. Let $x(0) \in \mathbb{R}^n_+ \setminus \{0\}$ and consider $z(t) = x(t)/\mathbf{e}^T x(t)$. Since A is an M-matrix, $\mathbf{e}^T x(t) \neq 0$, and $z(t)$ is well defined.

$$\frac{d}{dt} z(t) = \frac{d}{dt} \frac{x}{\mathbf{e}^T x} = \frac{\frac{d}{dt} x}{\mathbf{e}^T x} - \frac{x}{\mathbf{e}^T x} \frac{\frac{d}{dt} \mathbf{e}^T x}{\mathbf{e}^T x} = \frac{Ax}{\mathbf{e}^T x} - \frac{x}{\mathbf{e}^T x} \frac{\mathbf{e}^T A\, x}{\mathbf{e}^T x} = Az - z\mathbf{e}^T Az.$$

This is the equation for $y(t)$. Furthermore, let $\mathbf{e}^T y(0) = 1$. Since

$$\frac{d}{dt}(1 - \mathbf{e}^T y) = -\frac{d}{dt} \mathbf{e}^T y = -\mathbf{e}^T (I - y\mathbf{e}^T) Ay = -(1 - \mathbf{e}^T y)(\mathbf{e}^T Ay)$$

we find

$$1 - \mathbf{e}^T y(t) = (1 - \mathbf{e}^T y(0))\ e^{-\int_0^t \mathbf{e}^T A y(\tau)\, d\tau} = 0.$$

Hence also the invariance of $\mathcal{S}$ follows.

□

Now we may investigate the stationary points, i.e. solutions of $\dot{y} = 0$, the projected system.

Proposition 2.8: *A stationary point of $\dot{y} = (I - y\mathbf{e}^T)Ay$ corresponds to an eigenvector of A.*
Proof: Let u be a solution of $\dot{y} = 0$, i.e. $(I - u\mathbf{e}^T)Au = 0$. Hence,

$$Au = -(\mathbf{e}^T Au)\, u,$$

i.e. u is an eigenvector with eigenvalue $-(\mathbf{e}^T Au)$.

□

Remark 2.9: **(1)** Later, we will consider the Perron-Frobenius theorem. One important conclusion of this theorem is the fact, that there is exactly one non-negative eigenvector (and this eigenvector corresponds to the spectral radius ρ of the matrix, which is a simple eigenvalue and the only eigenvalue on $\{z \in \mathbb{C} || z| = \rho\}$). Hence, if $A_{i,j} > 0$ for $i \neq j$, there is only one stationary point in $\mathcal{S}$. It is possible to prove that this stationary point is attracting all trajectories in $\mathcal{S}$.

(2) Some of this theory can be generalized to differential equations that are homogeneous of degree one, $\dot{x} = f(x)$, $f(\alpha x) = \alpha x$.

Until now, we considered only one property of the ODE derived in the last paragraph: the fact, that A is an M-matrix. The second important fact is, however, that $\mathbf{e}^T A = 0$.

Proposition 2.10: *The solution of $\dot{x} = Ax$ with $\mathbf{e}^T A = 0$ conserves the total mass,*

$$\mathbf{e}^T x(t) = \mathbf{e}^T x(0).$$

The proof is straight-forward.

General linear compartmental models

Linear compartmental models utilize this structure. The idea is to define different states, a directed graph that denotes possible transitions between the states; each edge is equipped with a rate. This construction describes a closed system. If the system is not closed, there may be emigration or immigration, i.e. there may be an in- and an outflow from the system. The total number of particles is not preserved. However, also these events are simple to integrate into our picture: If an edge goes outside of the system, we have a death process, where the individuals never reappear in a class of the system. An edge

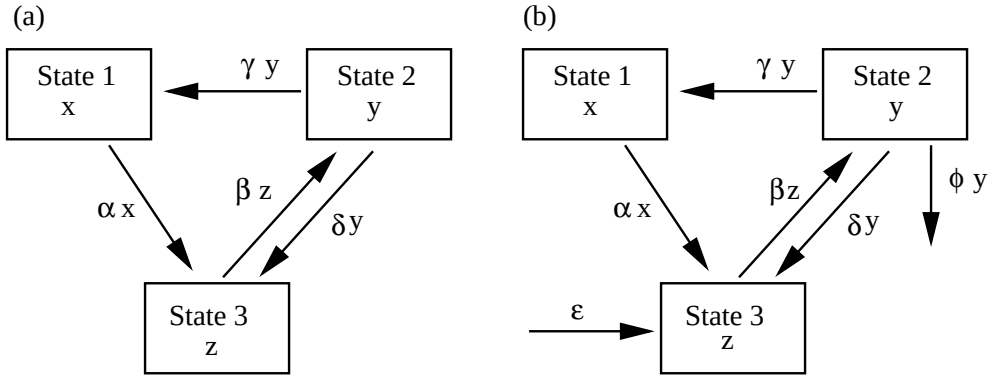

Figure 15: Linear compartmental models. (a) closed system, (b) open system.

pointing insight yields to a constant inflow of newborn individuals into a certain class. Perhaps an example is of higher use than formal definitions. Consider Fig. 15. Let x, y and z be the densities in state 1, state 2 and state 3 respectively. Consider subfigure (a). The equation reads

$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} = \begin{pmatrix} -\alpha & \gamma & 0 \\ 0 & -(\gamma+\delta) & \beta \\ \alpha & \delta & -\beta \end{pmatrix} \begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix}, \qquad \begin{pmatrix} x(0) \\ y(0) \\ z(0) \end{pmatrix} = \begin{pmatrix} x_0 \\ y_0 \\ z_0 \end{pmatrix}.$$

The equation for subfigure (b) reads

$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} = \begin{pmatrix} -\alpha & \gamma & 0 \\ 0 & -(\gamma+\delta+\phi) & \beta \\ \alpha & \delta & -\beta \end{pmatrix} \begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ \epsilon \end{pmatrix}, \qquad \begin{pmatrix} x(0) \\ y(0) \\ z(0) \end{pmatrix} = \begin{pmatrix} x_0 \\ y_0 \\ z_0 \end{pmatrix}.$$

One has to be careful in interpreting the term with ϵ. In all other cases, we had to multiply the density in a certain state with the rate in order to obtain the incidence of corresponding events (i.e. the number of transitions per time unit). The arrow with ϵ comes in from nothing. We have to be sure, that ϵ is not a rate but the incidence of particles entering state 2 from outside.

In the remaining part of our considerations about the death process and linear compartmental models, we want to consider three examples.

Further reading: You find more (and more literature) about compartmental models and the connection between matrices, ODE's and graph theory in the review article [33].

2.4 Examples for compartmental models

2.4.1 Receptor-Ligand Binding

The aim of this section is to describe the dynamics of ligands and receptors. Obviously, these interaction are necessary to understand, if one aims at cell-signaling systems. We follow examples from the book [42], where you may also find more and more detailed models in this direction.

In the basic situation we have receptors and ligands, which may react to receptor-ligand complexes; this may then dissociate (see Fig. 16). Receptors are located on the cell surface, while the ligands are solved in the medium. The basic assumption in the following considerations is that ligands are present in excess, s.t. the number/density of free ligands is not changed in an significant way by the reaction of some of them with free receptors.

Experimentally, one uses a certain cell line that express a kind of receptors. The experiment consist of three steps: (1) The cells are incubated in a medium with a given density of ligands. (2) After incubation for a relatively long time, the medium is changed and the cells are washed, s.t. only ligands bound to receptors are present in the experimental system. (3) It is now possible to add substances that cause a dissociation of the receptor-ligand complex, s.t. the ligand again is in solution. Now, one can measure the density of ligands.

State: Since we assume that there is a large reservoir of free ligands, s.t. the density of free ligands L is not changes by the reaction of receptor and ligand to a complex, we only have to keep track for the density of free receptors (state 1) and receptor/ligand-complexes (state 2).

$$R(t) = \#\text{Free Receptors/Cell}, \qquad C(t) = \#\text{Receptor-ligand-complexes/Cell}.$$

Dynamics: We have two processes: reaction and dissociation. While the rate k_2 for dissociation will not depend on the density of free ligands L, $k_2 = k_r$, we may assume that the rate for the production of complexes k_1 is proportional to L, $k_1 = k_f\, L$.

Thus we obtain the ODE's

$$\begin{aligned} \frac{d}{dt}R(t) &= -(k_f\, L)R + k_r C \\ \frac{d}{dt}C(t) &= (k_f\, L)R - k_r C \end{aligned}$$

Since we have conservation of mass ($C(t) + R(t) = \text{constant} =: R_T$, we find

$$\frac{d}{dt}C(t) = (k_f\, L)(R_T - C) - k_r C$$

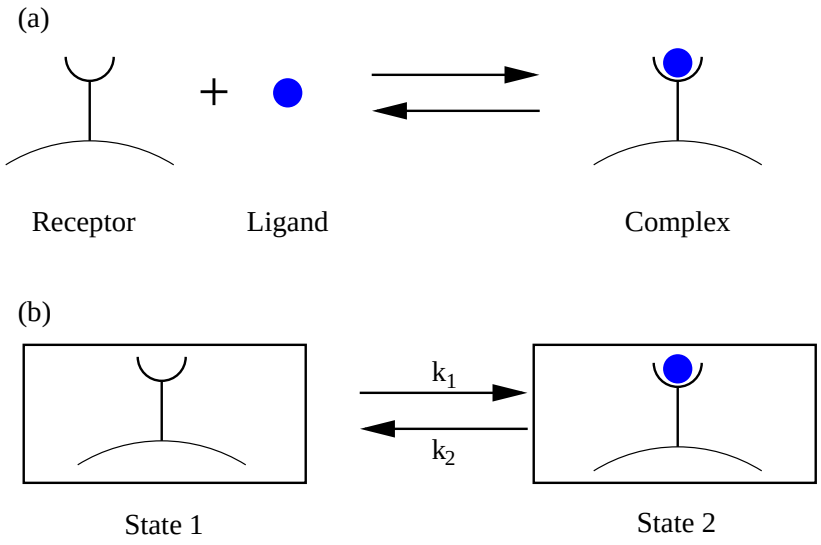

Figure 16: Reaction of ligand and receptor to the complex, respectively dissociation of the complex. **(a)** The reaction of receptor and ligand to the receptor-ligand complex. **(b)** The compartmental model for the situation that the ligand density is constant over time.

Define $K_D = k_f/k_r$. Then, the equilibrium for C reads

$$\frac{d}{dt}C(t) = 0 \quad \Rightarrow \quad C = \frac{k_f\, R_T\, L}{k_f\, L + k_r} = R_T\, \frac{L}{L + K_D}.$$

This formula predicts the amount of ligands bound to the receptor in equilibrium. We can compare the prediction with the result of an experiment (see Fig. 17).
After fitting the parameter K_D and R_T, we find a nice agreement of experiment and theoretical predictions. However, we are not able to estimate all parameter of the model. Especially, we only estimate the quotient of the rates k_r and k_f, since we only have data about the equilibria. We cannot expect to be able to reconstruct the whole dynamics from the equilibria - e.g. all information about time scales are lost. Other experiments aiming at the dynamics are necessary to obtain information about every single parameter. An example for such an experiment is [15].

2.4.2 Positron-Emission-Tomography

In some sense, the second example is a direct generalization of the first example. In positron-emission-tomography, a dose of radioactive marked ligands are injected into the blood of a patient. These ligands are called “tracer”. The tracer spreads over the body via the blood and diffuses into the tissue. There it may bind to specific receptors (f they are expressed in the corresponding tissue type). The dynamics of the tracer will be different for different types of tissue (which express receptors in a different number). In this way, it is e.g. possible to distinguish between cancer and healthy tissue for some

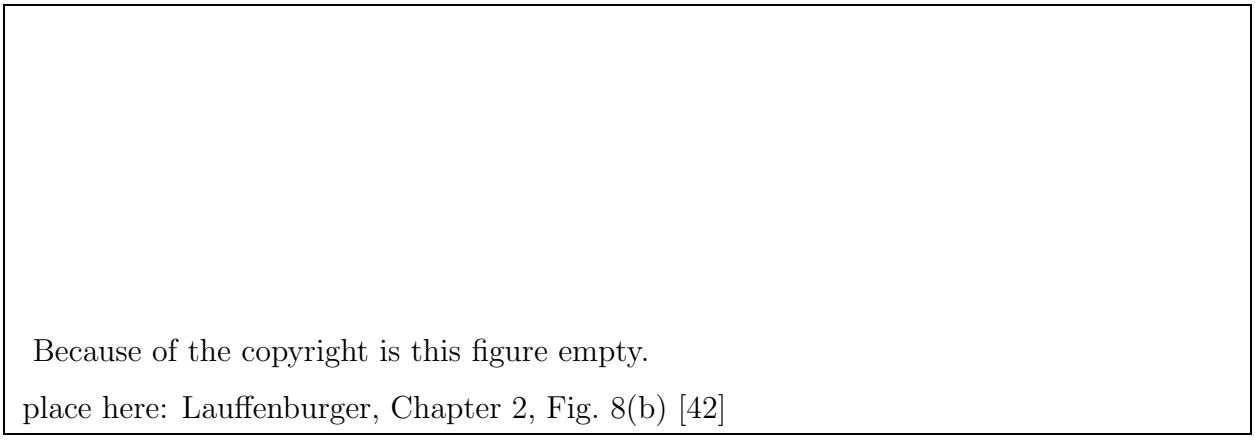

Figure 17: Density of bound ligands C in equilibrium as a function of free ligand concentration in the medium L.

specific cancer species. The radioactive tracer will decay. A positron is produced in such a decay (see Fig. 18). This positron will recombine with an electron. In this reaction, two γ-quantums are produced. They spread nearly exactly in opposite directions. Thus, it is possible **(1)** quite exactly to determine decays coming from a positron (two γ quantums have to be detect simultaneously) and **(2)** to determine a straight line, on which this decay has happend. More details of this principle can be found in [46]. Hence we obtain informations about the density of the radioactivity in the tissue, integrated over straight lines. With the Radon transformation one can recompute the density of radioactivity at a certain location in the tissue (the Radon transformation yields an inverse problem that is ill posed; also here, interesting mathematics is involved, which we will not discuss here. You may find more in [44]).

Compartmental models

For the dynamics of the tracer in a certain tissue, one may now use a linear compartmental model. Of course, this model has to take into account the knowledge about the special tracer under consideration. However, it turns out, that there is something like a standard model, that is valid for a lot of tracers. Here, one has to distinguish between three complements: tracer in the blood, tracer in the tissue that did not bind to its specific receptor, and tracer in the tissue that did bind to an receptor (Fig. 19).

State: Let $C_a(t)$ be the amount of tracer in the blood (at time t), $C_1(t)$ be the amount of tracer in the tissue not bounded to a receptor, and $C_2(t)$ be the tracer bounded to an receptor.

Dynamics: We obtain directly the model equations (the rate k_1 describes the transition blood to tissue, the rate k_2 that of tissue to blood, the rate k_3 binding of the tracer to a receptor (where k_3 depends on the receptor density in the corresponding tissue) and k_4

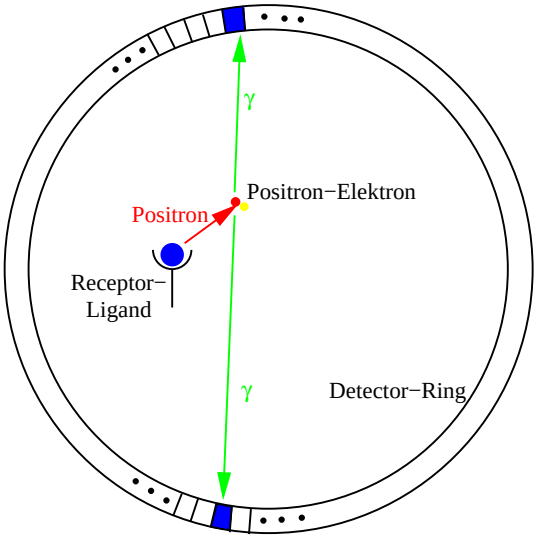

Figure 18: Principle of positron-emission-tomography.

the dissociation of tracer and receptor)

$$\begin{aligned} \frac{d}{dt}C_1 &= -k_2\,C_1 + k_1\,C_a - k_3\,C_2 + k_4\,C_2, & C_1(0) = 0 \\ \frac{d}{dt}C_2 &= -k_4\,C_2 + k_3\,C_1, & C_2(0) = 0. \end{aligned}$$

We assume that the infusion of the tracer starts ate time zero, and hence we obtain the initial values $C_1(0) = C_2(0) = 0$. The function $C_a(t)$ is an external function that describes the density of tracer in the blood (depending on the infusion etc.). There are different methods to deal with this function. We assume here the so-called invasive method, where blood samples are taken from the patient, and these blood samples are measured, s.t. this function is known.

This tracer aims at two different tissue types: one type, where almost no specific receptors are present. Hence, in this region, $k_3 = 0$ and we are left with a two-compartmental model (blood and tracer in tissue that is not bound specifically to anything). The second tissue type does express the tracer in an significant amount, s.t. here we do have to take the tracer into account.

The PET-scanner measures the total radioactivity. Hence, we only have information about $C_a(t) + C_1(t) + C_2(t)$. Fortunately, the size of the blood vessels are rather small relatively to the amount of tissue within one voxel (the smallest volume element that can be resolved by the scanner), s.t. we are able to neglect $C_a(t)$.

Interesting parameters

The primary goal of parameter estimation is not to obtain estimations about all of the parameters k_1,..,k_4, but to distinguish between tissue where k_3 is large and region where

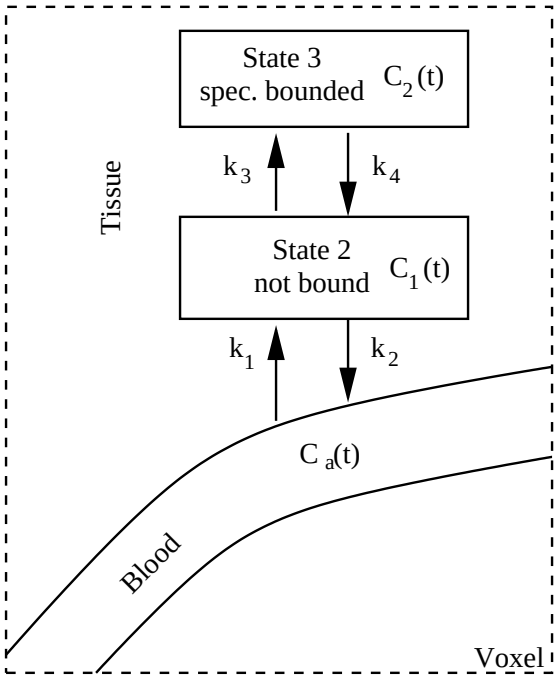

Figure 19: Compartmental model for the dynamics of the tracer in one voxel (smallest spatial unit that can be resolved).

$k_3 \approx 0$, i.e. where the specific receptors are present and where they are not. Of course, this parameter has to be simple and stable to estimate. Otherwise, one would directly use k_3 for these purpose.

Situation I ($k_3 \approx 0$):
It turned out, that a thought experiment yields quite good hints for which parameter to address: Assume that $C - a(t)$ is constant in time, $C_a(t) \equiv C_a$. We assume in situation 1, that $k_3 = 0$, i.e. that no specific receptors are present in the tissue under consideration. Asymprotically, the concentrations $C_1(t)$ and $C_2(t)$ will tend to an equilibrium (why?), and hence we find asymprotically

$$0 = \dot{C}_1 = -k_2 C_1 + k_1 C_a.$$

Thus

$$V_1 := \lim_{t\to\infty} \frac{C_1}{C_a} = \frac{k_1}{k_2}.$$

We will use V_1 as characteristic magnitude.
Of course, for real measures, C_a is by no means constant (see Fig. 21), s.t. we have to think about a method to estimate V_1.
Situation II ($k_3 > 0$):
We approach the problem in the same way like befor: we assume $C_a(t) \equiv C_a$ (constant in

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place here: J.H. Meyer and M. Ichise, *J. Neuroimag*(2001) 11, 03-39, Fig. 3 [46]

Figure 20: Data of a PET-scan (two types of tissue).

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place here: J.H. Meyer and M. Ichise, *J. Neuroimag*(2001) 11, 03-39, Fig. 4 [46]

Figure 21: Data of a PET-scan (concentration of the tracer in the blood).

time) and investigate the equilibrium concentrations.

$$\begin{aligned} 0 = \dot{C}_1(t) &= -(k_2 + k_3)C_1(t) + k_4 C_2(t) + k_1 C_a(t) \\ 0 = \dot{C}_2(t) &= -k_4 C_2(t) + k_3 C_1(t) \end{aligned}$$

We define the quotient of the densities in equilibria,

$$V_1 = C_1/C_a|_{\text{Equilibrium}}, \qquad V_2 = C_2/C_a|_{\text{Equilibrium}}.$$

(Remark: we define V_1 a second time. However, the model for situation I is a special case of the present model (for $k_3 = 0$). Thus the definition of V_1 in this slightly changed situation is appropriate). Division by C_a yields

$$0 = -(k_2 + k_3)V_1 + k_4 V_2 + k_1, \qquad 0 = -k_4 V_2 + k_3 V_1$$

and therefore

$$\frac{V_1}{V_2} = \frac{k_4}{k_3}, \qquad V_1 = \frac{k_1}{k_2}, \quad \Rightarrow \quad V_2 = \frac{k_1 k_4}{k_2 k_3}.$$

Estimating parameters: Logan-Plot
There are a lot approaches for parameter estimation around. Perhaps the most important (in the sense that this approach is very often used) is the Logan plot. The Logan plot is based on the fact, that $C_a(t)$ has a sharp peak at the very beginning of the measurement, and then tends very soon to zero (see Fig. 21). The Logan plot is a so-called graphical method, because the nonlinear data analysis is reduced to a linear regression (which can be plotted) [46].

Situation I ($k_3 = 0$):
We know from measurements $C_a(t)$ and we know $C_1(t) + C_a(t)$; we assume that $C_a(t)$ is rather small after an initial time interval, s.t. we may assume that $C_1(t) + C_a(t) \approx C_1(t)$ if t large (to be more precise: after ten or twenty minutes).
The aim is to estimate $V_1 = k_1/k_2$. According to the model, we find

$$\frac{d}{dt}C_1 = k_1 C_a - k_2 C_1, \qquad C_1(0) = 0.$$

Integrating this equation w.r.t. t (*not* integrating the differential equation as differential equation!) yields

$$C_1(t) = k_1 \int_0^t C_a(\tau)\, d\tau - k_2 \int_0^t C_1(\tau)\, d\tau.$$

and hence

$$C_1(t) = k_1 \int_0^t C_a(\tau)\, d\tau - k_2 \int_0^t C_1(\tau)\, d\tau$$

Dividing by $k_2\, C_1(t)$ yields

$$\frac{\int_0^t C_1(\tau)\, d\tau}{C_1(t)} = \frac{k_1}{k_2}\frac{\int_0^t C_a(\tau)\, d\tau}{C_1(t)} - \frac{1}{k_2} = V_1 \frac{\int_0^t C_a(\tau)\, d\tau}{C_1(t)} - \frac{1}{k_2}.$$

V_1 can be estimated as the slope of a linear equation, where

$$\frac{\int_0^t C_1(\tau)\, d\tau}{C_1(t)}, \qquad \frac{\int_0^t C_a(\tau)\, d\tau}{C_1(t)}$$

are the dependent variables.

Situation II ($k_3 > 0$):
In order to estimate V_2, the informations about $C_a(t)$ and the measurement in the corresponding voxel (i.e. $C_a(t) + C_1(t) + C_2(t)$ is not enough. In addition, we need information about V_1, i.e. we need to analyze a reference region, where we assume $k_3 = 0$. Under this assumption, we are able (by the approach for Situation I) to estimate V_1. Hence, three different measurements are necessary to evaluate an voxel of the interesting region (so-called "Region Of Interest", ROI):

(1) Measurements of the blood $C_a(t)$.

(2) Measurement of an reference region. We will attach a prime to the corresponding magnitudes for the reference region, i.e. C_1', k_1' etc.

(3) The measurements of the voxel in the ROI. We will denote these magnitude still with $C_1(t)$, k_1 etc.

Assumption: We assume, that $k_3' = 0$ (i.e. there are no specific receptors in the reference region), and

$$V_1' = \frac{k_1'}{k_2'} = \frac{k_1}{k_2} = V_1.$$

This assumption is necessary in order to obtain information about V_2 in the ROI. However, this assumption is arbitrary, and there may be many reasons to doubt it. The only justification is pragmatically: this approach with this assumption yields reasonable results.

(A) Reference Region: (Estimation of V_1)
Here we use the method of Situation I.

(B) ROI: (Estimation of $V_1 + V_2$)
Now we cannot assume $k_3 = 0$. We have to reconsider the computations done for Scenario I. The state in the ROI is determined by $C_a(t)$, $C_1(t)$ and $C_2(t)$, the measured signal reads

$$S(t) = \epsilon\, C_a(t) + C_q(t) + C_2(t) \approx C_1(t) + C_2(t)$$

Let

$$A = \begin{pmatrix} -(k_2 + k_3) & k_4 \\ k_3 & -k_4 \end{pmatrix}, \qquad \mathbf{e}_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}.$$

We find

$$\begin{aligned} \frac{d}{dt}\begin{pmatrix} C_1 \\ C_2 \end{pmatrix} &= A \begin{pmatrix} C_1 \\ C_2 \end{pmatrix} + C_a(t) k_1 \mathbf{e}_1 \\ \Rightarrow \qquad \frac{d}{dt} A^{-1} \begin{pmatrix} C_1 \\ C_2 \end{pmatrix} &= \begin{pmatrix} C_1 \\ C_2 \end{pmatrix} + C_a(t) k_1\, A^{-1} e_1 \end{aligned}$$

With $\mathbf{e} = (1,1)^T$ and $\overline{C}(t) = C_a(t) + C_1(t)$ it follows, that

$$\mathbf{e}^T A^{-1} \begin{pmatrix} C_1(t) \\ C_2(t) \end{pmatrix} = \int_0^t \overline{C}(\tau)\, d\tau + \int_0^t C_a(\tau)\, d\tau \quad k_1\, \mathbf{e}^T A^{-1} \mathbf{e}_1$$

Division by $\overline{C}(t)$ yields

$$\frac{\int_0^t \overline{C}(\tau)\, d\tau}{\overline{C}(t)} = \frac{\mathbf{e}^T A^{-1} \begin{pmatrix} C_1(t) \\ C_2(t) \end{pmatrix}}{\overline{C}(t)} - k_1\, \mathbf{e}^T A^{-1} \mathbf{e}_1\, \frac{\int_0^t C_a(\tau)\, d\tau}{\overline{C}(t)}.$$

After an initial phase, we may assume that $C_a(t) \approx 0$. Hence we are left with a system of linear, autonomous ordinary differential equations. Asymptotically, the solutions of such an system will approach an exponentially increasing (or decreasing) function,

$$\begin{pmatrix} C_1(t) \\ C_2(t) \end{pmatrix} \propto e^{\hat{\lambda}\, t} \begin{pmatrix} \hat{C}_1 \\ \hat{C}_2 \end{pmatrix} \qquad \text{for } t \to \infty,$$

where $\hat{\lambda}$ denotes the largest eigenvalue of the matrix A and $(\hat{C}_1,\, \hat{C}_2)^T$ is the corresponding positive eigenvector (why is this eigenvector positive?). Hence, asymptotically, we find

$$\frac{\mathbf{e}^T A^{-1} \begin{pmatrix} C_1(t) \\ C_2(t) \end{pmatrix}}{\overline{C}(t)} \approx \text{ const}$$

and a linear connection

$$\frac{\int_0^t \overline{C}(\tau)\, d\tau}{\overline{C}(t)} \;=\; \text{const} - k_1\, \mathbf{e}^T A^{-1} \mathbf{e}_1\, \frac{\int_0^t C_a(\tau)\, d\tau}{\overline{C}(t)}.$$

The slope of this linear function reads

$$\begin{aligned} -k_1\, \mathbf{e}^T A^{-1} \mathbf{e}_1 &= -k_1 \frac{1}{\det(A)} \mathbf{e}^T \begin{pmatrix} -k_4 & -k_4 \\ -k_3 & -(k_2+k_3) \end{pmatrix} \mathbf{e}_1 \\ &= k_1 \frac{k_3 + k_4}{k_4\, k_2} = \frac{k_1}{k_2} + \frac{k_1\, k_3}{k_4\, k_2} = V_1 + V_2 \end{aligned}$$

(C) ROI: (Estimation of V_2)
V_2 may be estimated as the difference of the estimation of $V_1 + V_2$ (done in (B)) and the estimation of V_1 (done in (A)).

Remark: Of course, many problems are related to these considerations.

2.4.3 Treatment of Hepatitis C

Hepatitis C is a viral infection. It is quite prevalent in the population (2-15% infected individuals). Mostly, it is asymptomatically. However, individuals infected with Hepatitis C have a higher risk to develop liver cancer. The present treatment strategy is a high dose of interferon-α over a long period (one year). The mechanisms of this treatment is poorly understood. Also early time prediction about the success of this treatment are not too well. The latter is of special interest, since this treatment causes high fever - individuals who will be not successfully treated will be happy to stop the treatment as soon as possible. Only if the virus is eradicated this torture pays out.
The question that can be approached by a model is two-fold: can we say something about the mechanisms of interferon-α? Can we predict the success/failure of this treatment for one individual early in the treatment? Can we perhaps enhance the treatment, if it fails?

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place here: Neumann et al., Science (1998) 282, p. 103-107, Fig. 1 [51]

Figure 22: Data about the decline of the virus load during the treatment with interferon-α (data of two patients; left hand side are data of the first two days, right and side the first two weeks).

These questions are approached in a series of articles [51]. We report here especially the ideas of the authors about the evaluation of different possible mechanisms that interferon-α uses to fight the infection and the interpretation of some of the structures in the data we do have from infected persons under treatment.

We find data describing the decline of virus-load under interferon-α (see Fig. 22). After the onset of treatment, these data show three phases:
(1) Delay (1-3h)
(2) Phase 1: sharp decrease of the total virus load ($\approx$ 2 Days)
(3) Phase 2: slow decrease of the total virus load (Months)
The authors start off with a description of the life cycle of a viron (a free viral particle of Hepatitis C). Virons infect a target cell. These infected target cells can be detected by the immune system and thus have a higher clearance rate. Furthermore, infected cells release new virons, that in turn may infect more target cells (see Fig. 23).

State: The state of the system is given by the density of target cells T, the density of free virons V and the density of infected cells I.

Dynamics: For the dynamics, we make a simplifying assumption: the population of target cells should be quite large and stable, s.t. we may assume that $T(t) = T$ is constant and is only slightly influenced by infection. Basically we assume that - even if the viral infection is quite prevalent - only a small fraction of target cells are infected. Then, the number of newly infected cells per time unit (the incidence) is proportional to the free virons, i.e. the incidence is βT. We furthermore assume that the infection is in (a stable) equilibrium before the beginning of the treatment. The natural death rate of infected cells is δ. These dying cells are translated by a certain factor into new virons, s.t. we have $p\,I$ new virons

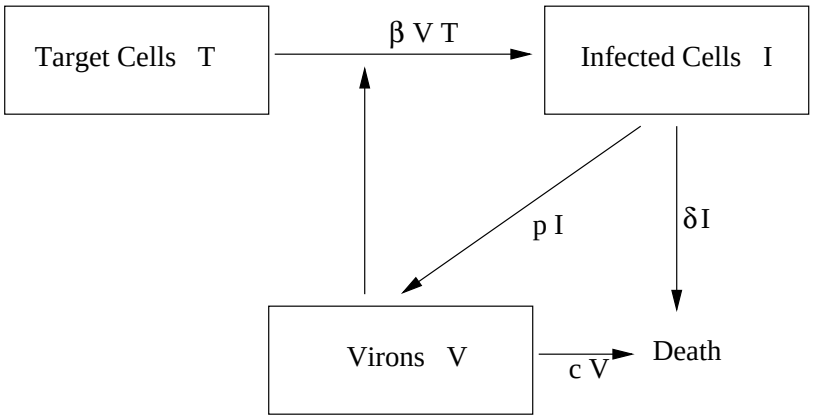

Figure 23: Basic model of viral infection.

per time unit. The clearance rate for free virons reads c. We obtain the model euqations,

$$\begin{aligned} \dot{I} &= \beta T V - \delta I \\ \dot{V} &= pI - cV. \end{aligned}$$

Now possible treatment effects are included. There are two ideas:
(1) The production rate for new virons are reduced. We replace p by $(1-\epsilon)p$, $\epsilon \in [0,1]$.
(2) The infection rate is reduced. We replace β by $(1-\eta)p$, $\eta \in [0,1]$.

$$\begin{aligned} \dot{I} &= (1-\eta)\,\beta T V - \delta I \\ \dot{V} &= (1-\epsilon)\,pI - cV. \end{aligned}$$

We have to inspect the effects of η and ϵ on the dynamics, in order to obtain an idea which effect is more likely to meet the data.

Time scales and treatment effect:
We need to know some time scales. From experiments it is known that

$$\begin{aligned} \delta \approx 0.1 \text{ day}^{-1} &\Leftrightarrow \text{ Mean time } \approx 10 \text{ Days} \\ c \approx 0.6 \text{ day}^{-1} &\Leftrightarrow \text{ Mean time } \approx 4 \text{ h} \end{aligned}$$

For the first phase after treatment, we can consider the effect of partially blocking new infection of target cells ($\eta > 0$) or partially blocking de novo production of virons. The first effect would lead to an decline infected T-cells with a time scale of the magnitude of the mean life span of an infected cell, i.e. with $1/\delta \approx 10$ Days. We expect a rather slow and long-lasting decline in the initial phase, if $\eta > 0$. The second effect, $\epsilon > 0$, leads to a smaller production rate of virons. Thus the clearance of virons that runs on a time scale of hours reduces fast the load with free viruses in the initial phase, that should range in a time scale of hours to days. Hence, from the data it seems much more plausible that

interferon-α primarily blocks the de novo production of virons than blocks the infection pathway.

Analysis of the model

However, where do these two phases come from? We have a two-dimensional, linear differential equation that is to analyze. From the considerations above, we choose $\eta = 0$. Thus we need the eigenvalues of the corresponding matrix

$$A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} = \begin{pmatrix} -\delta & \beta T \\ (1-\epsilon)\, p & -c \end{pmatrix}.$$

Formulas for the eigenvalues of a two times two matrix:

Let

$$A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}.$$

The characteristic polynomial for the eigenvalues λ reads

$$\lambda^2 - (a_{11} + a_{22})\lambda + a_{11}a_{22} - a_{21}a_{12} = 0$$

Hence, using the definition for trace and determinant, we find

$$\lambda_\pm \;=\; \frac{1}{2}\left(\mathrm{tr}(A) \pm \sqrt{\mathrm{tr}(A)^2 - 4\det(A)}\right)$$

A further useful formula follows from

$$\mathrm{tr}(A)^2 - 4\,\det(A) = (a_{11} + a_{22})^2 - 4\,a_{11}a_{22} + 4\,a_{21}a_{12} = (a_{11} - a_{22})^2 + 4\,a_{21}a_{12}$$

i.e.

$$\lambda_\pm \;=\; \frac{1}{2}\left(a_{11} + a_{22} \pm \sqrt{(a_{11} - a_{22})^2 + 4a_{21}a_{12}}\right).$$

Thus,

$$\lambda_\pm(\epsilon) = \frac{1}{2}\left(-(\delta + c) \pm \sqrt{(\delta - c)^2 + 4(1 - \epsilon p)\beta T}\right)$$

Case 1, no treatment:

In this case, we assume the system to be in a locally stable, non-trivial equilibrium, i.e. in an equilibrium with $I,\ V > 0$. Hence, either $\lambda_+(0) = 0$ or $\lambda_-(0) = 0$. Since we assume local stability, we conclude $\lambda_\pm(0) \leq 0$. Thus,

$$\lambda_+(0) = 0 > \lambda_-(0).$$

The condition $\lambda_+(0) = 0$ can be solved for T. We obtain a line of stationary points, that attract all other initial values (see Fig. 24). This model is degenerated, because we do not include the dynamics of T. If we explicitly model the influence of the infection on

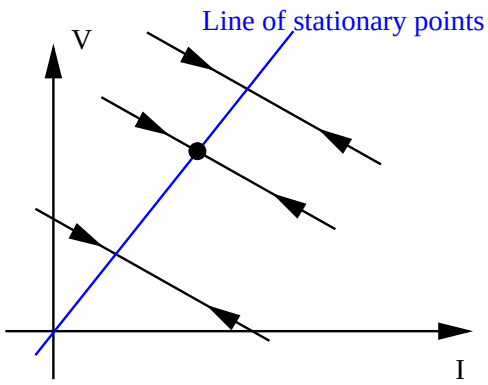

Figure 24: Dynamics for $\epsilon = 0$.

the population of target cells, we find a unique, (locally) attracting fixed point. We will return to this complete model later in this lecture.

Case 2, treatment:
We now choose $0 < \epsilon \ll 1$, i.e. we switch on the proposed treatment effect. In this case, we find from the explicit formula for $\lambda_\pm(\epsilon)$ that

$$0 > \lambda_+(\epsilon) \gg \lambda_-(\epsilon).$$

We deal with a stiff system, respectively with a system that exhibits two time scales (see Fig. 25). We start at the stationary point on the line with stationary points for $\epsilon = 0$. The eigenvectors will slightly change, if we set ϵ to a value larger than zero. Along the fast manifold (the eigendirection for $\lambda_-(\epsilon)$) we will approach the new slow manifold (the eigendirectionof $\lambda_+(\epsilon)$, that did correspond to a line of stationary points before) and then go along this line slowly into the unique stationary point, where $I = V = 0$, i.e. where the infection is gone. This picture explains very nicely the two phases we have seen in the data. However, it does not explain the delay, that appears between the first does of interferon-α and start of the decline of the virus load.

One may even learn something about failures of the treatment: if we do not find the fast decline of phase I, then the reduction of the production rate of virons by infected cells is not effective enough. One should enhance this process. If the decline in the second phase is not present or very slow, this may be a hint that the death rate for infected cells c is not large enough. One should therefore enhance this death rate. It is possible to modify treatment in these directions. In this way, this simple mathematical model may help to tailor the treatment against Hepatitis C for a given patient.

2.5 Summary/Conclusion

• *In biology, most entities that are to describe are discrete (molecules, cells, individuals). We started with the description of one individual, that only has one possible behavior: it*

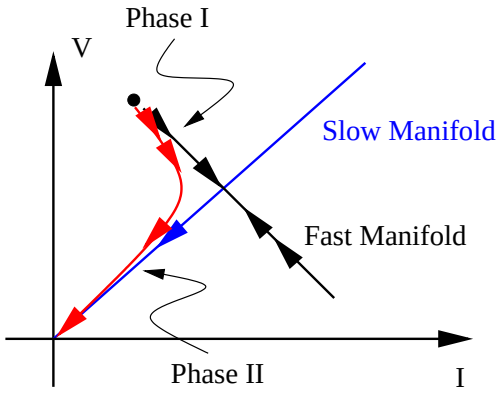

Figure 25: Dynamics for $\epsilon > 0$.

may die, or - more general - it may change its present state. Here we met the first time the basic structure of dynamical models: a model is given by the states that the entities can assume, and by the characterization of the transition between these states (the dynamics).

- *The investigation of one individual yields a stochastic model about the duration that a particle spends in the given state. If the rate does not depend on the time that the particle already belongst to this state (i.e. the transition rate is constant), we find the exponential distribution for this time ("exponentially distributed waiting times").*
- *Next we considered a small population of particles. Here, we have to be clear about the fact that we consider only independent individuals - there is no competition for resources or alike. In general, models about independent individuals yield linear equations. The distribution of individuals that are a certain time in a given state after a certain time can be described by a Binomial distribution, where the parameter p of this distribution is given by the survival probability of one individual.*
- *Now we aimed at a justification for deterministic models. A deterministic model, in the present case, assumes the form of an ordinary differential equation. This yields numbers in $\mathbb{R}$, while the population consists of discrete entities. This seemingly contradiction can be solved with two different approaches: either one describes the expectation of the size of the population. For this argumentation, it is necessary to focus on independent individuals. The second approach considers large population. Relatively to the size of the population the random fluctuations tend to zero. However, one has to normalize the population size (one has to consider fractions or densities). This approach still works out with nonlinear models.*
- *Linear compartmental models are the straight forward generalization of models with only two states (dead of alive) and one transition to models with n states and an arbitrary number of transitions between these states. These models can be graphically represented by directed graphs, and translated into stochastic or deterministic model equations. It must be clear, that the state is described only by numbers/densities of particles in the corresponding state, which does not include the time, that a particle already did spend in this state. Hence, we only can use constant rates (exponentially distributed waiting times).*

This may not be appropriate in some cases.

2.6 Exercise

Exercise 2.1:
The population density of independently acting individuals (bacteria, animals etc.) that do have unlimited resources can be described by a linear equation,

$$\dot{x} = b\,x$$

where b denoted the net-reproduction rate.
Develop a model for a population of independently acting individuals (and unlimited resources) that consists of n phenotypes (behavioral types); every phenotype has its own reproduction rate. During reproduction, however, offspring may mutate to one of the other phenotypes.
Can you draw some conclusions from your model?

Exercise 2.2:
Consider an experiment that only has one of two results $\{0, 1\}$ (e.g. dead or alive). The experiment is repeated N times, s.t. we have results x_1,..,x_N, $x_i \in \{0, 1\}$. Assume the corresponding random variables X_i to be i.i.d. (independent and identically distributed) (what does this mean for the experiment?)
(a) Compute the maximum-likelihood-estimator
(b) Compute the Bayes-estimator, if we assume the prior for $p = P(X_i = 1)$ to be the uniform distribution between zero and one.

Exercise 2.3:
Let $f : \mathbb{R}^n \to \mathbb{R}^n$ and $f(\alpha\, x) = \alpha f(x)$. Compute the projection of $\dot{x} = f(x)$ to the simplex $\mathcal{S} = \{x \in \mathbb{R}^n_+ \,|\, \mathbf{e}^T x = 1\}$. Assume $f \in C^1$. Are there fixed points of the projected system? If there are fixed points of the projected system, which solutions are projected to these fixed points?

Exercise 2.4:
(Programming exercise) Consider a population of individuals, all of them born at time $t = 0$. Assume that these individuals do have a death rate that depends on a, $\mu = \mu(a)$ Extend the simulation method 1 (transformation of a uniformly distributed random variable) to this case.
Choose $\mu(a) = 0.01 \exp(0.001\, a)$. Simulate a population with 10, 100 and 1000 particles and the given death rate. Draw one realization of these simulation together with the expected value.

Part One:
Independent Entities - The Linear Case

We now start with a systematic description of modeling methods for a population of entities that act independently of each other. In this part (not in Part II, where we look at non-linear models) we emphasize the methodological aspects. I.e., we consider systematically the different models mentioned in the upper part of the table at page 2. We first concentrate on discrete time, going from small to large populations, and then we will focus on continuous time, again moving from small to large populations.

Many of the tools we develop here are the foundation for a profound understanding of the models in Part II. There are two connections between nonlinear and linear models:
(1) First of all, even for stochastic models, there is often enough a possibility to "linearize" a model locally. I.e., if some magnitude becomes small (e.g. the time interval under consideration), then the nonlinear model will not behave very differently compared with an appropriate chosen linear model. However, the long term behavior of nonlinear models often show a completely new behavior. Nevertheless, much of this new behavior can be understood if one uses the linear methods in a clever way.
(2) A second connection, that proves to be useful in certain situations, is the fact that - by blowing up the state space - one can embed nonlinear dynamics into a linear structure. Perhaps this may sound magic, the principle how to construct this embedding is quite straight forward. We will consider an example at the end of Part I.

3 Discrete Time

Of course, biological systems evolve in chronological time, i.e. discrete time seems on the first glance to by an artificial simplification. However, two situations that are quite typical to occur suggest in a natural way the description of the evolution by a model with discrete time: the model may be periodically forced, or one is not interested in chronological time but in generations.

Perhaps the best and simplest example for a periodically forced system is an ecosystem in Europe. The conditions of this ecosystem will be changed by the seasons, i.e. the parameters undergo an annual periodicity. In order to reduce the dimension, one may not inspect the ecosystem all over the year (indeed, in some months there will be almost no activity), but only at one certain day in the year. E.g., the state in every 10'th October is measured. These measurement points form a discrete time series, that one desires to describe by a mathematical model, that - of course - will be then also discrete. This procedure is known in mathematics as the introduction of a Poincaré map (see [40]).

In the second case, that frequently appears, one concentrates on generations rather than on chronological time. Obviously, in population genetics this point of view is appropriate. But it turns out, that also in many other fields this approach if fruitful: e.g., in

epidemiology one may introduce the "generation of infecteds", which does mean that one starts with one primary infected person in a population. The individuals infected by the primary infected person form the second generation of infecteds and so on. Using these ideas, the central theorem for epidemic models (that also we will derive in Part II) can be understood in a quite natural manner, much better than using a model in chronological time.

3.1 Small Population Size: The Galton-Watson-Process

3.1.1 Example: QPCR

PCR (Polymerase Chain Reaction) is meanwhile a standard technique of molecular biology that multiplies a small amount of DNA (or RNA), such that it can be detected. The fingerprinting-technique, well known from crime novels, relays on PCR. QPCR (Quantitative Polymerase Chain Reaction) is a sophisticated version of PCR. One is not only interested in the sequence/fingerprint of the DNA fragment, but also in the mass of these fragments in a probe [52]. A typical application of this technique is the estimation of the virus load of a patient, like we used in the example in section 2.4.3.

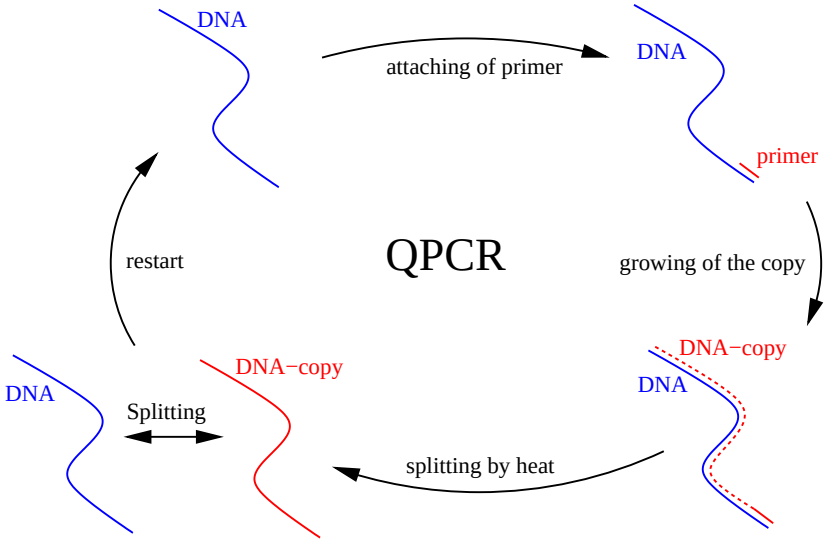

Figure 26: Sketch of the (Q)PCR-cycle .

The basic mechanism of the (Q)PCR is the following (see Fig. 26): start with a (small) amount of single (not double) DNA-strings (single strings can be produced from double strings simply by heating). This amount of DNA-mass is incubated in a mixture of primers and nukleoides. In the first step, a primer - a very short pice of DNA, 6-8 nucleotides long, is attached to the string. This is necessary for the second step, where nucleotides subsequentially attach to the end of the primer, and in this way produce a double string from the single string. After finishing this doubling procedure, using heat, the double

string is split again. This cycle can be repeated over and over again, in principle always doubling the amount of DNA, until the mass of DNA is sufficient for other experimental techniques (e.g. finger-printing).

The heating-splitting-cycle yields a natural structure of "generations", i.e. discrete time. For PCR, the detailed structure of the process is not really important. This is different in QPCR. Here, after typically ten to twenty cycles, there is enough material s.t. the density of DNA-strings can be measured. The measurements in two subsequential cycles can be used to recompute the amount of DNA in the beginning. The basic problem in this computation if a consequence of a non-deterministic component of this process: the primer only attaches with a certain probability to a DNA-string. However, if the primer does not attach to a certain string, this string will not be copied in the corresponding cycle. Hence, the "population" of DNA-stings will not be doubled in each cycle but reproduce according to a stochastic law. If this law is known and analyzed, it will be possible to derive an estimator for the initial mass of DNA-strings. We have to model this process more in detail.

Model for QPCR:
State: Let Z_n be the number of single DNA-strings in generation n.
Dynamics: Every single string replicates independently on each other string with probability

$$P(\text{ doubling a single string}) = p_d.$$

Remark: **(1)** The independence of the replication behavior basically assumes, that there is at each point of time enough primers and nucleotides present in the system. I.e., the DNA-stings do not have to compete for resources.
(2) The probability p_d is also called "amplification factor". Typically, the amplification factor ranges between 0.6 and 0.8 for the PCR.

Question:
How to estimate Z_0, given Z_n and Z_{n+1} for n large (typically $10 \leq n \leq 20$)?

3.1.2 Galton-Watson-Process

The Galton-Watson process (GW-process) is the mathematical framework that describes the process above. The books [35, 3, 25] give introductions into this subject.

Definition
We consider - in a slightly more abstract framework - a population of reproducing individuals. We use the successful approach to start off with one individual and then to construct the population where we assume as most important ingredients independency of individuals.

One Individual:
Let X be a random variable with values in $\mathbb{N}$ that describes the number of children of one individual, i.e. the probability for i children is given by $P(X = i)$. Let p_i defined by

$$P(X = i) = p_i.$$

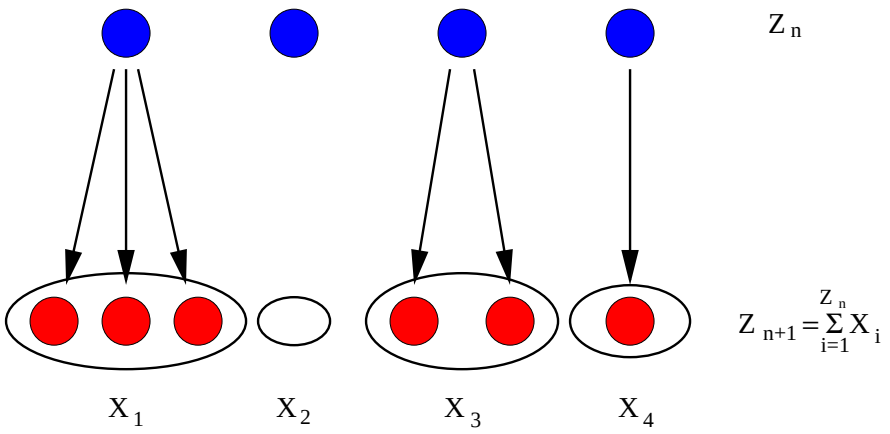

Figure 27: The population in generation $n+1$ is the sum over the children of generation n.

The Population:
Let Z_n be the size of the population in generation n, i.e. an $\mathbb{N}$-valued random variable. Let furthermore X_1,..,X_{Z_n} be i.i.d. random variables, distributed like X (the number of offspring of one individual). Then,

$$Z_{n+1} = \sum_{i=1}^{Z_n} X_i$$

i.e. the population in generation $n+1$ consists of the offspring of generation n (see Fig. 27). This process is called branching process, and more specifically (a general branching process may also live in continuous time) a Galton-Watson process.

Expectations of Functions of Random Variables

Let Y be a random variable that assumes values only in $\mathbb{N}$, $g : \mathbb{N} \to \mathbb{R}$ a function. Then,

$$E(g(Y)) := \sum_{i \in \mathbb{N}} g(i) P(Y = i).$$

Of course, $E(g(Y))$ may not exists, even if $E(Y)$ exists and $g(Y)$ is well defined. We find the well known formula

$$\mathrm{Var}(Y) = E(Y^2) - (E(Y))^2.$$

Generating function of an $\mathbb{N}$-valued random variable

The generating function of the random variable Y is defined as a power sequence

$$f : [0,1] \to [0,1], \quad f(s) \mapsto \sum_{i=0}^{\infty} s^i P(X = i).$$

Formally, we may write

$$f(s) = E(s^Y).$$

Since $0 \leq P(X = i) \leq 1$, the power series converges for all $s \in [0,1]$ and thus also all derivatives in $[0,1)$. Furthermore,

$$f(1) = \sum_{i=0}^{\infty} P(X = i) = 1, \qquad E(Y) = \sum_{i=1}^{\infty} i\, 1^{i-1}\, P(X = i) = f'(1)$$

and

$$P(Y = i) = \frac{1}{i!} \frac{d^i}{ds^i} f(s)|_{s=0}.$$

All informations about Y are coded in f.

In the example above (the QPCR), we have either one "child" with probability $1 - p_d$ (the string that did not replicate), or two children with probability p_d (if the string replicates). Hence,

$$\begin{aligned} P(X = 0) &= 0 \\ P(X = 1) &= 1 - p_d \\ P(X = 2) &= p_d \\ P(X = 3) &= 0 \\ &\dots \end{aligned}$$

In this case we find

$$f(s) = (1 - p_d)\, s + p_d\, s^2.$$

Analysis

The interesting questions are:

- $E(Z_n)$
- $\mathrm{Var}(Z_n)$
- The probability that the population goes extinct, $P(\lim_{n\to\infty} Z_n = 0)$.

In the following, let $f_n(s)$ be the generating function of Z_n. If we know $f_n(s)$, we know $P(Z_n = i)$, i.e. we are able to derive all these informations.

In order to prepare for our central theorem, we prove a rather technical lemma.

Lemma 3.1: *Let Y, X_1, X_2,... random variables with values in $\mathbb{N}$, and let X_i be i.i.d. Let furthermore*

$$S = \sum_{i=1}^{Y} X_i,$$

and $h_1(.)$ the generating function of X_i, $h_2(.)$ the generating function of Y and $h_3(.)$ the generating function of S. Then,

(1) $h_3(s) = h_2 \circ h_1(s)$
(2) $E(S) = E(X_1)\,E(Y)$
(3) $\mathrm{Var}(S) = \mathrm{Var}(X_1)\,E(Y) + E(X_1)^2\ \mathrm{Var}(Y)$.

Note, that the formula for the expectation of S is symmetric in X_i and Y, but not the formula for the variance.

Proof:
ad 1)

$$\begin{aligned}
h_3(s) &= E(s^S) = E(E(s^S|Y)) \\
&= \sum_{i=0}^{\infty} P(Y=i) E(s^S|Y=i) \\
&= \sum_{i=0}^{\infty} P(Y=i) E\left(s^{\sum_{j=1}^{i} X_j}\right) \\
&= \sum_{i=0}^{\infty} P(Y=i) E\left(\Pi_{j=1}^{i}\, s^{X_j}\right) \\
&\overset{X_i \text{ independent}}{=} \sum_{i=0}^{\infty} P(Y=i) \Pi_{j=1}^{i}\, E\left(s^{X_j}\right) \\
&= \sum_{i=0}^{\infty} P(Y=i) E\left(s^{X_1}\right)^i \\
&= \sum_{i=0}^{\infty} P(Y=i) (h_1(s))^i \\
&= h_2(h_1(s)) = h_2 \circ h_1(s)
\end{aligned}$$

ad 2)

$$E(S) = \left.\frac{d\,h_3(s)}{ds}\right|_{s=1} = \left.\frac{d\,h_2(h_1(s))}{ds}\right|_{s=1} = \left. h_2'(h_1(s)) h_1'(s)\right|_{s=1} \overset{h_1(1)=1}{=} h_2'(1) h_1'(1) = E(Y)E(X).$$

ad 3) Exercise 3.2

□

Theorem 3.2: $f_{n+1}(s) = f \circ f_n(s)$

Proof: The lemma above with $Z_{n+1} = \sum_{i=1}^{Z_n} X_i$ and X_i are i.i.d. with generating function $f(.)$.

□

Theorem 3.3: *Let* $r = E(X)$, $\sigma = \mathrm{Var}(X)$, $Z_0 = z_0 \in I\!N$. *Then,*

$$\begin{aligned} E(Z_n) &= z_0\, r^n \\ \mathrm{Var}(Z_n) &= \begin{cases} z_0 \sigma r^{n-1} \frac{r^n - 1}{r-1} & \text{for} \quad r \neq 1 \\ z_0 \sigma n & \text{for} \quad r = 1 \end{cases} \end{aligned}$$

Proof:
Expected value: Since $E(Z_{n+1}) = f'_{n+1}(1) = f'(1) f'_n(1) = r E(Z_n)$, the proof for the expected value follows with induction.
Variance: Exercise 3.3

□

Theorem 3.4: *Assume* $f(0) > 0$, *i.e.* $P(X = 0) > 0$. *If* $E(X) = f'(1) > 1$, *then there is exactly one root* $\overline{p}$ *of* $f(s) = s$ *for* $0 < s < 1$. *If* $E(X) = f'(1) \leq 1$, *define* $\overline{p} := 1$. *The probability for extinction reads*

$$P(\lim_{n \to \infty} Z_n = 0) = \overline{p}.$$

Proof: *Step 1 (Uniqueness of the root of* $f(s) = s$ *for* $s \in [0, 1]$, *if* $f'(1) < 1$*:*
Since $f(s) = \sum_{i=0}^{\infty} s^i P(X = i)$, we obtain

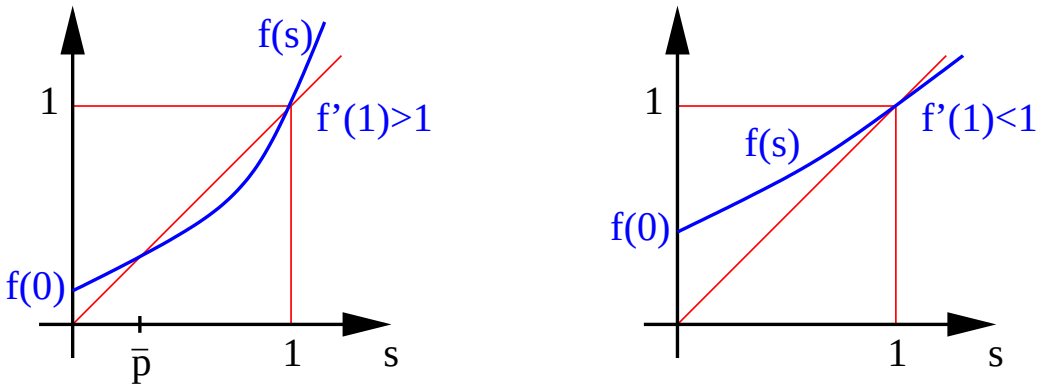

Figure 28: Function $f(.)$ for the two cases: $f'(1) > 1$ and $f'(1) < 1$.

$$\begin{aligned} f(0) &> 0, & f(1) &= 1, \\ f'(s) &\geq 0, & f''(s) &\geq 0. \end{aligned}$$

Hence, the function $g(.)$ is monotonously increasing and concave. Therefore, the root $\overline{p} \in [0,1]$ of $f(s) = s$ is unique (see Fig. 28).

Step 2 (Probability for extinction):
Let $q_n = P(Z_n = 0)$. Then,

$$q_n = f_n(0) = f \circ f_{n-1}(0) = f(q_{n-1})$$

and $q_0 = P(Z_0) = 0$. This is a discrete, deterministic iterative system for q_n. We aim at the limit point for $n \to \infty$ (if it exists). Since $f(.)$ is non-decreasing in $[0,1]$ and $f(s) > s$ in $[0,\overline{p})$ and $f([0,\overline{p}]) \subset [0,\overline{p}]$, we find (per induction)

$$q_n = f(q_{n-1}) \geq q_{n-1}, \qquad q_0 = 0 < \overline{p}, \qquad q_n = f(q_{n-1}) < \overline{p}.$$

I.e., q_n is a non-decreasing sequence that is bounded by $\overline{p}$. Thus this sequence converges. Since f is continuous,

$$f(\lim_{n\to\infty} q_n) = \lim_{n\to\infty} f(q_n) = \lim_{n\to\infty} q_n$$

and thus the limit point is a fixed point of f. We conclude

$$\lim_{n\to\infty} q_n = \overline{p}.$$

□

Interpretation:

We will find this law in several versions during the lecture. The basic structure is the following dichotomy:
Case 1: Extinction. If the expected number of children is below one, the population will die out with probability one. In average, a member of the population will not be replaced by at least one child, s.t. eventually the population is bound to decrease. However, there may be a large number of individuals present until finally the population dies out (if our population consists of infected individuals, this information may be of value)
Case 2: Persistence. Even if the population may persist, there is still a positive probability to get extinct (if $f(0) > 0$, i.e. if an individual is allowed to die without any offspring). If the population does not die out, it will tend to infinity with probability one (see Jagers [35]). By the way, the information is only available within a stochastic model. A deterministic model, that addresses the expected value for the population size is not able to give information about realizations that die out. This may be an important difference between the stochastic and the deterministic approach.

The magnitude $E(X)$, i.e. the average number of children, often is called reproduction number, or basic reproduction number R_0. In many (at least mathematically important) examples, we find that

$$P(\text{Extinction}) = 1/R_0, \quad \text{if} \quad R_0 > 1.$$

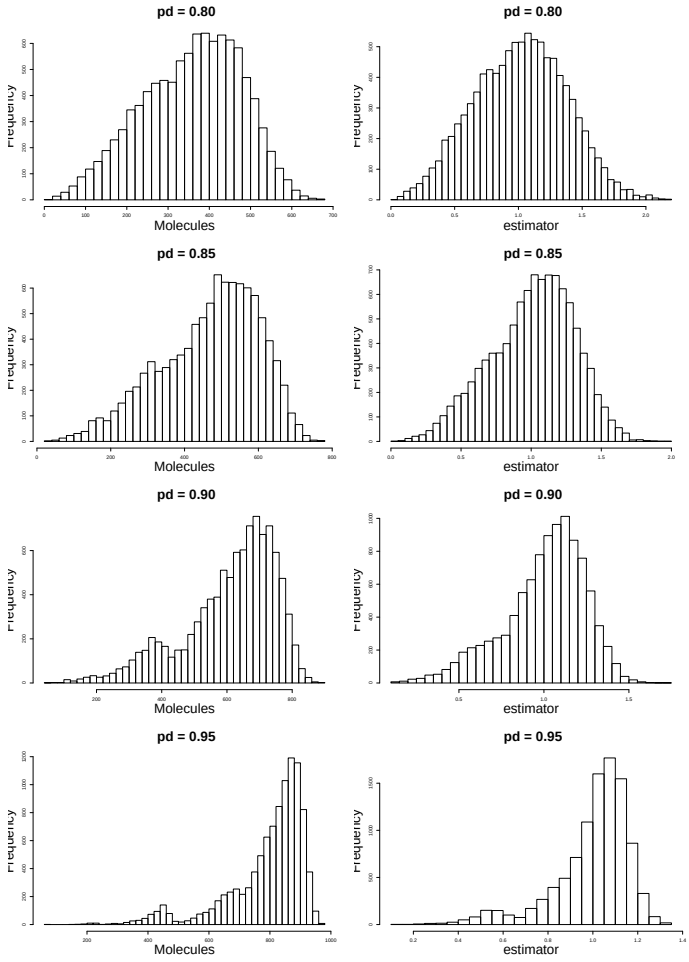

Figure 29: Simulations of the QPCR using the Galton-Watson process. The histograms are the results of 10000 runs. The simulations have been performed for different parameter values ($p = 0.95,\ 0.9,\ 0.85$ and 0.8; $n = 10$; $z_0 = 1$ Left hand side: mass after ten cycles. Right hand side:estimated number of strings z_0.

3.1.3 Back To QPCR

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place here: M.K.Hansen at al., J. Neurosc. 18(1998) 2247–2253, Fig. 1 [29]

Figure 30: Data of a QPCR. See text for further explanation.

Using the analysis of the Galton-Watson process, we are able to derive estimators for the QPCR. We know that

$$E(Z_n) = r^n z_0, \qquad E(Z_{n+1}) = r^{n+1} z_0.$$

Hence,

$$r = E(Z_{n+1})/E(Z_n)$$

and we define the estimator

$$\hat{r} = \tilde{Z}_{n+1}/\tilde{Z}_n$$

(where $\tilde{Z}_i$ denotes the measurement of the mass after the i'th cycle). Knowing r and n, we find

$$z_0 = E(Z_n)/r^n.$$

This yields in a straight forward way the estimator

$$\hat{z}_0 = \tilde{Z}_n/\hat{r}^n = \frac{\tilde{Z}_{n+1}^n}{\tilde{Z}_n^{n-1}}.$$

Of course, this estimator is a naive estimator. The performance of this estimator has to be analyzed (e.g. variance), confidence intervals have to be determined etc. It may also be possible to improve it, e.g. by taking into account not only Z_n and Z_{n+1} but also $Z_n, .., Z_{n+i}$ with $i > 1$.

A simple way to approach such problems are computer simulations. It is possible to simulate the process, generating artificial measurements $\tilde{Z}_n$ and $\tilde{Z}_{n+1}$ and then to compare the estimated number z_0 with number z_0 that has been chosen for simulations (see Fig. 29). We observe, especially for p_d high, shoulders in the distributions. These shoulders are the

result of early events: the effect of a failure to double in the first generation will spread and cause these shoulders (which, of course, may be also found back in the estimates).

A picture of data are shown in Fig. 30. Here, the amount of mRNA is determined by RT-PCR (a special kind of QPCR that uses reverse transcription). Wild type and mutant rats are treated with IL-1β, a substance, that is an important messenger for the immune system. Left part of the picture shows the data from liver cells, while the right part of the picture shows data for brain cells (open triangles: wild type, closed triangles: mutant). The logarithm of the density is plotted over PCR-cycles. According to our theory, the data should approximately be located on a line. From these data one can interfere the amplification factor and then estimate the original amount of mRNA in the substrate. l

3.1.4 Exercise

Exercise 3.1:
Consider the following (sub)model for the fate of one individual / the probability distribution of offspring:
State: Number of children.
Dynamics: In every step the individual decides if he/she dies or gets another child. I.e.,

$$P(i+1 \text{ children in step } i+1 | i \text{ children in step } i) = q$$

and

$$P(\text{dead in step } i+1 | \text{alive in step } i) = 1-q.$$

(a) Compute the distribution of children of one individual.
(b) Compute the probability for extinction.
(c) If the probability for extinction is one, how large is the expected value of the total population
over all generations $\sum_n Z_n$?

Exercise 3.2:
Show part (c) of Lemma 3.1. I.e., let Y, X_1, X_2,... random variables with values in $\mathbb{N}$, and let X_i be i.i.d. Let furthermore

$$S = \sum_{i=1}^{Y} X_i,$$

and $h_1(.)$ the generating function of X_i, $h_2(.)$ the generating function of Y and $h_3(.)$ the generating function of S. Show that

$$\mathrm{Var}(S) = \mathrm{Var}(X_1)\, E(Y) + E(X_1)^2\, \mathrm{Var}(Y).$$

Exercise 3.3:

Show the part about the variance in Theorem 3.3. I.e., let Z_n be the population size of a Galton-Watson process, X be the random variable that counts the offspring of one individual. Let furthermore $r = E(X)$, $\sigma = \mathrm{Var}(X)$, $Z_0 = z_0$. Show that

$$\mathrm{Var}(Z_n) \quad = \quad \begin{cases} z_0 \sigma r^{n-1} \frac{r^n - 1}{r-1} & \text{for} \quad r \neq 1 \\ z_0 \sigma n & \text{for} \quad r = 1 \end{cases}$$

Exercise 3.4:
Consider a population that consists of two types of individuals (where each individual acts independently of each other).
(a) Formulate a Galton-Watson process for these two types.
(b) Find a recursive equation for the expected number of individuals (structured by type).
(c) Find a necessary and sufficient condition, s.t. the expected number of individuals will tend to infinity respectively tends to zero.

3.2 Large Population, Discrete State

If we consider large population, we again derive deterministic models. Since we consider independent individuals, these models assume the form of linear difference equations. Like in part about the death process, we have two possibilities to justify a deterministic model. Consider the Galton-Watson Process. We may either consider expectations, or investigate the importance of random fluctuations for large population sizes.
(1) $E(Z_{n+1}) = R_0\, E(Z_n)$.
(2) $\sqrt{\mathrm{Var}(Z_n)}/E(Z_n) \to 0$ for $Z_0 \to \infty$ (i.e. relative size of fluctuations tends to zero if the populationsize tends to ∞).

3.2.1 Example 1: Fibonacci numbers

Consider animals (rabbits?) that become exactly three years old. In the second and third year, one animal produces exactly one child.

First formulation:

- State: x_n = Number of newborn animals in year n.
- Dynamics: $x_n = x_{n-1} + x_{n-2}$.

Assume $x_0 = 0$, $x_1 = 1$. We obtain the sequence

$$0,\ 1,\ 1,\ 2,\ 3,\ 5,\ 8\ \cdots.$$

Second formulation:

- State in year n:

$y_1^{(n)}$ = No. of animals of age one, $\quad y_2^{(n)}$ = No. of animals of age two, $\quad y_n = \begin{pmatrix} y_1^{(n)} \\ y_2^{(n)} \end{pmatrix}$.

- Dynamics: $y_2^{(n)} = y_1^{(n-1)}, \qquad y_1^{(n)} = y_1^{(n-1)} + y_2^{(n-1)}$

i.e.

$$y_n = \begin{pmatrix} 1 & 1 \\ 1 & 0 \end{pmatrix} y_{n-1} = A y_{n-1}.$$

Thus we find $y_n = A^n y_0$. Questions: How to deal with these models? How does the dynamics look like - is a classification possible? How does the asymptotic behavior looks like?

3.2.2 Linear, discrete dynamical systems

Generic Case / real Jordan normal form
Consider

$$y_{n+1} = A y_n, \qquad y_n \in \mathbb{R}^m.$$

This system can be simplified and reduced using invariant eigenspaces; later we will see, that this approach may be not appropriate in all case - properties like positivity of the solution may become invisible. Generically, there are m different eigenvalues

$$\lambda_1, .., \lambda_m.$$

Of course, there also cases where two eigenvalues coincide. However, a generic perturbation of the matrix will split these eigenvalues. Hence, these cases are not important here (they may be important because they separate regions with different behavior, but in itself they are less interesting, since we will never find them).
Let $\lambda_1 = r_1 e^{\mathrm{i}\phi_1}, \lambda_2 = r_1 e^{-\mathrm{i}\phi_1}, .., \lambda_{2k+1} = r_k e^{-\mathrm{i}\phi_k} \in \mathbb{C} \setminus \mathbb{R}$ and $\lambda_{2k+2}, .., \lambda_m \in \mathbb{R}$ and

$$\tilde{A} = \begin{pmatrix} A_1 & & & & & \\ & \cdots & & & 0 & \\ & & A_k & & & \\ & & & \lambda_{2k+2} & & \\ & 0 & & & \cdots & \\ & & & & & \lambda_m \end{pmatrix}.$$

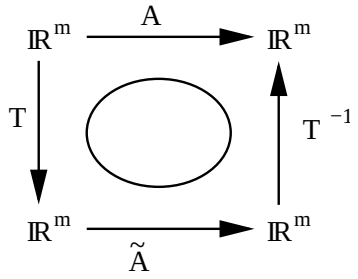
where

$$A_i = r_i \begin{pmatrix} \cos(\phi_i) & \sin(\phi_i) \\ -\sin(\phi_i) & \cos(\phi_i) \end{pmatrix}.$$

Then, there is a linear transformation T s.t.

$$A = T^{-1} \tilde{A} T,$$

i.e. the diagram



commutes. Thus we may restrict ourself to the analysis on one-dimensional systems and 2×2-systems with complex eigenvalues.

Case 1: $\lambda \in I\!R$.
We iterate with a real number. I.e., the system is one-dimensional. We may distinguish four generic cases:

1. $\lambda > 1$ (y_n tends to $\pm$ infinity monotonously)
2. $1 > \lambda > 0$ (y_n tends to zero monotonously)
3. $0 > \lambda > -1$ (y_n tends to zero in an alternating way)
4. $-1 > \lambda$ ($|y_n|$ tends to infinity while y_n alternate)

Like before, the cases $|\lambda| = 1$ or $\lambda = 0$ are not this important since they are not generic cases. The corresponding behavior can be found in Fig. 31.
Case 2: $\Im(\lambda) \neq 0$.
In this case, we find a two-dimensional system (the Gaussian plane). Since $\lambda = |\lambda| e^{i\theta}$, the trajectory will spiral; if $|\lambda| < 1$ it spirals into the origin, if $|\lambda| > 1$ to infinity (see Fig. 31).

Remark 3.5: Of course, a simple criterion for $|\lambda| < 1$ is of interest. We find, that for a 2×2-matrix

$$|\lambda_\pm| < 1 \quad \Leftrightarrow \quad 2 > 1 + \det(A) > |\mathrm{tr}(A)|.$$

Proof: We distinguish two cases, $\mathrm{tr}(A)^2 - 4\,\det(A) \geq 0$ and $\mathrm{tr}(A)^2 - 4\,\det(A) < 0$.
Case 1: $(\mathrm{tr}(A)^2 - 4\,\det(A) \geq 0)$
Let $f(\lambda) = \lambda^2 - \mathrm{tr}(A)\lambda + \det(A)$. Due to the condition $\mathrm{tr}(A)^2 - 4\,\det(A) \geq 0$ we find $\lambda_\pm \in I\!R$. Hence, in order to satisfy $|\lambda_\pm| < 1$ we need (see Fig. 32 (a)).

$$\begin{array}{rcl@{\qquad}rcl} f(-1) & > & 0, & f'(-1) & < & 0, \\ f(1) & > & 0, & f'(1) & > & 0. \end{array}$$

Hence,

$$\begin{array}{rcl} f(-1) & = & (-1)^2 - \mathrm{tr}(A)(-1) + \det(A) > 0 \\ f(\ 1) & = & (\ \ 1)^2 - \mathrm{tr}(A)(\ \ 1) + \det(A) > 0 \end{array}$$

which is equivalent with $1 + \det(A) > \max\{\mathrm{tr}(A), -\mathrm{tr}(A)\} = |\mathrm{tr}(A)|$.

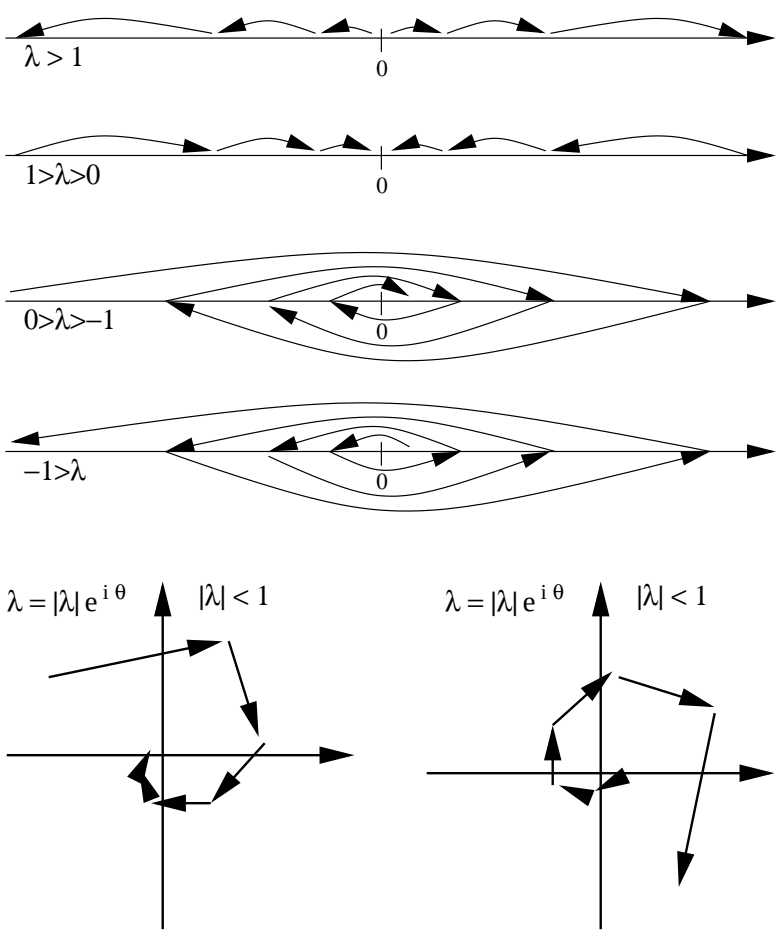


Figure 31: The behavior of a linear iterative equation for certain ranges of eigenvalues.

Similarly,

$$\begin{aligned} f'(-1) &= 2\,(-1) - \mathrm{tr}(A) > 0 \\ f'(\ 1) &= 2\,(\ \ 1) - \mathrm{tr}(A) < 0 \end{aligned}$$

which is equivalent with $2 > \max\{\mathrm{tr}(A), -\mathrm{tr}(A)\} = |\mathrm{tr}(A)|$ (see Fig. 32 (b)). Since $\mathrm{tr}(A)^2 - 4\,\det(A) = 0$ for $\det(A) = 1$, $\mathrm{tr}(A) = 2$, we find

$$|\lambda_\pm| < 1, \quad \mathrm{tr}(A)^2 - 4\,\det(A) \geq 0 \quad \Leftrightarrow \quad 2 > 1 + \det(A) > |\mathrm{tr}(A)|, \quad \mathrm{tr}(A)^2 - 4\,\det(A) \geq 0.$$

Case 2: $(\mathrm{tr}(A)^2 - 4\,\det(A) < 0)$
In this case, $\lambda_\pm \in \mathbb{C} \setminus \mathbb{R}$, i.e. (the determinant of a matrix is the product of its eigenvalues)

$$|\lambda_\pm|^2 = \lambda_\pm \overline{\lambda_\pm} = \lambda_+ \lambda_- = \det(A)$$

Hence, $|\lambda_\pm| < 1$ and $\mathrm{tr}(A)^2 - 4\,\det(A) > 0$ is equivalent with $\det(A) < 1$ and $\mathrm{tr}(A)^2 - 4\,\det(A) > 0$.

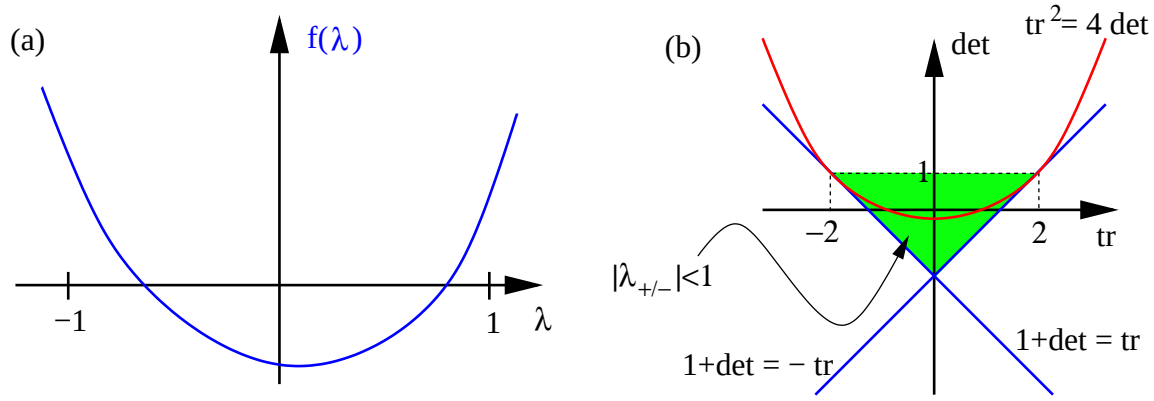


Figure 32: (a) The characteristic polynomial $f(.)$ in case 1. (b) The allowed region for case 1.

Combining these two cases yields (see again Fig. 32 (b)),

$$|\lambda_\pm| < 1 \qquad \Leftrightarrow \qquad 2 > 1 + \det(A) > |\mathrm{tr}(A)|.$$

□

Remark 3.6: The region

$$\Delta = \{(\mathrm{tr}(A), \det(A)) \,|\, \sigma(A) \subset \{|z| < 1\}\}$$

has the shape of a triangle. The part of the boundary of Δ with $\det(A) = 1$, $\mathrm{tr}(A) \in (-2, 2)$ corresponds to complex eigenvalues ($|\lambda_\pm| = 1$, $\lambda_\pm \notin \mathbb{R}$), while the two other lines of the boundaries correspond to real eigenvalues (either $+1$ or -1). On the first glance, this seems to be strange: the boundary of $\{|z| < 1\}$ consists of the two real points ± 1 that separate two connected lines of values with non-vanishing imaginary part. The structure of the two sets, $\{|z| < 1\}$ and Δ, seems not to fit.
The solution is the fact that two eigenvalues leave the unit circle simultaneously, if the point $(\mathrm{tr}(), \det)$ cross the boundary Δ with $\det = 1$ and $-1 < \mathrm{tr}() < 1$. Hence, the two disconnected non-real parts of the boundary of the unit circle can be identified.

Positive Matrices
Positive matrices play an important role in mathematical biology (we observed this several times before). We state a few important theorems about positive matrices.

Main questions:
• Under which conditions can/cannot a system, governed by

$$y_{n+1} = A\, y_n, \qquad ((A))_{i,j} \geq 0$$

be split into two independent subsystems?
• What can be concluded about the asymptotic behavior?

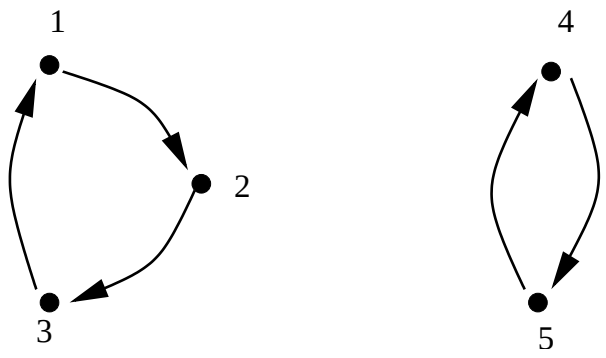


Figure 33: Transition graph of a reducible system.

Splitting of a system:

Consider five states, with transitions shown in Fig. 33. These transitions form a directed graph.

Definition 3.7: *A (directed) graph $G = (V, E)$ consists of a set of vertices V and (directed) edges E.*

In our example, we find $V = \{1, .., 5\}$, $E = \{1 \to 2, 2 \to 3, 3 \to 1, 4 \to 5, 5 \to 4\}$.

Definition 3.8: *An incidence matrix of the directed graph with vertices $V = \{v_1, .., v_n\}$ and directed edges E is a matrix $A \in \{0, 1\}^{n \times n}$, s.t.*

$$((A))_{i,j} = \begin{cases} 1 & \text{if } v_i \to v_j \in E \\ 0 & \text{else} \end{cases}$$

In our example, we find

$$A = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

Obviously, this system can be split into two independent subsystems. In order to get a grip on this phenomenon, we introduce the concept of irreducibility.

Definition 3.9: *Let A be a non-negative matrix, and $\hat{A} \in \{0, 1\}^{n \times n}$ defined by*

$$((\hat{A}))_{i,j} = \begin{cases} 1 & \textit{if} \quad ((A))_{i,j} > 0 \\ 0 & \textit{if} \quad ((A))_{i,j} = 0 \end{cases} .$$

$\hat{A}$ is an incidence matrix of a directed graph $G = (V, E)$, $V = \{v_1, .., v_n\}$. If this directed graph is connected (i.e. for all $v_i, v_j \in V$ there is a directed path $v_i = v_{l_1} \to v_{l_2} \to v_{l_3} \to \cdots \to v_{l_{m-1}} \to v_{l_m} = v_j$, where $v_{l_k} \to v_{l_{k+1}} \in E$ for $k = 1, .., m-1$), then A is called irreducible.

Remark 3.10: The graph in Fig. 34 is not connected, though it is not possible to cut it into two independent subsystems. There is no possibility to come into node one, though node one is connected with nodes two and three. It nevertheless makes sense to reduce the graph to $\tilde{G} = (\tilde{V}, \tilde{E})$ with $\tilde{V} = \{2, 3\}$ and $\tilde{E} = \{2 \to 3,\ 3 \to 2\}$: if we are once in state 1 or 2, we will never leave $\tilde{G}$; moreover, $\tilde{G}$ is connected. We find here an example for the concept of a trap: a subgraph $\tilde{G} = (\tilde{V}, \tilde{E})$ that is connected, and where no edge points "outwards", i.e. if $v_i \to v_j \in E$, $v_i \in \tilde{V} \Rightarrow v_j \in \tilde{V}$. Obviously, an irreducible transition matrix corresponds to a graph that exhibits exactly one trivial trap: the graph itself.

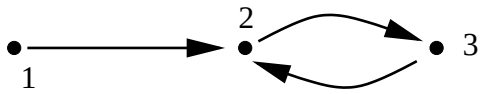


Figure 34: This directed graph is not connected.

Proposition 3.11: *If $A \in \mathbb{R}^{n\times n}$ is irreducible, then*
(1) *there is for every pair $(i, j) \in \{1, .., n\}^2$ a number $m \in \mathbb{N}$, s.t. $((A^m))_{i,j} > 0$*
(2) *$(I + A)^{n-1}$ is strictly positive.*

Proof: (Exercise!)

Theorem 3.12: *(Perron) If $A \in \mathbb{R}^{n\times n}$ is strictly positive, then the spectral radius $\rho(A)$ is a simple eigenvalue. The corresponding eigenvector is strictly positive. The absolute value of all other eigenvalues are strictly smaller than $\rho(A)$; they do not have a non-negative eigenvector.*

Theorem 3.13: *(Frobenius) If $A \in \mathbb{R}^{n\times n}$ is non-negative and irreducible, then the spectral radius is a simple eigenvalue with a non-negative eigenvector.*

Remark 3.14: In the case of the Theorem of Frobenius, there may be more eigenvalues with $|\lambda| = \rho(A)$.

We do not want to prove booth of these theorems; one may find the proofs (and more) in the book of Gantmacher [22]. Let us sketch the idea for the theorem of Perron (we follow Gantmacher [22], who in turn follows a proof due to Wieland).

Proposition 3.15: *If $A \in \mathbb{R}^{n\times n}$ is strictly positive, then the spectral radius $\rho(A)$ is a simple eigenvalue. The corresponding eigenvector is strictly positive.*

Proof: (Perron's Theorem)
Step 1: Find a candidate for the largest eigenvalue.
Define $N := \{Ax \,|\, x \in \mathbb{R}^n_+ \setminus \{0\}\}$ and

$$r : N \to \mathbb{R}_+, \quad x \mapsto r(x) = \min_{1\le i\le n} \frac{(Ax)_i}{(x)_i}.$$

Since A is strictly positive, also N consist of vectors that are strictly positive. Hence, $r(.)$ is continuous on N. Furthermore, with

$$\alpha = \min\{((A))_{i,j} \,|\, 1 \leq i,j \leq n\,\},$$

we find $(Ax)_i \geq \alpha(x)_i$ for $x \in \mathbb{R}^n_+$ and $i = 1,..,n$, i.e. $r(.)$ is bounded from below. Since $r(.)$ is homogeneous of degree zero ($r(\zeta x) = r(x)$ for $\zeta > 0$), we find

$$\sup_{x \in N} r(x) = \sup_{x \in N \cap \{x^T x = 1\}} r(x).$$

Since $r(.)$ is continuous on N and $N \cap \{x^T x = 1\}$ is compact, $r(.)$ assumes its maximum on this set.

Step 2: The maximum of $r(.)$ is an eigenvalue with a positive eigenvector.
Since $r(x) \geq \alpha > 0$, the maximum of $r(.)$ is strictly positive. Let $x_0 \in N$, s.t. $r_0 := r(x_0) = \max_{x \in N} r(x)$. Assume $Ax_0 \neq r_0 x_0$. Then,

$$r_0 \leq \frac{(Ax_0)_i}{(x_0)_i} \quad \Rightarrow (Ax_0)_i \geq r_0\,(x_0)_i \qquad\qquad \text{for } i = 1,..,n$$

i.e. $Ax_0 - r_0 x_0 \geq 0$, and $Ax_0 - r_0 x_0 \neq 0$. Hence (A is strictly positive), we find $A(Ax_0) - r_0(Ax_0) > 0$. Hence, there is $\epsilon > 0$ s.t. $A(Ax_0) - (r_0 + \epsilon)(Ax_0) > 0$, i.e. $\max_{x \in N} r(x) \geq r_0 + \epsilon$, which is a contradiction to the definition of r_0. Thus,

$$Ax_0 = r_0 x_0, \qquad (x_0)_i > 0 \quad \text{for } i = 1,..,n.$$

Step 3: r_0 is the spectral radius
For $y \in \mathbb{C}^n$ define as y^+ the vector with enries that are the absolute values of y. Assume $Ay = \lambda y$. Then,

$$Ay^+ \geq (Ay)^+ = |\lambda| y^+ \qquad \Rightarrow \qquad A(Ay^+) \geq |\lambda|(Ay^+).$$

Since $Ay^+ \in N$, we find $|\lambda| \leq r_0$. If $|\lambda| = r_0$, then Ay^+ is already an eigenvector of A (since $Ay^+ \in N$).

Step 4: The spectral radius is a simple eigenvalue.
Step 4(a): There is no linear independent second eigenvector.
Assume that apart of $x_0 \in N$ a second (linearly independent) vector x_1 is eigenvector for r_0. Then, also $x_2 = \zeta_1 x_0 + \zeta_2 x_1$ are eigenvalues. We may choose ζ_1, ζ_2 s.t. $x_2 \in \mathbb{R}^n_+$, and exactly one entry becomes zero, i.e. there is an $i_0 \in \{1,..,n\}$ with $(x_2)_{i_0} = 0$. Thus,

$$0 < (Ax_2)_{i_0} = r_0 (x_2)_{i_0} = 0.$$

This is an contradiction.

Step 4(b): $\rho(A)$ is a simple root of the characteristic polynomial.

Introduce the adjoint matrix $B(\lambda)$ for $\lambda I - A$. I.e.,

$$(\lambda I - A)^{-1} = p(\lambda)^{-1} B(\lambda)$$

for $\lambda \notin \sigma(A)$ ($p(\lambda)$ denotes the characteristic polynomial). We will investigate the structure of $B(\lambda)$ in the following steps.

• *$B(\lambda)$ is either non-negative or non-positive.*

For $\lambda > r_0$ we may compute $(\lambda I - A)^{-1}$ by the Neumann series and find

$$(\lambda I - A)^{-1} = \frac{1}{\lambda} \sum_{i=0}^{\infty} (A/\lambda)^i > 0.$$

Hence, $(\lambda I - A)^{-1}$ is strictly positive. Furthermore, $p(\lambda)$ has no real root larger than $\rho(A)$. Hence, $p(\lambda) > 0$ for $\lambda > \rho(A)$ and n even, resp. $p(\lambda) < 0$ for $\lambda > \rho(A)$ and n odd. Since the entries of $B(\lambda)$ are polynomials in λ, $B(\lambda)$ depends on λ in a smooth manner, and thus

$$B(\rho(A)) = \lim_{\lambda \to \rho(A)+} B(\lambda) = \lim_{\lambda \to \rho(A)+} p(\lambda)(\lambda I - A)^{-1}.$$

The expression on the r.h.s. is either strictly positive or strictly negative for $\lambda > \rho(A)$, hwncw the entries of $B(r_0)$ are either non-negative or non-positive. It is not possible that $B(r_0)$ has a positive and a negative entry at the same time.

• *$B(\lambda)$ cannot vanish.*

Let $T : \mathbb{R}^n \to \mathbb{R}^n$ be a linear transformation, i.e. T^{-1} exists. The characteristic polynomial will not be changed by a linear transformation of $\mathbb{R}^n$. Furthermore,

$$TB(\lambda)T^{-1} = T\, p(\lambda)(\lambda I - A)^{-1} T^{-1} = p(\lambda)(\lambda I - T^{-1}AT)^{-1}$$

i.e. if $B(\lambda) = 0$, then also the adjoint matrix of $T^{-1}AT$ vanishes for any transformation T. Thus, we only have to show that the adjoint of $J(\lambda I - A) =: J(\lambda)$, the Jacobi normal form of $\lambda I - A$, does not vanish. Let

$$J(\lambda) = \text{Block-Diagonal}(J_1(\lambda), J_2(\lambda), .., J_k(\lambda))$$

where the J_i are the Jordan-blocks of A. Since we know (step 4(a)) that we only have one eigenvector for $\rho(A)$, there is only one Jordan-block for $\lambda - \rho(A)$; without restriction this block is $J_1(\lambda)$. Thus,

$$\det(J_i(\rho(A)) \neq 0 \qquad \text{for } i > 1.$$

Now we show that at least one entry or the adjoint of $J(\rho(A))$ is non-zero. Consider the Jordan-Block $J_1(\lambda)$ for $\lambda(\rho(A))$. Since the diagonal elements are $\lambda - \rho(A)$, they vanish for $\lambda = \rho(A)$. Hence, $J_1(\rho(A))$ is zero but the upper secondary diagonal: in the upper secondary diagonal all entries are one.

$$J_1 = \left(\begin{array}{c|cccc} 0 & 1 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 1 & \cdots & 0 & 0 \\ & & \vdots & & \vdots & \\ 0 & 0 & 0 & \cdots & 0 & 1 \\ \hline 0 & 0 & 0 & \cdots & 0 & 0 \end{array}\right).$$

Let the dimension of J_1 be l, and consider $\mathrm{adj}_{l,1}(J_1(\rho(A)))$, i.e. the determinant of J_1, if we skip the first column and the last row.

$$\mathrm{adj}_{l,1}(J_1(\rho(A))) = (-1)^{l+1}\det(I) = (-1)^{l+1}.$$

Hence, the entry $(l,1)$ of adjoint of $J(\rho(A))$ is non-zero and thus also $B(\rho(A)) \neq 0$.
• $p'(\rho(A)) \neq 0$.
We find for $\lambda \notin \sigma(A)$ that

$$\begin{aligned} (\lambda I - A)^{-1} &= \frac{1}{p(\lambda)} B(\lambda) \\ \Rightarrow \qquad p(\lambda) I &= B(\lambda)(\lambda I - A) \\ \Rightarrow \qquad p'(\lambda) I &= B'(\lambda)(\lambda I - A) + B(\lambda) \end{aligned}$$

Since the last equation is the equality of polynomials, this equation also holds if $\lambda = \rho(A)$. Plugging in $\rho(A)$ for λ and multiplying with x_0 yields

$$p'(\rho(A))x_0 = B'(\rho(A))(\rho(A)I - A)x_0 + B(\rho(A))x_0 = B(\rho(A))x_0 \neq 0$$

where $B(\rho(A))x_0$ does not vanish (since $B(\rho(A)) \neq 0$ and $B(\lambda)$ is either non-negative or non-positive, and since x_0 is strictly positive). Thus, $p'(\rho(A)) \neq 0$.

Step 5: There is no other non-negative eigenvector of A but x_0.
Assume that there is $x_3 \in \mathbb{R}^n_+ \setminus \{0\}$, and

$$Ax_3 = \lambda x_3.$$

Since x_3 is non-negative, we find $0 < \lambda$. Since $r_0 = \rho(A)$ is simple (step 4), we obtain $0 < \lambda < r_0$. Let $\hat{u}$ be the left-eigenvector of A for the eigenvalue $\rho(A)$, i.e.

$$\hat{u}^T A = \rho(A)\hat{u}^T.$$

Since A and A^T do have the same properties (strictly positive), also $\hat{u}$ is strictly positive. Thus, $<\hat{u}, x_3> > 0$, and

$$\rho(A) <\hat{u}, x_3> = <A^T\hat{u}, x_3> = <\hat{u}, Ax_3> = \lambda <\hat{u}, x_3> .$$

Therefore $\lambda = \rho(A)$, which contradicts our conclusion that $\lambda < \rho(A)$.

□

In order to use these results for the Matrix-Iteration, we prove the following lemma.

Lemma 3.16: *Let $A \in \mathbb{R}^{m\times m}$. Then, there is $C > 0$ s.t. $\|A^k x\| \leq C\rho(A)^k k^m$.*

Proof: It is sufficient to show this inequality for a Jordan-Block. Let

$$J = \begin{pmatrix} \lambda & 1 & 0 & \cdots & 0 & 0 \\ 0 & \lambda & 1 & \cdots & 0 & 0 \\ & & \vdots & & \vdots & \\ 0 & 0 & 0 & \cdots & \lambda & 1 \\ 0 & 0 & 0 & \cdots & 0 & \lambda \end{pmatrix}.$$

By induction it is easy to show that

$$J^n = \begin{pmatrix} a_1^n\lambda^n & a_2^n\lambda^{n-1} & a_3^n\lambda^{n-3} & \cdots & a_{m-1}^n\lambda^{n-m+2} & a_m^n\lambda^{n-m+1} \\ 0 & a_1^n\lambda^n & a_2^n\lambda^{n-1} & \cdots & a_{m-2}^n\lambda^{n-m+3} & a_{m-1}^n\lambda^{n-m+2} \\ & & \vdots & & \vdots & \\ 0 & 0 & 0 & \cdots & a_1^n\lambda^n & a_2^n\lambda^{n-1} \\ 0 & 0 & 0 & \cdots & 0 & a_1^n\lambda^n \end{pmatrix}.$$

The coefficients a_i^n are real numbers that satisfy

$$a_1^n = 1, \quad a_i^0 = 0 \text{ for } i > 1, \quad a_i^n = a_i^{n-1} + a_{i-1}^{n-1}.$$

We show by induction that that $a_i^n \leq Cn^{i-1}$:
Case $i = 1$: $a_1^n = 1 \leq Cn^{i-1}$ for $C > 1$.
Step $i \to i + 1$:

$$a_i^{n+1} = a_i^n + a_{i-1}^n = a_i^{n-1} + a_{i-1}^{n-1} + a_{i-1}^n = \cdots = a_i^0 + \sum_{l=0}^{n} a_{i-1}^l$$

Since $a_i^0 = 0$ and $a_{i-1}^l \leq Cl^{i-2} \leq Cn^{i-2}$ we find

$$a_i^{n+1} \leq \sum_{l=0}^{n} Cn^{i-2} = Cn^{i-2}(n+1) \leq C(n+1)^{i-1}.$$

Thus, all entries of J^n are smaller than $C\lambda^n n^m$, and therefore

$$|J|^n \leq \tilde{C}\lambda^n\, n^m$$

□

Proposition 3.17: Consider a strictly positive matrix A with spectral radius $\rho(A)$, and the corresponding right eigenvector $\hat{x}$ and left eigenvector $\hat{u}$. We assume without restriction that $\hat{u}^T\hat{x} = 1$. Let furthermore

$$\sigma(A) \setminus \{\rho(A)\} \subset \{|z| \leq r < \rho(A) - \epsilon\}.$$

Then, asymptotically, we find

$$A^n x =< \hat{u}, x > \hat{x}\, \rho(A)^n + g_n$$

where the residuals g_n can be estimated by

$$|g_n| \leq C(\rho(A) - \epsilon)^n,$$

i.e. they grow slower than $\rho(A)^n$.

Proof: Define the spectral projector

$$Pi_0 = \hat{x}\,\hat{u}^T = \hat{x} < \hat{u}, . > .$$

we find easily that $\Pi_0^2 = \Pi_0$, $\Pi_0 A = A\Pi_0$ and $A^n\Pi_0 = \rho(A)^n\Pi_0$. Let $\Pi_1 = I - \Pi_0$ be the complementary projector. Define $A_1 = \Pi_0 A\Pi_0$, $A_2 = \Pi_1 A\Pi_1$. Since for any $\lambda \in \sigma(A)$ with eigenvector $x \in \mathbb{C}^n$, we find (like above) that

$$\rho(A) < \hat{u}, x >=< A^T\hat{u}, x >=< \hat{u}, Ax >= \lambda < \hat{u}, x > .$$

From $\lambda \neq \rho(A)$ we conclude that $< \hat{u}, x >= 0$. Hence, $\Pi_1 x = x$ and $A_2 x = \lambda x$. Then,

$$\sigma(A) \setminus \{\rho(A)\} \subset \sigma(A_2).$$

On the other hand, if $\lambda \in \sigma(A_2)$, then there is $x \in \mathbb{C}^n$ s.t. $A_2 x = \lambda x$, i.e.

$$\Pi_1 A\Pi_1 x = \lambda x \quad \Rightarrow \quad \Pi_1^2 A\Pi_1 x = \Pi_1 A\Pi_1 x = \lambda\Pi_1 x \quad \Rightarrow \quad A\Pi_1^2 x = A\Pi_1 x = \lambda\Pi_1 x.$$

Hence, either $\Pi_1 x = 0$, or $\Pi_1 x$ is eigenvector of A for eigenvalue λ. Since the eigenvalue of $\rho(A)$ is simple with an eigenvector that is mapped to zero by Π_1, we find

$$(\sigma(A) \setminus \{\rho(A)\}) \cup \{0\} = \sigma(A_2).$$

Especially, $\rho(A_2) \leq r < \rho(A) - \epsilon$.
Furthermore, (since $\Pi_0\,\Pi_1 = 0$)

$$\begin{aligned} A^n &= (A\,(\Pi_0 + I - \Pi_0))^n = (A\Pi_0 + A\Pi_1)^n = (A\Pi_0^2 + A\Pi_1^2)^n = (\Pi_0 A\Pi_0 + \Pi_1 A\Pi_1)^n \\ &= (\Pi_0 A\Pi_0)^n + (\Pi_1 A\Pi_1)^n = A_1^n + A_2^n. \end{aligned}$$

Hence,

$$A^n x = A_1^n x + A_2^n x = \rho(A)^n < \hat{u}, x > \hat{x} + g_n$$

where $|g_n| \leq C\,n^m\,r^n$, s.t. $|g_n| \leq \tilde{C}(\rho(A) - \epsilon)^n$.

□

Back to Fibonacci
If we want to know the asymptotic behavior of the Fibonacci-numbers, we have to compute the leading eigenvalue and the corresponding eigenvector for the matrix

$$A = \begin{pmatrix} 1 & 1 \\ 1 & 0 \end{pmatrix}.$$

We find

$$\lambda_\pm = \frac{1}{2}(\mathrm{tr}(A) \pm \sqrt{\mathrm{tr}(A)^2 - 4\,\det(A)}) = \frac{1}{2}(1 \pm \sqrt{1+4}) = \frac{1 \pm \sqrt{5}}{2}.$$

Hence the spectral radius is

$$\rho(A) = \frac{1+\sqrt{5}}{2},$$

the "golden ratio". The corresponding eigenvector is

$$x_0 = \begin{pmatrix} (1+\sqrt{5})/2 \\ 1 \end{pmatrix}.$$

We find asymptotically

$$\begin{pmatrix} y_1^{(n)} \\ y_2^{(n)} \end{pmatrix} \sim \left(\frac{1+\sqrt{5}}{2}\right)^n \begin{pmatrix} (1+\sqrt{5})/2 \\ 1 \end{pmatrix}.$$

3.2.3 Example 2: Leslie Matrices - Age Structured Population

While the Fibonacci-numbers are a toy model, discrete age structured population model are used in "real-world-applications". The basic model has been introduced by Leslie [43], and the corresponding matrices are thus also called "Leslie-Matrices". This technique is not only able to describe natural age. If one keeps track of the time a particle belongs to a state, we assign an artificial clock/age to this particle. At the time of the entry this clock is set to zero. Matrices, resemble the Leslie matrix describe the evolution of this age of the particle. An example could be for an infected person to introduce the time since infection. Infectivity as well as recovery rates do depend on this time (and are, in general, not really exponentially distributed).

Leslie-Model

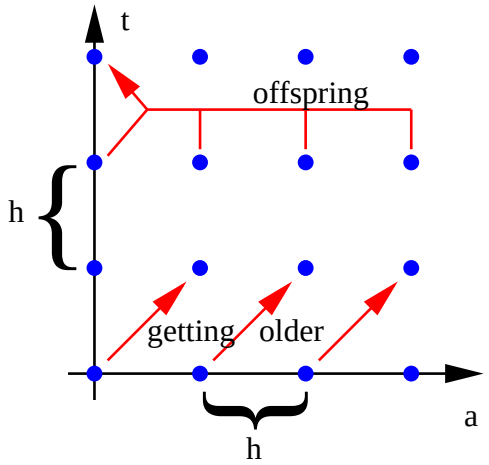


Figure 35: Time discretization for the Leslie-model.

Consider an age-structured population. Discretize age and time,

$$t_i = i\,h \qquad a_i = i\,h, \qquad i = 1, .., m.$$

State: Let $x_i^{(n)}$ be the number of individuals at time $t = n\,h$ with age in $[(i-1)\,h, i\,h)$.
Dynamics: There are two processes to consider: becoming older/death and birth
• *becoming older/death*
If there is no death at all, we find immediately (see Fig. 35)

$$x_i^{(n)} = x_{i-1}^{(n-1)},$$

i.e. age and chronological time pass with the same velocity. If we introduce death, not everyone is able to survive. Hence, there are parameters $p_i \in [0, 1]$ that can be interpreted as survival probabilities, and

$$x_i^{(n)} = p_{i-1} x_{i-1}^{(n-1)}.$$

• *birth*
We know from $x^{(n)}$ the vector $x_i^{(n+1)}$ for $i > 0$. The element $x_0^{(n+1)}$ is governed by birth (see Fig. 35). Let F_i be the expected number of children for a person in the age interval $[(i-1)\,h,\, i\,h)$ during one time step. Then,

$$x_0^{(n+1)} = \sum_{i=0}^{m} F_i x_i^{(n)}.$$

All in all we find

$$x^{n+1} = Ax^{(n)}$$

with

$$A = \begin{pmatrix} F_1 & F_2 & F_3 & \cdots & F_{m-2} & F_{m-1} & F_m \\ p_1 & 0 & 0 & & 0 & 0 & 0 \\ 0 & p_2 & 0 & & 0 & 0 & 0 \\ 0 & 0 & p_3 & & 0 & 0 & 0 \\ \vdots & \vdots & & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & & p_{m-2} & 0 & 0 \\ 0 & 0 & 0 & \cdots & 0 & p_{m-1} & 0 \end{pmatrix}$$

Analysis
Consider the graph of the incidence matrix corresponding to a Leslie matrix with $p_i, F_i > 0$ (Fig. 36). Obviously, the graph is connected. Thus, the corresponding Leslie matrix is irreducible.
If $F_{i_0} = .. = F_m = 0$, i.e. the older age classes are not fertile any more, the corresponding graph becomes reducible. These age classes do not influence the population dynamics and hence can be (from this point of view) skipped.

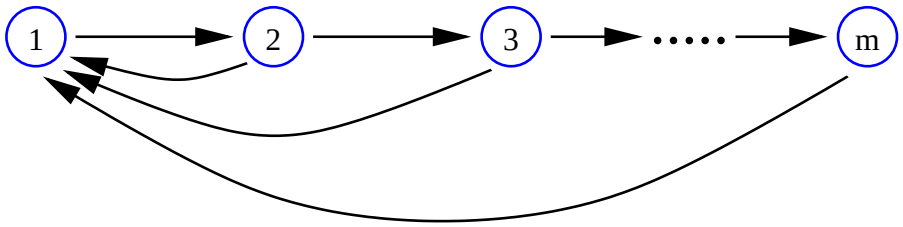


Figure 36: Graph of a Leslie matrix.

Corollary 3.18: *If $|\lambda| \neq \rho(A)$ for $\lambda \in \sigma(A) \setminus \{\rho(A)\}$, there is $\hat{x} \in \mathbb{R}_+^m$ (the eigenvector corresponding to $\rho(A)$) s.t.*

$$A^n y / \|A^n y\| \to \hat{x}.$$

I.e., with any initial condition we approach an unique stationary age distribution.

This is not the necessarily the case, if there are more eigenvalues with an absolute value of $\rho(A)$.

Definition 3.19: *If we find $\mathbf{e}^{\mathrm{i}\phi}\rho(A) \in \sigma(A)$ for $\phi \notin \{0, \pi\}$ we are in the "lattice case".*

Lattice Case
What happens in the lattice case?

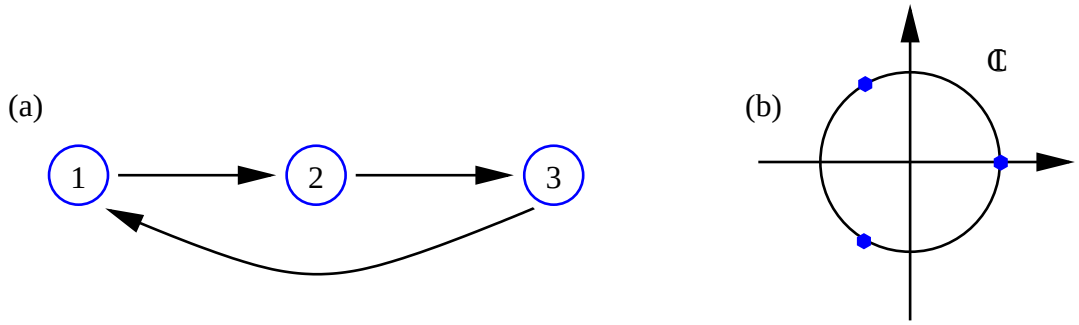


Figure 37: (a) Transition graph of the salmon-example. (b) Spectrum of the Leslie matrix.

Example: Consider salmon [16]. It is natural to divide the population of salmon in three age classes: newborn, one year old and two year fish. Only the last class reproduces (and then dies).

$$A = \begin{pmatrix} 0 & 0 & F_3 \\ p_1 & 0 & 0 \\ 0 & p_2 & 0 \end{pmatrix}.$$

The transition graph is shown in Fig. 37 (a). The spectrum of A is

$$\sigma(A) = \{(p_1\, p_2\, F_3)^{1/3} e^{2\pi \mathrm{i}/3\, j} \,|\, j = 0, 1, 2\}$$

i.e. we find a kind of resonance (Fig. 37 (b)). A population can be split into three independent subpulations that live with a shifted phase. There are interesting phenomena. For example, a rare mutant with a period of four years may invade the primary population; however, by a shift in the phase of the resident the invader may be out-competed again. This phenomenon is called "the resident strikes back" [49].

Interestingly enough, populations in lattice case can be observed in many examples (for example a certain species of Bamboo (17 years), grasshoppers (7 or 17 years),..). Furthermore, the populations live synchronized, i.e. of all the possible phases only one is realized; there is e.g. the large outbreak of grasshoppers every 17 years. It is intriguing that all these periods are prime numbers. It is by no means clear, why this is the case. The main hypothesis is the idea that predators have to be synchronized with the prey if they want to survive. If the period of the prey is not prime, the period of the predator may be any number that divides the period of the prey. With a prime number as period, the predator is forced to hit exactly this prime number (or multiples of this prime number). This is much more difficult, and this advantage possibly leads to the strategy of these lattice-case populations to live in one synchronized homogeneous population and to choose a prime period.

3.2.4 Summary/Conclusion

We focused on matrix iterations. Especially the asymptotic behavior is interesting (will the solution tend to zero? Or grow to infinity? Does the – normalized – state converge?)

Generic Case: If we do not have additional structure like positivity (see below), then the only thing that can be done is to reduce the matrix using eigenspaces. Generically all eigenvalues are simple. In this case, one classifies the dynamics of a scalar iteration resp. the dynamics of a two-dimensional system (where the corresponding matrix has non.real eigenvalues, i.e. is a rotational matrix.

Non-Negative Matrices: In this case, we aim to exploit the positivity. Again, the quesion of reduction to more simple systems (keeping the positivity) appears. This leads to the connection to graph theory, and the question if/if not the corresponding graph of possible transitions is connected.

We find different degrees of connectivity:
- *Matrices that are strictly positive correspond to graphes where every node is directly connected to evry node. This is the strongest connectivity one can think of.*
- *If the graph corresponding to a matrix is connected, it is possible to go with a finite number of steps from one node to another node. Still, this situation leads to conclusions about the asymptotic dynamics that are non-trivial.*
- *The weakest case is given if the graph is not connected. However, in this situation it is possible to define subsystems that are connected. In this sense, the classification of matrices is complete and it is only necessary to understand the dynamics for irreducible and strictly positive matrices.*

Results about long term behavior:
These results are due to the detailed analysis of the spectrum of non-negative matrices, the Perron-Frobenius Theory.
- *For a generic strictly positive Matrix we find that a trajectory with any generic initial condition will either tend to infinity of to zero. If we normalize the iterated vectors to one, then we find that these normalized vectors ("densities", "distributions") tend to a unique positive vector that is given by the eigenvector of the matrix.*
- *If we only have a non-negative matrix, we may have more than one eigenvalue with an absolute value the equals the spectral radius. Also here, we find exponential grow/decrease. However, there may be oscillations/different phases in the solutions.*
- *In general, it is possible to find subsystems that behave according to one of the two previous cases.*

It is interesting and intriguing to find such a strong connection between dynamical systems, linear algebra and graph theory. It is by no means obvious that e.g. the spectrum of a matrix tells us something about the structure of the corresponding graph. More can be found in the review article [33].

3.2.5 Exercise

Exercise 3.5:
Let $A \in \mathbb{R}^{n\times n}$ be a non-negative and irreducible matrix. Show that
(1) $\forall (i,j) \in \mathbb{N}_n \times \mathbb{N}_n \, \exists m = m(i,j) \in \mathbb{N}: \;\; ((A^n))_{i,j} > 0$.
(2) $(I + A)^{n-1} > 0$.

Exercise 3.6:
Consider the incidence matrix

$$A = \begin{pmatrix} 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 1 \\ 1 & 0 & 1 & 1 \end{pmatrix}.$$

Draw the directed graph coded by this matrix. Is this matrix irreducible?

Exercise 3.7:
Let A be the incidence matrix of a directed graph $G = (V, E)$. A loop of length l is defined as a path $v_1 \to v_2 \to v_3 \cdots \to v_{l-1} \to v_1$, where every step is an edge, $v_i \to v_{i+1} \in E$. Let loop(l) be the number of these loops. Show that

$$\text{loop}(l) = \text{tr}(A^l).$$

Exercise 3.8:
Consider a directed graph $G = (V, E)$ with incidence matrix A. A trap is defined as a subgraph $\tilde{G} = (\tilde{V}, \tilde{E})$ with $\tilde{V} \subset V$ and

$$\tilde{E} = \{v_i \to v_j \,|\, v_i, v_j \in \tilde{V}, \quad v_i \to v_j \in E\}$$

such that $\tilde{G}$ is connected and there are no edges pointing outward of $\tilde{G}$, i.e. $v_i \in \tilde{V}$, $v_i \to v_j \in E$, then $v_j \in \tilde{V}$.
Show that the number of positive left-eigenvectors of A is at least the number of traps of the system.

Exercise 3.9:
Model the fate of a fish population with different stages like egg, larvae etc.

3.3 Markov Chains

We want to put the stochastic models in a more general framework. The Galton-Watson process can be seen as a special case of a Markov Chain. Also the deterministic models are in a certain sense included in this framework.

3.3.1 Socio-Biology: Dunging behavior of pigs

If pigs are allowed to move freely in the stable (unfortunately not really the typical fate of a pig), pigs are quite clean animals. They have a common latrine, the dunging area. In order to be able to build stables that are well suited for pigs, Wechsler and Bachmann [61] investigate the eliminative behavior of pigs. First different behavioral elements are defined. Then, the animals are observed and a sequence of these behavioral pattern is measured. These data are then evaluated. One may find more information about the statistical aspects (planning and evaluation of such experiments) of behavioral biology in [45].

Setup of the scene:
• The behavioral pattern are (in quotation marks: verbal quotations from [61]):
(1) *Outside:* The pig is outside of the dunging area.
(2) *Sniff:* "a pig withdraws the outer part of the snout at least twice".
(3) *Posture:* "a pig turns its hind quarters at least 90^0 around the spot it has sniffed at or makes a few steps by which the hind quarters are placed within a maximal distance of 30 cm from the spot it has sniffed at."
(4) *Defaecate.*
(5) *Urinate.*

In the article, the state "outside" is not explicitely introduced. Instead there are actions "enters the dunging area" and "leaves the dunging area", which is of course equivalent to transition from state 1 to any of the states 2,..,5, respectively the transition from one of the states 2,..,5 into state 1.

• Measure protocol:
An animal is observed while it is in the dunging area. The sequence of different behavioral pattern is protocoled. Thus, there is no information about the time duration of each pattern available, but only the sequence of these pattern. A trivial conclusion is, that in this sequence a state appears never twice in a row.

Evaluation of the data:
A first common approach is to draw a histogram of the frequency of these pattern. It is then possible, to compare different animals, say. However, this approach is completely static. It neglects all correlations between states, and thus may be criticized.

A slightly more sophisticated approach is to construct the first order dynamics in the following way.
State: The state is either of the states 1,..,5.
Dynamics: We define a matrix A, where the entries $p_{i,j} = ((A))_{i,j}$ denote transition probabilities to change from state i into state j.

We here assume implicitly two things:
• The transition probability only depends on the state, where I am, and the state I'm going to. There is no further dependency on the history. Of course, this assumption is very often (also in the present case) not true. However, a model is never "true" but always neglect phenomena. In this sense, the present model is sensible, since the effects of the

		Previous state				
		outside	sniff	posture	defaecate	urinate
next state	outside	0	0.4505495	0	0.25	0.1
	sniff	0.8301887	0	0.05263158	0.725	0.85
	posture	0	0.2087912	0	0	0
	defaecate	0.1320755	0.2197802	0.631579	0	0.05
	urinate	0.03773585	0.1208791	0.3157895	0.025	0

Table 1: Transition probabilities for the model about the eliminative behavior of a pig.
.

history long ago should not influence the behavior of the pig as much as the close history. And the last state is possibly the most important part of the history that the pig takes into account in his/her decisions.
• The transition probabilities are constant in time. Also this may not be given (perhaps the behavior of a pig is different in the morning and in the evening).

In principle, both restrictions can be removed: one may take more states than the very last state into account in prediction the next states. This approach leads to semi-Markovian processes. Or, one may introduce transition probabilities that depend on time. In this case, we go into the field of non-stationary Markov chains.

The authors count the transitions of i $\rightarrow j$. From this, we obtain naive estimators for the transition probabilities

$$((\hat{A}))_{i,j} = \hat{p}_{i,j} \frac{\#\text{transitions } j \rightarrow i}{\#\text{transitions } j \rightarrow \text{any state}}.$$

The corresponding probabilities are shown in Table 1. All in all, we have data about 52 visits of the dunging area. Using these probabilities, we draw a transition graph between the different states Fig. 38. We find the a picture of the behavior of a pig within a dunging ares. However, we also find the weakness of Markov models (where the state space is very small): the main path is outside $\rightarrow$ sniff $\rightarrow$ outside. It is to expect that mostly a real pig will go through states 4 or 5 before it leaves the dunging area. However, it will sniff after entering and before leaving the dunging area. The Markov process cannot decide if the pig sniffs because it wants to go to states 4 or 5, or if it sniffs because it is coming from the states 4 or 5. Hence, a Markov-chain-pig will (unrealistically) quite often leave the dunging area without using it.

3.3.2 Basic definitions

In this chapter, we briefly browse trough some basic definitions and facts about Markov chains. There are many books concerned with Markov chains, e.g. in [11] a nice presentation of the basic theory can be found.

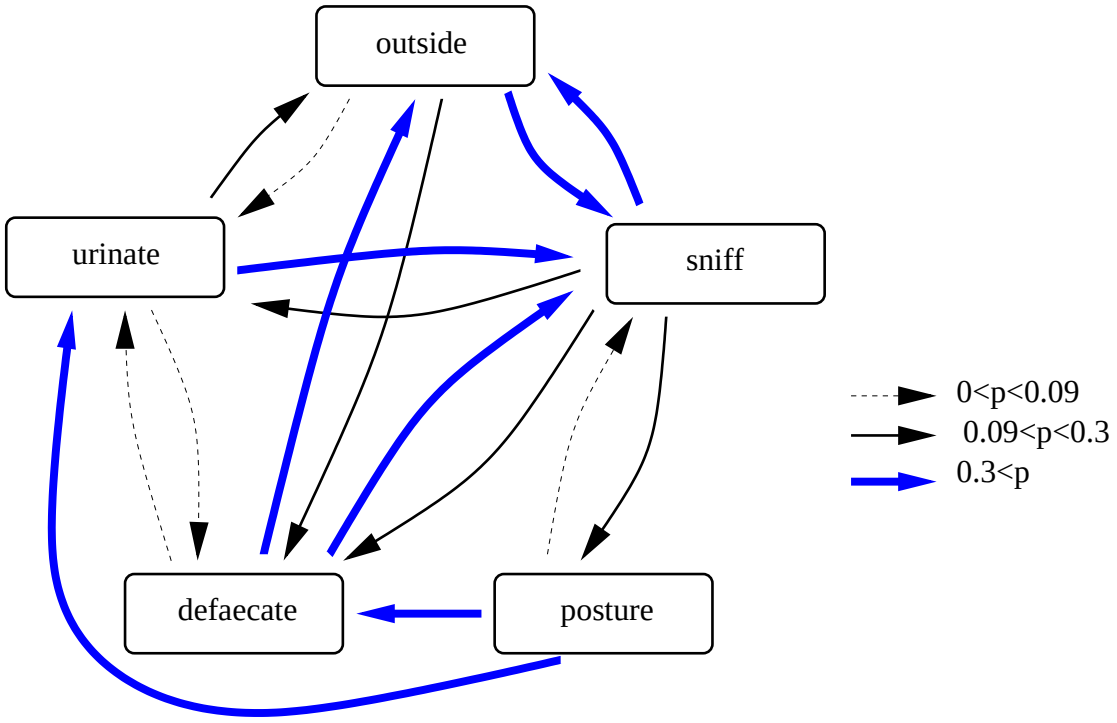


Figure 38: Transition graph for the pig-example.

Definition 3.20: *Let $I = \{a, b, ..\}$ be a set (finite or infinite) and X_n a sequence of I-valued random variables. If $i_1, .., i_n \in I$ and for all $n \in \mathbb{N}$, $n \geq 1$ we find*

$$P(X_n = i_n \,|\, X_1 = i_1, .., X_{n-1} = i_{n-1}) = P(X_n = i_n \,|\, X_{n-1} = i_{n-1})$$

then the sequence of random variables is called a Markov chain.

Remark 3.21:
• The matrix A given by

$$((A))_{i,j} = p_{i,j} := P(X_2 = i \,|\, X_1 = j)$$

is called transition matrix. The transition matrix contains all informations that describe the dynamics of the Markov process. If π_n gives the probability density in time step n, i.e.

$$\pi_n = (P(X_n = a), P(X_n = b), P(X_n = c), \ldots)^T$$

then we find

$$P(X_{n+1} = i) = \sum_{c \in I} P(X_{n+1} = i \,|\, X_n = c) P(X_n = c) = \mathbf{e}_i^T A \pi_n.$$

Hence

$$\pi_{n+1} = A \pi_n.$$

This is a deterministic, linear iterative system describing the dynamics of a probability distribution. Since A is non-negative, the Perron-Frobenius Theorems from the last section can be applied.

• The important property is the Markov-property: the next state only depends on this state but not on the history - one calls a Markov process "memoryless". This structure allows to prove a lot of statements that are in general not valid for a process that remembers the total history. However, it is possible to generalize the Markov process and to allow the process to recall - say - the last N states. Also the property that A is not changed during the iterations may be released; we then obtain non-stationary Markov chains. E.g. simulated annealing is based on non-stationary Markov-processes.

• One may interprete the vector π_n in two ways (these are two general concepts): either we consider one individual, and ask for the probability to find one individual at time step n in a given state. Or, one does not consider only one individual but an ensemble of individuals. In this case, we ask for the relative part of the population that is in a certain state. The latter interpretation does not need (at population level) any probabilistic interpretation. In this sense, the Markov process is a framework for the stochastic as well as for the deterministic models of this section.

• Though a lot of models can be seen as Markov models, it is not always wise to take this point of view. For example, a Galton-Watson process is a Markov chain. It is in principle possible to derive the transition matrix and prove all theorems from the section about Galton-Watson processes in this formalism. However, the specific property that the state of the Galton-Watson process consists of a finite number of individuals is hidden in the transition matrix. Markov chains offer an abstract framework for a wide class of processes. From an abstract framework we cannot expect too many tools for a specific model/problem. Thus it is sometimes better to stick with a specific formulation of the problem that allows to use the specific structure instead using the general formulation as a Markovian process.

Definition 3.22:
(a) *Let $p_{i,j}^{(n)} = (A^n \mathbf{e}_i)_j$ the probability to be after n steps in state j if we started in state i. Then, a state j (represented by $\mathbf{e}_j$) is called recurrent, if*

$$\sum_{n=0}^{\infty} p_{j,j}^{(n)} = \infty$$

and transient else.
(b) *A state j is called periodic with period s, if s is the greatest common divisor of*

$$\{n \,|\, p_{j,j}^{(n)} > 0\}.$$

(c) *A state is called absorbing, if*

$$A\mathbf{e}_j = \mathbf{e}_j.$$

In this case, only transitions into this state are possible. The state itself is invariant under A.
(d) *A state i is called essential, if* $\forall j \in I, . \quad n \in I\!N, \quad p_{j,i}^{(n)} > 0 \quad \exists m > 0 : p_{i,j}^{(n)} > 0.$
(e) *A Markov chain is called irreducible, if the transition Matrix is irreducible.*

Remark 3.23:
(a) If a state is recurrent, the expected number of returns to this state are infinite. If the expected number of returns is finite, the point is transient (eventually the particle leaves this state and will never return).
(b) If the Markov chain is finite and irreducible, then all states are recurrent.
(c) If there is an absorbing sate, then the Markov chain is not recurrent.
(d) The essential states are a generalization of absorbing states. They form a trap, and a states once in this trap can never leave this trap.
(e) If the Markov chain is irreducible, and one state is periodic of period s, then all states are periodic with this period.
Proof: (of **(e)**) Let state j be periodic. Consider state k. Since the Markov chain is irreducible, there are m and r, s.t.

$$p_{j,k}^{(m)} > 0, \qquad p_{j,k}^{(r)} > 0.$$

Since $0 < p_{j,k}^{(m)} p_{k,j}^{(r)} \leq p_{j,j}^{(m+r)}$, s divides $m + r$. Furthermore,

$$p_{k,k}^{(m+r+i\,s)} \geq p_{k,j}^{(r)} p_{j,j}^{i\,s)} p_{j,k}^{(m)} > 0$$

and s divides $m + r + i\,s$ for $i \in \mathbb{N}$. Hence, the period of k is smaller or equal s, the period of j. By symmetry, we find immediately that also the period of j must be smaller than the period of k. Hence, the period of j and k are equal.

□

Theorem 3.24: *For a finite Markov chain, there is a non-negative, stationary distribution* $\hat{\pi}$ *(also called invariant random measure),*

$$\hat{\pi} = A\hat{\pi}.$$

Proof: (Exercise 3.10).

Remark 3.25: For a reducible Markov chain, there may be more than one invariant measure. Furthermore, if the Markov chain is not finite, there may be no invariant measure (consider $A\mathbf{e}_i = \mathbf{e}_{i+1}$).

Theorem 3.26: *For a finite, irreducible Markov chain, there is a unique non-negative, stationary distribution* $\hat{\pi}$*. Furthermore,* $A^n \pi_0 \to \hat{\pi}$ *for* $\to \infty$*.*
Proof: This is a direct conclusion of the Theorem of Perron.

□

Total number of infecteds	Number of families (empirical)	Number of families (predicted)
1	$F_1 = 112$	112
2	$F_2 = 35$	32.3
3	$F_3 = 17$	18.5
4	$F_4 = 11$	12.0
5	$F_5 = 6$	6.2

Table 2: Data for the final size distribution (taken from [7]). F_i denotes the number of families with i infecteds at the end of the epidemic. The third column shows the predicted values by a model.

3.3.3 A model for common cold in households

In this section we develop technics for dealing with a non-linear birth-death process. We already know *linear* birth-death processes, where each individual acts independent of each other. For many systems in biology, this hypothesis is not completely appropriate: a growing population eventually reaches the limits of the carrying capacity of the ecosystem (individuals start to compete for resources), an infection cannot grow exponentially (eventually all susceptibles are infected). If the correlations between individuals are strong then a linear model is no longer appropriate and the dependence between the individuals must be taken into account.

As an example we consider the common cold in households (see [4, 7]). Consider a family of N persons with $N = 5$, say. Assume that one member catches the cold somewhere. At least in principle, the disease will spread. In [30] data have been collected from 181 families (see Tab. 2): All infected family members have been counted. Our aim is to describe/predict this distribution. Since our "population" is quite small, a linear birth-death process ("birth" means infection and "death" means recovery) won't do it. We have to look into the mechanisms of the spread more in detail.

State of a household: At each point of time, we find a certain number of susceptibles, infecteds and recovereds (this model is a close relative of the model for the virus dynamics we considered in section 2.4.3; we will come back to this point later in the part about nonlinear models). We may characterize the state by (i, r), where i and r denote the number of infectives and recovereds respectively (see Fig.39). The number of susceptibles is $N - i - r$.

Dynamics: Next we specify the rates, at which the system changes the state. Like in the classical SIR-model, we assume that the recovery rate is a constant α. At a transition from state (i, r) to state $(i - 1, r + 1)$, one of i infected persons recovers. Hence, the rate is $i\alpha$. The rate to get infected for one susceptible individual will be proportional to the number of infecteds. Accordingly, the rate for the transition from (i, r) to $(i + 1, r)$ reads $\beta\, i(N - i - r)$.

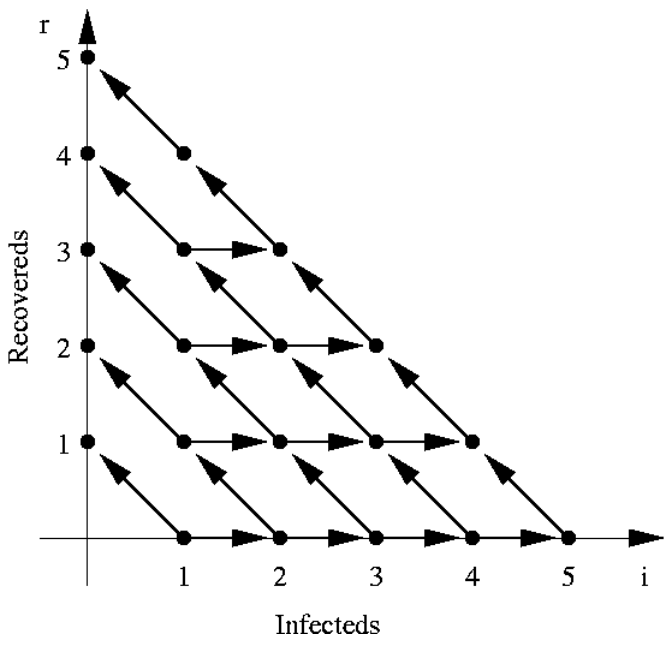


Figure 39: Possible states and transitions for a family of size $N = 5$. We start with one infected person, i.e. in state $(1, 0)$.

Model equations: Let $p_{i,r}(t)$ be the probability to find the system in state (i, r) at time t. We are able to obtain a Master equation for $p_{i,r}(t)$ (if an index exceeds N or is below 0, formally the corresponding probability has to be taken to zero):

$$\begin{aligned} \tfrac{d}{dt}p_{i,r}(t) &= -(i\,\alpha + \beta\, i(N-i-r))p_{i,r}(t) \\ &\quad +(i+1)\alpha p_{i+1,r-1}(t) + (i-1)(N-i-r)\beta p_{i-1,r}(t) \end{aligned} \tag{1}$$

with $i = 0, \cdots, N$ and $r = 0, \cdots, N-i$. We start with one infected and $N-1$ susceptible persons, i.e.

$$p_{1,0}(0) = 1, \qquad p_{i,r}(0) = 0 \quad \text{for} \quad (i,r) \neq (1,0).$$

Embedded time-discrete Markov process and final size distribution
The data in Tab.2 show the total number of infected during the epidemic which we call *final size of the epidemic*. A good test of our model is to reproduce these data. We need the probabilities that the system is at state (i, r) under the condition that the epidemic has come to an end, i.e. $\lim_{t\to\infty} p_{i,r}(t)$. If the time tends to infinity, no infecteds are present any more and the total mass of the probability $p_{i,r}$ is contained in the states $(0, r)$, $r = 1, .., 5$ (this means $p_{i,r} = 0$ if $i \neq 0$). One way to obtain the distribution for $t \to \infty$ is to implement the system of ordinary differential equations (1) and to solve it numerically for a long, long time interval. At the end of this interval we can check that almost all mass is concentrated in states with $i = 0$.

Faster, and more elegant, is not to use the differential equations directly. Instead of using time, we count the *events*. One event is either "infection" or "recovery" of an individual.

An event is a transition form one state (i, r) to a different state (i', r'). We can use the number of events as a new "time"-variable. Then we obtain a time-discrete dynamical system. This system is called the *embedded time-discrete Markov process* or the *embedded Markov chain*. After a finite number of iterations we will end up with a probability distribution that has no mass at all in states with infected individuals (why?).

In order to develop this *embedded time-discrete Markov* model, we need the transition probabilities from one state (i, r) into another (i', r') (this time really probabilities, not rates!). Assume that we are in state (i, r), which event will take place first? Recovery or infection?

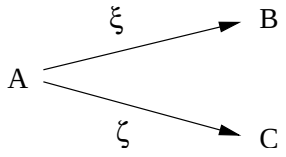


Figure 40: We go from state A to state B with rate ξ, and to state C with rate ζ. In which state we will end up?

We formulate this problem in a slightly more abstract way (see Fig. 40): Assume we are in state A, going to state B with rate ξ and to state C with rate ζ. What is the probability $P(A \to B)$ to end up in state B and not into state C? Let $p_A(t)$, $p_B(t)$ and $p_C(t)$ be the probability for state A, B, and C at time t. Then,

$$\frac{d}{dt}p_A(t) = -(\xi+\zeta)p_A(t), \qquad \frac{d}{dt}p_B(t) = \xi\, p_A(t), \qquad \frac{d}{dt}p_C(t) = \zeta\, p_C(t),$$
$$p_A(0) = 1, \quad p_A(0) = 0, \quad p_A(0) = 0.$$

The solutions of these linear equations are simple enough to find:

$$p_A(t) = e^{-(\xi+\zeta)t}, \quad p_B(t) = \frac{\xi}{\xi+\zeta}\left(1 - e^{-(\xi+\zeta)t}\right), \quad p_C(t) = \frac{\zeta}{\xi+\zeta}\left(1 - e^{-(\xi+\zeta)t}\right).$$

Hence,

$$\lim_{t\to\infty} p_B(t) = P(A \to B) = \frac{\xi}{\xi+\zeta}, \qquad \lim_{t\to\infty} p_C(t) = P(A \to C) = \frac{\zeta}{\xi+\zeta}.$$

The transition probability from one state to another is the rate of this transition to occur divided by the sum of all rates of all possible transitions leaving the first state.
With this rule in mind we come back to our problem and define a discrete Markov chain: Let $P_{(i,r),(i',r')} = P((i, r) \to (i', r'))$ be the transition probability from state (i, r) to state (i', r'). Like in our example with states A, B and C, also here we have two possibilities to leave a state: recovery and infection. Let $R_0 = \beta/\alpha$. Then,

$$\begin{aligned} P_{(i,r),(i+1,r)} &= \frac{\beta\, i(N-i-r)}{\beta\, i(N-i-r) + i\alpha} = \frac{(\beta/\alpha)\, i(N-i-r)}{(\beta/\alpha)\, i(N-i-r) + i} \\ &= \frac{R_0\,(N-i-r)}{R_0\,(N-i-r)+1} \end{aligned} \tag{2}$$

for $i = 1, ..., N$ and $r = 0, ..., N - i - 1$.

$$\begin{aligned} P_{(i,r),(i-1,r+1)} &= \frac{\alpha\, i}{\beta\, i(N-i-r) + i\alpha} = \frac{i}{(\beta/\alpha)\, i(N-i-r) + i} \\ &= \frac{1}{R_0\,(N-i-r)+1} \end{aligned} \tag{3}$$

for $i = 1, ..., N$ and $r = 0, ..., N - i$. If we are in one of the states $(0, r)$ then we will not leave them. These states are the *absorbing states*. Hence,

$$P_{(0,r),(0,r)} = 1 \qquad\qquad \text{for } r = 0..N$$

and $P_{(i,r),(i',r')} = 0$ for all index combinations not mentioned so far. There is only one parameter R_0 in these equations, though our original model includes two parameters (α and β). The reduction of the number of parameters is possible since we disclaim the time course of the disease. The finial size is all the information we need.
Finally we use the transition probabilities $P_{(i,r),(i',r')}$ to find the probabilities $q_{i,r}(n)$ to be in state (i, r) after n events:

$$q_{i,r}(n) = \sum_{(k,l)} P_{(k,l),(i,r)} q_{k,l}(n-1), \tag{4}$$

for $i, r = 1, ..., N$. In (4) we sum over all possible states (k, l). The system of equations (4) forms a discrete model for our household.

From nonlinear to linear models
It is possible to embed nonlinear models in linear models. We already did this in the last paragraph, without mentioning it explicitely. This fact is closely related to the two different interpretation of a Markov chain (see remark 3.21).

We may either assume as state space the set $\Delta = \{(i, r) \,|\, 0 \le i, r, \quad i + r \le N\}$. In this case, we look at a single realization of the Markov process, and follow the fate of one family. The transition probabilities depend in a nonlinear way on the state of the system, i.e. we do have a nonlinear model (a model describing interacting individuals).
We may change our point of view, and consider an ensemble of families that undergo an attack of common cold. The state space becomes the set of probability distributions over Δ,

$$\mathbf{P} : \Delta \to \mathbb{R}_+.$$

The dynamics is an iteration by the linear operator $P_{(.,.),(.,.)}$, i.e.

$$\mathbf{P}_{n+1}(i, r) = \sum_{(i',r') \in \Delta} P_{(i,r),(i',r')} \mathbf{P}_m(i', r')$$

Though, of course, we still have a model about interacting particles, the nonlinear vanishes, if we blow up the state space and consider functions over Δ instead of Δ itself.

This principle can be also applied e.g. to ordinary differential equations. Consider

$$\dot{x} = f(x) \qquad x \in \mathbb{R}^n.$$

This (nonlinear) differential equation exhibits solutions $x(t; x_0)$, where $x(0; x_0) = x_0$. In order to derive a linear model, we consider functions over $\mathbb{R}^n$ instead of $\mathbb{R}^n$ itself. The idea is to interprete a time-dependent function $u(t, x)$ over $\mathbb{R}^n$ as the description of the transport of mass along solutions of the ordinary differential equations $\dot{x} = f(x)$. Thus, $u(t, x)$ is constant along trajectories, i.e. $u(t, x(t; x_0)) =$ constant. Taking the derivative with respect to t yields

$$u_t + (\nabla u)^T \dot{x}(t, x_0) = 0 \qquad \Rightarrow \qquad u_t = -f(x)^T \nabla u.$$

This is a linear equation in u. The trajectories can be derived from u as level sets,

$$x(.; x_0) = \{x \,|\, \exists t \geq 0 : u(t, x) = u(0, x_0)\}$$

(if $u(0, .)$ assumes the value $u(0, x_0)$ only for $x = x_0$). This is the characteristics-method for the solution of partial differential equations of first order in backward-direction (going from characteristics to the partial differential equation).

Application to data

We now apply our theory to data that are given in Tab. 2. We have to come up with an estimate for R_0. One possibility would be to do a least-square fit: vary R_0 until the error between data and theoretical prediction is minimal. Using statistical tools, one may refine this approach, taking an appropriate variance structure into account. However, we use a shortcut: Let us consider the probability to find exactly one infected person during the epidemic within our family. Since there is exactly one path from state $(1, 0)$ to state $(0, 1)$, the probability for this absorbing state is already given after one iteration, i.e. by the element $P_{(1,0),(0,1)}$. Since $P_{(1,0),(0,1)} = 1/(R_0\,(n-1)+1)$, we find

$$R_0 = \frac{1}{(n-1)} \left(\frac{1}{\text{Prob. for one infected}} - 1 \right).$$

Furthermore, we have a simple estimate for the probability to find exactly one infected person during the epidemic: let F_i be the number of families with i infected persons, then this probability is approximately F_1/F with $F = \sum_{i=1}^{n} F_i$. Hence, R_0 may be estimated by $\hat{R}_0$,

$$\hat{R}_0 := \frac{1}{(n-1)} \left(\frac{F}{F_1} - 1 \right).$$

For our data we obtain $\hat{R}_0 = 0.154$, the numerical value we used in our program in order to calculate the final size distribution.

We find that data and theoretical prediction agree surprisingly well (see Fig. 41 and Tab. 2). In order to judge the agreement in more detail one has to use statistical methods (see e.g. [1, 7]), and this is out of our present scope.

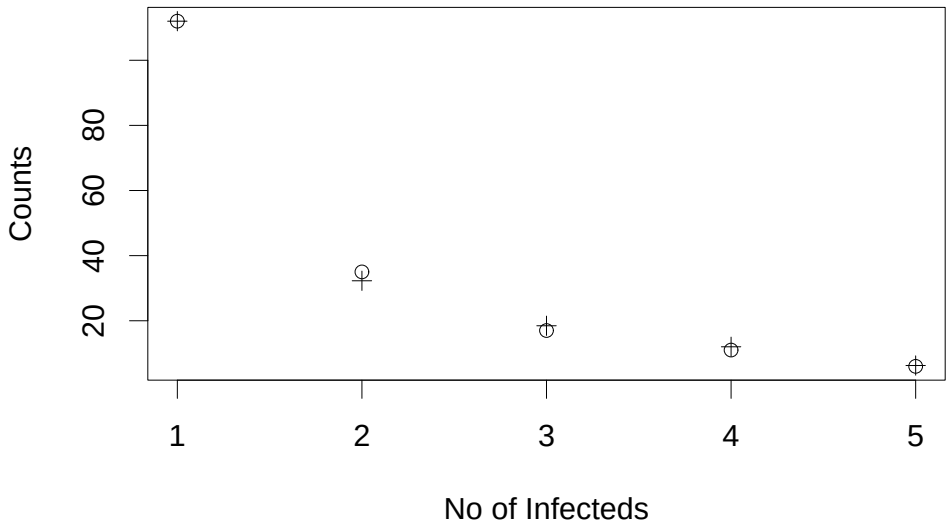


Figure 41: Comparison of data (opern circle) and model (cross).

Project: Paths of an epidemic
In section 3.3.3 we have considered a model for the final size of an epidemic of common cold in a household. The data collected by Haesman and Reid in [30] are even more detailed. Let the primary infected person of a family be "the first generation", the persons infected by him/her are called "the second generation" and so on (do not confuse these generations by the usual ones, i.e. grandmother, mother, child, etc.) We have data about the number of infected in each generation (to obtain the data, i.e. to decide who is in the first, second... generation is quite a difficult task, see [7, 30]). The data are shown in Tab. 3. Find a model describing these data, and fit the model parameter (somehow).

Summary/Conclusion
• *The central characteristics of a Markov chain is the Markov property: the transition probabilities for time step n do not depend on the history, but only on the state in time step n. These probabilities are assumed to be constant in time. This structure is compatible with the basic rule of modeling: first define the state space, then the dynamics within this state space. This fact is the deeper reason that almost all models do have the Markov property (provided that the state space is chosen in an appropriate way).*

• *The dynamics of Markov chains are strongly connected with the structure of the corresponding transition graph. Here we find ideas about connectivity/irreducibility, essential states and traps or periodicity and periodic cycles. If the Markov chain is finite, an*

1. Gen.	2. Gen.	3. Gen.	4. Gen.	5. Gen.	Number of families
1					413
1	1				131
1	1	1			36
1	2				24
1	1	1	1		14
1	1	2			8
1	2	1			11
1	3				3
1	1	1	1	1	4
1	1	1	2		2
1	1	2	1		2
1	1	3			2
1	2	1	1		3
1	2	2			1
1	3	1			0
1	4				0

Table 3: Data for the number of infecteds, structured by "generation" (taken from [7])

individual moves along the transition graph, and will end up in a subgraph that is connected (and forms a trap/consists of essential states). Especially, the Markov chain can be reduces to these subgraphs/sub-Markov-chains. Irreducibility superimposes another important structure (in addition to the Markov property).

- *Though the underlying system may describe interacting particles/nonlinear structures, the Markov chain itself is linear. The description level is not directly that of the states of the system, but the set of random measures over these states. This blowing-up of the state space allows to imbed a nonlinear process in a linear one.*

- *The Markov chain is a quite general framework to describe time-discrete stochastic processes. One may obtain very fast some general properties of a process (e.g. convergence to a unique probability measure in case a strictly positive Markov chain). However, since this framework is quite general, in some cases it hides the special structure of a process. In these cases, another level of description may be more appropriate.*

3.3.4 Exercise

Exercise 3.10:
(a) Show that a finite Markov chain (i.e. a chain with a finite number of states) has at least one essential state.
(b) Show that there is at least one invariant measure of the Markov chain.

Final infecteds	Number of families		
	overcrowded	crowded	uncrowded
1	112	155	156
2	35	41	55
3	17	24	19
4	11	15	10
5	6	6	2

Table 4: Data for the final size distribution, structured by degree of "crowededness" of the families. (taken from [7])

Exercise 3.11:
Heasmen and Reid [30] divide all households (with five members) into three classes: overcrowded, crowded and uncrowded. The data are given in the table 4.
(a) Estimate R_0 in all cases.
(b) Implement a computer program that yields the theoretical and empirical final size distribution.
(c) Is R_0 different for the three types of households? Can you explain the results?

Exercise 3.12:
In contrast to the Reed-Frost model, where the infection probability is increased by the number of infecteds, the Greenwood model assumes a constant infectivity, i.e. the incidence of infection is βs if $i > 0$ without direct dependency on i.
(a) Find estimators for the parameters (use the data of the table above).
(b) Implement a computer program that yields the theoretical and empirical final size distribution. Which model is better: The Greenwood or the Reed-Frost model?

Exercise 3.13:
Consider an infectious disease, where a recovered person is susceptible again. Formulate a model. How is the transition matrix changed, if you only consider realizations, where the disease does not die out?

4 Continuous Time

In this section, we investigate continuous time. We will define the time continuous analogue to Galton-Watson processes. We briefly have a look at linear systems of ordinary differential equation. However, the emphasize of this chapter will be time-continuous systems with continuous state space: age-structured and spatially structured models. While the approach how to model age structure is quite clear, the "best" model of spatial structure is still a matter for discussions. Thus, we will consider and discuss several attempts to model movement in space.

4.1 Small Population Size: The Birth-Death Process

Like in the Galton-Watson process, we investigate a small population, where we count the number of individuals (at a certain time).

State: The state of the population is given by by the number of individuals (at time t). Define

$$Z_t = \#\text{ of individuals at time } t.$$

Dynamics: Since we still investigate independent acting entities, the dynamics is defined by the behavior of only one individual. The birth rate for one individual is β (meaning that the time between two births is exponentially distributed with rate β), and the death rate is μ (the life span is exponentially distributed with rate μ).

Master equation and Generating Function

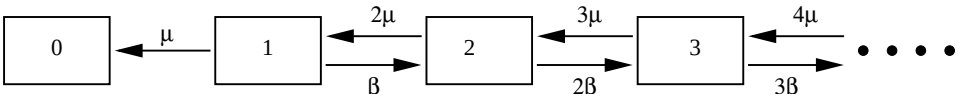


Figure 42: Structure of the master equations.

Define the probability to find the population at time t in state i,

$$p_i(t) = P(Z_t = i).$$

The master equation is the differential equation that describes the time evolution of the $p_i(t)$. We derive these master equations as a translation of the compartmental model in Fig. 42 into a system of differential equations,

$$\begin{aligned} \frac{d}{dt}p_0 &= \mu p_1 \\ \frac{d}{dt}p_i &= -i(\beta+\mu)p_i + (i-1)\beta p_{i-1} + (i+1)\mu p_{i+1}, \qquad i \geq 1. \end{aligned}$$

These equations are not straight-forward to solve. A standard trick is to introduce generating functions (similar to those used in the analysis of the Galton-Watson-Process).

$$f : [0,1] \times \mathbb{R}_+ \to \mathbb{R}_+, \quad (s,t) \mapsto f(s,t) = \sum_{i=0}^{\infty} s^i p_i(t).$$

It is possible to derive a closed partial differential equation for $f(s,t)$. If we re able to solve this PDE, then we know $p_i(t)$ (at least implicitly), since they are coded in $f(.,t)$ via

$$p_i(t) = \frac{1}{i!}\frac{d^i}{ds^i} f(s,t)|_{s=0}.$$

Proposition 4.1: *The generating function for the birth-death process with death rate μ and birth rate β is given by*

$$f(s,t) = \frac{\mu(s-1) - (\beta s - \mu)e^{(\beta-\mu)t}}{\beta(s-1) - (\beta s - \mu)e^{(\beta-\mu)t}}.$$

Proof: We find for the time derivative of f

$$\begin{aligned}
\frac{\partial}{\partial t} f(s,t) &= \sum_{i=0}^{\infty} s^i \dot{p}_i(t) \\
&= \mu p_1 + \sum_{i=1}^{\infty} s^i \left[-i(\beta+\mu)p_i + (i-1)\beta p_{i-1} + (i+1)\mu p_{i+1}\right] \\
&= \mu s^0 p_1 - (\beta+\mu)\sum_{i=1}^{\infty} i s^i p_i + \beta \sum_{i=1}^{\infty}(i-1)s^i p_{i-1} + \mu \sum_{i=1}^{\infty}(i+1)s^i p_{i+1} \\
&= -(\beta+\mu)\sum_{i=1}^{\infty} i s^i p_i + \beta \sum_{i=0}^{\infty} i s^{i+1} p_i + \mu \sum_{i=1}^{\infty} i s^{i-1} p_i \\
&= -(\beta+\mu)s\frac{\partial}{\partial s}\sum_{i=1}^{\infty} s^i p_i + \beta s^2 \frac{\partial}{\partial s}\sum_{i=0}^{\infty} i s^i p_i + \mu \frac{\partial}{\partial s}\sum_{i=1}^{\infty} i s^{i-1} p_i \\
&= (\beta x^2 - (\beta+\mu)x + \mu)\frac{\partial}{\partial s} f(s,t) \\
&= (s-1)(\beta s - \mu)\frac{\partial}{\partial s} f(s,t).
\end{aligned}$$

Let us assume that we start with one individual, i.e. $p_1(0) = 1$ and $p_i(0) = 0$ for $i \neq 1$. In this case, we find the initial value problem

$$\begin{aligned}
\frac{\partial}{\partial t} f(s,t) &= (s-1)(\beta s - \mu)\frac{\partial}{\partial s} f(s,t) \\
f(s,t) &= s.
\end{aligned}$$

The solution of this problem can be approached by the method of characteristic curves. We look for curves $X(s,t)$, s.t. $X(s,0) = s$ and $f(s,t)$ does not change along these curves

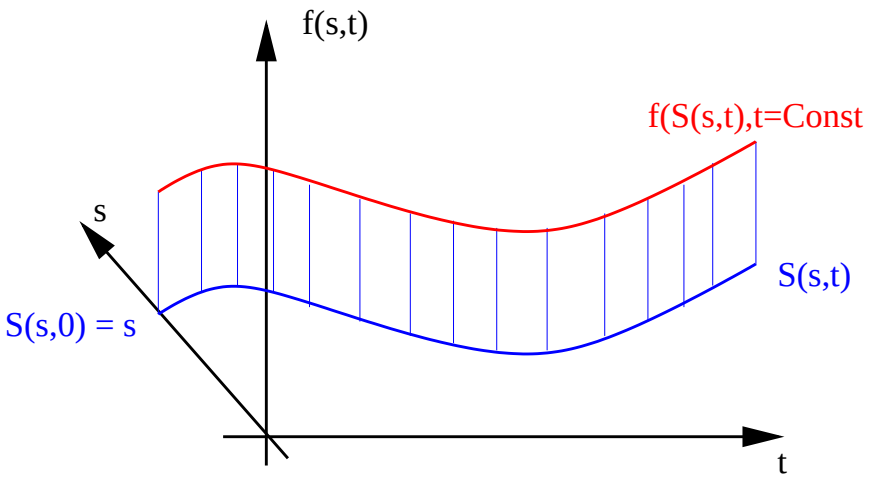


Figure 43: Method of characteristic lines.

(see Fig. 43; we discussed that method already when we considered a method to embed a nonlinear ODE into a linear PDE),

$$f(S(s,t),t) = \text{constant} \qquad \Rightarrow \qquad f_t(S(s,t),t) + S_t(s,t)\, f_s = 0.$$

Comparison with the PDE yields immediately that

$$\dot{S}(s,t) = -(S-1)(\beta S - \mu), \qquad S(s,0) = s,$$

where dot does mean derivation with respect to t. This ODE can be explicitely solved, using the method of separation of variables,

$$\begin{aligned}
-t = -\int_0^t d\tau &= \int_s^{S(s,t)} \frac{ds'}{(s'-1)(\beta s' - \mu)} \\
&= \int_s^{S(s,t)} \frac{(\beta-\mu)^{-1}}{s'-1}\, ds' - \int_s^{S(s,t)} \frac{(\beta(\beta-\mu)^{-1}}{\beta s' - \mu}\, ds' \\
&= \frac{1}{\beta-\mu}\, \log\left(\frac{S(s,t)-1}{s-1}\right) - \frac{1}{\beta-\mu}\, \log\left(\frac{\beta S(s,t) - \mu}{\beta s - \mu}\right) \\
&= \frac{1}{\beta-\mu}\, \log\left(\frac{S(s,t)-1}{\beta S(s,t) - \mu}\, \frac{\beta s - \mu}{s-1}\right)
\end{aligned}$$

Hence we find

$$\begin{aligned}
e^{-(\beta-\mu)t} &= \frac{S(s,t)-1}{\beta S(s,t) - \mu}\, \frac{\beta s - \mu}{s-1} \\
\Rightarrow \qquad (S(s,t)-1) &= \frac{s-1}{\beta s - \mu}\, e^{-(\beta-\mu)t}\, (\beta S(s,t) - \mu) \\
\Rightarrow \qquad S(s,t)\left(1 - \beta \frac{s-1}{\beta s - \mu} e^{-(\beta-\mu)t}\right) &= 1 - \mu \frac{s-1}{\beta s - \mu} e^{-(\beta-\mu)t}
\end{aligned}$$

$$\Rightarrow \qquad S(s,t) = \frac{(\beta s-\mu)-\mu(s-1)e^{-(\beta-\mu)t}}{(\beta s-\mu)-\beta(s-1)e^{-(\beta-\mu)t}}$$

From $S(s,t)$ we are able to derive the value of $f(S(s,t),t)$ by

$$f(S(s,t),t) = f(S(s,0),0) = f(s,0) = s = S^{-1}(s,t).$$

We solve the equation for $S(s,t)$ for s and obtain

$$f(S,t) = f(S(s,t),t) = s = \frac{\mu(S-1)-(\beta S-\mu)e^{-(\beta-\mu)t}}{\beta(S-1)-(\beta S-\mu)e^{-(\beta-\mu)t}}$$

or (renaming S by s),

$$f(s,t) = \frac{\mu(s-1)-(\beta s-\mu)e^{-(\beta-\mu)t}}{\beta(s-1)-(\beta s-\mu)e^{-(\beta-\mu)t}}.$$

□

Probability of extinction

The possibility for a population to die out is one of the most important differences between stochastic and deterministic model. Like in the Galton-Watson process, also now, we are interested in the probability of extinction.

Proposition 4.2: *The probability for extinction reads*

$$q = \begin{cases} \mu/\beta & \text{if} \quad \beta > \mu \\ 1 & \text{if} \quad \beta < \mu \end{cases}.$$

Proof: We find

$$q = \lim_{t\to\infty} P(Z_t = 0) = \lim_{t\to\infty} f(0,t) = \lim_{t\to\infty} \frac{-\mu+\mu e^{-(\beta-\mu)t}}{-\beta+\mu e^{-(\beta-\mu)t}}.$$

The assertion is an immediate consequence of this formula.

□

We did some similar computations in the context of the Galton-Watson process before. This fact raises the question, if there is a relationship between the birth-death process and the Galton-Watson process. Here, we focus on time while the Galton-Watson process focus on generations. We now derive for the time-continuous birth-death process the embedded Galton-Watson process (see Fig. 44). We use generations instead of time.

In order to find the corresponding Galton-Watson process, we determine the number of children that one individual produces during his/her live span.

Proposition 4.3: *Let X be the number of children of one individual. Then, X is geometrically distributed, $X \sim Geom(\mu/(\beta+\mu))$, i.e.*

$$P(i \text{ children}) = \left(\frac{\beta}{\mu+\beta}\right)^i \left(\frac{\mu}{\mu+\beta}\right).$$

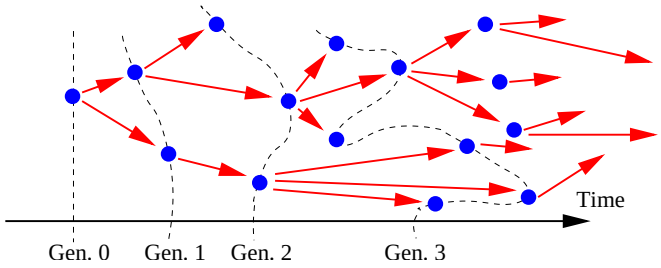


Figure 44: Connection between the birth-death and the Galton-Watson process.

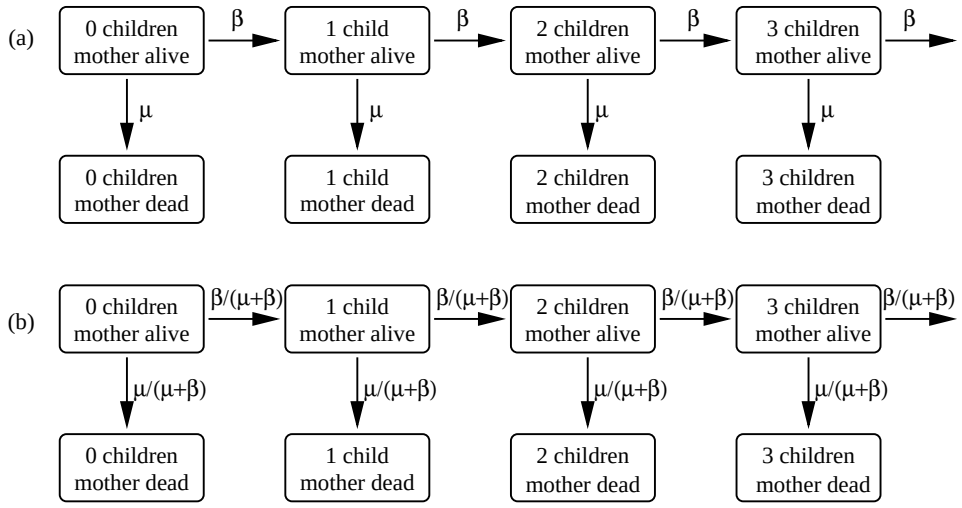


Figure 45: Number of children (in the time-continuous (a) and the discrete version (b)).

Proof: Consider an individual born at time $t = 0$ and

$$q_i(t) = P(i \text{ children at time} t, \text{ mother alive}) \qquad r_i(t) = P(i \text{ children at time} t, \text{ mother dead}).$$

We are able to derive the master equations (see Fig. 45). We now could define a generating function and solve this problem with the same approach like that of Proposition 4.1. However, we are not really interested in the timing but only in the final numbers of children. Thus, instead of time we may use transition probabilities. Here, we find the embedded discrete process for the number of children. From each state where the mother is alive, there are two transitions possible (either to die or to get another child), we obtain directly the transition probabilities

$$\begin{aligned} P(i \text{ children, mother alive} \to i+1 \text{ children, mother alive}) &= \frac{\beta}{\beta+\mu}, \\ P(i \text{ children, mother alive} \to i \text{ children, mother dead}) &= \frac{\mu}{\beta+\mu}. \end{aligned}$$

If we denote with $q_{i,n}$ ($p_{i,n}$) the probability to be after step n in the state with i children

and mother alive (respectively dead), then we find for $i > 0$

$$q_{i,n} = \frac{\beta}{\beta+\mu}\, q_{i-1,n-1}, \qquad p_{i,n} = \frac{\beta}{\beta+\mu}\, q_{i,n-1}$$

and $q_{0,n} = 1$ for $n = 0$ and zero else. From that, we find immediately the assertion. □

Remark 4.4: The probability for extinction of a branching process with death rate μ and birth rate σ coincides with that of a Galton-Watson process, where the number of children of one individual is given by $X \sim \text{Geom}(\mu/(\beta+\mu))$. From exercise 3.1 we already know, that the probability for extinction in the case of geometrically distributed offspring with parameter r reads

$$q = \begin{cases} (1-r)/r & \text{if} \quad r > 1 \\ 1 & \text{else} \end{cases}$$

Using $r = \mu/(/\beta+\mu)$ we find directly $q = \beta/\mu$ if $r > 1 \Leftrightarrow \beta > \mu$.

Remark 4.5: The Galton-Watson process is insofar more general, as that it is often possible to derive the distribution of children also for age-dependent death rates. However, going form the birth-death process to the Galton-Watson process we through away information which may be often interesting.

4.2 Linear Deterministic Dynamics

We already discussed the connection between positive solutions and the corresponding r.h.s. of differential equations in Section 2.3.
At this point, we only briefly mention that one may split a real, linear dynamical system with simple eigenvalues into at most two-dimensional invariant subsystems (in the spirit of the generic case in section 3.2.2). One may classify the behavior into different types (according to the eigenvalues)

(I) stable node

(II) unstable node

(III) stable spiral

(IV) unstable spiral

(V) saddle.

It is easily possible to find the corresponding behavior according to the eigenvalues (see Fig. 46). E.g., a saddle has two eigenvalues with different sign, or a stable spiral imaginary eigenvalues with negative real part. Fig. 46 figure parallels Fig. 31. You may find more in [2].

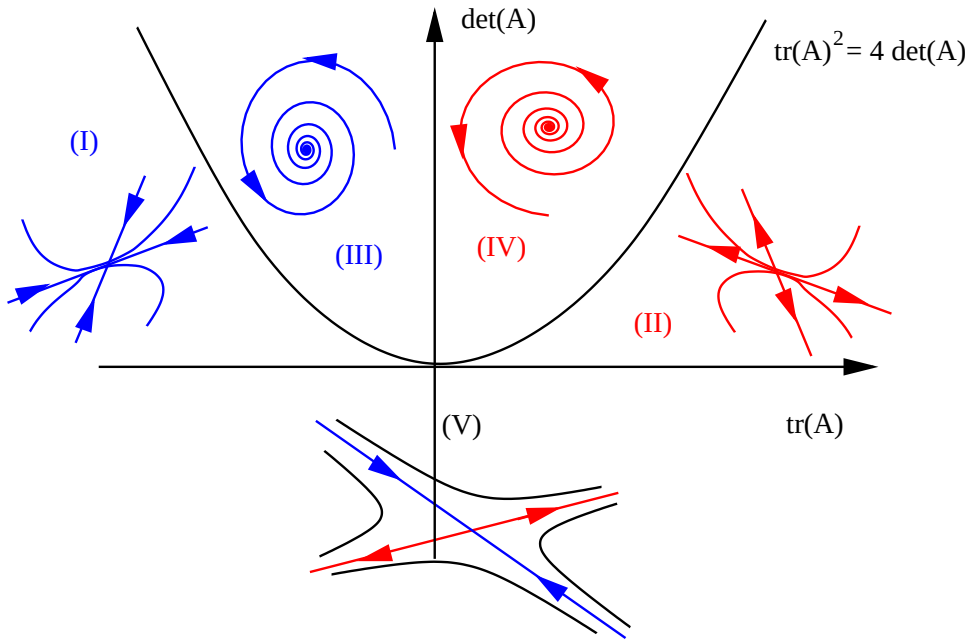


Figure 46: Dynamics for linear, planar systems.

4.3 Age Structure

In this section, we consider age structure and in the next section spatial structure. With respect to the finite-dimensional state space we considered until now, the infinite dimensional state space adds a new quality. Especially concerning the spectrum and argumentation about asymptotic behavior by investigation of the spectrum of linear operators are not this straight forward any more. Mostly one may derive results about the point spectrum. However, other parts of the spectrum, e.g. the essential spectrum, are not this simple to control and - in principle - may lead to incorrect conclusions if only the point spectrum is considered.

Luckily, in our cases the point spectrum determines the behavior of the system, indeed; other parts of the spectrum are either empty or bounded away from the region in $\mathbb{C}$ that governs the dynamics. Since in this lecture we aim on modeling methods rather than on the analysis of models, we will only use the (relatively simple) point spectrum. One has to be aware that these arguments are thus only heuristic. Often enough, we even do not specify the space that our operators are acting on (terrible! and this in a math's lecture!).

The Model

Since becoming older is a purely deterministic effect, a stochastic model does not add too much. Thus, we consider here only a deterministic model (the stochastic version can be easily formulated using the ideas of the previous sections). We start off by the ideas / the structure developed for the Leslie model (section 3.2.3). Then, we use the continuum

limit in order to find the appropriate time-continuous model.

(Discrete) State: x_i^n is the number of persons at time t_n and age class a_i, where

$$a_i = h\,i, \qquad t_n = h\,n$$

and h denotes the discretization size.

(Discrete) Dynamics:

$$\begin{aligned} x_0^{n+1} &= \sum_i b_i x_i^n \\ x_i^{n+1} &= p_i x_{i-1}^n \qquad \text{for } i > 0 \end{aligned}$$

Here, b_i denotes the expected number of births in the age interval $(i\,h, (i+1)h]$. Thus, the coefficients b_i depend on h. It is reasonable to assume that b_i are derived from a rate

$$b_i = b_i(h) = \beta(i\,h)\,h + \mathcal{O}(h^2), \qquad \beta(a) \in C_+^0.$$

C_+^0 denotes the set of continuous non-negative functions. A reasonable further assumption on $\beta(a)$ is that $\beta(a)$ is not identically zero but vanishes for $a > \overline{a}$, i.e. there is a maximal fertile age $\overline{a}$.
Similarly, also the survival probabilities p_i are assumed to be related to a continuous death rate via

$$p_i = 1 - \mu(i\,h)h + \mathcal{O}(h^2), \qquad \mu(a) \in C_+^0.$$

In this case, we want to assume not only that the death rate is non-negative, but also that it is equally bounded away form zero,

$$\mu(a) \geq \overline{\mu} > 0.$$

Now we consider these equations, if h tends to zero. We *assume* that x_i^n approximate a smooth function

$$x_i^n = u(ih, nh) + \mathcal{O}(h).$$

If this is the case, we find

$$u(0,t) = \sum b_i(x_i^n + \mathcal{O}(h)) = \sum h(\beta(ih)\,u(ih,t) + \mathcal{O}(h)) \overset{h\to 0}{\to} \int_0^\infty \beta(a)\,u(a,t)\,da.$$

Furthermore,

$$\begin{aligned} u(a+h,t+h) &= (1 - h\mu(a) + \mathcal{O}(h^2))u(a,t) \\ \Rightarrow \qquad \frac{u(a+h,t+h) - u(a+h,t) + u(a+h,t) - u(t,a)}{h} &= (\mu(a) + \mathcal{O}(h))u(a,t) \\ &\downarrow \quad h \to 0 \\ \frac{\partial}{\partial t}u(a,t) + \frac{\partial}{\partial a}u(a,t) &= -\mu(a)u(a,t). \end{aligned}$$

The age-structured model:
All in all, we derived at the model

$$\begin{aligned} \frac{\partial}{\partial t}u(a,t) + \frac{\partial}{\partial a}u(a,t) &= -\mu(a)u(a,t) \\ u(0,t) &= \int_0^\infty \beta(a)u(a,t)\,da \\ u(a,0) &= u_0(a) \end{aligned}$$

where $u(a,t)$ denotes the population density at time t, $u_0(a)$ is the initial condition, and $\mu(a)$ ($\beta(a)$) the death (birth) rate. We assume

$$\begin{aligned} &(H1) \qquad \mu \in C^0_+, \quad \mu(a) > \overline{\mu} > 0 \\ &(H2) \qquad \beta \in C^0_+, \quad \beta(a) = 0 \text{ for } a > \overline{a}, \quad b(.) \not\equiv 0. \end{aligned}$$

Analysis
Like in the discrete models with a finite number of states, also in this case we expect asymptotically exponential growth. Like discussed before, one has to be more carefully in models with a continuous state space. It is not clear at all, that the point spectrum governs the system. However, if we consider the solution in C^n, The assumptions (H1) and (H2) imply that (1) the essential spectrum is part of $\{z \in \mathbb{C} \| \, \Re(z) < -\overline{\mu}\}$, i.e. does not play a role for stability / instability of the trivial solution. Furthermore, (2), we find that the semigroup (the solution operator) eventually becomes compact (the reason is, that $u(0,t)$ is given by an integration. Hence, we gain smoothness. Since furthermore $b(a)$ has compact support, after a time interval $\overline{a}$, we gained one degree of differentiability. Since smooth function spaces are embedded in non-smooth spaces in a compact way, the semigroup eventually becomes compact). Again, this tells us that essentially only the point spectrum plays a role in the dynamics (find the proofs for these two statements in [60]).

Proposition 4.6: *Consider the operator* $L : D(L) \subset C^1 \to C^0$,

$$Lu = -\partial_a u(a) - \mu(a)u(a)$$

with $D(L) = C^1_{bd}$,

$$C^1_{bd} = \{\phi \in C^1 \,|\, \phi(0) = \int_0^\infty b(a)\,\phi(a)\,da\}.$$

The age-structured model can be written as $u_t = Lu$. *The point spectrum of* L *is*

$$\sigma_p(L) = \{\lambda \in \mathbb{C} | \, g(\lambda) = 1\}$$

where

$$g(\lambda) = \int_0^\infty b(a)\, e^{-\int_0^a \mu(\tau) + \lambda\, d\tau}\, da$$

and the corresponding eigenfunctions read

$$v_\lambda(a) = e^{-\int_0^a \mu(\tau) + \lambda\, d\tau}$$

Proof: We us use the ansatz

$$Lv_\lambda = \lambda\, v_\lambda(a).$$

Then,

$$\begin{aligned} \dot{v}_\lambda(a) &= -(\mu(a)+\lambda)v_\lambda(a) \\ v_\lambda(0) &= \int_0^\infty b(a)\, v_\lambda(a)\, da \end{aligned}$$

Hence $v_\lambda(a) = e^{-\int_0^a \mu(\tau)\, d\tau - \lambda a}$ and

$$v_\lambda(0) = \int_0^\infty b(a)\, v_\lambda(0)\, e^{-\int_0^a \mu(\tau)+\lambda\, d\tau}\, da.$$

Since $v(a)$ is an eigenfunction, $v_\lambda(a) \not\equiv 0$ and thus $v_\lambda(0) \neq 0$. Hence, we find an eigenfunction for λ if and only if $g(\lambda) = 1$.

□

Remark 4.7: **(1)** Since $g(\lambda)$ is strictly decreasing, then there is a unique real solution$\hat{\lambda}$ of

$$g(\lambda) = 1.$$

(2) Let $\lambda \in \mathbb{C}$, $g(\lambda) = 1$, then we find $\Re(\lambda) < \hat{\lambda}$. In order to show this inequality, consider $\lambda \in \mathbb{C}$, $\Im(\lambda) \neq 0$ and

$$\begin{aligned} 1 &= g(\lambda) = |g(\lambda)| \\ &= \left| \int_0^\infty b(a)\, e^{-\int_0^a \mu(\tau)+\lambda\, d\tau}\, da \right| \\ &\leq \int_0^\infty b(a) \left| e^{-\int_0^a \mu(\tau)+\lambda\, d\tau} \right| da \\ &< \int_0^\infty b(a)\, e^{-\int_0^a \mu(\tau)+\Re(\lambda)\, d\tau}\, da \\ &= g(\Re(\lambda)). \end{aligned}$$

Since $g(.)$ is strictly decreasing, we find that $\hat{\lambda} > \Re(\lambda)$.

Proposition 4.8: *Let $u(a,0) > 0$ and define*

$$R_0 = g(1).$$

Under the assumptions above (H1, H2), we find: If $R_0 > 1$, then $\|u(a,t)\| \to \infty$. If $R_0 < 1$, then $\|u(a,t)\| \to 0$.

Idea of the proof: (we will not strictly prove this proposition, since we only consider point spectrum). From our last remark, we find that

$$\sigma(L) \subset \{z \in C \,|\, \Re(z) \leq \hat{\lambda}\}$$

We know that $g(\hat{\lambda}) = 1$. Thus, if $R_0 = g(0) < 1$, then $\hat{\lambda} < 0$ and the (point) spectrum of L is contained in the left half plane of C. All solutions will die out. Otherwise, if $g(0) > 1$,

then $\hat{\lambda} > 1$. Since the initial condition is strictly positive, the solution will finally tend to infinity.

□

Remark 4.9: It is possible to interprete R_0.

$$R_0 = \int_0^\infty \underbrace{b(a)}_{\text{birth rate}} \quad \underbrace{e^{-\int_0^a \mu(\tau)\,d\tau}}_{\substack{\text{Probability to be} \\ \text{alive at age a}}} \quad da,$$

i.e. R_0 is the average number of children of an individual. Only if one individual has in average more than one child, the population will tend to infinity. If the average number of children is below one, then the population will die out (be careful with the meaning of "the number of children". In a certain sense, this model only considers females. Thus, one should more precisely state "the number of female children").

Remark 4.10: Asymptotically, the shape of the population tends to $v_{\hat{\lambda}}(a)$, i.e. against the function

$$e^{-\int_0^a \mu(\tau)\,d\tau - \hat{\lambda}a}.$$

If $\hat{\lambda} > 0$, i.e. if the population is growing, then the population shape is monotonously decreasing. Since the death rate is (more or less) increasing and very small in young age classes (at least in developed countries), we find for $\hat{\lambda} < 0$ that the shape is a unimodal function: it first increases until it reaches a maximum. Then the function decreases again. We find this prediction in data about different countries, indeed (see Fig 47).

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place here: http://www.prb.org/Content/NavigationMenu/PRB/Educators/Human_Population/Change/Three-Patterns-of-Population-Change1.htm

Figure 47: Shape of populations with different net growth rates ($\hat{\lambda}$): Republic of Congo, USA and Germany.

4.4 Spatial Structure

While it is clear how to model age structure, it is not this clear how to model spatial structure. Different modes of movement may be considered. We present here especially two approaches: the parabolic approach (heat equation) and the hyperbolic model (correlated random walk).
Beware! Do not confuse this section with mathematics! All arguments are only heuristic, no argument is hard! It is possible to find a setting s.t. the arguments become strict. However, in order to avoid technicalities, we do not work in a formal context but present with hand-waving arguments the idea of the different modeling approaches.

4.4.1 Diffusion Equation

In order to obtain a deeper insight into the properties of the parabolic model for diffusion, we derive the heat equation in two ways: first, by a scaling argument of the discrete random walk. Second, by considerations about the change of densities and the relation to the flux (conservation law). Find more in [48, chapter 9].

Discrete Random Walk
Perhaps the most simple model for spatial movement is the discrete random walk. We consider one particle moving in one dimension.

State: Let $x_i = i\Delta x$, $i \in \mathbb{Z}$ be the location of the particle (at time $t_n = n\,\Delta t$; the choice of the state space already is a hint that we aim to scale this model and let Δx, Δt tend to zero).

Dynamics: If the particle is in state x_i at time step t_n, it will jump either to x_{i-1} or to x_{i+1} (with equal probabilities, see Fig. 48).

Analysis: Define

$$p(m,n) = P(\text{state } x_m \text{ in time step } t_n).$$

We find at once that $p(m,n) = 0$ for $|m| > n$. Let $|m| \leq n$. In order to reach state x_m we have to go (all in all) a steps to the left and b steps to the right, s.t. $a - b = m$. Furthermore, we have to do that in n time steps, $a + b = n$. Thus,

$$\begin{array}{rcl} a+b &=& n \\ a-b &=& m \end{array} \quad \Leftrightarrow \quad \begin{array}{rcl} a &=& (n+m)/2 \\ b &=& (n-m)/2 \end{array}$$

Obviously, $m + n$ has to be even in order to allow for an integer-solution. This becomes clear in Fig. 48 (b). Since we force a change of the state in every time step, in the even time steps only states with an even number can be visited, and in the odd time steps only odd x-states.
One certain, fixed combination of a steps to the right and b steps to the left (something like "+ + - - + - + - + + - -+ - + - +...") has probability $(1/2)^n$ (one step to the left and one step to the right, booth have probability 1/2). Hence, to find the probability to be in state x_m at time t_n, we have to count the number of possible combinations of "step

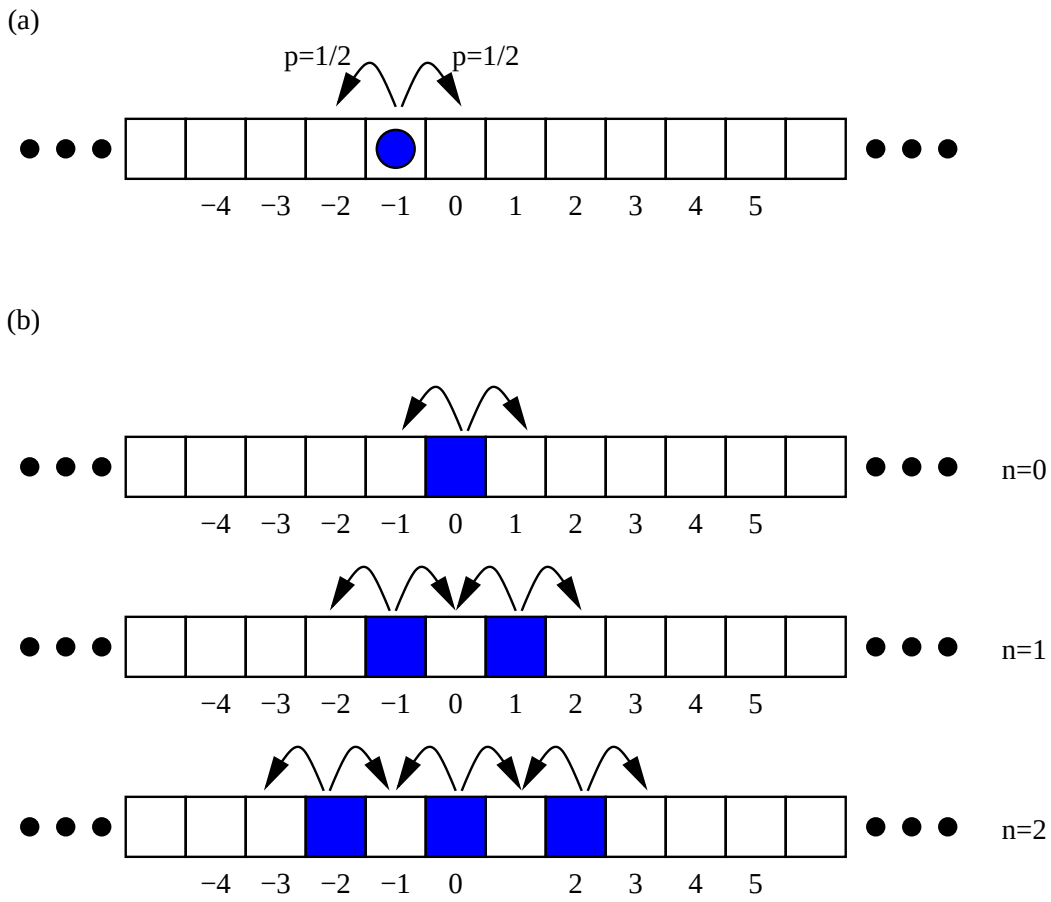

Figure 48: (a) Discrete random walk. (b) Possible states for the initial condition and the first two time steps.

to the right" and "step to the left", s.t. at the end we have (all in all) exactly a steps to the left among n steps altogether; i.e., we find here the binomial coefficients. Thus,

$$p(m,n) = \left(\frac{1}{2}\right)^n \begin{pmatrix} n \\ a \end{pmatrix} = \left(\frac{1}{2}\right)^n \frac{n!}{a!(n-a)!}$$

Remark 4.11: (1) The probabilities sum up to one: let $\chi_{m+n \text{ even}}(m)$ be one if $m+n$ even and zero else. Then,

$$\begin{aligned}
\sum_{m=-\infty}^{\infty} p(m,n) &= \sum_{m=-n}^{n} \left(\frac{1}{2}\right)^n \frac{n!}{a!(n-a)!} \chi_{m+n \text{ even}}(m) \\
&= \sum_{m=-n}^{n} \left(\frac{1}{2}\right)^n \frac{n!}{((n+m)/2)!((n-m)/2)!} \chi_{m+n \text{ even}}(m) \\
&= \sum_{k=0}^{n} \left(\frac{1}{2}\right)^k \left(1-\frac{1}{2}\right)^{n-k} \frac{n!}{k!(n-k)!}
\end{aligned}$$

$$= \quad (0.5 + 0.5)^n = 1.$$

(2) Using the Stirling's formula

$$n! \sim \sqrt{2\pi n} n^n e^{-n}$$

it is possible to show that ($|m|, n \gg 1$)

$$p(m,n) \sim \sqrt{\frac{2}{\pi n}} e^{-\frac{m^2}{2n}}.$$

I.e., $p(m,n)$ approaches the normal distribution for m, n large.

Scaling to the Heat Equation
The last remark in the previous section suggests a connection between the random walk and the heat equation (the scaled random walk as well as the the heat equation doe have the Gaussian distribution as solution). In order to make this connection more explicite, we scale the discrete random walk.
The master equations read

$$p(m,n) = \frac{1}{2} p(m-1, n-1) + \frac{1}{2} p(m+1, n-1).$$

We now scale the master equation, using

$$\Delta x \to 0, \qquad \Delta t \to 0, \qquad \frac{\Delta x^2}{2\Delta t} = D.$$

We assume that the scaled probabilities $p(m,,n)$ approach a continuous (and even twice differentiable!) function $u(x,t)$,

$$u(x,t) = p(x/\Delta x, t/\Delta t)$$

Then,

$$\begin{aligned} u(x,t) &= \frac{1}{2}\left(u(x-\Delta x, t-\Delta t) + u(x-\Delta x, t-\Delta t)\right) \\ \Rightarrow \quad \frac{u(x,t) - u(x,t-\Delta t)}{\Delta t} &= \frac{\Delta x^2}{2\Delta t} \frac{u(x-\Delta x, t-\Delta t) - 2u(x,t-\Delta t) + u(x-\Delta x, t-\Delta t)}{\Delta x^2} \\ &\downarrow \quad {\scriptstyle (\Delta t, \Delta x \to 0, \quad \Delta x^2/(2\Delta t) = D)} \\ u_t &= D\, u_{xx} \end{aligned}$$

If the mass is at time zero concentrated in the origin, $u(x,0) = \delta_0(x)$, then we find the well-known singularity solution for the heat equation,

$$u(x,t) = \frac{1}{2\sqrt{\pi D t}} e^{-x^2/(4Dt)}.$$

Remark 4.12: **(1)** We find, that with a (small, but) positive probability our particle is even after an arbitrary small time far away from the origin. We may interpreted this fact in the way that "the model allows for arbitrary high velocities". A particle is allowed (perhaps with a small probability) to travel very fast, also faster than the light. This conclusion shows, that the model is not realistic. However, this very fact can be found in most of the linear models in statistics: e.g. the size of adult, male African elephants can be well described by a normal distribution. However, a normal distribution predicts (with a very small probability) the existence of elephants with negative size. Even the basic rule that every elephant has positive size is not respected by linear statistical models. Only the fact that the probability is very, very small and can be neglected justifies the success of these models. Also in our case, often enough the diffusion model just works fine, because the discussed effects do not disturb the overall performance. Only in some cases we are forced to think about something else. However, we should be clear about the problems related to the parabolic mode of movement.

(2) It is an important fact that will come up over and over again, that we required a certain (the parabolic) scaling. If Δx tend to zero, $\Delta t = \mathcal{O}(\Delta x^2)$ tends faster to zero. Thus, the velocity $\Delta x/\Delta t = D/(2\Delta x)$ may tend to infinity. This is one part of the truth concerning the effect, that the model allows for arbitrary high velocities. We find this scaling as an invariance also in the heat equation: this equation is invariant if we rescale time and space by $\hat{t} = \varepsilon^2 t$, $\hat{x} = \varepsilon x$. Again, the scaling of time requires a second order, the scaling of space the first order in ε.
The second important observation is the Markov property of the stochastic process. The particle does not know where it has come from, when it decides where to go (left or right). By chance, there are some particles that keep for a longer time the direction, resp. do not change the direction this often (with smaller probability if the number of changes of direction becomes less). Since we scale time and space in the parabolic way, these particles have the opportunity to travel a long way. The escaping particles are described by the tail of the Gaussian distribution respectively the singularity solution of the heat equation.

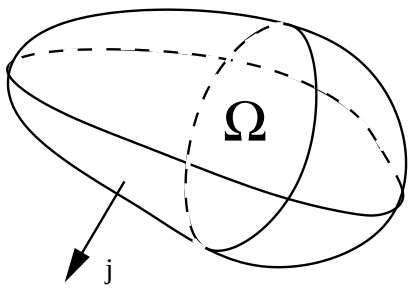

Figure 49: The region Ω and the flow j.

Conservation Law, Flux and the Heat Equation

A second approach is not concerned directly with a stochastic process, but connects the change of a density $u(x,t)$ with a flux $j(x,t)$. This connection yields the first law of Fick. In a second step, one chooses a connection between flux and density in a reasonable way (Fick's second law). The combination of the two laws will again yield the heat equation. This approach is in a certain sense more flexible, since it also allows for different definitions for the flux (the second law may be changed), with different outcomes for the models that are developed to describe diffusion.

Fick's first law / Conservation law:
Consider an arbitrarily chosen, compact region Ω with smooth boundary $\partial\Omega$. Let furthermore $u(x,t)$ denote the density of particles within this region. If we assume that no mass is created nor annihilated (no sinks or sources), the change of mass can only happen via a flux through the surface of Ω. The flux $j(x,t)$ is defined to point outward (see Fig 49). We then find

$$\frac{d}{dt}\int_\Omega u(x,t)\,dx = -\int_{\partial\Omega} j(x,t)\,d\vec{\sigma}.$$

Since everything is assumed to be smooth, the Theorem of Gauss (divergence theorem) yields

$$\int_\Omega \partial_t u(x,t)\,dx = -\int_\Omega \nabla j(x,t)\,dx.$$

Since we have chosen Ω as an arbitrary region, this equation holds true for every smooth region. Hence, the integrands from the r.h.s. and the l.h.s. coincide,

$$\partial_t u(x,t) = -\nabla j(x,t).$$

This is the first law of Fick; the statement of this fundamental law is the generic connection between time derivative of density and flux caused by the assumption of conservation of mass.

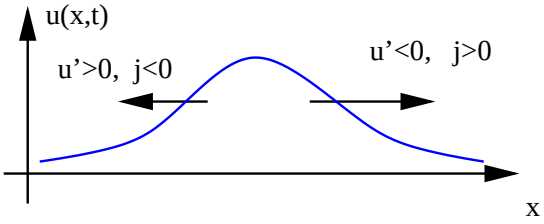

Figure 50: Choice of the flux according to Fick's second law.

Second law of Fick/ Choice of the flux:
In a second step we connect $j(x,t)$ to $u(x,t)$. In a certain sense, $u(x,t)$ corresponds to the zeroth moment of the velocity and $j(x,t)$ to the first moment. We now express the first moment by the zeroth moment. This idea is similar to the moment-closure methods we will consider later in the non-linear part of the lecture.

The idea how to choose j as a function of u is the observation, that (pure) diffusion flattens the density: e.g., if we consider the evolution of a temperature profile and assume an initial condition where at some points the temperature is high while it is low at other points, we find that the hills are decreased and the valleys are increased until the temperature slowly approaches the constant solution. Or, the concentration of a drop of milk poured into a cup of coffee will slowly diffuse over the whole cup until the milk is uniformly distributed (without steering; however, perhaps your coffee is cold at the time the equilibrium is reached). All in all, local maxima will be decreased and, during this process, valleys are filled s.t. we find in the end a constant solution. Thus (see Fig. 50), the flux should be positive if the gradient is negative and vice versa. The most simple way to model this structure reads

$$j(x,t) = -D\nabla u(x,t),$$

the flux is proportional to the negative gradient. Using this definition/model assumption, we find

$$\partial_t u(x,t) = D\Delta u(x,t),$$

i.e. again the heat equation.

Example: Spread of Muskrats
In order to validate the model in biological context, we consider the spread of muskrats over Europe (see [19, 56]). The muskrats escaped 1905 from a farm in Germany. In the following years they spread over a larger and larger region. Data about the habitat of the muskrats are shown in Fig. 51. The aim is to model this situation following the lines of thinking we developed above.

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place here: Edelstein-Keshet, p 439, Fig. 10.1 [19]

Figure 51: Spread of muskrats over Europe. Lefthand side: regions where the muskrats have been present at a given time. Right hand side: square root of the area over time.

State: The state of the muskrats population is the density of muskrats at time t and location x, $u(x,t)$.

Dynamics: The dynamics consists of two parts: diffusion and growth of the population.

- Diffusion only.

Diffusion is modeled by the heat equation,

$$u_t = D\Delta u, \qquad u(0,x) = u_0(x).$$

Since the muskrats spread from one point, we assume for the initial conditions a point mass, located in $x = 0$,

$$u_0(x) = \overline{u}_0\delta_0(x).$$

- Growth only.

Since we consider the spread of the population, we do not assume that the muskrats compete for resources with other muskrats (there may be competition with other species, but not within the species). Hence, we find a linear model for growth (a justification for this assumption will be found later, if we consider the "diffusion-competition-equation", the Fisher equation). Hence, we find for growth only

$$u_t = \alpha u$$

where $\alpha > 0$ is the growth rate.

- Complete model.

In order to find the complete model, we have to add the r.h.s. of the equations describing the booth processes. This procedure is a general concept: if several processes are to be combined in a differential equation, one has to add the r.h.s. of the models,

$$u_t = D\,\Delta u + \alpha u, \qquad u(0,x) = u_0(x).$$

Remark 4.13: This general "recipe" is quite non-trivial to understand. One argument can be found in exercise 4.7. Another argument (better: another approach to the same argument) is the reduction to the corresponding stochastic processes: We consider the discrete random walk, and combine this random walk with a birth process. The state at a time t_n consists of the number of particles N_i^n in x_i, $i \in \mathbb{Z}$. In each time step, we subsequentially realize the two processes: birth and movement. Fist, we let every particle decide if it wants to reproduce or not. Reproduction of one particle happens with probability $\alpha\Delta t = \alpha(t_{n+1} - t_n)$. This process leads to a new state $\hat{N}_i^n$ for the number of particles in location x_i after reproduction. We find (up to higher order terms)

$$\hat{N}_i^n = N_i^n + \mathrm{Bin}(N_i^n, \alpha\Delta t).$$

After reproduction, we perform with all (the old particles and the newborn particles) a random walk, where every particle moves independently of each other particle. We then find for every single location (we only consider a single location in order to avoid the correlation between cells x_i and $x_{i\pm1}$ that are caused by the fact that the particles in the location x_i will either go to the left or to the right)

$$P(N_i^{n+1} = k \,|\, \hat{N}_\cdot^{n-1}) = \mathrm{Bin}(\hat{N}_{i+1}^n, 1/2) + \mathrm{Bin}(\hat{N}_{i-1}^n, 1/2).$$

Hence, for the expected value, we find

$$E(N_i^{n+1}) = \frac{1}{2}\left(E(\hat{N}_{i-1}^{n+1}) + E(\hat{N}_{i+1}^{n+1})\right) = \frac{1}{2}\left((1+\alpha\Delta t)E(N_{i-1}^{n+1}) + ((1+\alpha\Delta t)E(N_{i+1}^{n+1})\right).$$

If we perform the parabolic scaling, assuming that $u(i\Delta x, n\Delta t) = E(N_i^n)$ approaches a smooth function, we obtain in the limit our desired equation

$$u_t = D\,\Delta u + \alpha u, \qquad u(0,x) = u_0(x).$$

The deeper reason for the additivity is that the particles move and reproduce independently. There is no correlation between the two processes (reproduction and diffusion).

Proposition 4.14: *The solution of $u_t = D\,\Delta u + \alpha u$, $u(0,x) = u_0(x)$ reads*

$$u(x,t) = \frac{\overline{u}_0}{2\sqrt{\pi D t}} e^{-\frac{|x|^2}{4Dt} + \alpha t}.$$

Proof: One may plug the function into the PDE, or observe that

$$v(x,t) = e^{-\alpha t} u(x,t)$$

satisfies the heat equation (with a delta peak as initial condition, i.e. is the singularity solution of the heat equation).

□

Remark 4.15: By now, we do know the density (according to our model). The data show the area, where the muskrats are present. We relate $u(x,t)$ to the area, where muskrats are observable, by the assumption that a minimal density $\underline{u}$ is necessary to find animals (recall that $u(x,t) > 0$ for all $x \in \mathbb{R}^2$, provided that $t > 0$; thus, $\{x \,|\, u(x,t) > 0\}$ will not do it).

Proposition 4.16: *Let $A(t) = \{x \,|\, u(x,t) \geq \underline{u}\}$. We find asymptotically, for large time*

$$\sqrt{|A(t)|} \sim 2\sqrt{\pi\alpha D}t \qquad \text{for } t \to \infty.$$

Proof: We find

$$\begin{aligned}
& \underline{u} \leq u(x,t) \\
\Leftrightarrow \quad & \underline{u} \leq \frac{\overline{u}_0}{2\sqrt{\pi D t}} e^{-\frac{|x|^2}{4Dt} + \alpha t} \\
\Leftrightarrow \quad & \frac{2\sqrt{\pi D t}\underline{u}}{\overline{u}_0} \leq e^{-\frac{|x|^2}{4Dt} + \alpha t} \\
\Leftrightarrow \quad & \frac{2\sqrt{\pi D t}\underline{u}}{\overline{u}_0} \leq e^{-\frac{|x|^2}{4Dt} + \alpha t} \\
& |x|^2 \leq 4\alpha D t^2 (1 - \underbrace{\log(2\underline{u}\sqrt{\pi D t}/\overline{u}_0)/(\alpha t)}_{(.)\to 0 \quad \text{for} \quad t\to\infty}) \\
\Rightarrow \quad & |x|^2 \leq 4\alpha D t^2 \qquad \text{for } t \to \infty.
\end{aligned}$$

Thus, we find asymptotically that

$$|A(t)| \equiv |\{x \,|\, |x|^2 \leq 4\alpha D t^2\}| = 4\,\pi\alpha D t^2.$$

□

Hence, $\sqrt{|A(t)|}$ should approximately be a linear function of t. Indeed, the data in Fig. 51 show a good agreement with our prediction. This is a hint, that the parabolic model for diffusion is not too bad.

4.4.2 Excursion: Porous Media Equation

The main drawback of the heat equation is the possible very fast spread of some particles. Though often enough this equation is an appropriate model for the spatial spread of entities (bacteria, cells, animals or information), sometimes this effect is too unrealistic to be acceptable. At least it is useful to think about different models that do not show this approach and their relation to the parabolic partial differential equation. We may also learn in this way more about the interpretation and the way how to handle the parabolic equation. Furthermore, sometimes we find new effects in non-parabolic models for spatial movement.

The model we want to consider now somehow does not fit in the overall structure of these considerations: it is **not** a linear model, but takes into account some interactions. The basic idea is the following: The overall velocity a population growing with rate α and diffusing according to the heat equation with diffusion constant D reads $\sqrt{\alpha D}$ (see the muskrat example above). Hence, if we reduce the diffusion constant D, we reduce the net velocity of a population. Furthermore, the spread of the population is basically driven by these few particles that move very rapidly (the tail of the Gaussian distribution). Note that the density in the tails is rather low. Hence, if we assume that the diffusion constant is a function on the population density, $D = D(u)$, and choose $D(u)$ to be very small if u becomes small, then the very fast spread of densities according to parabolic equations can be stopped.

Model and interpretation
In order to translate this idea in a model, we use the formulation of transport phenomena with the Fick's laws. We find always the first law of Fick,

$$\partial_t u(x,t) = -\nabla j(x,t)$$

i.e. the change in the density is related to a flux. This is a general principle for a population where we do not have sinks and sources but only transport. The formulation of a special transport model is done by relating the flux to the density (and, perhaps, also to the flux itself),

$$j = F(u, j).$$

E.g. for the heat equation we assume

$$F = -D\nabla u.$$

The age structured model (without death and birth, since at this point of time we do not want to have sinks or sources) can be derived via

$$F = u.$$

In the present case, we assume

$$F = -D\nabla u, \qquad D = D(u),$$

i.e. the model is similar to the heat equation but the diffusion constant depends on u. It is furthermore assumed that $D(u) \to 0$ for $u \to 0$. Hence,

$$u_t = \nabla(D(u)\nabla u).$$

The typical function $D(u)$ is shown in Fig. 52, it is a function that is zero for $D = 0$, strictly increasing and global bounded.

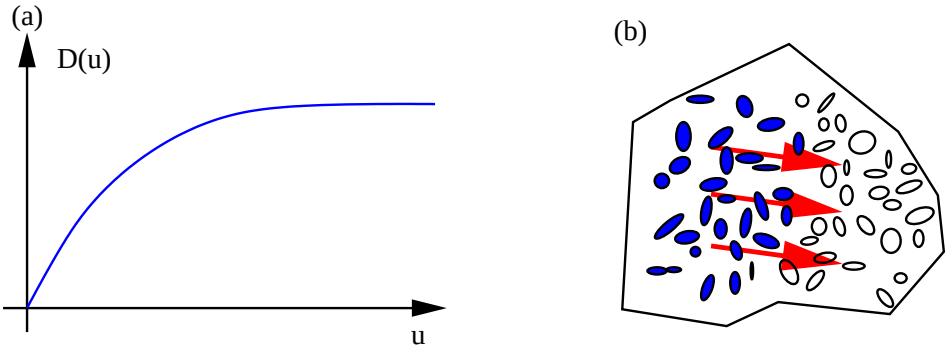

Figure 52: (a) The diffusion coefficient for the porous media equation. (b) Water in porous media.

The origin of this equation, the so-called porous media equation is the description of the spread of water in a media with numerous very small caverns. The water fills one cavern after the other, and only if the pressure/the local density is high enough, it will move forward ($D(.) > 0$), otherwise it just stays ($D = 0$). Though one may argue whether this equation is a good model for porous media, it had considerable impact. In mathematical biology, this model sometimes is used to describe the spread of insects [48].

Remark 4.17: The form $u_t = \nabla(D(u)\nabla u)$ conserves the total mass; assume $u \in L^1$, then (under appropriate assumptions)

$$\partial_t \int u(t,x)\,dx = \int \nabla(D(u(t,x))\nabla u(t,x))\,dx = 0.$$

An equation of the form $v_t = D(v)\Delta v$ leads to

$$\begin{aligned}
\partial_t \int v(t,x)\,dx &= \int D(v(t,x))\Delta v(t,x)\,dx \\
&= \int \nabla(D(v(t,x))\nabla v(t,x))\,dx - \int (\nabla D(v(t,x))(\nabla v(t,x))\,dx \\
&= -\int (\nabla D(v(t,x))(\nabla v(t,x))\,dx = -\int D'(v(t,x))\,|\nabla v(t,x)|^2\,dx.
\end{aligned}$$

Since in general $D'(v) > 0$, the last term does not vanish, i.e. we introduce by a description that does not use the formulation via the conservation law an artificial source/sink term of the form $D'(v(t,x))|\nabla v(t,x)|^2$.

Explicite solution of a special example
Perhaps the most simple function to chose for $D(u)$ reads

$$D(u) = D_0 \left(\frac{u}{u_0}\right)^n.$$

This function is not bounded, but tends to infinity if u goes to infinity; however, since we expect the effect to be triggered by the behavior of $D(u)$ for u small, this choice yields a reasonable model equation to study the behavior of the porous media equation. The nice point about this special choice of the nonlinearity is that an explicite solution is available. We find, that

$$u_t(x,t) = \left(D(u)u_x\right)_x$$

with $u(x,0) = Q\delta_0(x)$ has the solution

$$u(x,t) = \begin{cases} \frac{u_0}{\lambda(t)}\left[1 - \left(\frac{x}{r_0\lambda(t)}\right)^2\right]^{1/m} & \text{for} \quad |x| \le r_0\lambda(t) \\ 0 & \text{else} \end{cases}$$

with

$$\begin{aligned} \lambda(t) &= \left(\frac{t}{t_0}\right)^{1/2m} \\ r_0 &= \frac{Q\Gamma(1/m+3/2)}{\sqrt{\pi}n_0\Gamma(1/m+1)} \\ t_0 &= \frac{r_0^2 m}{2D_0(m+2)} \end{aligned}$$

and r_0 is determined by

$$Q = \int_{-\infty}^{\infty} u(x,t)\,dx = r_0 \int_{-r_0\lambda(t)}^{r_0\lambda(t)} \frac{u_0}{r_0\lambda(t)}\left[1 - \left(\frac{x}{r_0\lambda(t)}\right)^2\right]^{1/m} dx = r_0 \int_{-1}^{1} u_0\left[1-x^2\right]^{1/m} dx$$

It is easy to verify that this function sattisfies the partial differential equation for $|x| \neq r_0\lambda(t)$. At point $x = \pm r_0\lambda(t)$, the function is not differentiable. However, also $D(u)$ becomes zero at this point, s.t. formally the equation is also sattisfied at this point. In general, it is necessary to reconsider the definition of solution; we derive definitions of weak solutions [13].

The most important observation is that the solution defined above has a finite support. This behaviour is typically for solutions of the porous media equation [13]. Thus, it seems that this type of equation is a possible solution for the problem of finite propagation speed. However, this is only partially true. Indeed, the support of $u(x,t)$ will disperse with a finite maximal velocity. Particles of the corresonding stochastic process, though, may have locally within the support of $u(x,t)$ an arbitrary high velocity.

4.4.3 Correlated Random Walk in one dimension

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place here: M. Gulch et al., J. Bacteriol. 177(1995) 5473–5479, Fig. 4 [28]

Figure 53: Tracking of the path of *E. Coli*. Right side: Actual path of a bacterium. The points where the bacteria tumble are marked in black, the paths where they go (more or less) straight are denoted by open circles. Left hand side: Change of direction (angle) over time. The three images (a)-(c) correspond to different ambient temperatures.

Certain microorganisms, e.g. *E. Coli* show the following behavior: they either move at an approximative straight line with approximative constant velocity, or they stop, and "tumble". During this process they chose a new direction, where again they start to move straight (Fig. 53). This procedure has a physiological foundation. These microorganisms move by flagellants, small "hairs" on the cell membrane - the smallest natural motors known by now (see Fig. 54 or [59]). If they move straight, all of these flagellants are directed backward. During tumbling the flagellants stick out and in this way the bacterium performs a random rotation.

This behavior is well captured by the correlated random walk. We starts off with the description of a stochastic process in one dimension that incorporates a constant velocity for each particle. This stochastic process yields to coupled hyperbolic partial differential equations. These equations show truly finite propagation velocity for single particles and - as a consequences - also for the spread of mass/information.

Model

We consider a particle in one dimension. This particle moves with constant velocity γ either to the right or to the left. The time that this particle moves in one direction is exponentially distributed with rate μ.

State: $u^+(x,t)$ and $u^-(x,t)$, denote the probability density to find this particle at location x and moving to the right $(u^+(x,t))$ or to the left $(u^-(x,t))$.

Dynamics: We have two processes: to move straight and to change the direction.

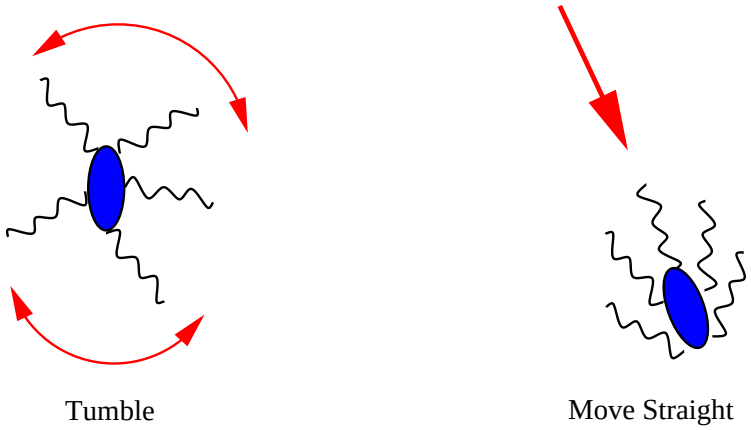

Figure 54: Modes of movement of E. Coli.

Movement: We now neglect that the particles change direction but assume that they go on for ever with velocity γ. From

$$u^+(x,0) = u^+(x+\gamma t, t), \qquad u^-(x,0) = u^-(x-\gamma t, t)$$

we conclude (taking the derivative with respect to time) that

$$(\partial_t + \gamma\partial_x)u^+(x,t) = 0, \qquad (\partial_t - \gamma\partial_x)u^-(x,t) = 0.$$

These equations correspond to the fact, that $\partial_t \pm \gamma\partial_x$ is the infinitesimal generator of the right (left) shift with velocity γ [62].
Change of direction: If we neglect the spatial structure and consider the direction as a property with two possible states ("+" and "-"), where our particle changes from one state to the other with exponentially distributed waiting times of average $1/\mu$, we obtain immediately

$$\partial_t u^+(.,t) = -\mu u^+(.,t) + \mu u^-(.,t), \qquad \partial_t u^-(.,t) = \mu u^+(.,t) - \mu u^-(.,t).$$

Total process: Like usual, we obtain the total process if we add the r.h.s. of the differential equations describing the single processes. Hence we find

$$\begin{aligned}(\partial_t + \gamma\partial_x)u^+(x,t) &= -\mu u^+(x,t) + \mu u^-(x,t)\\ (\partial_t - \gamma\partial_x)u^-(x,t) &= \mu u^+(x,t) - \mu u^-(x,t).\end{aligned}$$

The boundary conditions have to be chosen in an appropriate way to meet the situation one aims at (see Exercise 4.10).

Of course, $u^\pm(x,t)$ may also be interpreted as the population density of a large number of particles that do not interact and behave according to the rules above (we discussed these two possibilities of interpretation - as the probability of a single individual or the

density of a population – which is, in a way, that same due to the idea of an ensemble – before).

Remark 4.18: In contrast to the memoryless Brownian motion, we here explicitly include memory: a particle that is going to the right hand side now, is likely to do that also in the next moment. Therefore we obtain a hyperbolic system of equations (time and space scale with the same exponent), while the heat equation is memoryless (space scales with second order while time scales with first order). Hence, the correlated random walk belongs to the same class like the wave equations [36] or the age structured model [60]. The most obvious difference of the two types of equations is the smoothing behavior: if we start with a Heaviside function for the density at time zero, the heat equation will smooth out the step in the population density at once - after an arbitrarily small time step, the solution becomes arbitrarily often differentiable. The hyperbolic equation tends to preserve a jump - in the correlated random walk, the magnitude of the jump will become smaller in time but will never vanish. The solutions do not gain smoothness during the evolution.
This difference of the smoothing behavior is strongly connected with the finite propagation speed: while parabolic equations are this smoothing that they do not allow for a compact support of a solution, the hyperbolic equations allow for a jumps in the density, also jumps to zero s.t. solutions with finite support exist (in this case we have - like in the case of the porous media equation - to define a slightly modified definition of solution).

Parabolic Limit
In order to better understand the correlated random walk, we derive the connection to the heat equation - the parabolic limit. The heat equation can be derived via the Fick's laws, i.e. via the connection between density and flux. Thus, it is useful to rewrite the correlated random walk in these terms.

Lemma 4.19: *Define the total density $u(x,t)$ and the flux $j(x,t)$ via*

$$u(x,t) = u^+(x,t) + v^+(x,t), \qquad j(x,t) = \gamma(u^+(x,t) - u^-(x,t)).$$

If we assume that $u^+(x,t)$ and $u^-(x,t)$ are sufficiently smooth, we find

$$\begin{aligned} u_t(x,t) &= -j_x(x,t) \\ j(t,x) &= -\frac{1}{2\mu} j_t(t,x) - \frac{\gamma^2}{2\mu} u_x \end{aligned}$$

Proof: The proof is a direct computation (add resp. subtract the two equations for u^+ and u^-).

□

Remark 4.20: **(1)** The first equation, $u_t = -j_x$, only tells us, that the flux is well defined (i.e., j is a flux, indeed).
(2) The interesting term is the time derivative of j in the equation for j (the equation that replaced the second law of Fick). The hyperbolicity of the correlated random walk expresses itself by the appearence of the time derivative.

(3) We can now (at least formally) take the parabolic limit: let

$$\gamma,\ \mu \to \infty, \qquad \text{s.t.} \qquad \frac{\gamma^2}{2\mu} = \text{constant} =: D,$$

we find

$$\begin{aligned} u_t(x,t) &= -j_x(x,t) \\ j(t,x) &= -Du_x \end{aligned}$$

Though this limit is only a formal one, an approximation theorem can be [47, 32].

We find that the particles have to move faster and faster, and - at the same time - to turn around more and more often in order to derive the (memoryless) Brownian motion.
(4) We now know how to interprete the diffusion equation in the view of the correlated random walk. Conversely, also the correlated random walk may be interpreted in terms of the diffusion equation. Consider the inhomogeneous linear ordinary differential equation

$$\alpha\dot{y} + y = f(t),$$

If $f(t) = f$ is constant, then $y(t) \to f$, i.e. $y(t)$ adapts to the input signal $f(.)$. The time scale of this adaptation process is given by $1/\alpha$. I.e., if α is small, the adaptation is very fast, while for $1/\alpha$ large $y(t)$ needs a lot of time until it slowly approaches the asymptotic value $f(.)$.

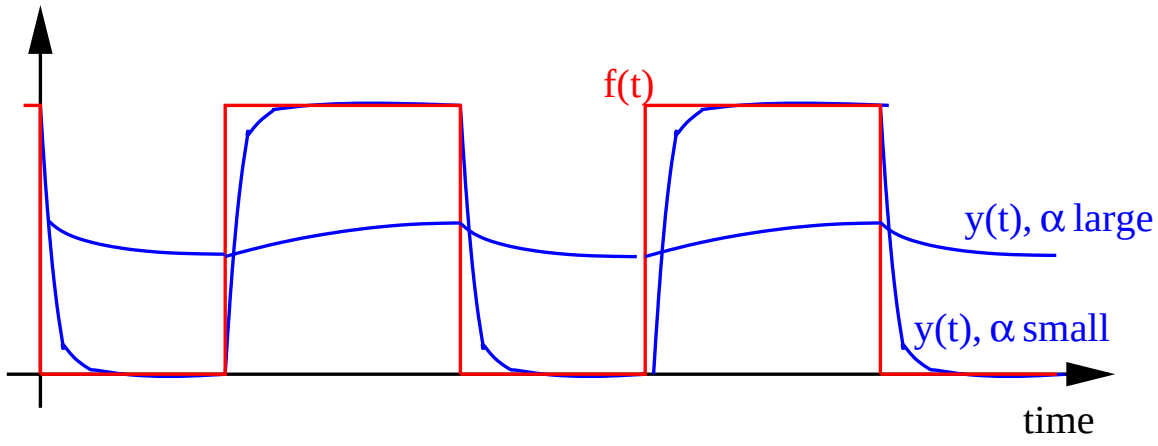

Figure 55: Behavior of the equation $\alpha\dot{y} + y = f(t)$.

If $f(t)$ is a periodic signal (see Fig. 55), α determines again the behavior of the equation. If α is small, $y(t)$ will follow closely to the signal; if α is large, the differential equation will average the signal, and $y(t)$ becomes almost constant over time. In other words, if we keep α constant but look at different signals $f(t)$ with different period, we understand that this equation has the behavior of a low pass filter.

In this sense, we may interprete the equation for the flux

$$\frac{1}{2\mu} j_t(t,x) + j(t,x) = -D\, u_x$$

as a kind of delay equation. The term $j_t/(2\mu)$ prevents the flux to adapt instantaneously to the gradient of the density (what is required by the second law of Fick, which leads to the heat equation). The time scale of this adaptation process is given by $1/(2\mu)$. If μ becomes large, the adaptation becomes faster and faster s.t. the second law of Fick is almost fulfilled and the correlated random walk approaches the heat equation. Only if μ is rather small, the character of booth equations differ.

Cattaneo System
From the structure density/flow, it is straight forward to define a system of equations that describe a generalization of the correlated random walk in higher dimensions $x \in \mathbb{R}^n$,

$$\begin{aligned} u_t(x,t) &= -\nabla_x j(x,t) \\ j(t,x) &= -D\nabla_x u. \end{aligned}$$

This system is called Cattaneo-system after the Italian physicist Cattaneo who introduced this model in the year 1948. This system is of interest and the properties of this system are investigated (see e.g. [31]). However, it is unknown if there is a stochastic process in $\mathbb{R}^n$ s.t. the probability density of a particle obeys this system of equations. Several attempts are made, and some articles are published; however, it seems that in all of these attempts problems arises that do not allow a strict derivation of the Cattaneo system from a stochastic process. Hence, different generalization of the correlated random walk to the n-dimensional situation are of interest.

4.4.4 Correlated Random Walk in higher dimensions

Of course, it is possible to extend the correlated random walk to higher dimensions. We will sketch here the basic idea how to formulate this model.

Model
Let us first consider one particle, and only then characterize probability densities.

State of one particle: A particle is characterized by its location and velocity. Let $x \in \mathbb{R}^n$ denote the state, and $v \in V \subset \mathbb{R}^n$ the velocity. Note, that we explicitly assume a that the velocity is element of a subset V of $\mathbb{R}^n$. In this way, we are able to exclude large velocities (V may be compact) and also small velocities (if a particle is allowed to stay for a certain while at one and the same location, this sometimes implies technical difficulties, especially if one aims at scaling arguments).

Dynamics: Like before, we have two processes, movement and choosing a new direction. *Movement:* If there is no change in the velocity, the location of a particle after Δt is

$$x(t+\Delta t) = x(t) + \Delta t v.$$

Time to move in one direction: The waiting times in between two changes of direction are distributed exponentially with parameter μ.
Choose a new direction/velocity: Assume that we do have the velocity v now and want to choose a new one (i.e., we tumble). In general (without further restrictions) we only can assume that there is a probability density over the set of velocities V that describes the probability density to choose $v' \in V$ (this probability density depends in general on v). Hence, there is a function $K(v', v)$

$$K : V \times V \to \mathbb{R}_+, \qquad \int_V K(v', v)\, dv' = 1.$$

Now we desire to derive an equation for the probability density of one particle at time t in the state (x, v) (resp. the population density of a lot of particles evolving according to the rules above).
State: Let $u(x, v, t)$ be the density to find a/the particle at location x with velocity v.
Dynamics: Again, let us first consider movement and change of direction separately.
Movement: Since we move straight with velocity v, we find

$$u(x + \Delta t v, v, t + \Delta t) = u(x, v, t)$$

and hence (taking the derivative with respect to Δt)

$$\partial_t u(x, v, t) + \nabla(v\, u(x, v, t)) = 0.$$

Change of velocity: The rate of change of velocity is μ, the new direction is given by the kernel $K(., v)$. Hence, neglecting space, we find

$$\partial_t u(., v, t) = -\mu u(., v, t) + \int_V K(v, v') u(., v', t)\, dv'.$$

Full process: The complete process is given by

$$\partial_t u(x, v, t) + \nabla(v\, u(x, v, t)) = -\mu u(., v, t) + \int_V K(v, v') u(., v', t)\, dv'.$$

This equation is related to the Boltzmann equation [10]. The difference is, that Boltzmann equation describes colliding gas particles, i.e. has a quadratic term at the r.h.s.

Flux and asymptotic velocity
We do not want to go into the detail and aim at an analysis of the model (even on the heuristic level we work on). In order to give a brief feeling for the behavior of this equation, we only want to mention three facts.

Remark 4.21: If we only aim at spatial information, we find with the definitions

$$\overline{n}(t, x) = \int_V u(x, v, t)\, dv, \qquad j(t, x) = \int_V v\, u(x, v, t)\, dv$$

that

$$\partial_t \overline{n}(t,x) = -\nabla j(t,x)$$

i.e. $j(t,x)$ is the flux for the (spatial) density $n(t,x)$. We again meet the first law of Fick.

Remark 4.22: Now we forget the space but only consider the distribution of velocities. Let

$$\nu(t,v) = \int_{\mathbb{R}^n} u(x,v,t)\,dx.$$

We find

$$\partial_t \nu(t,v) + \underbrace{\int_{\mathbb{R}^n} \nabla v u\,dx}_{=0} \;=\; -\mu\nu(t,v) + \mu \int_V K(v,v')\nu(t,v')\,dv'.$$

Hence, stationary distributions satisfy $\partial_t \nu(t,v) = 0$, i.e.

$$\nu(v) = \mu \int_V K(v,v')\nu(v')\,dv',$$

i.e. are eigenvectors for the eigenvalue one of the operator

$$A : V \to V, \quad \nu \mapsto \int_V K(v,v')\nu(v')\,dv'.$$

We are confronted with an integral operator (where we even did not define properly the space this operator acts on, though we want to draw conclusions about the spectrum of A!). For simplicity, we assume that V consists of a m discrete points, s.t. ν can be represented as a positive vector in $\mathbb{R}^m_+$ with l^1-norm one (this has been the case in our one-dimensional model, where $V = \{-\gamma, \gamma\}$). In this case, A is a non-negative matrix. If we assume furthermore that A is strictly positive, i.e. there is a positive probability to jump from any allowed velocity in V to any other velocity in V, we are able to apply the Perron-Frobenius theorem (in the setting of integral operators, we need some assumptions to derive the same results like compactness etc., but it is possible to extend this theory to quite a large classes op operators. See the theorem of Krein-Rutmann).
In this (relatively simple) setting, we have to prove that here is a positive eigenvector for eigenvalue one. Since $\int_V K(v,v')\,dv' = 1$ we find

$$\mathbf{e}^T A = \mathbf{e}^t,$$

i.e. $\mathbf{e}$ is a left-eigenvector for eigenvalue one. Since the matrix A is strictly positive, we conclude $\rho(A) = 1$ and thus there is a unique positive right-eigenvector $\overline{\nu}$ for the eigenvalue one. Furthermore, since the absolute value of all other eigenvalues are strictly smaller than one, we find

$$\Re(\lambda - 1) < 0 \qquad \forall \lambda \in \sigma(A) \setminus \{1\}.$$

Hence, the matrix $A - I$ has one eigenvalue zero and the remaining part of the spectrum has negative real part. Thus, the solution of the (ordinary(!)) differential equation

$$\frac{d}{dt}\nu(t) = \mu(A - I)\nu(t)$$

tends for positive initial values to $\overline{\nu}$.
Conclusion: We find asymptotically a well defined velocity distribution in our system.

Remark 4.23: With appropriate scaling methods (the parabolic scaling), also in this case we are able to derive a parabolic partial differential equation for

$$n(x,t) = \int_V u(x,v,t)\,dv$$

(see [21, 32]). We find in general the form

$$\partial_t \overline{n} = \sum_{i,j=1}^{n} \partial_{x_i}(a_{i,j}\partial_{x_j}\overline{n}(x,t)) + \sum_{i=1}^{n} b_i \partial_{x_i} n_{x_i}.$$

Remark 4.24: **(1)** We find again, that this form is "the right way" to write the differential equation: we consider here pure transport, i.e. no skins and no sources. Thus, $\int \overline{n}(x,t)\,dx \equiv$ const.. In the present form, this is trivially given. In general, an equation of the form $\partial_t \overline{n} = \sum_{i,j=1}^{n} a_{i,j}\overline{n}(x,t)_{x_i x_j} + \sum_{i=1}^{n} b_i \partial_{x_i} n_{x_i}$ will not do it.

(2) The term $\sum_{i=1}^{n} b_i \partial_{x_i} n_{x_i}$ corresponds to a drift term. How can we make his fact clear? There are two ways: either, we may write down the equation in terms of the flux,

$$\begin{aligned} \partial_t \overline{n}(x,t) &= -\nabla_x j(x,t) \\ \partial_t j(x,t) &= A\nabla_x \overline{n}(x,t) + b\overline{n}(x,t) \end{aligned}$$

where the matrix A denotes $((a_{i,j}))$ and b is the vector $(b_1,..,b_n)^T$. Hence, the flux incorporates a term $b\overline{n}(x,t)$, i.e. direct transport of mass in the direction b.
The second possibility to investigate this term is the use of a moving coordinate system. Let

$$v(x,t) = \overline{n}(x - b\,t, t).$$

Then,

$$\partial_t v(x,t) = \partial_t \overline{n}(x - b\,t, t) - b\nabla_x \overline{n}(x - b\,t, t) = \nabla_x A \nabla_x \overline{n}(x,t) = \nabla_x A \nabla_x v(x,t).$$

I.e. $v(x,t)$ does not incorporate the drift term but evolves only due to diffusive processes. Then, $\overline{n}(x,t) = v(x + bt, t)$ shows that the density of $\overline{n}(x,t)$ is moved with constant velocity b. Another way to introduce drift (via the stochastic random walk) can be found in exercise 4.6.

In the next section, we will present two examples for models incorporating drift terms.

Examples: Advection and Chemotaxis
Advection of an additive
In 1986, at the river Rhine an accident with a herbicide did take place. This herbicide (altogether two tons) has been measured at three control points along the river (or, better,

Because of the copyright is this figure empty.

place here: Matthis et al.??? [63]

Figure 56: Data of three control stations along the river Rhine, presenting the advection/diffusion of a pollutant (in the third point - Lobith - at booth sides of the river measurements have been performed). Units of the x-axis are days, the units of the y-axis is concentration [μg/l].

we do have data from these three control points). Diffusion and advection with the river superimpose. A one-dimensional model of the form

$$u_t = Du_xxx + bu_x$$

is appropriate for the transport/diffusion of the chemical substance. We find rather good agreement between the model and the data (see Fig. 56).

Chemotaxis - the Keller-Segel-Model

Many microorganisms or also certain cell lines in higher organisms (e.g. monocytes) perform chemotaxis. I.e., the cells follow a gradient of some chemical signal substance. Let $u(x,t)$ be the density of the cells itself, and $a(x,t)$ be the chemical signal. We then find not only the diffusion equation $u_t = D\Delta u$, but also a drift term. The velocity of this drift is proportional to the gradient of the signal. This proportionality constant is denoted by χ,

$$u_t(x,t) = D\Delta u(x,t) + \nabla(\chi u(x,t)\nabla a(x,t)).$$

Some microorganisms (*Dictostelium discoideum*) produce a chemical signal in order to initiate an agglomeration of the cells. Interesting patterns and waves can be observed during this process. From several reasons, this behavior draw much attention from the modeling community: it seems that this is one of the simplest and experimentally best studied examples of cell-cell communication; furthermore, these cells form something like a primitive animal (the slime mold) after aggregation. It is in some sense possible to study the first attempts to form an organisms from single cells, and in this way, to get some idea, how complex organisms may have developed. In order to model that, we add

the dynamics of the signal: it is produced by the cell line and will degrade. We find

$$\begin{aligned} u_t(x,t) &= D\,\Delta u(x,t) + \nabla(\chi(a)u(x,t)\nabla a(x,t)) \\ a_t(x,t) &= D_a\Delta u(x,t) + \beta u(x,t) - \mu a(x,t). \end{aligned}$$

This is the Keller-Segel model (1971) [38, 48]. Of course, many versions are investigated by now, introducing nonlinearities at all possible (and impossible) terms. Luckhaus and Jäger showed 1992 that this equation exhibits a blow-up in finite time for appropriate initial conditions [34], i.e. this structure is sufficient to explain the aggregation for *Dyctostelium*.

4.5 Exercise

Exercise 4.1:
Consider a linear, time-continuous birth-death process. Assume that we start with i individuals. Solve the master equations for this case. How large is the probability of extinction?

Exercise 4.2:
(a) Consider a population of bacteria reproducing in a (living) host with rate β (independent of the population size of the bacteria) and do not die. How large is the population size after time a, if the host is infected at time zero with one bacterium? Which distribution does the population follow?
(b) Now add to the model above the mortality of the host. The death rate of the host is (in dependence of the bacteria load)

$$\mu(i \text{ bacteria}) = \mu_0 + i\mu_1.$$

Which states do we have to consider? Derive the master equations and the PDE for the generating function. Find the expected load of bacteria at time a after infection under the condition that the individual is alive. Find the average mortality rate after time a of infection.
(c) *(Modeling)* Derive a deterministic model for the host population structured by age since infection. What can be said about this population (equilibrium age distribution, average virus load of a randomly chosen infected individual etc).

Exercise 4.3:
Consider a polymer that consists of simple molecules. These simple molecules (monomers) are small linear chains that are able to bind at booth ends to other molecules of the same type. Furthermore, the end points of a polymer may also bind together and then the polymer forms a ring. Assume (for simplicity) that only monomers are able to bind to other monomers or polymers (that are no rings). Assume furthermore, that monomers are present in a constant density (and thus the rate for prolonging a polymers by one monomer is constant). Also, assume that the rate to form a ring is constant and independent of the length of the polymers. Find the length distribution and density of rings (structured by length) if the reaction is stopped after time t.

Exercise 4.4:
A model for a population, structured by size, reads

$$u_t + (g(x)u)_x = -\mu(x)\, u, \qquad g(0)u(t,0) = \int_0^\infty b(x)u(t,x)\, dx.$$

Here, x denotes the size, $u(t,x)$ the population density structured by size, and $g(x)$ the growth rate from an individual of size x. Assume that it is sufficient to consider the point spectrum in order to determine if the population will grow or decrease. Find a criterion simular to R_0 that determines if the population tends to infinity or to zero.

Exercise 4.5:
Consider an age structured population of fish. Assume that this population is harvested with a certain rate. Assume that one harvested fish yields a certain gain (money per fish), and that the costs for the harvesting effort is proportional to the harvesting rate. Assume (for a given harvesting rate) the population to be in equilibrium. Determine the overall gain (gain for the fish minus effort for the harvest). Maximize the gain.

Exercise 4.6:
Consider a one-dimensional model for bacteria that are sensitive for the gradient of a chemical additive: They will move towards the positive gradient of this additive. Find a model (starting from the master equations, and then taking the limit until we reach a PDE).

Exercise 4.7:
Consider the following model for a growing and diffusing population. Let $u(x,t) = S_1(t)u_0$ the solution at time t of

$$u_t(x,t) = \alpha u(x,t), \qquad u(x,0) = u_0.$$

Let furthermore $u(x,t) = S_2(t)u_0$ the solution at time t of

$$u_t(x,t) = D\Delta u(x,t), \qquad u(x,0) = u_0.$$

Now assume that the population switches every Δt between growing and diffusion, i.e.

$$u(n\,\Delta t, x) = \Pi_{i=1}^n \left(S_1(\Delta t)S_2(\Delta t)\right) u_0.$$

Let Δt tend to zero while n tend to ∞, s.t. $t = n\,\Delta t$ is constant. Show that in the limit (do we really need the limit?) we obtain $u(x,t) = S_t u_0$, where S_t is the solution operator of the equation of

$$u_t = D\Delta u + \alpha u, \qquad u(x,0) = u_0(x).$$

Exercise 4.8:
Consider the conservation equation $\partial_t u(x,t) = -\partial_x j(x,t)$ with the flow

$$j = \frac{1}{2}u^2.$$

This equation is called Burger's equation (and is e.g. used to model traffic flow on a highway). Let furthermore

$$\phi(x;\alpha,\beta) = \begin{cases} \alpha & \text{for} \quad t < 0 \\ \alpha + (\beta - \alpha)x & \text{for} \quad t \in [0,1] \\ \beta & \text{for} \quad t > 1 \end{cases}$$

(a) Find characteristic curves, i.e. curves $x(t)$ s.t. $u(x(t),t) \equiv C$ = constant. (Note: these curves will depend on C).
(b) Under which condition on α, β does the Burger's equation exhibit a global, classical ($C^1(\mathbb{R})$) solution for the initial condition $u(x,0) = \phi(x;\alpha,\beta)$? What does happen, if there is no classical solution?

Exercise 4.9:
Consider a population that reproduce with rate α and stays in a region (one-dimensional, say) where outside this region the circumstances are hostile (e.g. the animals are only able to survive within forest but not outside). The *Spruce Budworm* may be an example. We obtain the first-order approximation for the dynamics

$$u_t = D\,u_{xx} + \alpha u, \qquad u(0,t) = u(L,t) = 0$$

where $[0,L]$ denotes the (one-dimensional) habitat of the population. Find a criterion that ensures that the population persists (does not die out).

Exercise 4.10:
(a) Consider the correlated random walk in a finite interval $[0,L]$. Find boundary conditions that are appropriate for the situation considered in Exercise 2.
(b) Develop a complete model for the situation of Exercise 2 and find conditions s.t. a positive stationary solution exists.

Exercise 4.11:
Consider the coupled equations

$$\begin{aligned} u_t &= D_1 u_{xx} + au + bv, \qquad u(0,t) = u(L,t) = 0 \\ v_t &= D_2 v_{xx} + cu + dv, \qquad v(0,t) = v(L,t) = 0. \end{aligned}$$

Find situations, where diffusion destabilizes the system. I.e., for $D_1 = D_2 = 0$ all eigenvalues do have negative real part, while it is possible to chose $D_1, D_2 > 0$ s.t. there emerge eigenfunctions which have eigenvalues with a positive real part.

Part Two:
Interacting Entities - The Nonlinear Case

5 Logistic Equation

The logistic equation describes one homogeneous population competing for a resource. This situation is the prototype to study interaction and nonlinear models. Many ideas we develop here will carry over to other situations. Thus we will spend quite a while to investigate this (on the first glance relatively simple) system.

5.1 Experimental Setup

One key experiment has been performed in the thirties of the last century. At this time, people have been interested to study laboratory-setups for population dynamics and to check quantitatively (not only qualitatively) the prediction of mathematical models. Unfortunately, this line of research almost died out; in these days, we find a reemerging of these approaches (we will discuss below an example by Cushing [12]). The biological model organisms investigated in the first half of the last century have especially related to bacteria, phyto- and zooplancton. These systems are small, relatively easy to handle (if you are a trained biologist) and show in relatively short time interesting behavior.

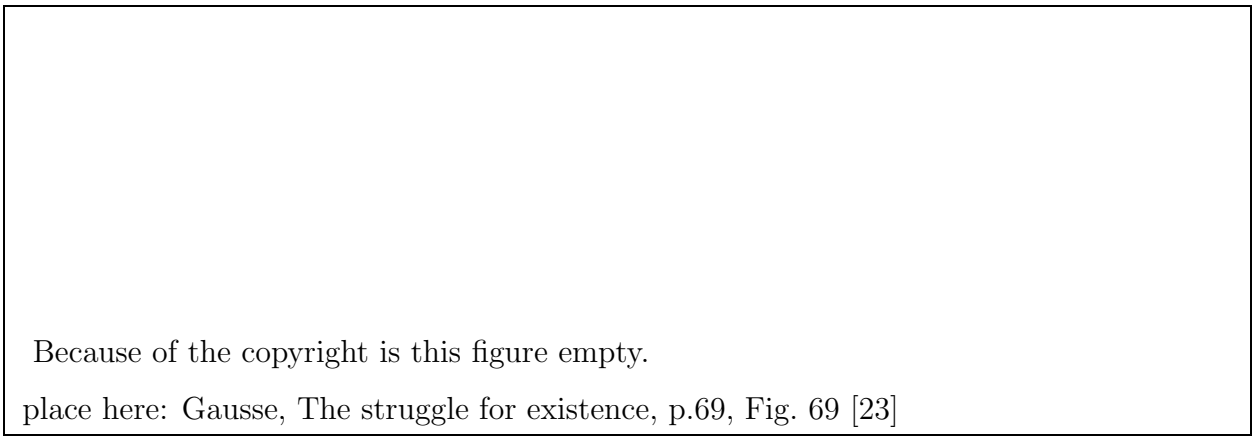

Figure 57: Population dynamics of yeast in a sugar solution.

Gausse [23] has been especially interested in yeast. The experiment we are interested in the population dynamics of only one yeast species *Saccharomyces cervesia* in a sugar solution (see Fig. 57). The experiment starts with a low amount of yeast, which shows in the initial phase an almost exponential growth. Later, the amount of sugar will decrease

and the yeast has to compete for resources (the sugar). Another component of this competition may be the poisoning by alcohol.

5.2 Deterministic Logistic Equation: Continuous Time

The first, and perhaps most simple approach is a time-continuous deterministic equation. Of course, this deterministic equation is only an approximation of the expected value of the underlying (nonlinear) birth-death process, the yeast performs. We will consider this birth-death process later.

The Model

Since this model is well known (and rather simple), we will keep the description rather short.

State: Density of yeast at time t, $x(t)$.

Dynamics: We do have two processes, birth and death. Due to competition, the birthrate is a decreasing and the death rate is an increasing function of the population size. The simplest assumption is a linear dependence.
Birth: Birth rate $\beta(x) = \beta_0 - \beta_1 x$
Death: Death rate $\mu(x) = \mu_0 + \mu_1 x$

Hence, we find the model

$$\dot{x} = \beta(x)\, x - \mu(x)\, x = (\beta_0 - \mu_0)x - (\beta_1 + \mu_1)x^2 = rx(1 - x/K)$$

with

$$r = \beta_0 - \mu_0, \qquad K = \frac{\beta_0 - \mu_0}{\beta_1 + \mu_1}.$$

This equation is called the logistic equation (or the time-continuous logistic equation).

Of course, this model is very simple, and it is easy to criticize this approach: E.g., if we start with a population size $x(0) > \beta_0/\beta_1$, the birth rate $\beta(x(0))$ becomes negative (this is rubbish! the birth rate may become zero, but never negative!). Or, the resources (sugar, alcohol) are not explicitly incorporated. On the other hand, one may view $\beta(x)$ and $\mu(x)$ as linearized net birth- and death rates of a more complex model (linearization taken at $x = 0$). Thus, the model is valid only if the population size x does not become too large; otherwise the second order terms cannot be neglected. In this sense, we do have some justification for the model. Also, we will test it against the data.

We expect some qualitative insight by the analysis of this model; if the model is also able to be used in a quantitative way can by only decided by the comparison with real world data.

Analysis

One can find an explicit solution for the ordinary differential equation,

$$x(t) = \frac{K\frac{x(0)}{K-x(0)}e^{rt}}{1+\frac{x(0)}{K-x(0)}e^{rt}}.$$

From the equation $\dot{x} = rx(1-x/K)$, we find at once the stationary points,

$$\dot{x} = 0 \quad \Leftrightarrow \quad x \in \{0, K\}.$$

We want to consider this structure more in detail. Therefore, we use the definition of K,

$$K = \frac{r}{\beta_1 + \mu_1} = \frac{r}{r_1}$$

with $r_1 = \beta_1 + \mu_1$. In this setting, we find the stationary points to be $x_0 = 0$ and $x_1 = r/r_1$. The stationary point x_1 is only positive if $r > 0$, i.e. $\beta_0 > \mu_0$: without competition, the birth rate has to be larger than the death rate in order to ensure the existence of an equilibrium with a positive population density.

We now consider the stability of the stationary points. Since we are in an one-dimensional setting, this "stability analysis" can be done in a graphical way. First we need some idea about stability.

Definition 5.1: *A stationary point $\overline{x}$ of an ordinary differential equation $\dot{x} = f(x)$ is called locally stable, if there is a neighborhood $U(\overline{x})$ s.t. for all trajectories $x(t)$ with $x(0) \in U(\overline{x})$, we find*

$$\lim_{t\to\infty} x(t) = \overline{x}.$$

If this is not the case, the point is called unstable.

Often enough, this definition is formulated in a slightly different way due to the following reason: consider a line of stationary points. According to our definition, every point is an unstable stationary point, because any small perturbation is never decreased to zero again. However, on the other hand, the perturbation will not increase. Thus, one may say that also these stationary points are locally stable.

Remark 5.2: If we consider $\dot{x} = f(x)$, and $x \in \mathbb{R}$, then $x(t)$ is increasing for $f(x) > 0$ and decreasing for $f(x) < 0$; if $f(\overline{x}) = 0$, we have an equilibrium. From this, we find that $f'(\overline{x}) < 0$ implies that $\overline{x}$ is locally stable, while the consequence of $f'(\overline{x}) > 0$ is instability of the stationary point (see Fig. 58). In general, this criterion can be extended: if we consider an ODE $\dot{x} = f(x)$, $x \in R^n$, $f(\overline{x}) = 0$, then this stationary point is locally stable, if the spectrum of the Jacobian of f at $\overline{x}$ is completely contained in the negative half plane of the complex plane [2].

Proposition 5.3: *We find for $r < 0$ that $x_0 = 0$ is locally stable while $x_1 = r/r_1$ is unstable, and the reversed stability structure for $r > 0$.*

The proposition is an immediate consequence of the remark about one dimensional ordinary differential equations. This situation we have is called transcritical bifurcation (see

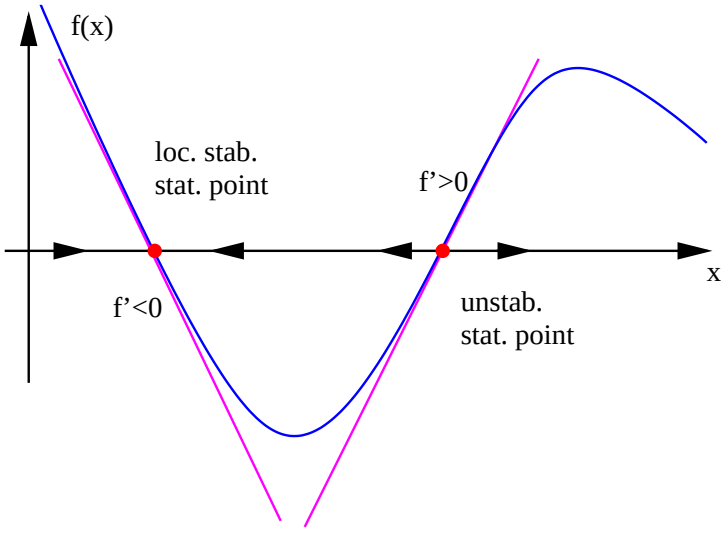

Figure 58: Stability of stationary points of $\dot{x} = f(x)$.

e.g. [27]). Two stationary points cross and exchange their stability (see Fig. 59). This bifurcation is quite typical for population dynamics: if the conditions are too poor, the population dies out; if the resources crosses a certain threshold, the population becomes endemic. Secondary bifurcations may then lead to periodic behavior or alike. We will find several examples for transcritical solutions later.

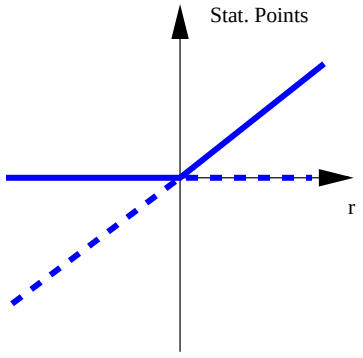

Figure 59: Branching diagram for the logistic equation.

Real World Data

Consider again the data from Fig. 57. It is easily possible to estimate the parameters r and K in a handwaving way: r can be estimated from the initial phase. There, the growth is approximately exponential. Hence, a semilogarithmic representation leads to a linear function with r as slope. The parameter K is just the asymptotic value. Using these methods, one derives the continuous function shown in Fig. 57. The logistic equation

seems to fit the data very well. Though is is a very simple model (perhaps the most simple model for interacting entities), it meets in this case the reality not only in a qualitative but in a quantitative way.

5.3 Deterministic Logistic Equation: Discrete Time

Like before, we will only briefly touch the time-discrete deterministic logistic equation. Much more can be found in the book of Devaney [14]. The discrete logistic equation is often introduced as discretization of the time-continuous logistic equation. This approach is not appropriate - if some of the effects discussed below appear in the time-discretization of an ordinary differential equation, this is a sign that the discretization parameter is chosen too large. Like discussed before, a better approach is an external clock like the seasons.

State: The state x_n denotes the population size at time step n.

Dynamics: The dynamics is given by

$$x_{n+1} = r\, x_n(1 - x_n/K).$$

Remark 5.4: **(1)** Rescaling ($y_n = x_n/K$) yields a one-parameter family of maps,

$$y_{n+1} = r y_n(1 - y_n) =: F_r(y_n).$$

This is the so-called quadratic family.

(2) The stationary points of this map are given by fixed points of F_r, $y = F_r(y)$. Hence,

$$y_0 = 0, \qquad y = 1 - 1/r.$$

In the discrete case, local stability can be defined in a similar way like in the continuous case:

Definition 5.5: *A stationary point $\overline{x}$ of an iterative equation $x_{n+1} = f(x_n)$ is called locally stable, if there is a neighborhood $U(\overline{x})$ s.t. we find for all trajectories x_n with $x_0 \in U(\overline{x})$,*

$$\lim_{n\to\infty} x_n = \overline{x}.$$

Remark 5.6: **(1)** The stability of the discrete and the continuous case are linked. If we consider the time-one map of a time-continuous system (an ordinary differential equation) we find a discrete map. If we look at a linear system,

$$\dot{x} = Ax$$

the time-one map is

$$F(x) = e^A x.$$

Assume that the eigenvalues of A are contained in the negative half-plane of $\mathbb{C}$ (and thus the stationary point $x = 0$ is locally stable). Then,

$$\sigma(e^A) \subset \{e^\lambda \,|\, \lambda \in \sigma(A) \subset \mathbb{C}^-\} \subset \{|z| < 1\}.$$

Thus, we find a similar criterion for stability in the discrete case:

If the spectrum of the linearization of a discrete iterative function is contained in the unit circle, the stationary point is locally stable (in a certain sense, this is another version of the Banach Fixed Point Theorem).

(3) We find easily, that $y = 0$ is stable for $r < 0$. For $r \in (0, 2)$, the fixed point $y_2 = 1-1/r$ is locally stable. What does happen for $r = 2$? An (the) eigenvalue crosses "-1" if r crosses $r = 2$. We find, that for $F_r \circ F_r(y)$ three fixed points appear at $r = 2$ (by a pitchfork bifurcation). Hence, F_r exhibits a period-two orbit for $r > 2$. If an eigenvalue crosses "-1", under generic conditions we have a period doubling bifurcations, i.e. a periodic orbit of period two appears.

(4) This period doubling is a whole cascade – periodic orbits of period 2, 4, 16, 32... appear subsequentially. These bifurcation points cumulate and then we find chaotic behavior of this dynamical system (Fig. 60).

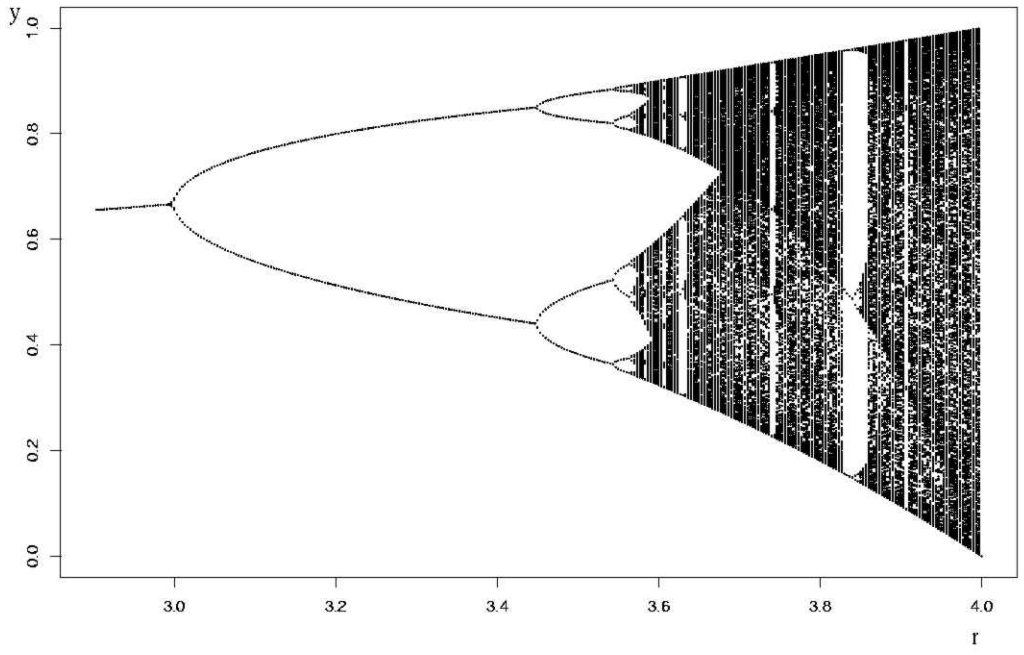

Figure 60: Period doubling cascade for the discrete logistic equation.

It is under debate, if this chaotic behavior appears in ecological systems or not. The basic problem comes from the fact that in most ecological systems, there is a strong stochastic perturbation (weather, temperature etc.) that makes it almost impossible to decide if irregular structure in data are due to stochastic perturbations or due to chaotic dynamics. In a sequence of papers, Constantino, Cushing [12] and coworkers tried to approach this problem. They did not consider a system that can be modeled by a function that maps the unit interval in itself, but they looked at an experiment that demands (at least) a three dimensional iterative equation: they considered certain strains of flour beatles *Tribolium*. These beatles lay eggs; from these eggs larvae hedge that eventually become adults. The system is non-trivial in the sense, that these beatles perform cannibalism. This behavior helps the species to survive if the food supply is short. However, cannibalism introduces a negative feedback (that is necessary to find nontrivial behavior). Cushing develops a three-dimensional discrete model. As the bifurcation parameter, the mortality of the adults is used. In the experiment, it is non-trivial to change this bifurcation parameter (i.e. to change the mortality of the adults). This has been implemented in the way, that the experimenters computed the expected number of animals that should have died in a certain time period (given a certain mortality rate), and then corrected the actual number of dead animals in removing or adding the difference (if too many animals died, then additional adults have been introduced in the system; if too many animals survived, the according number of animals have been removed from the system). This influence on the experiment has been subject of a quite controversy discussion. The measurements have not been taken from a free-running population, but from an influenced population. It is perhaps a kind of subjective opinion, if one believes that the resulting time series can be taken as that of a "real" population with given mortality or only that of an artificially system that does not give hints on real-world-population dynamics.
However, the result is quite striking (see Fig. 61). The time series of the biological system seems to meet quite well the predictions of the model equations. These experiments seem to hint, that the predictions of mathematical models do meet important features of reality, s.t. one expects also chaotic dynamics to contribute in certain ecological systems to the irregularity and unpredictability of ecological time series.

5.4 Branching Process

We now present a stochastic version of the logistic birth-death process. The stochasticity does not come from a stochastic perturbation (due to whether, ambient temperature etc., like assumed for ecological models), but due to an intrinsic variation of the number of children of one individual. We only consider the time-dependent case; it is straight forward to work out the parallel the arguments in the time-discrete case.

5.4.1 The Model

The idea of the logistic model is the competition for resources. Hence, the birth rate is decreased, and the death rate increased by the population size. For simplicity, we only

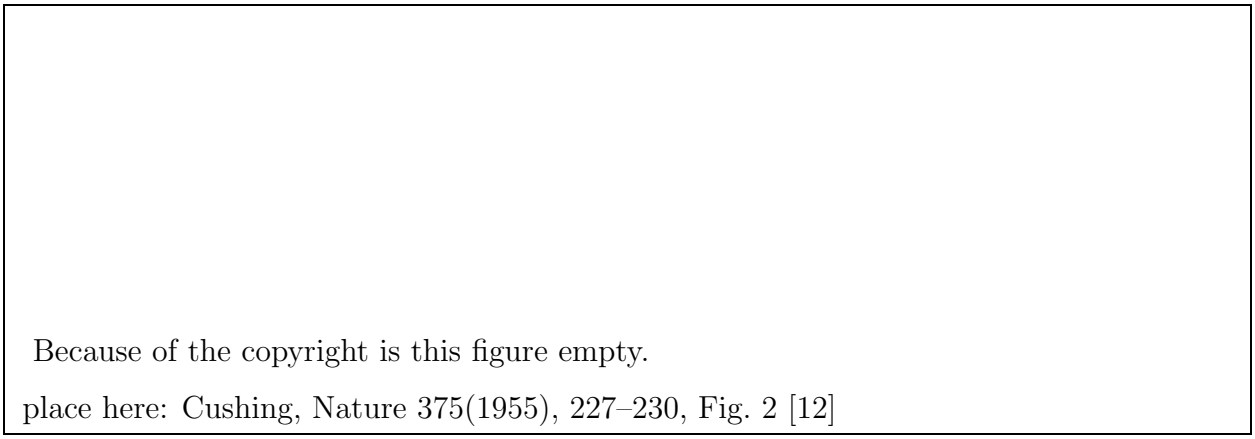

Figure 61: Predictions and data in the flour-beetle experiments.

look at the decrease in the birth rate and assume that the death rate is independent of the population size.

State: Let X_t =number of individuals at time t.

Dynamics: We have two processes, birth and death.

- Birth rate: $b(X_t) = \beta(1 - X_t/N)$, $N \in \mathbb{N}$, i.e.

$$P(X_{t+\Delta t} = X_t + 1) = \beta(1 - X_t/N)X_t\Delta t + o(\Delta t).$$

- Death rate: $\mu(X_t) = \mu$, i.e.

$$P(X_{t+\Delta t} = X_t + 1) = \mu X_t\Delta t + o(\Delta t).$$

The population size cannot exceed the maximal population size N, since for $X_t = N$ we find $b(X_t) = 0$. From this fact it is possible to conclude that the population dies out with probability one (see exercise 5.3). E.g. all species at the earth certainly do have a finite carrying capacity, i.e. the population on earth is bounded. Thus it has to die out. This is not what we observe. This seemingly contradiction is one of the interesting issues that has to be clarified.

5.4.2 Analysis I: Large population size

In order to analyze this process, one may scale it in certain (different) ways. We let always $N \to \infty$ (s.t. the nonlinearity becomes weaker and weaker). At the same time, one may rescale time resp. bound he time in a certain way. The scaling of the time is crucial for the result.

If $N \to \infty$, we may scale the process such that we derive an ODE. Let $Z_t = X_t/N$, then

$$\begin{aligned} P(Z_{t+\Delta t} = Z_t + 1/N) &= \beta(1 - Z_t)Z_tN\Delta t + o(\Delta t) \\ P(Z_{t+\Delta t} = Z_t + 1/N) &= \mu Z_tN\Delta\, t + o(\Delta t) \end{aligned}$$

If we rescale time $t = \tau/N$, we find for $N \to \infty$, that $Z_t \to z(t)$, where

$$\dot{z} = -\mu z + \beta(1 - z)\, z,$$

i.e. the scaled process approaches the logistic equation. The proof can be found in the paper by Kurtz [39].

5.4.3 Analysis II: Linearization

The second scaling let $N \to \infty$, but - at the same time - bounds the time. In this way, one derives a similar structure like the linearization at stationary points for nonlinear ordinary differential equations: Though the equation is nonlinear, under certain conditions (all eigenvalues of the linearization have non-vanishing real part), the dynamics of the linearized equations is locally homeomorph to the dynamics of the nonlinear system (Theorem of Hartman-Grobman [27]). We are able to prove a similar theorem for the stochastic system. The basic idea of the present section follow Ball and Donnelly [5]; however, we strongly simplify the proof and derive a weaker result.

Construction of the linear and the logistic birth-death process (coupling of the processes):

Let $(\Omega, \mathcal{F}, P)$ be a random space. Consider tow stochastic processes, defined simultaneously on this random space:

(1) Linear Birth-Death Process:
Let $Y_t(\omega)$, $\omega \in \Omega$, denote the population size of a realization of the linear birth-death process with birth rate β (independent of the population size) and death rate μ.

(2) Logistic Birth-Death Process:
We construct the population size X_t of the logistic birth-death process in the following way: apart from living individuals we define a population of ghosts with population size Z_t. X_t and Z_t are random variables that are defined on the same random space $(\Omega, \mathcal{F}, P)$, and thus we are able to relate single realizations $(X_t(\omega),\, Z_t(\omega))$ to $Y_t(\omega)$ s.t.

$$Y_t(\omega) = Z_t(\omega) + Y_t(\omega).$$

Birth:
• Every individual (Ghost or living individual) of the logistic process do have the constant birth rate β (independent of the population size).
• A newborn becomes with probability X_t/N a ghost.
• Children of a ghost are again ghosts.
Death:
All individuals ("normal individuals" or ghosts) die with the same death rate μ.

In a certain sense, the logistic process describes the linear birth-death process, where the individuals get one more attribute: they are either "normal individuals" or "ghosts". If we add the "normals" and the ghosts, we obtain the linear process. If we only consider the "normals", we obtain the logistic process. Booth processes agree until $Z_t(\omega) \neq 0$. We are now ready to prove the "linearization" result.

Approximation Result:

Theorem 5.7: *Let* $X_0 = 1$.
(a) *If* $\beta_0/\mu_0 < 1$, *then*

$$Z_t = 0 \qquad \text{a.s. for } N \to \infty, \qquad t \in I\!R_+.$$

(b) *If* $\beta_0/\mu_0 > 1$, *then for all* $T \in I\!R_+$, *we find*

$$Z_t = 0 \qquad \text{a.s. for } N \to \infty, \qquad t \in [0, T].$$

Proof: *Step 1:* Estimation of the number of birth events
Let $I = \mathbb{R}_+$ in case (a) and $I = [0, T]$ in case (b). For $\omega \in \Omega$, define

$$\hat{N}(\omega) = \sup_{t \in I} Y_t(\omega), \qquad \hat{B}(\omega) = \text{total number of birth events in } I \text{ of the linear process.}$$

We find $\hat{N}(\omega) \leq \hat{B}(\omega) + 1$. If we are in case (b), we may estimate the number of birth events by a pure birth process ($\mu = 0$) with birth rate β. The generating function of the population size in such a case is given by (see Proposition 4.1)

$$f(s,t) = \frac{-\beta s e^{\beta t}}{\beta(s-1) - (\beta s)e^{\beta t}}.$$

i.e. $\tilde{p}_i = P(i \text{ Individuals at time } T) \to 0$ for $i \to \infty$. Thus,

$$|\{\omega \in \Omega \,|\, \hat{B}(\omega) \text{ is not finite}\}| \leq \lim_{i \to \infty} p_i = 0.$$

If we are in case (a), we know from Proposition 4.2 that the population dies out with probability one. Hence, there is for every realization a stopping time $T(\omega)$, for that $Y_{T(\omega)}(\omega) = 0$. The argument above shows that again the number of births up to time $T(\omega)$ are bounded a.s., and thus again

$$|\{\omega \in \Omega \,|\, \hat{B}(\omega) \text{ is not finite}\} = 0.$$

Therefore, $B(\omega)$ is finite a.s.
Step 2: X_t and Y_t agree for $N \to \infty$.
The probability to create a ghost in an birth event at time t is

$$P(\text{Create ghost at time } t) = X_t/N \leq \hat{N}(\omega)/N.$$

The probability to nit create a ghost in a birth event taking place at time t reads

$$P(\text{no creation of a ghost at time } t) \geq 1 - \hat{N}(\omega)/N.$$

The probability to create no ghost at all in $\hat{B}(\omega)$ birth events is thus

$$P(\text{no ghost at all}) \geq (1 - \hat{N}(\omega)/N)^{\hat{B}(\omega)} \to 1 \qquad \text{for } N \to \infty.$$

Thus,

$$\lim_{N\to\infty} |\{\omega \in \Omega \,|\, Z_t(\omega) = 0 \text{ for } t \in I\}| = 0.$$

□

Remark 5.8: Ball and Donnelly are able to prove in the case $\beta_0/\mu_0 > 1$ that

$$Z_t = 0 \qquad \text{a.s for} \quad t \leq C\, \log(N)$$

where C has to be chosen in an appropriate way.

This is a first, partial answer to the problem that the population dies out for $N < \infty$ a.s.: If $\beta/\mu > 1$, the population is able to spread (without competition), while for $\beta/\mu < 1$, the population will die out anyway even if $N \to \infty$. However, in order to get an better idea of the two different cases (β/μ larger resp. smaller one) without taking the limit $N \to \infty$, we consider in the next section ideas about the time to extinction.

5.4.4 Analysis III: Quasi-Steady State

For the deterministic logistic equation, it has been possible to derive a nontrivial equilibrium (i.e. an equilibrium where the population is not extinct) if $\beta/\mu > 1$. This is not the case for the logistic birth-death process, since we know that the population dies out for sure (exercise 5.3). However, if $\beta \gg \mu$, we will (e.g. in a simulation) never find that the population dies out. In order to solve this seemingly contradiction, one considers the logistic process X_t under the condition that the process does not die out $\hat{X}_t = X_t | X_t > 0$. In the following we present some results due to Ingemar Nasell [50].

Definition 5.9: *The quasi-steady state of the logistic process is the asymptotical distribution of the random variable $\hat{X}_t = X_t|X_t > 0$, i.e. the asymptotic distribution of the logistic process under the condition that it does not die out.*

Proposition 5.10: *Let $\beta_i = i\,\beta(1 - i/N)$, $\mu_i = i\mu$ and*

$$A = \begin{pmatrix} 0 & \mu_1 & 0 & \cdots & 0 \\ 0 & -(\mu_1+\beta_1) & \mu_2 & \cdots & 0 \\ 0 & \beta_1 & -(\mu_2+\beta_2) & \cdots & 0 \\ 0 & 0 & \beta_2 & \cdots & 0 \\ & \cdots & \cdots & \cdots & \\ 0 & 0 & 0 & \cdots & -\mu_N \end{pmatrix} = \left(\begin{array}{c|cccc} 0 & \mu_1 & 0 & \cdots & 0 \\ \hline 0 & & & & \\ \vdots & & \hat{A} & & \\ 0 & & & & \end{array}\right)$$

The distribution of the quasi-stationary state

$$\hat{q}^* = (\hat{q}_1^*, .., \hat{q}_N^*)^T$$

is given by the nonlinear eigenvalue problem

$$\hat{A}\hat{q}^* = -\mu_1 \hat{q}_1^* \hat{q}^*.$$

Proof: First, we introduce some notations. Let

$$\begin{aligned} q_i(t) &= P(X_t = i), & \hat{q}_i(t) &= P(\hat{X}_t = i) \\ q(t) &= (q_0(t), .., q_N(t))^T, & \tilde{q}(t) &= (q_1(t), .., q_N(t))^T \\ \hat{q}(t) &= (\hat{q}_1(t), .., \hat{q}_N(t))^T, \end{aligned}$$

Then,

$$\dot{q} = Aq.$$

Since $\hat{X}_t = X_t | X_t > 0$, we find for $i = 1, .., N$

$$P(\hat{X}_t = i) = \frac{P(X_t = i \text{ and } X_t > 0)}{P(X_t > 0)} = \frac{P(X_t = i)}{1 - P(X_t = 0)}$$

i.e.

$$\hat{q}(t) = \frac{\tilde{q}(t)}{1 - q_0(t)}.$$

and

$$\begin{aligned} \frac{d}{dt}\hat{q}(t) &= \frac{1}{1-q_0(t)}\frac{d}{dt}\tilde{q}(t) + \frac{1}{(1-q_0(t))^2}\tilde{q}(t)\frac{d}{dt}q_0(t) \\ &= \frac{1}{1-q_0(t)}\hat{A}\tilde{q}(t) + \frac{1}{(1-q_0(t))^2}\tilde{q}(t)(\mu_1 q_1(t)) \\ &= \hat{A}\hat{q}(t) + \mu_1\hat{q}_1(t)\hat{q}(t) = (\hat{A} + \mu_1\hat{q}_1(t))\hat{q}(t) \end{aligned}$$

The quasi-steady state satisfies $\hat{q}'(t) = 0$, i.e.

$$(\hat{A} + \mu_1\hat{q}_1^*)\hat{q}^*(t) = 0$$

□

Remark 5.11: This nonlinear eigenvalue problem cannot be solved explicitly. However, there are several approximations possible (see [50]). The shape of the quasi-steady state will look completely different for $\beta/\mu < 1$ and $\beta/\mu \gg 1$ (Fig. 62): If $\beta/\mu < 1$, the distribution is monotonously decreasing with $\hat{q}_1$ is maximal: the trajectories "want" to die out, i.e. jump to population size zero, but are not allowed to. Thus, they are centered at small population sizes. If $\beta/\mu \gg 1$, then the distribution looks approximately normal with the mean given by the population size where birth and death balances,

$$i\mu = i\beta(1 - i/N) \qquad \Leftrightarrow \qquad i = N(1 - \mu/\beta).$$

Here, the population is naturally in its equilibrium, far away from zero population size. However, natural fluctuations (the normal distribution does have tails that reach to zero population size) will bring a trajectory from time to time (very seldom) close to extinction. In this case, the realizations of the original process $X_t(\omega)$ die out; thus these realizations eventually have to die out, though they are naturally centered around $N(1 - \mu/\beta)$, far away from zero.

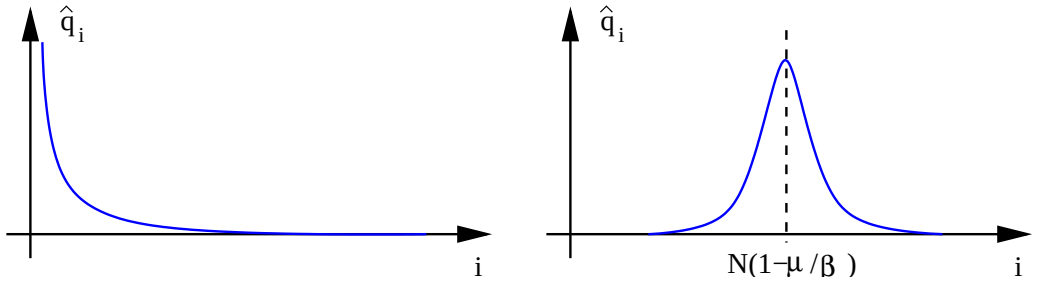

Figure 62: Sketch of the quasi-stationary distribution in the cases $\beta/\mu < 1$ and $\beta/\mu \gg 1$.

Another idea to characterize the two situations β/μ smaller resp. larger one is to consider the expected time to extinction. The time to extinction, however, depends on the initial population size. It is not clear how to choose this. The quasi-stationary state should represent the equilibrium distribution of the logistic process under th condition that it is not extinct jet. Thus it may be a good idea to define "the" time of extinction as the time of extinction if we start in the quasi-steady state. We find a relatively simple expression for expectation of the time to extinction.

Proposition 5.12: *Consider the logistic process starting in the quasi-stationary distribution $\hat{q}^*$. The expectation for the time to extinction is given by*

$$E(\text{time to extinction if } q(0) = (0, \hat{q}^*)^T) = 1/(\mu_1 \hat{q}_1^*).$$

Proof: We solve (with the nomenclature of the proof of the last theorem)

$$\dot{q} = Aq, \qquad q(0) = (0, \hat{q}^*)^T.$$

Thus,

$$\begin{aligned} \frac{d}{dt} q_0 &= \mu_1 \tilde{q}_1(t) \\ \frac{d}{dt} \tilde{q} &= \hat{A} \tilde{q}(t) \end{aligned}$$

Since $\tilde{q}(0) = \hat{q}^*$ is an eigenvector of $\hat{A}$, we find at once $\tilde{q}(t) = e^{-\mu_1 \hat{q}_1^* t} \hat{q}^*$. Thus

$$q_0(t) = \int_0^t \mu_1 (e^{-\mu_1 \hat{q}_1^* t} \hat{q}_1^*)\, dt = 1 - e^{-\mu_1 \hat{q}_1^* t}.$$

The expectation for the time to extinction now reads (where we used partial integration in the first step).

$$\begin{aligned} E(\text{time to extinction}) &= \int_0^\infty t \left(-\frac{d}{dt} P(\text{alive at time } t) \right) dt \\ &= \int_0^\infty (1 - q_0(t))\, dt = \int_0^\infty e^{-\mu_1 \hat{q}_1^* t}\, dt = 1/(\mu_1 \hat{q}_1^*). \end{aligned}$$

□

Application to ecological systems

The considerations above, concerning the time to extinction and to separate the cases β/μ larger or smaller one (if N is finite) are not of merely academic interest. At least in principle, these considerations can be used e.g. to get an idea how large to choose a nature reserve for a certain species. The aim would be to chose this reserve in such a way that the specie survives with a high probability a given time, e.g. 50 years. Unfortunately, a high effort is needed to set up a realistic model and to estimate the parameters of this model s.t. quantitative predictions are possible.

A case, where this has been done is the investigation about a planed reservoir for a certain butterfly (*Maculinea arion* [54, 26]). This butterfly has a funny live cycle: the eggs are placed in thyme. The larvae hedge and have to hibernate. They do this in a tricky way: the larvae "tell" a certain species of ants (*myrmica sabuleti*) that they are larvae of these ants. Consequently, the ants move the butterfly-larvae into their nests. There, the larvae hibernate (the butterfly hatch in the nests of the ants in the next spring, and then have to hurry out before the ants become aware that tasty butterflies are in their nests). The complete model takes into consideration the density of butterfly, thyme plants and ant nests etc., and - in this way - is able to predict the survival of the butterfly population. One result (dependence of the area size) is shown in Fig. 63. We find, that at least an area with a size of 4 ha is desirable.

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place here: E.M. Griebeler et al. Verh. Ges. Ökol. 29 (1995), p.201–206, Fig. 4 [26]

Figure 63: Probability of extinction (after 50 years) for the butterfly population over the protected area. Different ant nest-densities are assumed (cross: 150, circle: 200, closed diamond: 250, open diamond: 300 nests per ha.)

5.5 Spatially Structured Logistic Equation

The branching process has been concerned with a randomly mixing populations, i.e. ever entity interacts directly with any other entity. Of course, this setting is in general not realistic. Mostly, we find entities that interact locally, e.g. in a spatial setting. However, in the case that individuals move rather fast in comparison with the interaction, then one may neglect this structure (this is a typical time scale argument). Only if movement is slow or at a time scale comparable with the interaction, it is necessary to take into account booth aspects. We concentrate now on spatial structure, which is for sure the most important structure that should be considered. While the branching process is one extreme (spatial structure can be completely neglected), the contact process is the other extreme: the entities do not move at all, and only interact with the nearest neighbors. Since there are only very few strict results, we will investigate approximation techniques: the moment closure procedure and – more briefly – the rapid stirring limit. The latter yields the Fisher equation; since this equation plays a certain role in mathematical biology, we will investigate the Fisher (or KPP) equation more in detail.

5.5.1 Contact Process: Model

The contact process describes particles on a lattice (or a more general spatial structure). Briefly, particles die with a certain rate and give birth to other particles with a certain rate. The mother places these newborns at neighboring sites; if the site is already occupied, the newborn dies. Here we find the character of interaction/competition: the resource are (empty) sites. Now, let us introduce this stochastic process more precisely.

We first define the spatial structure (the grid Γ with the neighborhood of a site); then, we define the state of the system, and last, we define the dynamics (death and birth).

Definition 5.13: *Let $\Gamma = \mathbb{Z}^d$ or $\Gamma = \mathbb{Z}^d/\mathbb{Z}^d_m$ be a d-dimensional lattice or torus. Define for $x = 0 \in \Gamma$ the neighborhood $U(0)$; usual choices are $U(0) = \{x \in \Gamma \,|\, \|x\|_\infty \leq 1\}$ (Moore neighborhood) or $U(0) = \{x \in \Gamma \,|\, \|x\|_1 \leq 1\}$ (von Neumann neighborhood). Let $x + U(0)$ be the neighborhood of $x \in \Gamma$.*

A cell may be empty ("0") or occupied ("1"). The states of all sites yields the state of the system.

Definition 5.14: *Let $E = \{0, 1\}$ be the set of possible states of a site. The map*

$$\varphi : \Gamma \to E$$

yields the state of the system.

Now we introduce the dynamics; i.e., we define a random function $\varphi_t^{(\omega)}(x)$ that yields the state of the site x at time t in a certain realization ω.

Definition 5.15: *Let $(\Omega, \mathcal{F}, P)$ be a random space, and*

$$\varphi : \Omega \times \mathbb{R}_+ \times \Gamma \to E, \qquad \varphi(\omega, t, x) = \varphi_t^{(\omega)}(x)$$

a random variable that evolves according to

$$P(\varphi^{(.)}_{t+\Delta t}(x) = 0 \,|\, \varphi^{(.)}_t(x) = 1) = \mu\Delta t + \mathrm{o}(\Delta t)$$

and

$$P(\varphi^{(.)}_{t+\Delta t}(x) = 1 \,|\, \varphi^{(.)}_t(x) = 0) = \frac{\beta}{K}\#\{y \in U(x) \,|\, \varphi^{(.)}_t(x) = 1\}\,\Delta t + \mathrm{o}(\Delta t)$$

where $K = |U(0)| - 1$.

Here, K is introduced in order to compare different definitions of $U(0)$ in a fair way: The birth rate with that a site is occupied (given by the case that all neighboring sites of x are occupied) is always β, no matter how the shape of a neighborhood is chosen - Moore, von Neumann or different. Fig. 64 shows the time course of a realization of the 2-dimensional contact process. One finds that the number of occupied sites follow qualitatively a function similar to the solution of the deterministic logistic ordinary differential equation.

Remark 5.16: **(1)** If $|\Gamma|$ is not finite, it is non-trivial to prove that our definition yields a stochastic process, indeed. The problem is the fact, that in an infinite grid it is not clear that two events (change of a state) do not happen at the same time with probability one. The strategy to prove that the definition yields something that is reasonable is based on the observation (that has also to be proven) that in a small time interval Δt a cell is only influenced by the state of a finite number of cells close by. Thus, we find a certain form of localization of the process; for a finite number of cells, we find again that two events are separated by a positive time interval with probability one, and we are able to construct the stochastic process in the usual way (see [17]).

(2) If $|\Gamma| < \infty$, we find again that the process has to die out (the proof for the branching process can be reformulated for the contact process). However, also this case is of interest, since we will never find this extinction if the birth rate is high enough; we investigate this case in the moment closure approximation.

(3) Even for this simple process, there are only few hard results. There are some processes (e.g. voter model), where more is known - these processes can be related to peculation theory and the discrete random walk (see [17]). However, the contact process itself is of fundamental importance for many processes in biology, and therefore of special interest.

(4) The interesting questions are (like before) the probability of invasion (we place on an empty grid one particle and ask weather this particle may spread), and the persistence of a population (i.e. the existence of an invariant measure in the case that Γ is infinite resp. the time to extinction if Γ is finite). Unfortunately, there are no theorems that answer these questions completely; only partial answers are available. However, since even these partial answers require quite deep arguments, we will only consider approximation techniques that give in a heuristic way some hints about the behavior of the contact process.

5.5.2 Contact Process: Moment Closure Equations

Since there are (almost) no hard results, there is a large interest in approximation techniques. We find in simulations that the number of occupied sites follows an (almost)

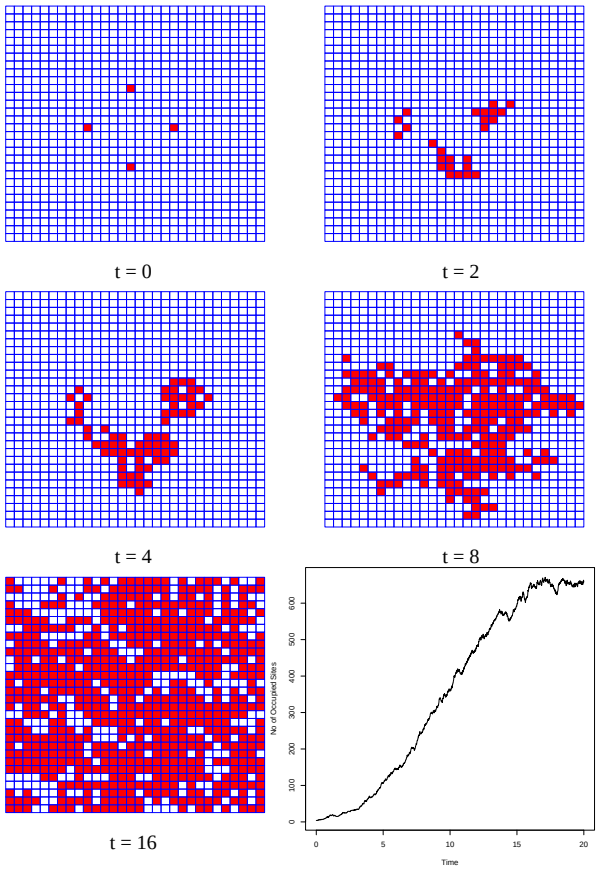

Figure 64: Time course of a 2-dimensional contact process ($\mu = 0.5$, $\beta = 2.0$). All sub-pictures show the state of the system at certain times, the last picture shows the number of occupied sites over time.

deterministic curve. Can we find an ordinary differential equation, describing (at least some features) of this curve? Early, the mean field approximation has been developed. In a certain sense, the mean field destroys all correlation; after every step (change of state), the particles are randomly re-distributed over Γ. Thus, the population is well mixed, and local correlations are destroyed. However, it is possible to derive an approximative ordinary differential equation for the number/the density of particles.

Mid of the 90's, one understood, that this technique can be generalized, and - in this way - it is possible to take spatial correlations into account (up to a certain degree). There are two approaches: the Japanese [63] and the European [37] approach. We present here (of course?) the European approach. The Japanese approach is concentrated on conditional probabilities (related to certain configurations), while the European approach focus on counting configurations. I.e., we count the number of, say, triplets (three neighboring cells) in the configuration "(0,1,1)", and try to develop an ordinary differential equation

for the expected value of the number of these configurations. In order to present the results without technicalities, we concentrate on the one dimensional case. The higher dimensional cases can be also approached in the same way; only some subtilities come in in addition.

This section is divided in four parts: (1) we derive equations for the expected values of the number of certain configurations; (2) we derive the mean field approximation; (3) we derive the pair approximation; (4) based on the pair approximation, we show numerically a threshold criterion that is different from that implied by the mean field approximation.

Counting Configurations
In order to do so, we need some definitions (basically, we follow [37]).

Definition 5.17: *Let $G_{v,v'}$ be the incidence matrix for the Graph implied by $(\Gamma, U(0))$, i.e.*

$$G(v,v') = \begin{cases} 1 & for \quad v' \in U(v) \setminus \{v\} \\ 0 & else \end{cases}$$

Then, define for one realization $\omega \in \Omega$ and $A, B, C \in E = \{0,1\}$

$$\begin{aligned} [A](t,\omega) &= \sum_{v\in\Gamma} \chi_{\varphi_t^{(\omega)}(v),A} \\ [A,B](t,\omega) &= \sum_{v_1,v_2\in\Gamma} \chi_{\varphi_t^{(\omega)}(v_1),A}\ \chi_{\varphi_t^{(\omega)}(v_2),B}\ G(v_1,v_2) \\ [A,B,C](t,\omega) &= \sum_{\substack{v_1,v_2,v_3\in\Gamma \\ v_1\neq v_2\neq v_3\neq v_1}} \chi_{\varphi_t^{(\omega)}(v_1),A}\ \chi_{\varphi_t^{(\omega)}(v_2),B}\ \chi_{\varphi_t^{(\omega)}(v_3),C}\ G(v_1,v_2)G(v_2,v_3) \end{aligned}$$

and the expectations

$$\begin{aligned} |[A]|(t) &= E([A](t,.)) \\ |[A,B]|(t) &= E([A,B](t,.)) \\ |[A,B,C]|(t) &= E([A,B,C](t,.)) \end{aligned}$$

Let furthermore (A,B,C) denote a corresponding configuration in the state of the system (in contrast to $[A,B,C]$ or $|[A,B,C]|$ that count the number of configurations).

Remark 5.18: **(1)** Note that due to symmetry, $[A,B](t,\omega) = [B,A](t,\omega)$ and $[A,B,C](t,\omega) = [C,B,A](t,\omega)$. Furthermore, $G(v,v) = 0$, i.e. a node of Γ is not its own neighbor. We will use this, when we sum $G(.,.)$ over Γ (see below).

(2) The number of configurations with symmetry is twice the number of configurations without symmetry, because we do not take into account the sequence/orientation of cells in the definition above. Consider the simple example in Fig. 65. We find for singletons

$$[0] = |\{v_1, v_2\}| = 2, \qquad [1] = |\{v_3, v_4\}| = 2.$$

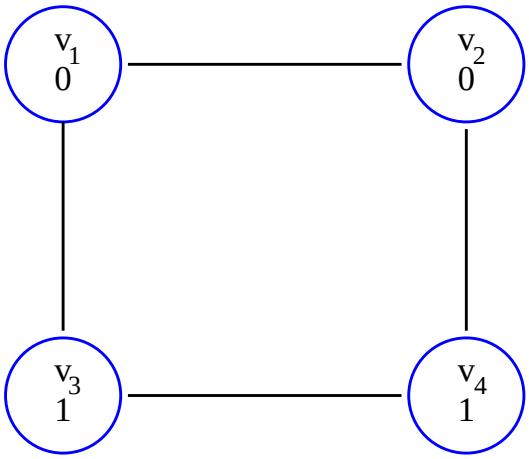

Figure 65: Example for counting of configurations.

and for pairs ((v_i, v_j) denotes here the ordered pair of the nodes v_i and v_j)

$$[00] = |\{(v_1, v_2), (v_2, v_1)\}| = 2,\ [01] = |\{(v_1, v_3), (v_2, v_3)\}| = 2,\ [11] = |\{(v_3, v_4), (v_4, v_3)\}| = 2.$$

While the number of $(0,1)$-pairs is exact, due to the symmetry we find that the pair (v_1, v_2) (which is the only pair with $(0,0)$) is counted twice. The same is the case for the number of $(1,1)$-pairs. Also in triplets, we find in general that $[1,0,1]$ are twice the number of triplets of this type that are actually there, while triplets without symmetry (like $(1,1,0)$) are counted with the correct number.

(3) It is now possible to write down at once differential equations for $|[A]|$, $|[A,B]|$ etc. However, we will derive these equations for the one-dimensional case in a more formal way, and only then interprete these equations s.t. we see how it is possible to derive the equations directly.

For the following considerations, we assume that Γ is a one-dimensional torus, i.e. the state is a finite sequence of zeros and one's, and, moreover, the last site is a neighbor of the first site. Let $K = 2 = |U(0)| - 1$. We first prove some statements about the relation between the number of certain configurations.

Proposition 5.19: *If $d = 1$, we find for any state that*

$$\begin{aligned}
[0] &= ([0,0] + [0,1])/2 = [0,0,0]/2 + [0,0,1] + [1,0,1]/2, \\
[1] &= ([0,1] + [1,1])/2 = [0,1,0]/2 + [0,1,1] + [1,1,1]/2, \\
[0,0] &= [0,0,0] + [1,0,0], \\
[0,1] &= [0,0,1] + [1,0,1], \\
[1,1] &= [0,1,1] + [1,1,1].
\end{aligned}$$

Note, that we suppressed the argument (t, ω) for $[.]$, since these relations are purely algebraic and hold for any configuration. They are not related to the construction of the

stochastic process. We will suppress this argument also within the proof (i.e. write $\varphi(v)$ instead of $\varphi_t^{(\omega)}(v)$).

Proof:
Step 1: Sum over G.
First, for any $v_1 \in \Gamma$ we find

$$\sum_{v_2 \in \Gamma} G(v_1, v_2) = K = 2$$

since this sum counts the numbers of neighbors of v_1. Furthermore, if $v_3 \in U(v_1) \setminus \{v_1\}$, we have

$$\sum_{\substack{v_2 \in \Gamma \\ v_2 \neq v_3}} G(v_1, v_2) = K - 1 = 1$$

since we again count the size of neighbors of v_1, but exclude one specific neighbor (i.e. v_3).

Step 2: From pairs to singletons.
Let $A \in E$, then

$$\begin{aligned}
[0, A] + [1, A] &= \sum_{v_1, v_2 \in \Gamma} \Big(\chi_{\varphi(v_1),0} \; + \; \chi_{\varphi(v_1),1} \Big) \, \chi_{\varphi(v_2),A} \; G(v_1, v_2) \\
&= \sum_{v_1 \in \Gamma} \chi_{\varphi(v_2),A} \sum_{v_2 \in \Gamma} G(v_1, v_2) = \sum_{v_1 \in \Gamma} \chi_{\varphi(v_2),A} \; K \\
&= 2\,[A].
\end{aligned}$$

Step 3: From triplets to pairs.
For every pair $[A, B]$, $A, B \in E$, we obtain

$$\begin{aligned}
[0, A, B] + [1, A, B] &= \sum_{\substack{v_1, v_2, v_3 \in \Gamma \\ v_1 \neq v_2 \neq v_3 \neq v_1}} \Big(\chi_{\varphi_t(v_1),0} \; + \; \chi_{\varphi_t(v_1),1} \Big) \, \chi_{\varphi(v_2),A} \; \chi_{\varphi(v_3),B} \; G(v_1, v_2) G(v_2, v_3) \\
&= \sum_{\substack{v_1, v_2, v_3 \in \Gamma \\ v_1 \neq v_2 \neq v_3 \neq v_1}} \chi_{\varphi(v_2),A} \; \chi_{\varphi(v_3),B} \; G(v_1, v_2) G(v_2, v_3) \\
&= \sum_{\substack{v_2, v_3 \in \Gamma \\ v_1 \neq v_2 \neq v_3 \neq v_1}} \chi_{\varphi(v_2),A} \; \chi_{\varphi(v_3),B} \; G(v_2, v_3) \sum_{v_1 \in \Gamma \setminus \{v_3\}} G(v_1, v_2) \\
&= \sum_{\substack{v_2, v_3 \in \Gamma \\ v_2 \neq v_3}} \chi_{\varphi(v_2),A} \; \chi_{\varphi(v_3),B} \; G(v_2, v_3)(K - 1) \\
&= [A, B].
\end{aligned}$$

Step 4: From triplets to singletons.

$$\begin{aligned}
\frac{1}{2}[0, A, 0] + [0, A, 1] + \frac{1}{2}[1, A, 1] &= \frac{1}{2}(\{[0, A, 0] + [1, A, 0]\}) + \frac{1}{2}(\{[0, A, 1] + [1, A, 1]\}) \\
&= \frac{1}{2}\left([A, 0] + 2[A, 1]\right) = [A].
\end{aligned}$$

□

Proposition 5.20: *We find for the expected values of the number of pairs and singletons in a certain configuration*

$$\begin{array}{rccccc}
\frac{d}{dt}|[0]| = & -|[0,0,1]|\frac{\beta}{K} & -\frac{1}{2}|[1,0,1]|\frac{2\beta}{K} & +\frac{1}{2}|[0,1,0]|\mu & +|[0,1,1]|\mu & +\frac{1}{2}|[1,1,1]|\mu \\
\frac{d}{dt}|[1]| = & |[0,0,1]|\frac{\beta}{K} & +\frac{1}{2}|[1,0,1]|\frac{2\beta}{K} & -\frac{1}{2}|[0,1,0]|\mu & -|[0,1,1]|\mu & -\frac{1}{2}|[1,1,1]|\mu \\
\frac{d}{dt}\frac{1}{2}|[0,0]| = & -|[0,0,1]|\frac{\beta}{K} & +0 & +2\,\frac{1}{2}|[0,1,0]|\mu & +|[0,1,1]|\mu & +0 \\
\frac{d}{dt}|[0,1]| = & 0 & -2\,\frac{1}{2}|[1,0,1]|\frac{2\beta}{K} & -2\,\frac{1}{2}|[0,1,0]|\mu & +0 & +2\frac{1}{2}|[1,1,1]|\mu \\
\frac{d}{dt}\frac{1}{2}|[1,1]| = & |[0,0,1]|\frac{\beta}{K} & +2\,\frac{1}{2}|[1,0,1]|\frac{2\beta}{K} & +0 & -|[0,1,1]|\mu & -2\frac{1}{2}|[1,1,1]|\mu
\end{array}$$

Proof: In order to derive these ordinary differential equations, we have to derive the probability for any event in a time interval Δt to occur (up to higher order). An event implies that the state of exactly one site is changed, either from "1" to "0" or vice versa. However, it is not enough to consider the site itself, but we have to keep track of configurations, i.e. we have to consider the whole neighborhood and to investigate the effect of this event (defined by the change of state in a certain neighborhood) on the vector

$$([0],[1],[0,0]/2,[0,1],[1,1]/2)^T.$$

Accordingly, we find five possible events: Death switches a "1" to "0"; this can happen in three neighborhoods,

$$(0,1,0)\to(0,0,0),\quad (0,1,1)\to(0,0,1),\quad (1,1,1)\to(1,0,1).$$

Birth toggles a "0" to "1"; here, only two neighborhoods are possible

$$(0,0,1)\to(0,1,1),\quad (1,0,1)\to(1,1,1),$$

since we need at least one "1" in the neighborhood and thus $(0,0,0)\to(0,1,0)$ is not possible. We discuss the birth event $(0,0,1)\to(0,1,1)$ in detail. The considerations of the other events parallel the arguments used here.

Probability for $(0,0,0)\to(0,1,0)$*:*

$$P((0,0,1)\to(0,1,1)) = [0,0,1]\beta/K\Delta t + o(\Delta t).$$

The probability for this event to occur in a (small) time interval Δt is the number of the configurations $(0,0,1)$ multiplied by the birth rate β, divided by the number of sites neighboring the central site in the triplet ($1/K$ is the probability that the child of the particle in the triplet $(0,0,1)$ is placed in the central site of this configuration) and multiplied by the length of the time interval. All following probabilities are derived in this way; one only has to take into account for birth the number of particles surrounding the

central (empty) site, and also the symmetry ($[A,B,A]$ has to be divided by two in order to obtain the actual number of triplets in the configuration (A,B,A)).

Effect of $(0,0,0) \to (0,1,0)$*:*

$$([0],[1],[0,0]/2,[0,1],[1,1]/2)^T \mapsto ([0]-1,[1]+1,[0,0]/2-1,[0,1],[1,1]/2+1)^T$$

i.e. one "0" vanishes and becomes a "1" ($([0],[1]) \mapsto ([0]-1,[1]+1)$). If we compare the configurations $(0,0,1)$ and $(0,1,1)$, we find that $(0,0,1)$ consists of one pair $(0,0)$ and one pair $(0,1)$, while $(0,1,1)$ consists of one pair $(0,1)$ and one pair $(1,1)$. Thus, one pair $(0,0)$ is destroyed and one pair $(1,1)$ created; the number of $(0,1)$-pairs is not changed,

$$([0,0]/2,[0,1],[1,1]/2)^T \mapsto ([0,0]/2-1,[0,1],[1,1]/2+1)^T$$

Again, the considerations are the same for all other events. We find

event	Birth (a) (0,0,1)→(0,1,1)	Birth (b) (1,0,1)→(1,1,1)	Death (a) (0,1,0)→(0,0,0)	Death (b) (0,1,1)→(0,0,1)	Death (c) (1,1,1)→(1,0,1)
Probabilities (up to higher order terms)	$[0,0,1]\frac{\beta}{K}\Delta t$	$\frac{1}{2}[1,0,1]\frac{2\beta}{K}\Delta t$	$\frac{1}{2}[0,1,0]\mu\Delta t$	$[0,1,1]\mu\Delta t$	$\frac{1}{2}[1,1,1]\mu\Delta t$
Effect on					
$[0]$	-1	-1	+1	+1	+1
$[1]$	+1	+1	-1	-1	-1
$\frac{1}{2}[0,0]$	-1	0	+2	+1	0
$[0,1]$	0	-2	-2	0	+2
$\frac{1}{2}[1,1]$	+1	+2	0	-1	-2

From that table, we are able to derive at once the ordinary differential equations. □

Proposition 5.21: *We find for the expectations of the number of pairs and singletons in a certain configuration*

$$\begin{aligned}
\frac{d}{dt}|[0]| &= -(\beta/K)|[01]| + \mu|[1]| \\
\frac{d}{dt}|[1]| &= +(\beta/K)|[01]| - \mu|[1]| \\
\frac{d}{dt}\left(\frac{1}{2}|[0,0]|\right) &= -(\beta/K)|[0,0,1]| + \mu|[0,1]| \\
\frac{d}{dt}|[0,1]| &= (\beta/K)\left\{|[0,0,1]| - |[1,0,1]| - |[0,1]|\right\} - \mu|[0,1]| + 2\mu\ \left(\frac{1}{2}|[1,1]|\right) \\
\frac{d}{dt}\left(\frac{1}{2}|[1,1]|\right) &= (\beta/K)\left\{|[1,0,1]| + |[0,1]|\right\} - 2\mu\ \left(\frac{1}{2}|[1,1]|\right).
\end{aligned}$$

Proof: We apply the rules from Proposition 5.19 to the differential equation of the last proposition and find e.g. for the first equation

$$\frac{d}{dt}|[0]| = -(|[0,0,1]|+|[1,0,1]|)\frac{\beta}{K}+(\frac{1}{2}|[0,1,0]|+|[0,1,1]|+\frac{1}{2}|[1,1,1]|)\mu = -|[0,1]|\frac{\beta}{K}+\mu|[1]|.$$

The other differential equations follow in a similar way.

□

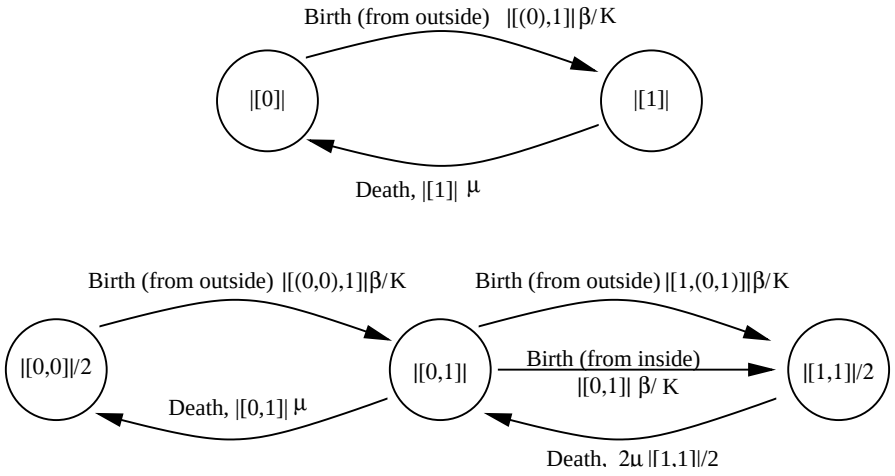

Figure 66: Dynamics of singletons and pairs as compartmental model.

Remark 5.22: The derivation of the ordinary differential equation has been quite tedious; moreover, obviously there is no unique representation of this differential equation, but one can derive also other forms (using the relations from proposition 5.19). However, one may interprete the form derived in the proposition above quite easily (and, following this interpretation, derive the corresponding differential equations also for more complex cases). We interprete the singletons and pairs as compartments. All we have to do is to specify the rates for transitions between these compartments (see Fig. 66). Consider the equation for [[0]]. There are two terms. The mortality term $\mu[1]$ is easily to interprete: a particle dies, and a "1" becomes a "0", with rate μ. The other term is concerned with birth. We consider a configuration "(0)". Birth can only take place, if a particle outside of this configuration places its offspring in this site. Hence, we find the event "birth from outside the configuration (0)", which takes place at the rate $[01]\beta/K$, since the configurations (01) describe exactly the configuration in which on individual (1) is able to place offspring in an empty site (0).
The same argumentation can be used for pairs: death is always simple to introduce, since no particle from outside of the configuration takes part in this event. Only in birth, one has to be aware that a particle outside of the configuration may place a child in an empty side of the configuration under consideration. These ideas yield immediately the transition graph in Fig. 66); the straight forward translation of this transition graph into differential equations yield the desired result.

Remark 5.23: **(1)** These equations for the expected values of singletons and doubles are exact. However, these equations do not help too much, since they are not closed (in the equation for singletons, the pair appear, and in the equations for pairs, also triplets show up). In order to derive differential equations we can work with, we have artificially to close these equations, i.e. (for the first order approximation that only takes into account the singletons) to express the number of pairs in terms of the singletons, and for the second order approximation (using singletons and pairs) to rewrite triples in terms of pairs and singletons. In this way we obtain the mean field approximation (first order) and the pair approximation (second order). Of course, it is possible to take into account larger and larger configurations, and derive equations for triplets, configurations with four, five,.. neighbors. If one approaches the size of the whole grid, one obtains a linear set of ordinary differential equations governing exactly the behavior of the system. This is nothing else but to derive the Perron-operator for this stochastic system (as we did in the example for the common cold Section 3.3.3), the state space is blown up until we derive a linear model. However, these equation do not help too much since they are quite high dimensional and do not provide insight. Thus the way how to deal with this structure is to close the moment equation at one point artificially, and - in this way - to obtain approximative equations.

(2) This foregoing is similar to the laws of Fick: The first law of Fick, that relates the zeroth moment (the density of mass) to the first moment of the velocity (the flux), is exact. However, in order to close the equation, the first moment (the flux) has to be related again to the zero moment (the density). This is the second law of Fick. Here, a certain ambiguity comes in; this law may be chosen in several ways.

First order dynamics: mean field equation

It is only possible to derive the equation for the moment closure in an heuristic way. The basic idea is to break the correlations on the corresponding level of the equation. Hence, in the mean field equation, no correlation at all is assumed to be there. There are different ways/models to derive the approximative equation [37]. We present here the most simple model.

We aim to know $|[0,1]|$, but we only know $|[1]|$ (and thus also $|[0]|$). If we assume, that Γ is large, and that there is no correlation between "0" and "1" (the last assumption is definitely wrong), we find that a cell has the probability $|[1]|/|\Gamma|$ to be in state "1". Assume that a site has state "0". This site has K neighbors, each of them with probability $|[1]|/|\Gamma|$ in state "1". Hence, the average number of pairs $(0,1)$ formed by one site with state "0" is $K|[1]|/|\Gamma|$, i.e. the expected number of pairs in the state $(0,1)$ is

$$|[0,1]| \approx K\ |[0]|\frac{|[1]|}{|\Gamma|}.$$

Using this idea – and $|[0]| = |\Gamma| - |[1]|$– we find the following mean field approximation.

Definition 5.24: *Let*

$$\begin{aligned}\frac{d}{dt}|[0]|_{(1)}(t) &= -\beta|[0]|_{(1)}\frac{|[1]|_{(1)}(t)}{|\Gamma|} + \mu|[1]|_{(1)}(t)\\ \frac{d}{dt}|[1]|_{(1)}(t) &= \beta|[0]|_{(1)}\frac{|[1]|_{(1)}(t)}{|\Gamma|} - \mu|[1]|_{(1)}(t)\end{aligned}$$

This equation is called the mean field equation for the contact process.

Remark 5.25: **(1)** We attach a one to $|[.]|$ in order to emphasize that this equation is (at least in some sense) the first order approximative equation for $|[.]|$.
(2) In the derivation, we assume a binomial distribution for the number of "1"-neighbors of a "0"-site. Indeed, it is a multinomial distribution, since we have information about the total number of "0" and "1". For large grids, however, this does not play a role.
(3) These equations yield

$$\frac{d}{dt}(|[0]|_{(1)}(t) + |[1]|_{(1)}(t)) = 0,$$

i.e. the ordinary differential equations respects the conservation law $|[0]| + |[1]| = |\Gamma|$. Hence, we may write

$$\frac{d}{dt}|[1]|_{(1)}(t) = \frac{\beta}{|\Gamma|}(|\Gamma| - |[1]|_{(1)})|[1]|_{(1)}(t) - \mu|[1]|_{(1)}(t),$$

i.e. we find in this case (again) the logistic equation. We already know the behavior of this equation. Especially, we find that the population may spread, if

$$\beta > \mu.$$

Unfortunately, especially for small dimensions ($d = 1, 2$), this threshold condition is much too optimistic. The simulations show, that the population is likely to go extinct for β much larger than μ (by the way: if Γ is finite, we know that the population goes extinct anyway. For Γ and β large enough, though, we expect the population to persist for a long time. And this long-time-persistence can be observed only for β much larger than μ). Partially, the correlations that lead to this threshold can be captured by the pair approximation.

Second order dynamics: pair approximation
With the same ideas in mind, we close the equation for the second moments, the pairs. In this case, we wish to derive the number of triplets of a certain configuration, if we only know the number of pairs (and thus, also the number of singletons). The idea is the same like in the mean filed approximation: Since we only know the pairs (i.e. correlations between neighbors), we only take these correlations into account and break all other correlations. One may think of this process as follows: We count the number of particles

(i.e. the number of "1") and pairs. Then, we "clear" all states and randomly redistribute the particles over the sites again. This step is repeated, until the number of pairs is exactly that from before. In this way, we keep the correlations over two sites (pairs) but completely destroy correlations over three sites (triplets). Thus, we are able to compute the number of triplets from the number of pairs. We assume that Γ is large. Then, the number of configurations $(0,0,1)$ can be written as the number of pairs $(0,0)$ times the probability to find a "1" next to a "0", i.e. times the number of pairs $[0,1]$ divided by the number of zeros, $[0]$. Hence,

$$[0,0,1] \approx ([0,0]/2)\,\frac{[0,1]}{[0]}.$$

We need the actual number of pairs of type $(0,0)$; thus we divide $[0,0]$ by two. We also could ask for the number of pairs $(1,0)$ multiplied by the probability to find a "0" next to a "0": this computation also yields $[0,1]\,[0,0]/[0]$. The procedure is symmetrically. Also the number of triplets of type $(1,0,1)$ can be found in this way,

$$[1,0,1]/2 \approx \frac{[0,1]^2}{[0]}.$$

Please note, that due to the symmetry $[1,0,1]$ is twice the number of triplets of this type; thus, we have to divide $[1,0,1]$ by two. If we close the equations with these terms, we find the pair approximation.

Definition 5.26: *The (classical) pair approximation of the contact process is defined as*

$$\begin{aligned}
\frac{d}{dt}|[0]|_{(2)} &= -\frac{\beta}{K}|[01]|_{(2)} + \mu|[1]|_{(2)} \\
\frac{d}{dt}|[1]|_{(2)} &= +\frac{\beta}{K}|[01]|_{(2)} - \mu|[1]|_{(2)} \\
\frac{d}{dt}\left(\frac{1}{2}|[0,0]|_{(2)}\right) &= -\frac{\beta}{K}\frac{|[0,1]|_{(2)}|[0,0]|_{(2)}}{|[0]|_{(2)}} + \mu|[0,1]|_{(2)} \\
\frac{d}{dt}|[0,1]|_{(2)} &= \frac{\beta}{K}\left\{\frac{|[0,0]|_{(2)}|[0,1]|_{(2)}}{|[0]|_{(2)}} - \frac{(|[0,1]|_{(2)})^2}{|[0]|_{(2)}} - |[0,1]|_{(2)}\right\} \\
&\qquad -\mu|[0,1]|_{(2)} + 2\mu\,\left(\frac{1}{2}|[1,1]|_{(2)}\right) \\
\frac{d}{dt}\left(\frac{1}{2}|[1,1]|_{(2)}\right) &= \frac{\beta}{K}\left\{\frac{(|[0,1]|_{(2)})^2}{|[0]|_{(2)}} + |[0,1]|_{(2)}\right\} - 2\mu\,\left(\frac{1}{2}|[1,1]|_{(2)}\right).
\end{aligned}$$

Remark 5.27: The nice aspect of this pair approximation (that is "the" pair approximation that can be found in literature) is the fact that the full system one starts with (Proposition 5.21) can be interpreted in terms of a compartmental system. The drawback is the fact, that only two of the three conservation laws is valid in the approximative equations; we find

$$\frac{d}{dt}\left([0]+[1]\right) = 0, \qquad \frac{d}{dt}\left(\frac{1}{2}[0,0] + [0,1] + \frac{1}{2}[1,1]\right) = 0$$

but we do not find that in general the expressions

$$\frac{d}{dt}\left([0]-([0,0]+[0,1])/2\right), \qquad \frac{d}{dt}\left([1]-([1,1]+[0,1])/2\right),$$

vanish. However, these two conditions reduce the five equations to three differential equations. We now propose an alternative pair approximation, starting directly from Proposition 5.21. The connection between pairs and triplets is the same like above, i.e.

$$[0,0,1] \approx ([0,0]/2)\,\frac{[0,1]}{[0]}, \quad [1,0,1]/2 \approx \frac{[0,1]^2}{[0]}, \cdots$$

Definition 5.28: *The alternative pair approximation of the contact process is defined as*

$$\begin{aligned}
\frac{d}{dt}|[0]|_{(\overline{2})} &= -\frac{|[0,0]|_{(\overline{2})}/2\,|[0,1]|_{(\overline{2})}}{|[0]|_{(\overline{2})}}\frac{\beta}{K} - \frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[0]|_{(\overline{2})}}\frac{2\beta}{K} + \frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[1]|_{(\overline{2})}}\mu \\
&\quad + \frac{|[0,1]|_{(\overline{2})}|[1,1]|_{(\overline{2})}/2}{|[1]|_{(\overline{2})}}\mu + \frac{1}{2}\frac{(|[1,1]|_{(\overline{2})}/2)^2}{|[1]|_{(\overline{2})}}\mu \\
\frac{d}{dt}|[1]|_{(\overline{2})} &= \frac{|[0,0]|_{(\overline{2})}/2|[0,1]|_{(\overline{2})}}{|[0]|_{(\overline{2})}}\frac{\beta}{K} + \frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[0]|_{(\overline{2})}}\frac{2\beta}{K} \\
&\quad - \frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[1]|_{(\overline{2})}}\mu - \frac{1}{2}\frac{(|[1,1]|_{(\overline{2})}/2)^2}{|[1]|_{(\overline{2})}}\mu \\
\frac{d}{dt}|[0,0]|_{(\overline{2})} &= -\frac{|[0,0]|_{(\overline{2})}/2|[0,1]|_{(\overline{2})}}{|[0]|_{(\overline{2})}}\frac{\beta}{K} + 2\,\frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[1]|_{(\overline{2})}}\mu + \frac{|[0,1]|_{(\overline{2})}|[1,1]|_{(\overline{2})}/2}{|[1]|_{(\overline{2})}}\mu \\
\frac{d}{dt}|[0,1]|_{(\overline{2})} &= -2\,\frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[0]|_{(\overline{2})}}\frac{2\beta}{K} - 2\,\frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[1]|_{(\overline{2})}}\mu + 2\frac{1}{2}\frac{(|[1,1]|_{(\overline{2})})^2}{|[1]|_{(\overline{2})}}\mu \\
\frac{d}{dt}|[1,1]|_{(\overline{2})} &= \frac{|[0,0]|_{(\overline{2})}/2\,|[0,1]|_{(\overline{2})}}{|[0]|_{(\overline{2})}}\frac{\beta}{K} + 2\,\frac{1}{2}\frac{(|[0,1]|_{(\overline{2})})^2}{|[0]|_{(\overline{2})}}\frac{2\beta}{K} \\
&\quad - \frac{|[0,1]|_{(\overline{2})}|[1,1]|_{(\overline{2})}/2}{|[1]|_{(\overline{2})}}\mu - 2\frac{1}{2}\frac{(|[1,1]|_{(\overline{2})})^2}{|[1]|_{(\overline{2})}}\mu
\end{aligned}$$

Remark 5.29: **(1)** We find

$$\frac{d}{dt}\left(|[0]|_{(\overline{2})}+|[1]|_{(\overline{2})}\right)=0, \qquad \frac{d}{dt}\left(\frac{1}{2}|[0,0]|_{(\overline{2})}+|[0,1]|_{(\overline{2})}+\frac{1}{2}|[1,1]|_{(\overline{2})}\right)=0,$$
$$\frac{d}{dt}\left(|[0]|_{(\overline{2})}-(|[0,0]|_{(\overline{2})}+|[0,1]|_{(\overline{2})})/2\right)=0$$

and from these equations it is possible to conclude that also

$$\frac{d}{dt}\left(|[1]|_{(\overline{2})}-(|[1,1]|_{(\overline{2})}+|[0,1]|_{(\overline{2})})/2\right)=0.$$

Hence, we have three invariant expressions. Using these expressions, we may reduce the five differential equations to two equations. We find

$$\begin{aligned} |[0]|_{(\overline{2})} &= (|[0,0]|_{(\overline{2})} + |[0,1]|_{(\overline{2})})/2, \\ |[1]|_{(\overline{2})} &= |\Gamma| - (|[0,0]|_{(\overline{2})} + |[0,1]|_{(\overline{2})})/2, \\ |[1,1]|_{(\overline{2})} &= 2\,|\Gamma| - |[0,0]|_{(\overline{2})} - 2|[0,1]|_{(\overline{2})}, \end{aligned}$$

and the dynamics of $(|[0,0]|_{(\overline{2})}/2, |[0,1]|_{(\overline{2})})$ is governed by

$$\begin{aligned} \frac{d}{dt}\left(\frac{1}{2}|[0,0]|_{(\overline{2})}\right) &= -\frac{(|[0,0]|_{(\overline{2})}/2)|[0,1]|_{(\overline{2})}}{|[0,0]|_{(\overline{2})}/2 + |[0,1]|_{(\overline{2})}/2}\ \frac{\beta}{K} + 2\frac{(|[0,1]|_{(\overline{2})})^2}{|\Gamma| - (|[0,0]|_{(\overline{2})} + |[0,1]|_{(\overline{2})})/2}\,\mu \\ &\quad + \frac{|[0,1]|_{(\overline{2})}(|\Gamma| - |[0,0]|_{(\overline{2})}/2 - |[0,1]|_{(\overline{2})})}{|\Gamma| - (|[0,0]|_{(\overline{2})} + |[0,1]|_{(\overline{2})})/2}\,\mu \\ \frac{d}{dt}\left(\frac{1}{2}|[0,0]|_{(\overline{2})}\right) &= -4\,\frac{(|[0,1]|_{(\overline{2})})^2}{|[0,0]|_{(\overline{2})}/2 + |[0,1]|_{(\overline{2})}/2}\ \frac{\beta}{K} - \frac{(|[0,1]|_{(\overline{2})})^2}{|\Gamma| - (|[0,0]|_{(\overline{2})} + |[0,1]|_{(\overline{2})})/2}\,2\mu \\ &\quad + 2\frac{(|\Gamma| - |[0,0]|_{(\overline{2})}/2 - |[0,1]|_{(\overline{2})})^2}{|\Gamma| - (|[0,0]|_{(\overline{2})} + |[0,1]|_{(\overline{2})})/2}\,\mu. \end{aligned}$$

(2) The mean field is the deterministic counterpart of a stochastic process that mixes all particles are randomly distributed in space after each event. The classical pair approximation does not have such an interpretation. The alternative pair approximation, however, does have again an interpretation of this type: here, after each event, the particles are randomly redistributed in such a way that the number of pairs of the three types (00), $(0,1)$ and $(1,1)$ are conserved.

(3) In Fig. 67 the dynamics of realizations of the contact process together with mean field and the two pair approximations are shown (the offset in time is chosen in such a way, that all four processes cross at the same time (In case of the stochastic process, for the first time) the point of 50 occupied sites. We find, that the pair approximations seem to agree better with the stationary distributions of occupied sites of the contact process than the mean field approximation; furthermore, the alternative pair approximation seems quite well describe the dynamics, if more than 20 sites are occupied; below this number, the growth of the alternative pair approximation is much too slow. The (classical) pair approximation does not meet the timing at all. Under this aspect, the alternative pair approximation seems to be superior to the classical approximation.

Threshold condition, revised

We now investigate the stationary solutions of the alternative pair approximation. We expect a new threshold condition, that is closer to the (numerically) observed threshold conditions. It is tedious but straight forward to compute the stationary points of the different approximations. The result is shown in Fig. 68. We find that the critical threshold

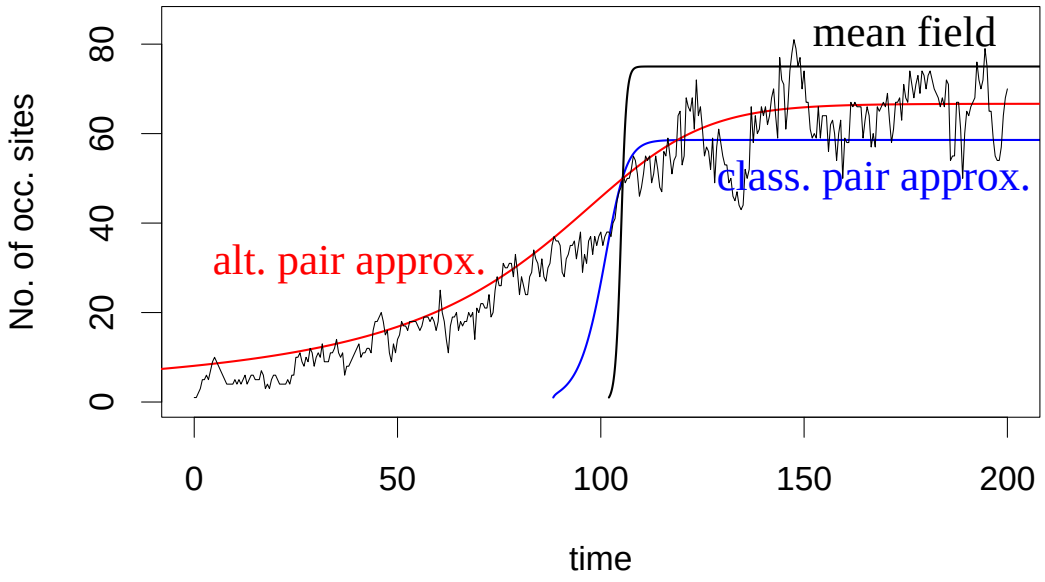

Figure 67: Dynamics of a realization of the contact process, together with the mean field approximation and the two pair approximations ($\beta = 2$, $\mu = 0.5$, $|\Gamma| = 100$). The curves are shifted in time s.t. all curves cross the value 50 at the same time.

for *beta* that is necessary for the process to survive is not met by the mean field. The two pair approximations are closer to this value, but also do not meet the threshold exactly - the classical pair approximation underestimates and the alternative overestimates the critical value for β. Please note the jump in the curve for the stationary solution of the alternative pair approximation; instead of a transcritical bifurcation, we find here a saddle-node bifurcation.

5.5.3 Contact Process: Rapid Stirring Limit

A second approximation to the contact process introduces movement of the particles. Under appropriate (the parabolic) scaling, it is possible to obtain a partial differential equation, the Fisher equation.

Definition 5.30: *Let $\epsilon > 0$. The contact process with rapid stirring is defined as the contact process with birth rate β/ϵ and death rate μ/ϵ with an additional process that exchange two states: Let for $x \in U(y)$*

$$P(\varphi_{t+\Delta t}(x) = i, \quad \varphi_{t+\Delta t}(y) = j \,|\, \varphi_t(x) = j, \quad \varphi_t(y) = i) = \Delta t/\epsilon^2 + \mathcal{O}(\Delta t).$$

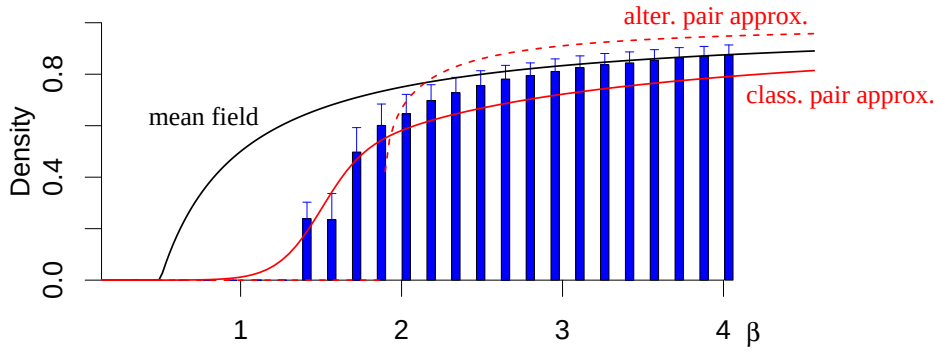

Figure 68: Stationary solutions of the three approximations (mean field: black, solid, classical pair approximation: blue, solid, alternative pair approximation: blue,dashed) and simulated stationary distribution of the contact process ($N = 100$, $\mu = 0.5$) with standard deviation (blue bars with whiskers).

For the scaled density $u(\epsilon t, \epsilon x) = P(\varphi_t(x) = 1)$, we are able to derive the Fisher equation.

Theorem 5.31: *Let* $u(\epsilon t, \epsilon x) = P(\varphi_t(x) = 1)$ *and* $v(t, y) = \lim_{\epsilon \to 0} u(t, y)$. *Then, under suitable conditions for* $\varphi_0(x)$, *we find*

$$v_t = \Delta v + \beta v(1 - v) - \mu v.$$

The proof is quite non-trivial. It can be found in [18]. However, this theorem is the stochastic justification for the large interest in the Fisher equation.

Remark 5.32: **(1)** The rapid stirring limit is basically a combination of the heat equation (consequence of the parabolic scaling) and the mean field approximation (consequence of the rapid stirring, that breaks all short range correlations - exactly, what we need to get the mean field).

(2) The pair approximation aims at local correlations (the pairs) but completely neglects long range correlation (the long range spatial structure). Thus, we find a ordinary differential equation for the pair approximation. The rapid stirring limit does the opposite thing: here, we destroy all local correlations by the stirring, but keep the long range correlations. Hence, we obtain a partial differential equation.

5.5.4 Fisher Equation

The Fisher equation [20] has been introduces simultaneously by Fisher and Kolmogoroff, Petrovsky and Piscunoff. Thus, this equation is often also called the KPP equation. Originally, Fisher has been interested in the spread of a gene in an environment. However, we have seen that the much broader background can be found in the contact process together with the rapid stirring limit. A rescalation of the PDE in Theorem 5.31 yields the common form of Fisher's equation,

$$u_t = \Delta u + u(1-u).$$

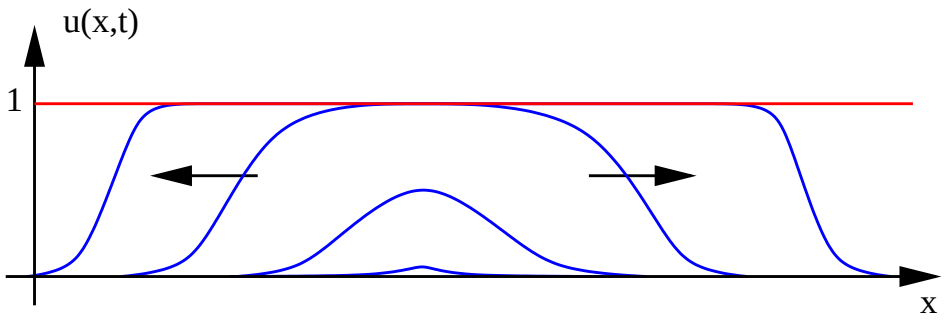

Figure 69: Spread of a small, local perturbation.

The most interesting question is the long-term behavior of this equation. Numerical simulations give a hint that a local, small perturbation of the trivial solution $u = 0$ will grow and then spread over the whole region. Consider the partial differential equation in one dimension. We expect that the population will spread asymptotically with a constant speed (Fig. 69). We show that such traveling fronts do exist.

Theorem 5.33: *For the Fisher's equation, there is for each $c \geq 2$ a unique positive solution of the form $u(x,t) = \varphi(x - c\,t)$ with*

$$\lim_{x\to-\infty} u(x,t) = 1, \qquad \lim_{x\to-\infty} u'(x,t) = 0$$

and

$$\lim_{x\to+\infty} u(x,t) = 0, \qquad \lim_{x\to+\infty} u'(x,t) = 0$$

For $c < 2$, there is no solution of this form.

Proof: *Step 1: Write the equation of the traveling font as an ODE*
Let $\eta(\xi) = \varphi'(\xi)$. Using the ansatz $u(x,t) = \varphi(x - ct)$, we find

$$-c\varphi'(x-ct) = \varphi''(x-ct) + \varphi(x-ct)(1-\varphi(x-ct))$$

and thus

$$\begin{aligned} \varphi'(\xi) &= \eta(\xi) \\ \eta'(\xi) &= -c\eta(\xi) - \varphi(\xi)(1-\varphi(\xi)). \end{aligned}$$

We look for a solution with

$$\varphi(\xi) \geq 0, \quad \lim_{\xi\to\infty}(\varphi(\xi),\eta(\xi)) = (0,0) \quad \text{and} \quad \lim_{\xi\to-\infty}(\varphi(\xi),\eta(\xi)) = (1,0).$$

Step 2: Stationary points and local dynamics
We find immediately the stationary points $(\varphi,\eta) = (0,0)$ and $(\varphi,\eta) = (1,0)$. The asymptotic behavior of $((\varphi(\xi),\eta(\xi)$ for $\xi \to \pm\infty)$ corresponds to these stationary points. This fact enables us to identify running fronts with heteroclinic orbits (orbits connecting different stationary points). The local stability/dynamics of these stationary points is given by the eigenvalues of the linearization.
• Stationary point $(\varphi,\eta) = (1,0)$:
The Jacobian reads

$$J = \begin{pmatrix} 0 & 1 \\ 1 & -c \end{pmatrix}$$

with eigenvalues $\lambda_\pm = (-c \pm \sqrt{c^2+4})/2$; i.e., $\lambda_+ > 0 > \lambda_-$. This point is always a saddle.
• Stationary point $(\varphi,\eta) = (0,0)$:
Here, the Jacobian reads

$$J = \begin{pmatrix} 0 & 1 \\ -1 & -c \end{pmatrix}$$

with eigenvalues $\lambda_\pm = (-c \pm \sqrt{c^2-4})/2$; we find imaginary eigenvalues for $c < 2$. Thus, the solution will spiral around zero for $c < 2$ and does not allow for a positive φ-component with $\lim_{\xi\to\infty}(\varphi(\xi),\eta(\xi)) = (0,0)$. Hence, we need $c \geq 2$ (this is already one claim of the theorem). For $c > 2$, this stationary point becomes a stable node.

Step 3: Phase Plane Analysis
We now show that the heteroclinic orbit exists, indeed. We construct an invariant region; every trajectory within this region will tend to the stationary point $(0,0)$, especially one unstable manifold of $(1,0)$.
Let $\epsilon > 0$, small, and

$$\Omega_\epsilon = \{(\varphi,\eta) \,|\, 0 \leq \varphi \leq 1-\epsilon, \quad 0 > \eta > -\varphi\}.$$

We show that Ω_ϵ is invariant. Therefore, we do have to show that the flow points inward on the boundary of Ω_ϵ except on $(0,0) \in \partial\Omega_\epsilon$, since $(0,0)$ is a stationary point. On $\partial\Omega_\epsilon$, we find for $\eta = 0$ that $\eta' = -\varphi(1-\varphi) < 0$ (if $0 < \varphi \leq 1-\epsilon$); for $\varphi = 1-\epsilon$, we have $\varphi' = \eta < 0$. The only part of the boundary that is more complicated is the line $\eta = -\varphi$. The outer normal vector on this line is $(-1,-1)^T$ and thus the scalar product of normal vector with vector field reads

$$\begin{aligned} < \begin{pmatrix} -1 \\ -1 \end{pmatrix}, \begin{pmatrix} \eta \\ -c\eta - \varphi(1-\varphi) \end{pmatrix} > &= < \begin{pmatrix} -1 \\ -1 \end{pmatrix}, \begin{pmatrix} -\varphi \\ c\varphi - \varphi(1-\varphi) \end{pmatrix} > \\ &= -\varphi\,(c - (2-\varphi)) < 0 \end{aligned}$$

for $c \leq 2$ since $0 < \varphi < 1$. Since in $\mathrm{int}(\Omega_\epsilon)$ we have $\varphi' < 0$, all trajectories have to move to the stationary point $(0,0)$. The proof is completed by the fact that one unstable manifold

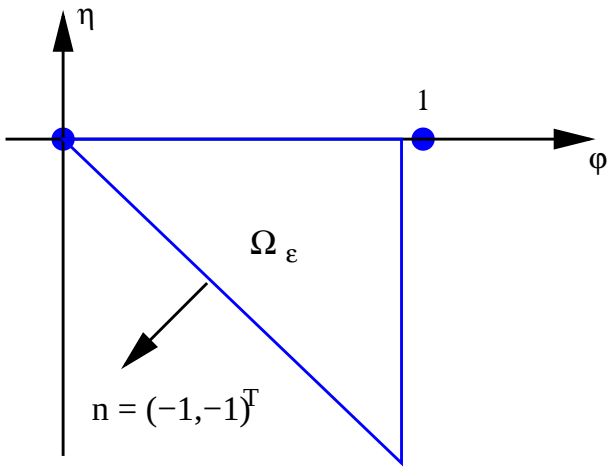

Figure 70: The invariant region Ω.

of $(1, 0)$ points inward to Ω_ϵ, if $\epsilon \to 0$.

□

Remark 5.34: It is possible to show, that all bounded, positive perturbation of the trivial solution approach the front with $c = 0$. In this sense, this front is stable. All other fronts are only stable within certain function spaces (the asymptotic decline of the perturbation has to be appropriate).

5.6 Exercises

Exercise 5.1:
The Ricker model has been developed especially for insect populations. The state x_n denotes the population size in autumn (year n). The population will reproduce almost linearly during the year (we find then a population of αx_n) and only compete for resources at the end of the year. The result of this competition is modeled by an exponential decrease,

$$x_{n+1} = \alpha x_n e^{-\beta x_n} =: g(x_n; \alpha, \beta).$$

(a) Find a transformation $y_n = f(x_n; \alpha, \beta)$ s.t. the dynamics of the transformed variable y_n does only depend on one parameter r, $y_{n+1} = \tilde{g}(y_n; r)$. Find the stationary points, i.e. solutions of the fixed point equation $y = \tilde{g}(y)$.
(b) Compute the spectrum (i.e. in the present case the derivative) of the linearization near the stationary points. Where does the stability of the stationary solutions changes? What happens?

Exercise 5.2:
Consider a time-discrete stochastic version of the logistic equation: Let X_n denote the number of individuals in time step n. The number of children of one individual is assumed

to be distributed according to

$$\text{No. of children} \,|\, X_n = k \quad \sim \quad \text{Geom(q(k))}$$

with $q(k) = q_0 e^{-\alpha k/N}$. Let $C_i(k)$ be i.i.d. random variables distributed according to this geometric distribution, and

$$X_{n+1} = \sum_{i=1}^{X_n} C_i(X_n)$$

be the population size in the time step $n+1$.
(a) Define a "linearized" stochastic process for $N \to \infty$.
(b) Prove an approximation theorem.

Exercise 5.3:
Consider the time-continuous stochastic logistic process,

$$P(X_{t+\Delta t} = X_t + 1) = \beta\, X_t\, (1 - X_t/N)\Delta t + o(\Delta t), \qquad P(X_{t+\Delta t} = X_t - 1) = \mu\, X_t \Delta t + o(\Delta t).$$

Show that the population eventually goes extinct with probability one:
(a) Prove that there is $\epsilon > 0$ s.t.

$$P(X_{t+\Delta t} = 0 | X_t = k) \geq \epsilon$$

for $k \leq N$.
(b) Define $p_n = P(X_{n\,\Delta t} = 0)$. Find a recursive equation for a lower bound of p_n using part (a).
(c) Show that $\lim_{n\to\infty} p_n = 1$.

Exercise 5.4:
Consider a finite, one-dimensional lattice, closed to a torus (i.e. $\mathbb{Z}/\mathbb{Z}_n$). The states in each cell are allowed to be an element of a finite set E. The neighborhood of a cell consists of the two next neighbors. Let $A \in E$. Express the number of sites in state A by the number of all pairs of any kind,

$$[A] = F([A, X], X \in E).$$

Exercise 5.5:
Consider a finite, one-dimensional lattice, closed to a torus (i.e. $T_n = \mathbb{Z}/\mathbb{Z}_n$). The states in each cell are allowed to be an element of the set $E = \{0, 1\}$. The neighborhood of the site 0 is only the cell itself and the next cell to the right,

$$U(0) = \{0, 1\}$$

and, like usual, $U(x) = x + U(0)$ in $\mathbb{Z}/\mathbb{Z}_n$. Please show, that (though the neighborhood is not symmetric and hence the incidence matrix is not symmetric) still

$$[0, 1] = [1, 0]$$

and that $[0,0]$ is the true number of pairs with $(\varphi(x), \varphi(x+1)) = (0,0)$ (recall that for the symmetric neighborhood, $[0,0]$ is just twice the number of these pairs!).

Exercise 5.6:
Consider the contact process on the lattice defined in the last exercise (with non-symmetric neighborhood). Find the mean field approximation.

Exercise 5.7:
Consider the logistic equation with delay,

$$\frac{d}{dt}u(t) = ru(t)(1 - u(t-\tau)).$$

i.e. the feedback depends on the population size τ time units ago rather than on the population size at time t.
(a) $u = 1$ is a stationary solution of this equation. Linearize the equation using the ansatz $u(t) = 1 + n(t)$, and eliminating all nonlinear terms.
(b) Compute a formula for the eigenvalues of the resulting linear equation, i.e. use the ansatz

$$n(t) = n_0 e^{\lambda t}$$

and derive an equation for λ.
(c) Show that there is a delay $\tau > 0$, s.t. we find λ with $\Re(\lambda) = 0$.

6 Population Dynamics and Ecology

Population dynamics is "the" classical field of biomathematics. Many results are common knowledge by now; the effort needed to understand the structures is not visible any more. Population dynamics (where one associates first of all fox and rabbits) is a prototype to study the interaction of individuals. The ideas developed here can then be translated to quite different fields, from molecular dynamics and immunology to the description of the spread of a disease among humans. Also in (statistical) physics, interacting particles is a well investigated field, and quite a number of tools have been developed there. However, in physical systems there are often symmetries and conservation laws (mass, energy, impulse etc.) which help to understand the behavior. This is in general not the case in biological application. Hence, often enough the tools developed in physics cannot be taken over in a trivial way but have to be adapted.

6.1 Competitive Exclusion

The logistic equation describes competition within one species. We are now interested in the case of two species which compete, i.e. we are interested in competition between species. The basic question here will be if two species that compete for resources may persist, or if one species will crush the other.

Modeling competition between species
State: $x(t)$ population density of species one, $y(t)$ population density of species two.

Dynamics: We consider the ordinary differential equations

$$\begin{aligned} \dot{x} &= \overbrace{\beta_1 y - \mu_1(1+\zeta_1 x}^{\text{logistic part}} + \overbrace{\zeta_2 y)}^{\text{interaction}} \\ \dot{y} &= \underbrace{\beta_2 y - \mu_2(1+\zeta_4 y}_{\text{logistic part}} + \underbrace{\zeta_3 x)}_{\text{interaction}} \end{aligned}$$

We rescale the system. Choose

$$u_1 = \frac{\zeta_1}{\beta_1 - \mu_1} x, \quad u_2 = \frac{\zeta_4}{\beta_2 - \mu_2} y, \quad \tau = (\beta_1 - \mu_1)t$$

and define

$$\rho = \frac{\beta_2 - \mu_2}{\beta_1 - \mu_1}, \quad a_{12} = \frac{\zeta_2}{\beta_1 - \mu_1}(\beta_2 - \mu_2), \quad a_{21} = \frac{\zeta_3}{\beta_2 - \mu_2}(\beta_1 - \mu_1),$$

then

$$\begin{aligned} \dot{u}_1 &= u_1(1 - u_1 - a_{12}u_2) \\ \dot{u}_2 &= \rho u_2(1 - u_2 - a_{21}u_1). \end{aligned}$$

Analytic Tools

The system above is a planar system (i.e. a system in the plane). Much is known about such systems (though a lot more is not known). We need two theorems that are concerned with the asymptotic behavior: the negative criterion of Bendixon-Dulac and the theorem of Poincaré-Bendixon. While we sketch the proof of the first theorem, we only state the second theorem.

Theorem 6.1: (Poincaré-Bendixon) *Consider a trajectory $x(t) \in \mathbb{R}^2$ of the ordinary differential equation $\dot{x} = f(x)$, f smooth. If $x(t)$ is bounded, then asymptotically $x(t)$ tends to one of the three objects:*

- *a stationary point*
- *a periodic orbit*
- *a homoclinic orbit or heteroclinic cycle.*

A homoclinic orbit is an orbit that tends for $t \to \pm\infty$ to the same stationary point, while a heteroclinic orbit tends to different stationary points. A heteroclinic cycle is a closed chain of heteroclinic orbits. I.e., a homoclinic orbit resp. chain of heteroclinic orbits may be interpreted as a generalization of a periodic orbit: we allow for stationary points on this periodic orbit. This theorem can be found e.. in the book of Guggenheimer and Holmes [27].

Theorem 6.2: (Negative Criterion of Bendixon-Dulac) *Consider $\dot{x} = f(x)$, $x \in \mathbb{R}^2$. If there is a scalar function $g(x) \in C^1(\mathbb{R}^2, \mathbb{R})$, that never vanishes, $g(x) \neq 0$, and if*

$$\operatorname{div}(g(x)f(x)) < 0 \qquad \forall x \in \Omega$$

then there is no periodic orbit completely contained in Ω.

Proof: Rescaling of time yields the equivalent ordinary differential equation

$$\dot{y} = g(y)f(y).$$

If $\dot{x} = f(x)$ has a period orbit Γ, than also $\dot{y} = g(y)f(y)$ (we only rescaled time, i.e. the only thing that changes is the velocity of a trajectory; the trajectory as a set of points is not changed).

Assume that there is a periodic orbit $\Gamma \subset \Omega$. Γ bounds a smaller region $\hat{\Omega} \subset \Omega$. Let the outer normal of $\hat{\Omega}$ be $\mathbf{n}$. Since the vector field $f(x)$ is tangential to an trajectory (nothing else is the meaning of the ODE $\dot{x} = f(x)$) and $\partial\hat{\Omega}$ is a trajectory, we find that $\mathbf{n}(x) \perp f(x)$ for $x \in \partial\hat{\Omega}$. Thus, with the divergence theorem we find

$$0 = \oint_{\partial\hat{\Omega}} g(y)f(y)\mathbf{n}(y)\, d\sigma = \int_{\hat{\Omega}} \operatorname{div}(g(y)f(y))\, d\sigma < 0.$$

This is a contradiction, and therefore no periodic orbit is completely contained in Ω. □

Remark 6.3: With the same argument, we are able to rule out homoclinic orbits and heteroclinic cycles. Basically, the first theorem tells us that only stationary points or

periodic behavior is the asymptotics of a bounded, planar trajectory; the second theorem shows us how to rule out periodic behavior, s.t. only a stationary point can be the limiting object of a trajectory.

Analysis of the Model

There are no periodic orbits: Scale the system with $1/(u_1 u2)$, and then compute the divergence:

$$\left(\frac{1}{u_1 u_2} u_1(1 - u_1 - a_{12}u_2)\right)_{u_1} + \left(\frac{1}{u_1 u_2}\rho u_2(1 - u_2 - a_{21}u_1)\right)_{u_2} = -\frac{1}{u_1} - \frac{\rho}{u_2} < 0.$$

Stationary points: The stationary points are

$$\{(0,0), \quad (1,0), \quad (0,1), \quad \left(\frac{1 - a_{12}}{1 - a_{12}a_{21}}, \frac{1 - a_{21}}{1 - a_{12}a_{21}}\right)\}.$$

Thus, there may be a stationary point, where booth species persist (if the parameter values are chosen in such a way that booth components are positive). The next question will be, under which condition this point is (locally) stable. In order to investigate this phenomenon, we use a (rather heuristic) method and consider the isoclines.

Definition 6.4: *An isocline are points in the phase plane for which either* $\dot{u}_1 = 0$ *(the* u_1*-isocline) or* $\dot{u}_2 = 0$ *(the* u_2*-isocline).*

The intersections of an u_1-and an u_2-isocline are stationary points. In our case, the isoclines are the lines (u_1-isoclines:) $u_1 = 0$, $1 - u_1 - a_{12}u_2 = 0$ and (u_2-isoclines:) $u_2 = 0$, $1 - u_2 - a_{21}u_1 = 0$. Thus, the u_1 and u_2-axis and two straight lines are the isoclines.

We distinguish four cases (see Fig. 71):

(a) $1 < 1/a_{12}$, $1 < 1/a_{21}$

The isoclines bound regions, where a quadrant into that the vector field points does not change. Thus, we can read out the direction, where the trajectory tends to. Since we know, that in the long run any trajectory tends to a stationary point, we are able to decide to which stationary point the trajectory will run.

We find that in case (a) two isoclines intersect in the interior of the positive quadrant. We have a stationary point, where persistence of booth species is possible. The vector field shows us, that this stationary state is (locally) stable. Thus, case (a) gives us a situation, where booth species persist.

(b) $1 > 1/a_{12}$, $1 < 1/a_{21}$

Here, we only have the stationary states on the boundary of the positive cone, i.e. persistence is not possible. If we consider the vector field, we find that we finally enter the region between the two isoclines. Here the flow is directed towards the u_1-axis. Thus, species two will vanish and finally we only find species one.

(c) $1 < 1/a_{12}$, $1 > 1/a_{21}$

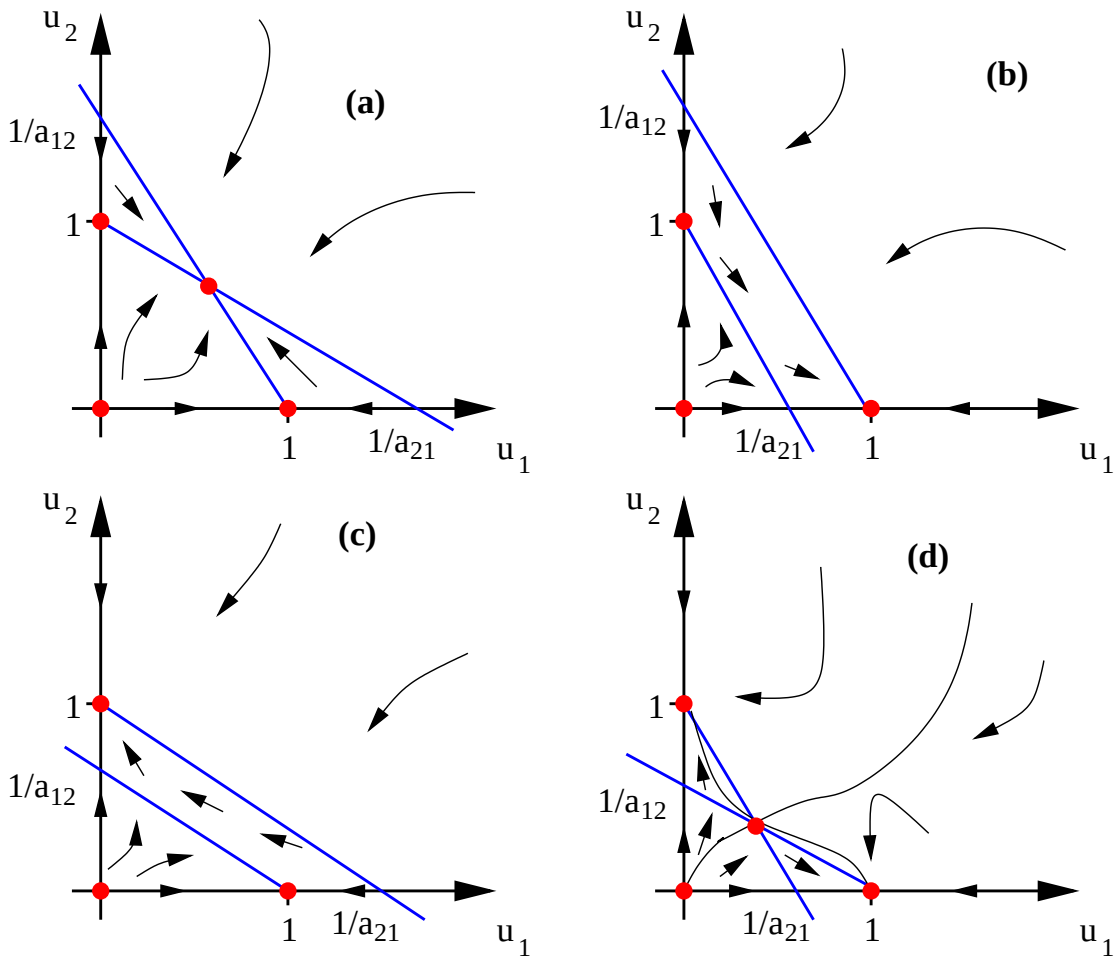

Figure 71: Isoclines for the four cases

By symmetry, we find that this is the same case like before, only that u_1 and u_2 interchange their role.

(d) $1 > 1/a_{12}$, $1 > 1/a_{21}$
Like in case (a), we do have a stationary state, where booth species may persist. However, the vector field shows us, that this stationary state is unstable. It is a saddle. It does play a role in intersecting the phase plane: the stable manifold of this point is connected to the point $(0, 0)$. Every trajectory that starts to the left of this unstable manifold will tend to the stationary point where only species two is present, while every trajectory that starts to the right tends to the stationary point where we find species one only. Hence, only one species persists, but which one depends on the initial state (bistable behavior).

All in all we find, that only in case (a) persistence of the species is possible. However, case (a) implies $a_{12}, a21 < 1$, i.e. the interaction of the two species is rather weak. Thus, we have the found the rule of Competitive Extinction.

Bio-Theorem: (Competitive Extinction) *If the competition of two species is strong enough, only one species survives. It may depend on the initial conditions which of the species goes extinct.*

Experimental Investigation
Of course, this conclusion attracted experimental investigators. One of them is (again) Gausse, who looked at cultures with different microorganisms (*Parametricum caudatum* and *Parametricum aurelia*). We find nice agreement with the prediction (Fig. 72). However, not all of the experiments of Gausse clearly show the principle of competitive exclusion. One possible explanation is that this principle only shows up in the long run. For intermediate time scales, the populations may persist.

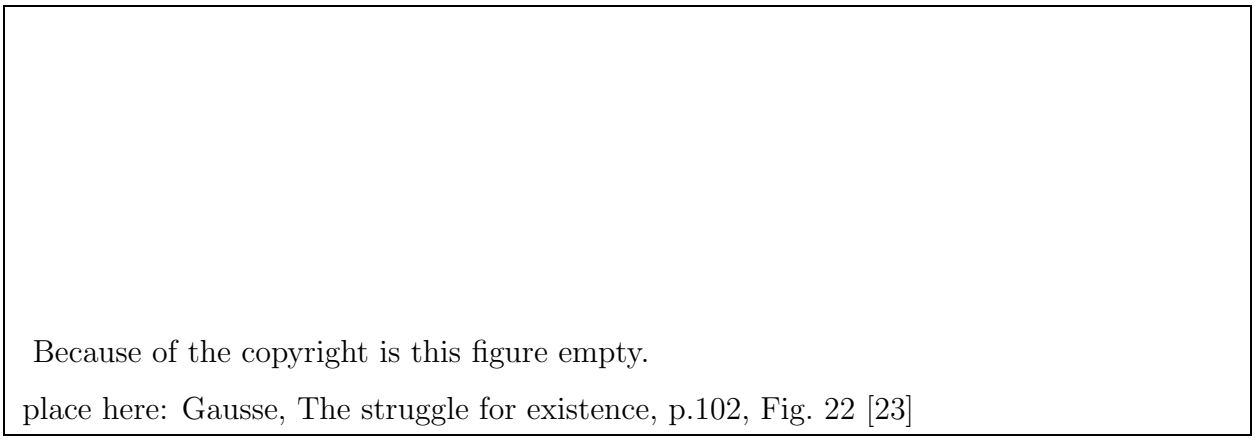

Figure 72: Population dynamics of yeast in a sugar solution.

6.2 Predator-Prey Systems

Predator-prey models are perhaps "the" example of biomathematics. If someone does know something about biomaths, then it is the oscillatory behavior of predator-prey systems. Also here, we have a brief look at these models.

Lotka-Volterra-Model
The most simple model takes into account only two trophic levels: the prey and the predator with density $N(t)$ (prey) resp. $P(t)$ (predator). The prey is assumed to be not limited by bounded resources; i.e., we expect in absence of the predator an exponential growth of the prey, $\dot{N} = aN$. The predator acts like a mortality rate that is proportional to the density of predator. Thus we find

$$\dot{N} = aN - bP\,N.$$

In absence of prey, the predator will starve to death. This is modeled by a linear death process, $\dot{P} = -dP$. However, if there is prey, the consumed prey is converted into offspring, i.e. we have a birth term of the form cNP,

$$\dot{P} = cNP - dP.$$

This model has been proposed by Volterra (1926) for predator-prey systems. Somewhat earlier, 1920/1925, Lotka proposed the very same equation in order to describe a hypothetical reaction kinetics that may lead to oscillations. Therefore, the model is called the Lotka-Volterra model.

We first rescale this model. Define $N = a\,N/c$, $P = av/b$, $t = \tau/c$ and the lumped parameter $\alpha = d/a$. Then,

$$\begin{aligned} \dot{u} &= u(1-v) \\ \dot{v} &= v(u-\alpha). \end{aligned}$$

Now we find an invariant functional (a special case of a Ljapunov-function). Define

$$L(u,v) = u - \alpha\ln(u) + v - \ln(v).$$

Then,

$$\begin{aligned} \frac{d}{dt}L(u(t),v(t)) &= L_u\dot{u} + L_v\dot{v} \\ &= [1-\alpha/u][u(1-v)] + [1-1/v][v(u-\alpha)] \\ &= 0. \end{aligned}$$

Thus, the function $L(u,v)$ is constant on trajectories. From the shape of $L(u,v)$, we find that the trajectories are nested periodic orbits. This model predicts a periodic behavior. The unattractive property is the lack of stability: if we change the state slightly, it will jump to another periodic orbit and never return to the original periodic orbit. Furthermore, if we perturb the model itself slightly (e.g. introduce a logistic term for the growth of the prey, see exercise 6.2) the oscillations vanish. These considerations gave rise to a variety of proposals how to change the Lotka-Vorlterra-model.

Generalizations of the Lotka-Volterra-Model
Obviously, the points that are quite unrealistically are the dynamics of prey only and the predation term.

- Incorporating limited resources for the prey:
Replace linear growth by logistic growth,

$$aN \qquad \rightarrow \qquad aN(1-N/K).$$

- Handling time for predator:

After a predator did capture a prey, the animal needs time to handle this animal. The predator will not immediately try to capture another prey. Thus, even if the density of prey becomes very large, the predated animals per time unit will tend to a saturation (given a constant predator density),

$$bNP \qquad \rightarrow \qquad bP\frac{N^n}{N_0+N^n}.$$

• In consequence, also the incidence of offspring tends to a saturation, even if the prey available tends to infinity,

$$cNP \qquad \rightarrow \qquad cP\frac{N^n}{N_0+N^n}.$$

All in all we find

$$\begin{aligned}\dot{N} &= aN(1-N/K) - bP\frac{N^n}{N_0+N^n}\\ \dot{P} &= cP\frac{N^n}{N_0+N^n} - dP.\end{aligned}$$

Indeed, for appropriate chosen parameter values, we find for this model a single, locally stable periodic orbit.

The Hudson Bay Data
The perhaps most prominent data that show this oscillatory behavior are the data of the Hudson Bay Company. This company sold pelts of animals that have been hunted by trappers in the Hudson Bay. The idea is, that the number of sold pelts give a hint about the abundance of the corresponding species. Expecially lynx and hare form a predator-prey system. The data show indeed a slow oscillation of roughly twelve years (Fig. 73. This seems to support the prediction of the model. However, if we look more in detail, we find that the lynx go up before the hare increase their density. This does mean, that the hare play the role of predators while the lynx are the prey! One possible explanation would be a (for lynx) deadly disease that is carried by the hares. Then, in a certain sense, hare are deadly for lynx, indeed. Another possible explanation is the presence of at least one more predator: the trappers. They kill lynx and hare. In this way, may perturb the dynamics strong enough to produce the observed pattern.

6.3 Chemostat

The importance of the chemostat is the application in industry: if certain metabolites are to be produced by microorganisms, often enough the set-up for the production is chosen in form of a chemostat. This device (Fig. 74) is a tank (often assumed to be stirred such that we do not spatial effects, like growth of microorganisms at the wall of the chemostat, i.e. a biofilm etc.). There is a continuous inflow of nutrient and substrate, and also continuous outflow. Within the outflow, there are metabolites, microorganisms,

Because of the copyright is this figure empty.

place here: Murry, Mathematical Biology [48]

Figure 73: Data of the Hudson Bay Company.

substrate and (of course) nutrient. The aim of the investigations is the prediction of the long-term dynamics (will we tend to a stationary state? Are there oscillations possible?) in order to control the system into a regime where the harvest of metabolites is optimal. The set-up can be very complicated, with a multitude of species, nutrient and metabolites, connected and interacting in a quite complicated way. In general, it soon becomes hard to investigate the dynamics. However, we will only consider the most simple case. One may find more in the book of Hale Smith [57]

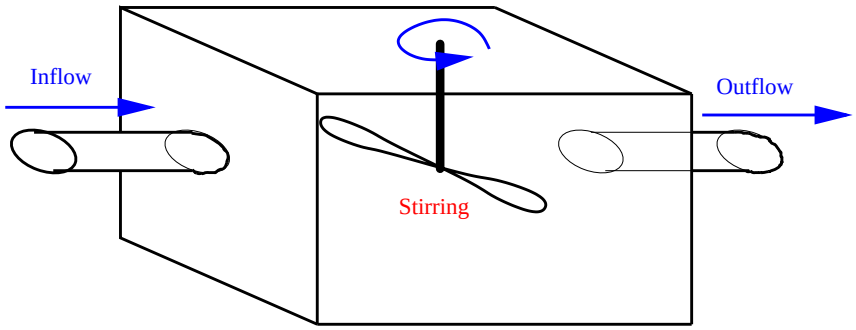

Figure 74: Schematic figure of a chemostat.

Model:

We consider a chemostat with only one species of microorganisms. Thus we model the density of the microorganisms x and the density of nutrient S.

The nutrient is introduced into the system with constant rate D (determined by the velocity of the inflow) and constant density S_0. The outflow occurs again with rate D (inflow is the same like outflow in order to keep the total volume constant). It is consumed

by a rate $f(x)$ that depends on the density of microorganisms x. We will discuss the properties of this function below. Thus,

$$\dot{S} = DS_0 - DS - xf(S).$$

The microorganisms transform consumed nutrient into offspring with an efficacy given by some proportionality constant α. With the outflow, also microorganisms are lost. Thus, we have a death term Dx, and we find

$$\dot{x} = -Dx + \alpha x f(S).$$

We assume that $f(0) = 0$, $f'(S) > 0$ and $\lim_{S\to\infty} f(S) = f_\infty < \infty$, reflecting that substrate is consumed by microorganisms. If there is substrate in excess, the consumption rate per microorganism tends to a saturation.

.

Analysis:

Stationary states:
The first (and simplest) step in the analysis is to determine the stationary points. One stationary point is $(x, S) = (0, S_0)$. Here, the microorganism is not present. Now let us find stationary points (x^*, S^*) s.t. $x^* > 0$. From $\dot{x} = 0$ we conclude

$$f(S^*) = D/\alpha.$$

A solution of this equation exists (and is then unique) if and only if

$$D/\alpha < f_\infty.$$

The interpretation of this finding is simple: If the wash-out rate D is too high resp. the efficiency of transforming food into offspring (given by α) is too low, then the microorganism is not able to persist. Else it may persist. From $\dot{S} = 0$ we find immediately the component x^* as

$$x^* = (S_0 - S^*)D/f(S^*) = \alpha(S_0 - S^*).$$

Here, the second condition for existence of the nontrivial state comes in: We need $S_0 > S^*$, i.e. $f(S_0) > f(S^*) = D/\alpha$ which leads to

$$\alpha f(S_0) - D > 0.$$

This condition does mean, that (for a very small population of microorganisms) the net growth rate $\alpha f(S_0) - D$ has to be positive. This condition implies the first one, since $f_\infty > f(S_0) > D/\alpha$.

Result 1:
There is always a trivial equilibrium $(x, S) = (0, S_0)$. There is a nontrivial equilibrium $(x, S) = (x^*, S^*)$, if and only if

$$\alpha f(S_0) - D > 0.$$

In this case, this equilibrium is unique.

Local stability:
The local stability can be found by the linearization,

$$J|_{x^*,S^*} = \begin{pmatrix} -D - x^* f'(S^*) & -f(S^*) \\ \alpha x^* f'(S^*) & -D + \alpha f(S^*) \end{pmatrix} = \begin{pmatrix} -D - x^* f'(S^*) & -D/\alpha \\ \alpha x^* f'(S^*) & 0 \end{pmatrix}$$

where we used the conditions for stationary the stationary state to remove $f(S^*)$ from the Jacobian. Thus,

$$\det(J|_{x^*,S^*}) = -D - x^* f'(S^*) < 0, \qquad \mathrm{tr}(J|_{x^*,S^*}) = -D/\alpha \; \alpha x^* f'(S^*) < 0$$

i.e. the stationary state (x^*, S^*) is always locally stable if existent. If we consider the other stationary state $(0, S_0)$, we find for the linearization

$$J|_{0,S_0} = \begin{pmatrix} -D - x f'(S) & -f(S) \\ \alpha x f'(S) & -D + \alpha f(S) \end{pmatrix}_{x=0,S=S_0} = \begin{pmatrix} -D & -f(S_0) \\ 0 & \alpha f(S_0) - D \end{pmatrix}$$

Thus,

$$\mathrm{tr}(J|_{0,S_0}) = \alpha f(S_0) - 2D, \qquad \det(J|_{0,S_0}) = -D \; (\alpha \; f(S_0) - D)$$

Hence if $\alpha f(S_0) - D < 0$, we have $\mathrm{tr}(J|_{0,S_0}) < 0$ and $\det(J|_{0,S_0}) < 0$ s.t. the trivial state is locally stable. If $\alpha f(S_0) - D$ becomes positive, the determinant (and eventually also the trace) changes sign, and the trivial state looses stability; at the same time the nontrivial stationary point (for which necessarily $\alpha f(S_0) - D > 0$) appears and is locally stable. Thus, we find here a transcritical bifurcation.

Result 2:
If the nontrivial equilibrium exists, it is locally stable and the trivial equilibrium looses stability.

Exclusion of periodic orbits:
We scale the vector field by $1/x$. Then,

$$\partial_S \left\{ \frac{1}{x} \; [(S - S_0)D - x f(S)] \right\} + \partial_x \left\{ \frac{1}{x} \; [-Dx + \alpha x f(S)] \right\} = -\frac{D}{x} - x f'(S) < 0.$$

Thus, by the negative criterion of Bendixon-Dulac, we are able to rule out periodic orbits. Since furthermore one can exclude that a trajectory starting in the positive quadrant tends to infinity, all trajectories tend to stationary states.

Result 3:
If $\alpha S(S_0) - D < 0$, every positive trajectory tends to the equilibrium $(x, S) = (0, S_0)$. If $\alpha S(S_0) - D > 0$, a trajectory with initial conditions $S \geq 0$, $x > 0$ tends to the unique nontrivial equilibrium (x^*, S^*) with $x^* > 0$.

6.4 Exercise

Exercise 6.1:
Consider an epidemic model, where susceptibles S become infecteds I with the incidence βSI, infecteds recover at rate α and become immunes R. Immunity is lost again at rate γ,

$$\begin{aligned} \frac{d}{dt}S &= -\beta SI/N + \gamma R \\ \frac{d}{dt}I &= \beta SI/N - \alpha I \\ \frac{d}{dt}R &= \alpha I - \gamma R. \end{aligned}$$

Show by the negative Criterion of Bendixon-Dulac (dimension?), that this system cannot exhibit periodic orbits.

Exercise 6.2:
Change the Lotka-Volterra-Model slightly, in assuming logistic population dynamics for the prey alone,

$$\begin{aligned} \frac{d}{dt}N &= aN(1-N) - bNP \\ \frac{d}{dt}P &= cNP - dP \end{aligned}$$

(a) Compute the stationary points.
(b) Consider parameters, s.t. a stationary solution exists with predator and prey present. Show that this stationary point is locally stable, i.e. the eigenvalues of the linearization have negative real part.
(c) Use the negative criterion of Bendixon-Dulac to exclude periodic orbits (!).

7 Neuronal Activity

We start off with the description of a single ganglion or neuronal cell, that is stimulated by a given input. Experiments show basically, that a certain minimal activation is necessary to provoke a reaction. This reaction has a form of one spike, if the input signal is short, or periodic spiking, if there is a constant input. This behavior is model by the Hodgkin-Huxley model, resp. by the simpler (but treatable) Fitzugh-Nagumo equation. In the next step, we consider the most simplest network: one neuron that is recoupled, the output signal is feed in again as input signal. If this feedback is negative, then we find periodic spiking. We aim to understand the origin of this observation. Last, we go to large networks. Of course, in general one is not able to state any theorem about large networks of neurons. However, we assume a certain topology (a two-dimensional lattice with interaction of nearest neighbors only) and consider a further abstraction: we derive Greenberg-Hastings automata, a special case of cellular automata. Using combinatorial methods, it is possible to prove some theorems about the behavior, especially it is possible to derive a condition under that a the network stays activated and can never go completely to the resting state.

7.1 Hodgkin-Huxley Model

Hodgkin and Huxley describe 1952 their famous model the dynamics of ionic current in a ganglion. In experiments the activation pattern of a ganglion has been investigated. The experiments are patch-clamp experiments, where one uses something like a needle that is located within the ganglion to measure the voltage between insight and outside of the ganglion (Fig. 75). Then, a given stimulus is applied to the cell. The outcome has been basically, that an activation by a relatively small stimulus will not lead to a large reaction, but the system soon will return to the resting state, while a stimulus above a certain threshold leads to a spike, i.e. a high peak in the activation that comes eventually to rest again. At the time of Hodgkin and Huxley, one did only partially understand this pattern. The basic idea of these authors has been to introduce two kinds of ion channels, for potassium and for sodium. At this time, these channels have been purely hypothetical, and much debate took place if one should take them verbally, or if these channels are only artefacts of their model. Only later, one could identify the channels. Meanwhile, even the chemical structure and the genes that produce these channels are (at least partially) identified.

The model describes the dynamics for the potential $V(t)$ between inside of the ganglion and outside of the ganglion, $V(t) = V_{inside}(t) - V_{outside}(t)$ (be aware, that two versions of the model can be found in literature: The other version is to take $V(t)$ as $V_{outside}(t) - V_{inside}(t)$, s.t. the sign changes!). Furthermore, the membrane current $I(t)$ is described (positive ion current is directed from inside to outside). Basic physics tells us

$$\underbrace{I(t)}_{\text{total current}} = \underbrace{C\frac{d}{dt}V(t)}_{\substack{\text{Current due to the ca-}\\\text{pacity of the ganglion}}} + \underbrace{I_i(t)}_{\text{"real" ion flow}} .$$

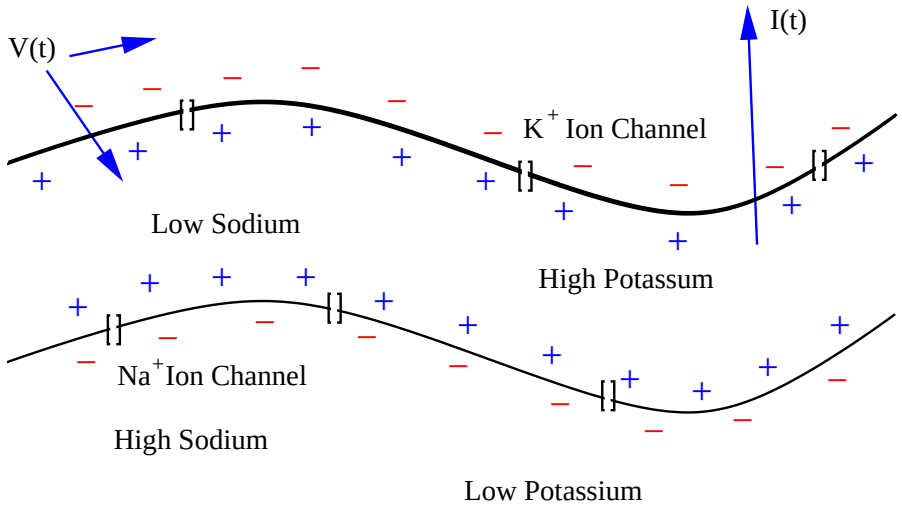

Figure 75: Caricature of a Ganglion: Low sodium, high potassium inside, reversed situation outside; ion flow is controlled by channels. The potential difference between outside and inside is modeled, together with ion flows.

The total ion flow I_i consists of the flow of sodium ions, I_{Na}, potassium ions I_K and all other ions (that are less important, the leakage flow) I_L.

$$I_i = I_K + I_{Na} + I_L.$$

These flows depend on $V(t)$ and the state of the gates (that are again controlled by the voltage $V(t)$). Thus, we have to model the dependence of the ion flows on $V(t)$.

Potassium

The law of Ohm tells us $I = VR$, i.e. voltage and current are proportional. Voltage does always mean a relative value. Thus, if all ion channels for potassium are open, we find

$$I_K = \kappa_K(V(t) - V_K),$$

the ion flow is proportional to the difference of the voltage with a reference voltage. If only a proportion g_K of channels are open, then

$$I_K = \kappa_K g_k(V(t) - V_K).$$

Until now, we shifted modeling the ion flow to modeling the proportion of gates that are open. This proportion will depend on $V(t)$.

The submodel that Hodgkin and Huxley developed for these ion channels introduces "gates" within the channel (see Fig. 76). On the level of one ion channel, g_K is the probability that this ion channel is open; i.e., that all doors are open. For the potassium channels, four doors with exactly the same features are assumed; at this point, this is a completely phenomenological approach. The assumption of "gates" cannot be justified

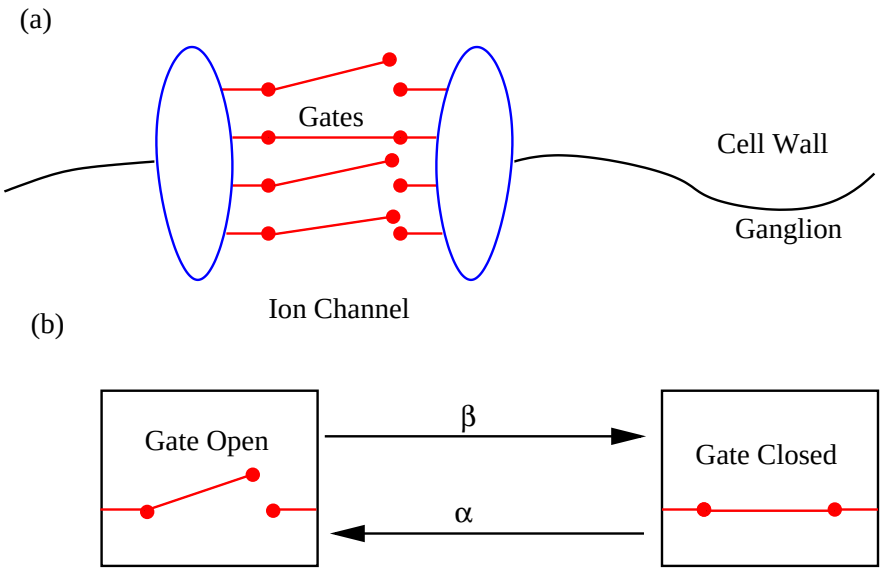

Figure 76: (a) Structure of a ion channel in the Hodgkin-Huxley model. (b) Submodel for one gate.

from, say, the stechiometric structure of ion channels. Hodgkin and Huxley used data to validate the model; and the assumption of four doors simply works fine.
If $n(t)$ is the probability that a door is open, we find $g_K(t) = n^4(t)$ to be the probability that the gate is open. First, the problem "model the ion flow" is reduced to the problem "model the probability that a ion channel is open". The latter task is reduced to "find a model for that describes the probability for one gate to be open". Here, a simple model is assumed: a gate is either open or closed; we have two states (see Fig. 76. It is assumed that we stay in the states for a time that is exponentially distributed (if $V(t) \equiv$ Const); thus, we have two constant rates for the transitions between the states. If $n(t)$ is the probability for a gate to be one, $1 - n(t)$ is the probability to be closed. Thus,

$$\frac{d}{dt}n(t) = \alpha_n(V)(1 - n(t)) + \beta_n(V)n(t).$$

The voltage $V(t)$ influences these rates; in this way, n and g_K depend on V. The functions $\alpha(V)$ and $\beta(V)$ have to be chosen. Hodgkin and Huxley used the from

$$\alpha_n(V) = \frac{1}{2}\hat{\alpha}_n^0 \frac{V_K - V}{1 - e^{\alpha_n^1(V_K - V)}}, \qquad \beta_n(V) = \beta_n^0 e^{-\beta_n^1 V}$$

s.t. $\alpha(V)$ increases in V while $\beta(V)$ decreases. These gates tend to be open if V is large, and are rather closed if V is near the resting state.

Estimation of the Parameters:
The interpretation of the equation $g_K(t) = n^4(t)$ as the description of single gates has been superimposed afterwards. Like remarked before, first of all these functions have

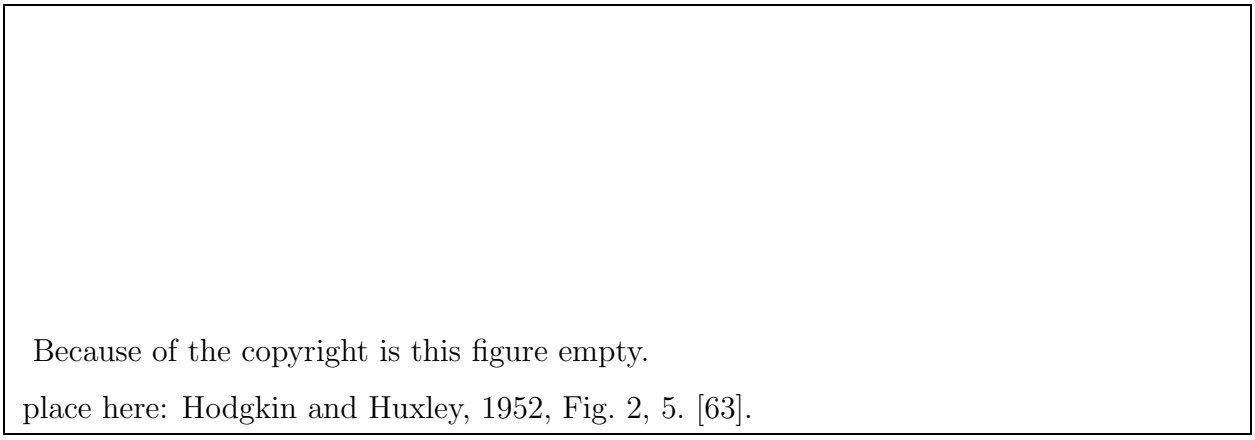

Figure 77: (a) Dynamics of potassium ion flow for $V = 25$mV above resting potential. (b) Curve of asymptotic values $n_\infty(V)$ in dependence of V.

been purely phenomenological well fitting functions that could be handled (Hodgkin and Huxley did their work 1952, where almost no computers have been available to do the computations!). The way how to obtain these parameter functions has been the following: First, fix a certain potential V. Then, determine the ion flux. For $V = v_0$ fixed, we can explicitly solve the differential equation, assuming $n(t)|_{t=0} = 0$,

$$n(t; v_0) = n_\infty(v_0) \left(1 - e^{-t/\tau_n(v_0)}\right)$$

with

$$n_\infty(v_0) = \frac{\alpha(v_0)}{\alpha(v_0) + \beta(v_0)}, \qquad \tau_n(v_0) = \frac{1}{\alpha_n(v_0) + \beta_n(v_0)}.$$

After the system is in equilibrium ($n \approx n_\infty(v_0)$, the voltage is changed to zero again. Then,

$$n(t) = n_\infty(v_0) e^{-t/\tau_n(v)}.$$

The data for one of these experiments are shown in Fig. 77 (a). Since $g(t) = n^4(t; n_\infty(v_0), \tau_n(v_0))$, it is possible to fit the two constants (since we only look at $V = v_0$ from these lines (to be more precise: one should say, that $g(t) = n^k(t; n_\infty(v_0), \tau_n(v_0))$, s.t. we fit three constants $n_\infty(v_0)$, $\tau_n(v_0) \in \mathbb{R}$ and $k \in \mathbb{N}$). These experiments are done for several values of V. The resulting curve for n_∞ is shown in Fig. 77 (b). This curve is fitted with a smooth function (like it is done with the corresponding curve for $\tau_n(V)$), and from these curves we are able recover $\alpha_n(V)$, $\beta_n(V)$.

Sodium

The same structure is used for sodium; only, that we have here two kinds of gates: one that opens and one that closes with increasing voltage. As a result, a "window" for the voltage is created, where the potassium channels are likely to be open. Outside the

window the channels will be closed. One channel consists of three gates that open and one gate that close with increasing V; we find

$$\begin{aligned} I_{Na} &= \kappa_{Na} g_{Na}(V - V_{Na}) = \kappa_{Na} m^3(t) h(t)(V - V_{Na}) \\ \frac{d}{dt} m &= \alpha_m(V)(1 - m(t)) + \beta_m(V) m(t) \\ \frac{d}{dt} h &= \alpha_h(V)(1 - h(t)) + \beta_h(V) h(t) \end{aligned}$$

where m describes the probability to be open for those gates that tend to be open for V large, and h is the probability to be open for the gate that tends to be closed for V large. Accordingly, the parameter functions have a inversed monotonicity: $\alpha_m(V), \beta_h(V)$ are increasing, while $\beta_m(V)$ and $\alpha_h(V)$ are decreasing in V,

$$\begin{aligned} \alpha_m(V) &= \alpha_m^0 \frac{V_{Na} - V}{e^{\alpha_m^2 (V_{Na} - V)} - 1}, \\ \beta_m(V) &= \beta_m^0 e^{-\beta_m^1 (V - V_{Na})}, \\ \alpha_h(V) &= \alpha_m^0 e^{-\alpha_m^1 (V - V_{Na})}, \\ \beta_h(V) &= \beta_h^0 \frac{V_{Na} - V}{e^{\beta_h^2 (V_{Na} - V)} + 1}. \end{aligned}$$

Leakage Ions

The leakage ions do not play an important role. It is assumed that no gates are there, i.e.

$$I_L = \kappa_L (V - V_L).$$

Hodgkin-Huxley Model

All in all we derive at the model

$$\begin{aligned} C \frac{d}{dt} V &= \kappa_K n^4 (V - V_K) + \kappa_{Na} m^3 h (V - V_{Na}) + \kappa_L (V - V_L) + I_0 \\ \frac{d}{dt} n &= \alpha_n(V)(1 - n(t)) + \beta_n(V) n(t) \\ \frac{d}{dt} m &= \alpha_m(V)(1 - m(t)) + \beta_m(V) m(t) \\ \frac{d}{dt} h &= \alpha_h(V)(1 - h(t)) + \beta_h(V) h(t) \end{aligned}$$

where the form of the parameter functions α_* and β_* are given above, and I_0 denotes the external stimulation. This model works quite well, and the desired behavior (the spiking) is reproduced by this model very nicely. From this starting point, research went in two directions: one direction tries to make the model even more realistically, taking into account more ion species or other phenomena (like synapses etc.). The other direction is a simplification of the model, such that it is possible to see clearly how the spike is produced. The most important of these simplifications is without doubt the Fizhugh-Nagumo model that we consider in the next paragraph.

7.2 Fitzhugh-Nagumo Model

The basic ingredient of the Fitzhugh-Nagumo-Model is the observation that the nerve pulse, described by the Hodgkin-Huxley model "lives" on different time scales. We will formulate these time scales; then, in a rather heuristic way, we develop the basic ideas of the singular perturbation theory - the mathematical structure that shows us how to deal with different time scales. We then will use this theory in order to understand how a spike is produced, and how we may obtain the different behavioral patterns of a nerve cell, that can be observed in experiments: either complete and long-lasting activation by a stiumulus, spiking or periodic spiking.

Simplified Model for Neuronal Activity
The key ingredients of the Hodgkin-Huxley model are Na^+ and K^+ ions, reflecting the activating and deactivating subsystems of the ganglion. The time scale of $m(t)$ is faster than that of $n(t)$ and $h(t)$. I.e., the activating part of the model is much faster than the deactivating part. Furthermore, we know that a minimal activating stimulus is necessary to provoke a reaction. A small stimulus is neglected; a stimulus above the threshold leads to a spike.

Let $v(t)$ be the variable describing the activating part of the system, and $w(t)$ the deactivating part. If we artificially remove the deactivating part, we are left with a system that - depending on the initial stimulus - either returns to the resting state (stimulus below a critical threshold a) or tends to a complete activated state (threshold above a) (see Fig. 78).
The simplest ordinary differential equation with this behavior reads

$$\dot{v} = -v(v-a)(v-1).$$

Now we describe the deactivating dynamics $w(t)$. It is stimulated by $v(t)$, and we assume a maximal possible deactivating reaction. Also here, we use the most simple model, a linear equation. In order to take into account that the time scale of w is much slower than that of v, we scale the r.h.s. by ϵ, $\epsilon \ll 1$ and derive

$$\dot{w} = \underbrace{\epsilon}_{\text{slow time scale}} \; (\; \underbrace{v}_{\text{activation}} \; - \; \underbrace{\gamma w}_{w \text{ bounded}} \;).$$

The effect on v is modeled by adding "$-w$" to the r.h.s. of the equation for v: if w becomes positive, it will reduce the activation v. All in all, we have the Fitzugh-Nagumo-model,

$$\begin{aligned} \dot{v} &= -v(v-a)(v-1) - w \\ \dot{w} &= \epsilon(v - \gamma w) \end{aligned}$$

We may include an explicite external stimulus $I(t)$,

$$\begin{aligned} \dot{v} &= -v(v-a)(v-1) - w + I \\ \dot{w} &= \epsilon(v - \gamma w) \end{aligned}$$

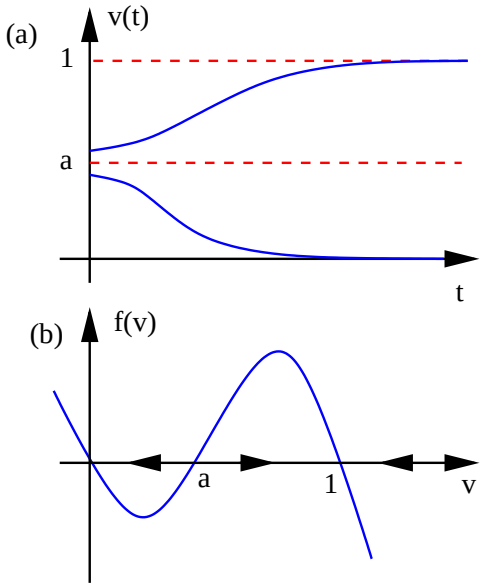

Figure 78: Activation only. (a) activation of the sytem over time, (b) right hand side of the corresponding ordinary differential equation $\dot{v} = f(v)$. The arrows on the x-axsis show the direction of $\dot{v}$

Analytizing Time Scales: Singular Perturbation Theory

Spikes and periodic Spiking

7.3 Small Networks: Periodic spiking

7.4 Large Networks: Greenberg-Hastings Automata

Deterministic Cellular Automata, Combinatorial methods.

8 Reaction Kinetics

8.1 Michaelis-Menton

8.2 Belouzov-Zhabotinskii

9 Immunology / Infectious diseases

9.1 Kermack-McKendrick/Standard Model for viral infection

9.2 Age-Structured Model, Vaccination (indirect effect)

10 Perhaps: System Biology / Regulatory Networks????

A Solutions of the Exercises

Solution of Exercise 3.2 : We use $\mathrm{Var}(S) = E(S^2) - (E(S))^2$. We find

$$\frac{d^2}{ds^2} h_3(s)\Big|_{s=1} = \sum_{i=1}^{\infty} i(i-1)P(S=i) = E(S^2) - E(S)$$

We find $\mathrm{Var}(S) = h_3''(1) + h_3'(1) - (h_3'(1))^2$

$$\begin{aligned}
\mathrm{Var}(S) &= (h_2 \circ h_1)''(1) + (h_2 \circ h_1)'(1) - ((h_2 \circ h_1)'(1))^2 \\
&= (h_2' \circ h_1\, h_1')'(1) + (h_2' \circ h_1\, h_1')(1) - ((h_2' \circ h_1\, h_1')'(1))^2 \\
&= h_2''(1)\,(h_1'(1))^2 + h_2'(1)\,h_1''(1) + h_2'(1)h_1'(1) - (h_2'(1))^2\,(h_1'(1))^2
\end{aligned}$$

We obtain with

$$\begin{aligned}
h_1'(1) &= E(X_1) & \qquad h_2'(1) &= E(Y) \\
h_1''(1) &= \mathrm{Var}(X_1) - E(X_1) + E(X_1)^2 & \qquad h_2''(1) &= \mathrm{Var}(Y) - E(Y) + E(Y)^2
\end{aligned}$$

that

$$\begin{aligned}
\mathrm{Var}(S) &= [\,\mathrm{Var}(Y) - E(Y) + E(Y)^2][E(X_1)]^2 + [E(Y)][\,\mathrm{Var}(X_1) - E(X_1) + E(X_1)^2] \\
&\quad + E(Y)E(X_1) - (E(Y))^2(E(X_1))^2 \\
&= \mathrm{Var}(Y)E(X_1)^2 + E(Y)\ \mathrm{Var}(X_1) - E(Y)E(X_1)^2 + E(Y)^2E(X_1)^2 \\
&\quad - E(Y)E(X_1) + E(Y)E(X_1)^2 + E(Y)E(X_1) - E(Y)^2E(X_1)^2 \\
&= \mathrm{Var}(X_1)\,E(Y) + E(X_1)^2\ \mathrm{Var}(Y).
\end{aligned}$$

Solution of Exercise 3.3 : We use induction and the relation

$$\mathrm{Var}(Z_{n+1}) = \mathrm{Var}(X)\,E(Z_n) + E(X)^2\ \mathrm{Var}(Z_n) = z_0 r^n \sigma + r^2\ \mathrm{Var}(Z_n)$$

For $r = 1$, the assertion follows immediately. If $r \neq 1$, then we have to work slightly more.
$n = 1$: $\mathrm{Var}(Z_1) = \sigma r^0 + r^2\ \mathrm{Var}(Z_0)$. Since we assume $Z_0 = z_0$, we have $\mathrm{Var}(Z_0) = 0$ and

$$\mathrm{Var}(Z_1) = \sigma r^0((r-1)/(r-1)).$$

$n \to n+1$: Hence we assume $\mathrm{Var}(Z_n) = z_0 \sigma r^{n-1}(r^n - 1)/(r-1)$. Thus we obtain

$$\begin{aligned}
\mathrm{Var}(Z_{n+1}) &= \sigma z_0 r^n + r^2 \left(z_0 \sigma r^{n-1} \frac{r^n - 1}{r-1} \right) \\
&= \sigma z_0 r^n \left(1 + r \frac{r^n - 1}{r-1} \right) \\
&= \sigma z_0 r^n \, \frac{r - 1 + r^{n+1} - r}{r-1} \\
&= z_0 \sigma r^n \, \frac{r^{n+1} - 1}{r-1}
\end{aligned}$$

Solution of Exercise 3.4 : ad **(a)** We formulate a two-type Galton-Watson process. Let Z_i^n be the population size for population type i, $i \in \{1,2\}$, in time step/generation n. In order to obtain the population size in the next time step, we need the information about number and type of children of one individual. Let $X_{i,j}$ be random variables that count the number of children of type i, if the mother is of type j. Then,

$$Z_i^{n+1} = \sum_{k=1}^{Z_1^n} X_{i,1} + \sum_{k=1}^{Z_2^n} X_{i,2}.$$

ad **(b)** Let $r_{i,j} = E(X_{i,j})$, $z_i^n = E(Z_i^n)$. Then,

$$\begin{pmatrix} z_1^{n+1} \\ z_2^{n+1} \end{pmatrix} = \begin{pmatrix} r_{1,1} & r_{1,2} \\ r_{2,1} & r_{2,2} \end{pmatrix} \begin{pmatrix} z_1^n \\ z_2^n \end{pmatrix}.$$

ad **(c)** If

$$A := \begin{pmatrix} r_{1,1} & r_{1,2} \\ r_{2,1} & r_{2,2} \end{pmatrix}$$

and A irreducible, we find immediately that

$$\lim_{n\to\infty} \| \begin{pmatrix} z_1^{n+1} \\ z_2^{n+1} \end{pmatrix} \| = \begin{cases} 0 & \text{for} \quad \rho(A) < 1 \\ \infty & \text{for} \quad \rho(A) > 1 \end{cases}$$

If the matrix is not irreducible, we may find two cases: Either one of booth or booth populations gives birth only to children of the own type. We define (!) that extinction does mean that booth population die out (one may also define extinction as the event that at least one population type has to vanish).

Case 1: A is a diagonal matrix.
In this case, booth populations give birth only to children of the own type. Hence, in order that the total population size tends to zero, we need

$$r_{1,1}, r_{2,2} < 1.$$

If either $r_{1,1}$ or $r_{2,2}$ is above one, then the expected population size of the corresponding type tends to infinity.

Case 1: Exactly one off-diagonal element of A is a zero.
Here, (without restriction) type 1 gives birth only to type 1 individuals, while type 2 gives birth to type 1 and type two individuals. However, in order to keep the total population alive, we need that either $r_{1,1}$ or $r_{2,2}$ is above one. If booth are below one, the population will die out.

Hence, in any case we find

$$\lim_{n\to\infty} \| \begin{pmatrix} z_1^{n+1} \\ z_2^{n+1} \end{pmatrix} \| = \begin{cases} 0 & \text{for} \quad \rho(A) < 1 \\ \infty & \text{for} \quad \rho(A) > 1 \end{cases}$$

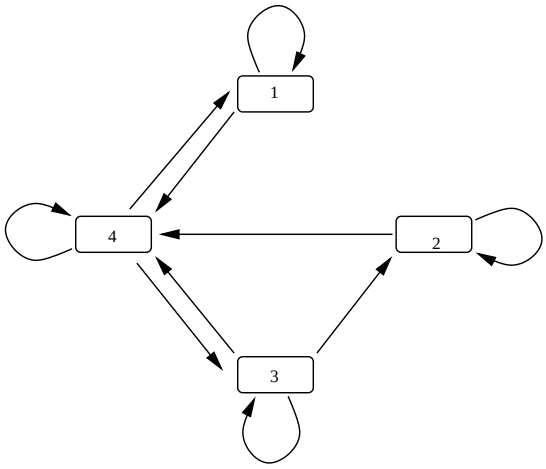

Figure 79: Graph of exercise 3.6.

Remark: It is possible to extend this conclusion to the stochastic process. If $\rho(A) > 1$, then the probability of extinction is strictly below one, i.e. the population may survive (and then tend to infinity but a number of realizations of zero measure). If $\rho(A) < 1$, then the probability of extinction is one (see e.g. Jagers [35]).

Solution of Exercise 3.5 : ad **(a)** Since A is irreducible, there is a path $i =: i_1 \to i_2 \to \cdots \to i_{l-1} \to i_l = j$. Thus, $(A^{l-1})_{j,i} > 0$.
ad **(b)** The irreducibility implies that there is a finite path between any of two states i and j. Let the length of this path be l,

$$i =: i_1 \to i_2 \to \cdots \to i_l \to i_{l+1} := j.$$

Since the number of states is n, the path $l \leq n-1$. Since we add the identity matrix, we ensure that the transitions $i \to i$ are possible. Thus, there is a path of length $n-1$,

$$i \to i \to \cdots i \to i_2 \to \cdots \to i_l \to i_{l+1}.$$

Thus, $(A+I)^{n-1}$ is strictly positive.

Solution of Exercise 3.6 : The graph shown in Fig. 79 is connected, hence A is irreducible.

Solution of Exercise 3.7 : A loop of length l has the structure

$$i_0 \to i_1 \to \cdots \to i_{l-1} \to i_0 \to i_1 \to \cdots$$

with $((A))_{i_j,i_{j+1}} = 1$. Hence

$$((A))_{i_0,i_1}((A))_{i_1,i_2}\cdots((A))_{i_{l-2},i_{l-1}}((A))_{i_{l-1},i_0} = \begin{cases} 1 & \text{if} \quad (i_0,..,i_{l+1}) \text{ is a cycle of length } l \\ 0 & \text{else} \end{cases}$$

Hence, the number of all these cycles is the summation over all possible combinations $(i_0, .., i_{l-1})$,

$$\begin{aligned} \text{loop}(l) &= \sum_{(i_0,..,i_{l+1})\in \mathbb{N}_n^{l+1}} ((A))_{i_0,i_1}((A))_{i_1,i_2}\cdots((A))_{i_{l-2},i_{l-1}}((A))_{i_{l-1},i_0} \\ &= \sum_{i_0\in\mathbb{N}_n} ((A\,A\cdots A\,A))_{i_0,i_0} \\ &= \sum_{i_0\in\mathbb{N}_n} ((A^l))_{i_0,i_0} = \text{tr}(A^l). \end{aligned}$$

Example: Consider the graph in Figure 80. The transition matrix reads

$$A = \begin{pmatrix} 0 & 1 \\ 1 & 1 \end{pmatrix}.$$

There is one loop of length one, the path $2 \to 2$. Accordingly, $\text{tr}(a) = 1$.
The paths of length two are $1 \to 2 \to 1$, $2 \to 1 \to 2$ and $2 \to 2 \to 2$. The trace of A^2 is

$$\text{tr}(A^2) = \text{tr}(\begin{pmatrix} 1 & 1 \\ 1 & 2 \end{pmatrix}) = 3$$

Paths of length four are $2 \to 1 \to 2 \to 2$, $2 \to 2 \to 1 \to 2$, $2 \to 2 \to 2 \to 1$ and $2 \to 2 \to 2 \to 2$. The trace of A^3 reads

$$\text{tr}(A^2) = \text{tr}(\begin{pmatrix} 1 & 2 \\ 2 & 3 \end{pmatrix}) = 4$$

One may also compute $\text{tr}(A^k)$ directly. The spectrum of A reads

$$\lambda_\pm = \frac{1}{2}(1 \pm \sqrt{5}).$$

Hence,

$$\begin{aligned} \text{tr}(A^k) &= \frac{1}{2^n}\left[(1+\sqrt{5})^k + (1-\sqrt{5})^k\right] = \frac{1}{2^n}\sum_{n=0}^{k}\begin{pmatrix} n \\ k \end{pmatrix}\sqrt{5}^n + \begin{pmatrix} n \\ k \end{pmatrix}(-1)^n\sqrt{5}^n \\ &= \frac{1}{2^{n-1}}\sum_{n=0}^{\lfloor k/2\rfloor}\begin{pmatrix} n \\ 2k \end{pmatrix}5^k \end{aligned}$$

Remark : Cycles that are shorter and divide l are also counted. Of course, one may subtract them if these should be removed (informations about cycles with a length that divides l can be obtained recursively. Furthermore, a specific cycle is counted with multiplicity due to the symmetry (phase). Hence, after subtracting all cycles with "true" smaller period, the remaining number has to be divided by l in order to factor out symmetry.

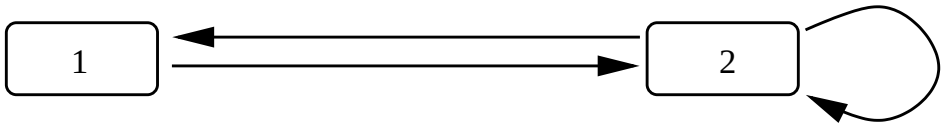

Figure 80: Example for exercise 3.7.

Solution of Exercise 3.8 : Assume that $\{v_1, .., v_l\}$ forms a trap. Then, the subset X in $\mathbb{R}^n$ spanned by $\{\mathbf{e}_{v_1}, .., \mathbf{e}_{v_l}\}$ (the unit vectors representing the states $v_1, .., v_l$ is invariant under the incidence matrix A. Furthermore, since the subgraph generated by $\{v_1, .., v_l\}$ is connected, the incidence matrix, projected to X is irreducible. Thus, there is a positive eigenvector x for the projected matrix $\Pi_X A \Pi_X$. Since the subgraph spanned by $\{v_1, .., v_l\}$ does not have an edge pointing outward of this subgraph (the subgraph is closed in a certain sense), we find

$$Ax = \Pi_X Ax.$$

and thus

$$Ax = \rho(\Pi_X A \Pi_X)x.$$

Since a trap is connected, different traps correspond to orthogonal invariant subspaces of the incidence Matrix. Hence, the number of positive eigenvectors is at least that of traps.

Solution of Exercise 3.9 : In order to model the ate of a fish, we have two possibilities. Either, we want to stick to natural time. Then, we obtain a Leslie-Matrix, where state 1,..,5 corresponds to "Egg", state 6,.,10 corresponds to "larvae" and state 11..50 corresponds to "adult", say.
The second possibility is to focus on the change of state. Then, we loose the information about time, but obtain a smaller set of states. However, we still have the form of a Leslie-Matrix. For fish that reproduce only once, we expect the model to be in the lattice-case. I.e., if the animals do not interact, we have several independent subpopulations. However, if these populations interact, we have exactly the salmon.example [49, 16].

Solution of Exercise 3.10 : ad **(a)** Assume that this is not the case. Hence, for every state $i \in I$, there is a natural number n and a state $j \in I$ with the properties:
• $p_{j,i}^{(n)} > 0$,
• There are no sequence of states $j_1 := j$,..,$j_k := i$ s.t. $p_{j_{l+1},j_l} > 0$, $l = 1, .., k-1$.
Now construct a chain of states in the following way: start with any state $i_0 \in I$. There is a state i_1 with the properties above. For state i_2 there is a state i_2 with the properties above, etc. If $|I| = n$, then $i_{n+1} \in \{i_1, .., i_n\}$, i.e. $i_{n+1} = i_l$ for some $l \in \{1, .., n\}$. This fact leads to a contradiction, since i_n can be reached from i_{n+1} via the finite chain $i_{n+1} = i_l, .., i_n$.
ad **(b)** According to **(a)** there is at least one essential state. Let

$$E = \{e \,|\, \text{e is essential state}\}.$$

We can define an equivalence relation on E,

$$e_1 \sim e_2 \qquad \Leftrightarrow \qquad \text{there is a path from } e_1 \text{ to } e_2.$$

Let $T \in E/\sim$ one equivalence class of E. Then, T is a trap (definition see exercise 3.8): obviously, T is connected. Furthermore, if there is any node v and an edge from $e \in T$ to v, then v belongs already to T. If we restrict the Markov chain to T, the Markov chain becomes irreducible, and thus there is an invariant measure (Theorem of Perron/Frobenius). Extending this measure to the complete Markov chain by putting the mass of all states apart form our essential states to zero will do it.

Solution of Exercise 3.11 : We developed a discrete Markov-chain model for the outbreak and transmission of a cold in a household. Here we show how to implement the model developed so far (in MAPLE). First we define the transition matrix P. We translate the formulas from above into a program. Let N be the family size, and the matrix $P_{(.,.),(.,.)}$ will be called `transition`.

```
# Family size
N := 5;
# Transition array, P(i,j)(k,l) = transition[i,j,k,l]
transition := array(0..N,0..N,0..N,0..N);
```

We first initialize the matrix `transition` with 0 and then we use the formulas (2) and (3).

```
# Initialize everything with zero
for n1 from 0 by 1 to N do
    for n2 from 0 by 1 to N do
        for n3 from 0 by 1 to N do
            for n4 from 0 by 1 to N do
                transition[n1,n2,n3,n4] := 0;
            od:
        od:
    od:
od: # First type of transitions:  infections.
for i from 1 by 1 to N-1 do
    for j from 0 by 1 to N-i-1 do
         transition[i,j,i+1,j] := R0*i*(N-i-j)/(R0*i*(N-i-j)+1);
    od:
od:
# Second type of transitions:  recovery.
for i from 1 by 1 to N do
    for j from 0 by 1 to N-i do
       transition[i,j,i-1,j+1] := 1/(R0*i*(N-i-j)+1);
    od:
od:
# Third type of transitions:  absorbing states.
for j from 0 by 1 to N do
    transition[0,j,0,j] := 1;
od:
```

Next, we choose the parameter R_0 and we define the state variable $q_{i,j}(n)$, i.e. the probability distribution over the states. Fort he MAPLE code we call it `probs` and we start in the state $(1, 0)$.

```
R0 := 0.154;
probs := array(0..N,0..N);
for n1 from 0 by 1 to N do
    for n2 from 0 by 1 to N do
       probs[n1,n2] := 0;
    od:
od:
probs[1,0] := 1;
```

The last step is to define a procedure that iterates our state from one event to the next event.

```
iter := proc( probs_in )
    # define local state variable
    local probs_new, n1, n2, n3, n4;

    # initialize the local state
    probs_new := array(0..N,0..N);
    for n1 from 0 by 1 to N do
        for n2 from 0 by 1 to N do
            probs_new[n1,n2] := 0;
        od;
    od:

    # now, iterate once
    for n1 from 0 by 1 to N do
        for n2 from 0 by 1 to N do
            for n3 from 0 by 1 to N do
                for n4 from 0 by 1 to N do
                    probs_new[n3,n4] := probs_new[n3,n4]
                            + probs_in[n1,n2]*transition[n1,n2,n3,n4];
                od:
               od:
            od:
        od:

    # return the new state
    RETURN( probs_new );
end;
```

Finally we have to iterate over many events until all probability mass is contained in the absorbing states. How often do we have to iterate? This is just the length of the longest path from state $(1, 0)$ into the states $(0, j)$ along the arrows of Fig. 39. The longest path ends up in $(N, 0)$, and all paths connecting $(0, 1)$ with $(0, N)$ have length $2N - 1$ (check!).

```
# now iterate 2*N-1 times:
for k from 1 by 1 to (2*N-1) do
    probs := iter(probs);
od:
# Plot the final size distribution
l := [];
for n1 from 1 by 1 to N do
    l := [op(l),[n1,probs[0,n1]]];
od:
with(plots);
myplot1 := plot(l, style=point, symbol = circle):
display(myplot1);
```

Given the parameter R_0, we are able to obtain the picture of the final size epidemics.

We add the empirical distribution to this plot.

```
# Data
final := [112,35,17,11,6];
total := final[1]+final[2]+final[3]+final[4]+final[5];

# empirical final size distribution
efsd := [];
for n1 from 1 by 1 to 5 do
    efsd := [op(efsd),[n1,evalf(final[n1]/total)]];
od:

myplot2 := plot(efsd, style=point, symbol=cross):
display(myplot1, myplot2);
```

Now we estimate R_0 (in the simple/heuristic way we discussed in section 3.3.3). We find

	overcrowded	crowded	undercrowded
R_0	0.154	0.139	0.138
χ^2	0.44	1.0	12.0

and the final size distribution is given in Table 5. We again see a good agreement. However, the crowdedness of the families seem not have a large influence on R_0.

Solution of Exercise 3.12 : The difference between Reed-Frost (exercise 3.11) and Greenwood is the incidence function: instead of $\beta\, s\, i$ (Reed-Frost) assumes the Greenwood model βs if $i > 0$ and zero else.
Thus, the trivial estimator does not change between Reed-Frost and Greenwood. Only the computer program for the final size distribu-

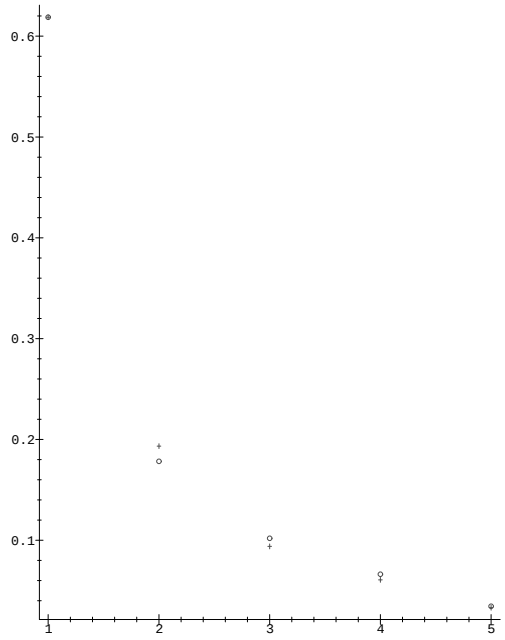

Figure 81: Comparizon of data and model.

tion has to be altered. Instead of (Reed Frost, see above, exercise 3.11

```
# First type of transitions:  infections.
for i from 1 by 1 to N-1 do
    for j from 0 by 1 to N-i-1 do
        transition[i,j,i+1,j] := R0*i*(N-i-j)/(R0*i*(N-i-j)+1);
    od:
od:
```

we write

```
# First type of transitions:  infections.
for i from 1 by 1 to N-1 do
    for j from 0 by 1 to N-i-1 do
        transition[i,j,i+1,j] := R0*(N-i-j)/(R0*(N-i-j)+1);
    od:
od:
```

We can now derive the final sie distribution (prediction shown in Tab. 5. The values for

Final infecteds	Number of families								
	overcrowded			crowded			uncrowded		
	Emp.	R-F	G	Emp.	R-F	G	Emp.	R-F	G
1	112	112	112	155	155	155	156	156	156
2	35	32.3	38.3	41	43.0	50.3	55	43.15	50.4
3	17	18.5	20.0	24	24.6	23.7	19	24.7	23.7
4	11	12	8.7	15	16.0	9.7	10	16.1	9.6
5	6	6.3	2.4	6	8.3	2.4	2	8.3	2.4

Table 5: Data and predictions (R-F: Reed-Frost model, G: Greenwood model) for the final size distribution, structured by degree of "crowdedness" of the families. (taken from [7])

R_0 and the χ^2-values are

	overcrowded	crowded	undercrowded
R_0	0.154	0.139	0.138
χ^2/Reed-Frost	0.44	1.0	12.0
χ^2/Greenwood	6.5	10.2	1.4

Solution of Exercise 3.13 : We consider an SIS-model (Suscepibles become Infected

Figure 82: SIS-model.

and then recover to be Susceptible again). Let N be the total population size.
State: The state of the population can be described by the number of infecteds i (since the number of susceptible individuals s is given by $N - i$).
Dynamics: The dynamics is given by the two processes, infection and recovery (see Fig. 82).
• Infection: The transition rate from state i to state $i + 1$ is $\beta si = \beta(N - i)i$.
• Revocery: We go from i to $i - 1$ at rate γi.

Let $p_i(t) = P(i \text{ infecteds at time } t)$. Then,

$$\dot{p}_i(t) = -i(\gamma + (N - i)\beta)p_i + (i - 1)\,(N - i - 1)\beta p_{i-1} + (N - (i + 1))\gamma p_{i+1}$$

where we formally define $p_{i-1}(t) = p_{N+1}(t) = 0$. Let $q_i(n)$ be the probability for the corresponding/embedded time discrete process, where we count the number of events.

$q_i(n)$ is the probability to be in state i after n events. Then,

$$\begin{aligned} q_i(n+1) &= \frac{(i-1)\,(N-i-1)\beta}{(i-1)\,(N-i-1)\beta+(N-i)\gamma}q_{i-1}(n) \\ &+\frac{(N-(i+1))\gamma}{(i+1)\,(N-(i+1))\beta+(i+1)\gamma}q_{i+1}(n). \end{aligned}$$

Like before, we let formally $q_{-1}(n) = q_{N+1}(n) = 0$. Define the vector $Q_n = (q_0(n), .., q_N(n))^T$, then we find a matrix A s.t.

$$Q_{n+1} = AQ_n.$$

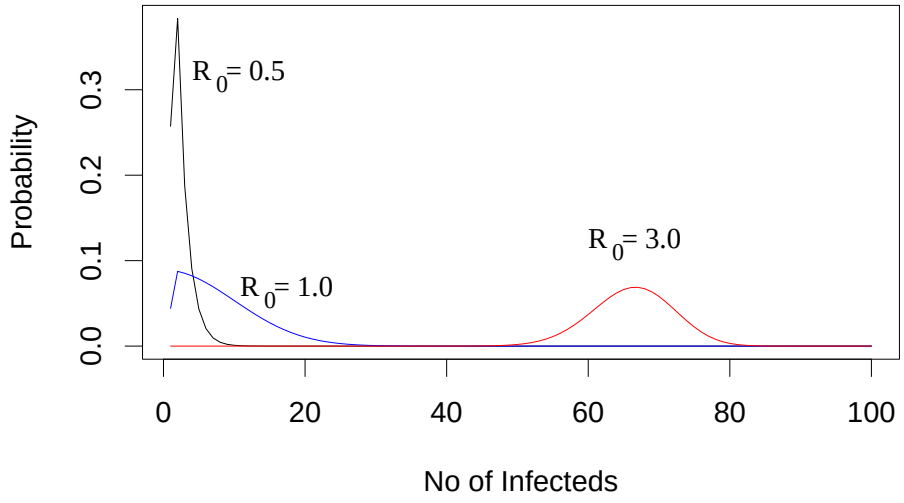

Figure 83: Quasi-stationary distributions (population size $N = 100$) for $R_0 = 0.5$, $R_0 = 1.0$ and $R_0 = 3$.

This Markov chain necessarily eventually dies out (all rates strictly positive), independent of the rates. However, if N is quite large, then we will never see this ion a simulation, provided that $\beta N \gg \gamma$. Thus, we are interested in all realizations that do not die out. Let

$$r_i(n) = P(\text{state } i \text{ after } n \text{ events} \,|\, \text{ Process did not die out}).$$

Then,

$$\begin{aligned} r_i(n+1) &= \frac{(i-1)\,(N-i-1)\beta}{(i-1)\,(N-i-1)\beta+(N-i)\gamma}r_{i-1}(n) \\ &+\frac{(i+1)\gamma}{(i+1)\,(N-(i+1))\beta+(i+1)\gamma}r_{i+1}(n). \end{aligned}$$

for $i > 2$ (again, formally $r_{-1}(n) = r_{N+1}(n) = 0$). Only the transition probabilities for $i = 1$ and $i = 2$ do change - we necessarily go form state $i = 1$ to state $i = 2$,

$$\begin{aligned} r_1(n+1) &= \frac{2\gamma}{2\,(N-2)\beta + 2\gamma} r_2(n) \\ r_2(n+1) &= \frac{3\gamma}{3\,(N-3)\beta + 3\gamma} r_3(n) + r_1(n) \end{aligned}$$

This Markov chain is irreducible and exhibits an invariant Measure. The shape of this measure is interesting. If $\beta N < \mu$, we find that the mass of this measure is concentrated at $i = 1$ and it is strictly decreasing in time. If $\beta N > \mu$ (and N large), then there is a maximum for some $i \gg 1$. This invariant measure is the so-called "quasi-stationary steady state" (see [50]). We show in Fig. 83 the shape of the asymptotic behavior (note: we start with the uniform distribution. Since we count events, one obtains only even or odd states if one starts in exactly one state; the kink for $R_0 = 0.5$ and 1.0 at state one is nevertheless a consequence of the fact that one has necessarily to leave state one in the next time step once one has reached this state. It does not appear in the time-continuous version of this process).
We know approximately the distribution for $R_0 \ll 1$, N large: In this case, we find an geometric distribution. If $R_0 \gg 1$, N large, one can show that the quasi-stationary distribution approximates (after appropriate rescaling) a normal distribution. The transitions between these two distributions are considered in [50]. This problem is related to the question for the minimal population size, where an disease is able to become endemic/to persist.

Solution of Exercise 4.1 : If we start with i individuals, the PDE for the generating function of the process reads

$$\frac{\partial}{\partial t} f(s,t) = (s-1)(\beta s - \mu)\frac{\partial}{\partial s} f(s,t), \qquad f(s,0) = s^i.$$

Let

$$f_0(s,t) = \frac{\mu(s-1) - (\beta s - \mu)e^{(\beta-\mu)t}}{\beta(s-1) - (\beta s - \mu)e^{(\beta-\mu)t}}.$$

be the solution for $i = 1$. Since the PDE is linear and of first order, we find

$$f(s,t) = (f_0(s,t))^i\,.$$

Especially, the probability of extinction reads

$$q = \lim_{t\to\infty} (f_0(s,t))^i = \left(\frac{\beta}{\mu}\right)^i$$

if $\beta > \mu$ and one else.
Another argumentation uses directly the independency of the particles: let q_1 be the probability that the population dies out, if we start with one particle. Since all particles act

independently of each other, the probability that all i subpopulations (each subpopulation consists of the ascendents of one of the i initial individuals) die out simultaneously is the product of the probability that one subpopulation dies out, i.e.

$$q = q_1^i.$$

Solution of Exercise 4.2 : ad **(a)** We consider a population of bacteria that only reproduce and never dies. Thus, from the birth-death process we obtain that the generating function reads (note that we start with one bacterium and $\mu = 0$)

$$\begin{aligned} f(s,t) &= \left.\frac{\mu(s-1)-(\beta s-\mu)e^{-(\beta-\mu)t}}{\beta(s-1)-(\beta s-\mu)e^{-(\beta-\mu)t}}\right|_{\mu=0} = \frac{se^{-\beta t}}{1-s+se^{-\beta t}} = se^{-\beta t}\ \frac{1}{1-s(1-e^{-\beta t})} \\ &= se^{-\beta t}\ \sum_{i=0}^{\infty}(1-e^{-\beta t})^i s^i \end{aligned}$$

Hence, if $p_i(t)$ denote the probability to have i bacteria at time t, we find

$$p_i(t) = \begin{cases} e^{-\beta t}(1-e^{-\beta t})^i & \text{for} \quad i>0 \\ 0 & \text{for} \quad i=0 \end{cases},$$

I.e.,

$$\text{number of bacteria} - 1 \ \sim\ \text{Geom}(e^{-\beta t}).$$

ad **(b)** Now we add the possibility for the host to die. We consider the states "i bacteria, host alive" and "i bacteria, host dead". With

$$p_{+,i}(t) = P(i \text{ bacteria, host alive}), \qquad p_{-,i}(t) = P(i \text{ bacteria, host dead})$$

we find

$$\begin{aligned} \frac{d}{dt}p_{+,i} &= -(\mu_0 + i\mu_1 + i\beta)p_{+,1} + (i-1)\beta p_{+,i-1} \\ \frac{d}{dt}p_{-,i} &= -(\mu_0 + i\mu_1)p_{+,1} \end{aligned}$$

with $p_{+,0}(t) \equiv 0$, $p_{+,1}(0) = 1$ and $p_{+,i}(0) = 0$ for $i \neq 1$, $p_{-,i}(0) = 0$ for all $i \in \mathbb{N}$. Let $\hat{p}_i(t) = e^{+\mu_0 t}p_{+,i}(t)$, then

$$\frac{d}{dt}\hat{p}_i = -i(\mu_1+\beta)\hat{p}_i + (i-1)\beta\hat{p}_{i-1}, \qquad \hat{p}_i(0) = \delta_{1,i}.$$

Define the generating function

$$g(s,t) = \sum_{i=0}^{\infty} s^i \hat{p}_i(t).$$

Then,

$$\begin{aligned}
\partial_t g &= \sum_{i=0}^{\infty} s^i \left(-i(\mu_1+\beta)\hat{p}_i + (i-1)\beta\hat{p}_{i-1}\right) \\
&= -(\mu_1+\beta)s\partial_s \sum_{i=0}^{\infty} s^i\hat{p}_i + \beta s^2\partial_s \sum_{i=0}^{\infty} s^i\hat{p}_i \\
&= s(\beta s - (\mu_1+\beta))\partial_s g \\
g(s,0) &= s.
\end{aligned}$$

We find the characteristic equation

$$\frac{d}{dt}S(s,t) = -S(s,t)(\beta S(s,t) - (\mu_1+\beta)), \qquad S(s,0) = s.$$

This equation can be solved by the method of separation of variables

$$\begin{aligned}
-t &= -\int_0^t d\tau = \int_s^S \frac{dS'}{S'(\beta S' - (\mu_1+\beta))} \\
&= -\frac{1}{\mu_1+\beta}\int_s^S \frac{-\beta S' + \beta S' - \mu_1 + \beta}{S'(\beta S' - (\mu_1+\beta))}\, dS' \\
&= -\frac{1}{\mu_1+\beta}\left(\int_s^S \frac{-\beta}{(\beta S' - (\mu_1+\beta))}\, dS' \int_s^S \frac{1}{S'}\, dS'\right) \\
&= -\frac{1}{\mu_1+\beta}\log\left(\frac{(\beta s - (\mu_1+\beta))S}{(\beta S - (\mu_1+\beta))s}\right)
\end{aligned}$$

Solving this equation for s (not for S) yields

$$s = \frac{(\mu_1+\beta)}{\beta S(1-e^{(\mu_1+\beta)t}) + (\mu_1+\beta)e^{(\mu_1+\beta)t}}.$$

Since $g(S,t) = s$, we find

$$g(S,t) = \frac{(\mu_1+\beta)S}{\beta S + (\mu_1+\beta(1-S))e^{(\mu_1+\beta)t}}.$$

Average load of bacteria We assume that an individual is alive at age a of infection. If we do not take into account that the host is alive, then we find (by part (a) of the exercise)

$$E(i)(a) = 1 + e^{\beta a}.$$

However, we know that the individual is alive. Heuristically this yields to a higher number of hosts that have (by chance) a lower number of bacteria. We expect that

$$E(i)(a)|\text{Host alive} < E(i)(a).$$

We find

$$P(\text{Host alive at age of infection } a) = \sum_{i=1}^{\infty} p_{+,i}(a) = e^{-\mu_0 a} g(1,a) = e^{-\mu_0 a} \frac{(\mu_1+\beta)}{\beta + \mu_1 e^{(\mu_1+\beta)a}}.$$

Hence,

$$\begin{aligned}
& P(\text{No of bacteria is } i \text{ age of infection is } a \,|\, \text{Host alive}) \\
= \; & \frac{P(\text{No of bacteria is } i \text{ age of infection is } a \text{ and Host alive})}{P(\text{age of infection is } a \text{ and Host alive})} \\
= \; & \frac{e^{-\mu_0 a} \frac{1}{i!} \frac{d^i}{ds^i} g(s,a)\Big|_{s=0}}{e^{-\mu_0 a} \frac{(\mu_1+\beta)}{\beta+\mu_1 e^{(\mu_1+\beta)a}}} \\
= \; & \frac{1}{i!} \frac{d^i}{ds^i} \frac{(\mu_1+\beta)s(\beta+\mu_1 e^{(\mu_1+\beta)a})}{(\beta s + (\mu_1+\beta(1-s))e^{(\mu_1+\beta)a})(\mu_1+\beta)}\Big|_{s=0} \\
= \; & \frac{1}{i!} \frac{d^i}{ds^i} s \, \frac{(\beta+\mu_1 e^{(\mu_1+\beta)a})}{(\mu_1+\beta)e^{(\mu_1+\beta)a} - \beta s(e^{(\mu_1+\beta)a}-1)}\Big|_{s=0} \\
= \; & \frac{1}{i!} \frac{d^i}{ds^i} s \, \frac{\frac{\mu_1}{\mu_1+\beta} + \frac{\beta}{\mu_1+\beta} e^{-(\mu_1+\beta)a}}{1 - \frac{\beta}{\mu_1+\beta} s(1-e^{-(\mu_1+\beta)a})}\Big|_{s=0} \\
= \; & \frac{1}{i!} \frac{d^i}{ds^i} s \, \frac{(1 - \frac{\beta}{\mu_1+\beta}(1-e^{-(\mu_1+\beta)a}))}{1 - \frac{\beta}{\mu_1+\beta} s(1-e^{-(\mu_1+\beta)a})}\Big|_{s=0}
\end{aligned}$$

and therefore

$$P(\text{No of bacteria is } i \text{ age of infection is } a \,|\, \text{Host alive}) - 1 \sim \text{Geom}\left(1 - \frac{\beta}{\mu_1+\beta}(1-e^{-(\mu_1+\beta)a})\right)$$

If $X \sim \text{Geom(q)}$, then $E(X) = (1/q) - 1$. Thus, the average number of bacteria in living hosts at time a after infection reads

$$1 + \left(\frac{1}{1 - \frac{\beta}{\mu_1+\beta}(1-e^{-(\mu_1+\beta)a})} - 1\right) = \frac{\mu_1+\beta}{\mu_1+\beta-\beta(1-e^{-(\mu_1+\beta)a})} = \frac{\mu_1+\beta}{\mu_1+\beta e^{-(\mu_1+\beta)a}}$$

Note, that the number of bacteria do not tend to ∞ for $a \to \infty$. This boundedness of the load is a consequence of the increased death rate in the case of a high bacteria load.

Death Rate: Hence, the death rate $\mu(a)$ after time a of infection reads

$$\mu(a) = \mu_0 + \mu_1 \frac{\mu_1+\beta}{\mu_1+\beta e^{-(\mu_1+\beta)a}}$$

Alternatively, it is possible to derive the death rate $\mu(a)$ if one takes the derivative of $P(\text{Host alive at age of infection } a)$ with respect to a. We find by a straight forward computation

$$\frac{d}{da} P(\text{Host alive at age of infection } a) = -\mu(a) P(\text{Host alive at age of infection } a).$$

ad **(c)** Let $u(t)$ be the density of healthy hosts and $v(t,a)$ the infected hosts with age of infection a. Assume that the infectivity does depend on the load of bacteria; this translates into a coefficient $\kappa(a)$ in the incidence function. We assume mass action law (perhaps the true mass action law would be more suitable? I.e., a function that is homogeneous of degree one?). Assume a constant inflow of Λ individuals per time into the population (birth or immigration). Then,

$$\begin{aligned} \frac{d}{dt}u &= \Lambda - \mu_0 u - u\int_0^\infty \kappa(a)v(t,a)\,da \\ \frac{\partial}{\partial t}v + \frac{\partial}{\partial a}v &= -\mu(a)v \\ v(t,0) &= u\int_0^\infty \kappa(a)v(t,a)\,da \end{aligned}$$

We assume(!) that the population tends to an equilibrium. Then, the "age of infection-distribution" of infected hosts read

$$\overline{v}(a) = \frac{e^{-\int_0^a \mu(\tau)\,d\tau}}{\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db}$$

we find that the average bacterium load is given by the formula above,

$$\text{average number of bacteria of a living individual at age of infection } a = \frac{\mu_1+\beta}{\mu_1+\beta e^{-(\mu_1+\beta)a}}$$

Thus,

$$\begin{aligned} \text{Average bacterium load} &= \frac{\int_0^\infty e^{-\int_0^a \mu(\tau)\,d\tau}\frac{\mu_1+\beta}{\mu_1+\beta e^{-(\mu_1+\beta)a}}\,da}{\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db} \\ &= \frac{\int_0^\infty e^{-\mu_0 a}\frac{d}{da}e^{-\int_0^a \mu_1\frac{\mu_1+\beta}{\mu_1+\beta e^{-(\mu_1+\beta)\tau}}\,d\tau}\,da/\mu_1}{\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db} \\ &= \frac{1}{\mu_1}\,\frac{1+\mu_0\int_0^\infty e^{-\mu_0 a}e^{-\int_0^a \mu_1\frac{\mu_1+\beta}{\mu_1+\beta e^{-(\mu_1+\beta)\tau}}\,d\tau}\,da}{\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db} \\ &= \frac{1}{\mu_1} + \frac{\mu_0}{\mu_1\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db} \end{aligned}$$

This expression cannot be simplified (at least in an obvious way). One may interprete the term $\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db$ using the observation

$$\int_0^\infty e^{-\int_0^b \mu(\tau)\,d\tau}\,db = \int_0^\infty b\left(-\frac{d}{db}e^{-\int_0^b \mu(\tau)\,d\tau}\right)\,db$$

i.e. this integral is the average time that an individual is infectious.

Solution of Exercise 4.3 : We define the states
(1) Polymer has length i, not closed to a ring
(2) Polymer has length i, closed to a ring
with the probabilities

$$p_i(t) = P(\text{Polymer has length } i, \text{ not closed to a ring, time is } t),$$

$$q_i(t) = P(\text{Polymer has length } i, \text{ closed to a ring, time is } t).$$

The master equations read (rate of attaching one more monomer is k, rate of closing to a ring is a),

$$\dot{p}_i = -(k+a)p_i + kp_{i-1}, \qquad \dot{q}_i = ap_i.$$

with initial conditions $p_1(0) = 1$ and all other points are zero. Define $\hat{p}_i(t) = e^{at}p_i(t)$. Then,

$$\frac{d}{dt}\hat{p}_i = -k\hat{p}_i + k\hat{p}_{i-1}.$$

This modified master equation describes the number of children of a particle that produces children at a constant rate (and never dies), or, more precisely: the number of events of a Poisson process with rate k. Hence,

$$\hat{p}_i(t) = \frac{1}{i!}(kt)^i e^{-kt}$$

and

$$p_i(t) = \frac{1}{i!}(kt)^i e^{-(k+a)t}, \qquad q_i(t) = \frac{1}{i!}\int_0^t a(k\tau)^i e^{-(k+a)\tau}\,d\tau.$$

Remark: (1) If $t \to \infty$, then

$$\lim_{t\to\infty} q_i(t) = \frac{a}{k+a}\ \left(\frac{a}{k+a}\right)^{i-1}.$$

(2) This model is for sure at most a first approximation to the growth of polymers. However, the structure of this model is appropriate also for more realistically models. See e.g. the description of histamine release in response to immunoglobolines, Perelson [53].

Solution of Exercise 4.4 : We look for exponentially growing solutions

$$u(x,t) = e^{\lambda t}v(x)$$

of the partial differential equation

$$u_t + (g(x)u)_x = -\mu(x)u, \qquad g(0)u(0,t) = \int_0^\infty b(x)u(x,t)\,dx.$$

Thus, we find the ODE

$$(g(x)v)' = -(\mu(x)+\lambda)v, \qquad g(0)v(0) = \int_0^\infty b(x)v(x)\,dx.$$

Since $(\mu(x)+\lambda)v(x) = [(\mu(x)+\lambda)/g(x)](g(x)v(x))$, we have

$$v(x) = \frac{g(0)v(0)}{g(x)} e^{-\int_0^x \frac{\mu(y)+\lambda}{g(y)}\,dy}$$

and

$$g(0)v(0) = \int_0^\infty g(0)v(0)\frac{b(x)}{g(x)} e^{-\int_0^x \frac{\mu(y)+\lambda}{g(y)}\,dy}\,dx.$$

We are only interested in solutions with $v \not\equiv 0$, i.e. $g(0)v(0) \neq 0$. Thus,

$$1 = \int_0^\infty \frac{b(x)}{g(x)} e^{-\int_0^x \frac{\mu(y)+\lambda}{g(y)}\,dy}\,dx.$$

The r.h.s. of this equation is strictly monotonously decreasing in λ, and hence (under non-pathologic conditions) there is a unique solution for λ. Furthermore, defining

$$R_0 = \int_0^\infty \frac{b(x)}{g(x)} e^{-\int_0^x \frac{\mu(y)}{g(y)}\,dy}\,dx$$

we find heuristically the usual threshold theorem: if $R_0 > 1$, the population will grow exponentially, if $R_0 < 1$ the population will die out.

Solution of Exercise 4.5 : First of all, the assumption is that for every harvesting rate there is a stationary point. This can only happen, if we assume a nonlinear model. The (perhaps) most simple nonlinear model reads

$$\begin{aligned} u_t + u_a &= -(\mu_0 + \overline{u}\mu_1 + \psi)u \\ u(0,t) &= \int_0^\infty b(a)u(a,t)\,da \\ \overline{u} &= \int_0^\infty u(a,t)\,da \end{aligned}$$

where μ_0 denotes the baseline of the mortality, μ_1 is the proportionality constant that describes the competition within the species, $\overline{u}(t)$ is the total population size and ψ the harvesting rate.
The (monetary) harvesting effort then reads

$$\text{Effort} = A\psi, \qquad \text{Gain} = B\,\psi\,\overline{u}.$$

Note: These equations and terms for effort and gain are model assumptions. They can be chosen in a different way - the only point is, that a reasonable interpretation has to be possible. In the present case, we have chosen the model as simple as possible.

The condition for a stationary solution reads

$$1 = \int_0^\infty b(a)e^{-(\mu_0+\mu_1\overline{u}+\psi)a}\,da$$

and thus

$$\overline{u}\mu_1 + \psi = \underline{u}$$

where $\underline{u}$ denotes the total population size without harvesting in the equilibrium. Thus, we maximize

$$g(\psi) = B\,\psi\,\overline{u} - A\psi = B\,\psi\,(\underline{u} - \psi/\mu_1) - A\psi.$$

Thus, there is a unique harvesting rate that maximizes the net gain,

$$\psi^* = \frac{\mu_1(A\underline{u} - B)}{2A}.$$

Solution of Exercise 4.6 : We consider a random walk on $\mathbb{Z}$. The probability to go to the left/to the right hand side depends on the gradient of a chemical signal $v(x)$, i.e. $P(\text{jump to the left}) = 1/2 - \alpha(m)$, $P(\text{jump to the right}) = 1/2 + \alpha(m)$ where m denotes the spatial location. The master equation for $p(m,n)$ (the probability to be in location m after time step n) reads

$$p(m,n) = \frac{1}{2}(p(m-1,n-1)+p(m-1,n-1))+\alpha(m-1)p(m-1,n-1)-\alpha(m+1)p(m+1,n-1).$$

Now define the spatial and temporal scale, and make the dependence of α on the signal $v(x)$ more explicite

$$\begin{aligned} p(m,n) &\approx u(x/\Delta x, t/\Delta t) \\ \alpha(m) &\approx -\chi\left[v((x-\Delta x)/\Delta x) - v((x+\Delta x)/\Delta x)\right] \end{aligned}$$

where $u, v \in C^2$, $t = n\Delta t$, $x = m/\Delta x$. We use the parabolic scaling, i.e.

$$\frac{\Delta x^2}{2\Delta t} = D$$

and find

$$\begin{aligned} u(x,t+\Delta t) &= \frac{1}{2}(u(x-\Delta x,t) + u(x-\Delta x,t)) \\ &\quad -\chi\left[(v(x-2\Delta x) - v((x)))u(x-\Delta x,t) - (v(x) - v((x+2\Delta x)))u(x+\Delta x,t)\right]. \end{aligned}$$

Thus,

$$\begin{aligned} \frac{u(x,t+\Delta t) - u(x,t)}{\Delta t} &= \frac{\Delta x^2}{2\Delta t}\frac{(u(x-\Delta x,t) - 2u(x,t) + u(x-\Delta x,t))}{\Delta x^2} \\ &\quad -\chi\frac{4\Delta x^2}{\Delta t}\frac{(v(x-2\Delta) - v((x)))u(x-\Delta x,t) - (v(x) - v((x+2\Delta)))u(x+\Delta x,t)}{4\Delta x^2} \\ &= \frac{\Delta x^2}{2\Delta t}\frac{(u(x-\Delta x,t) - 2u(x,t) + u(x-\Delta x,t))}{\Delta x^2} \\ &\quad -\chi\frac{4\Delta x^2}{\Delta t}\frac{\frac{v(x-2\Delta)-v(x)}{2\Delta x}u(x-\Delta x,t) - \frac{v(x)-v(x+2\Delta)}{2\Delta x}u(x+\Delta x,t)}{2\Delta x} \end{aligned}$$

Hence, for Δx, $\Delta t \to 0$ in the parabolic limit, we find

$$u_t = Du_{xx} - \overline{\chi}(v_x u)_x$$

where $\overline{\chi} = \chi D/8$.

Solution of Exercise 4.7 : We find for an initial condition $u_0(x)$

$$(S_1(t)u_0)(x) = e^{\alpha t}u_0(x)$$

and

$$(S_2(t)u_0)(x) = \int_{-\infty}^{\infty} \frac{1}{2\sqrt{\pi D t}} e^{|x-y|^2/(4t)} u_0(y)\, dy.$$

Thus,

$$S_1(t_1)S_2(t_2)u_0 = S_2(t_2)S_1(t_1)u_0$$

and

$$\Pi_{i=1}^n \left(S_1(\Delta t)S_2(\Delta t)\right) u_0 = \left(\Pi_{i=1}^n S_2(\Delta t)\right) \;\; \Pi_{i=1}^n \left(S_1(\Delta t)\right) u_0$$

Since S_1 and S_2 are semigroups, we have $S_\cdot(t_1)S_\cdot(t_2) = S_\cdot(t_1 + t_2)$ and thus

$$\Pi_{i=1}^n \left(S_1(\Delta t)S_2(\Delta t)\right) u_0 = S_1(t)S_2(t)u_0.$$

Hence,

$$\begin{aligned}
\frac{\partial}{\partial t}\Pi_{i=1}^n \left(S_1(\Delta t)S_2(\Delta t)\right) u_0 &= \frac{\partial}{\partial t}\left(S_1(t)S_2(t)\right) u_0 \\
&= \left(\frac{\partial}{\partial t}S_1(t)\right) S_2(t)u_0 + S_1(t)\left(\frac{\partial}{\partial t}S_2(t)\right) u_0 \\
&= \alpha \left(S_1(t)S_2(t)\right) u_0 + \left(S_1(t)D\frac{\partial^2}{\partial x^2}S_2(t)\right) u_0 \\
&= Du_{xx} + \alpha u.
\end{aligned}$$

We have to add the r.h.s. of the differential equations in order to obtain the complete solution. Here, the proof has been simple because S_1 and S_2 commute. The proof is less simple, if this is not the case: in this case, we have to show the Trotter formula [63, chapter??]. However, the stochastic approach in remark 4.13 and the present approach have in common that only very small time units are considered. Within these time units, the process are independent (n the deterministic case this does mean that we can apply the multiplication rule for the derivation, in the stochastic case this does mean that only one of the two processes are active/yield an event).

Solution of Exercise 4.8 : From $u_t = -j_x$ and $j = u^2/2$, we conclude

$$u_t + u\, u_x = 0.$$

(a) Characteristic lines.

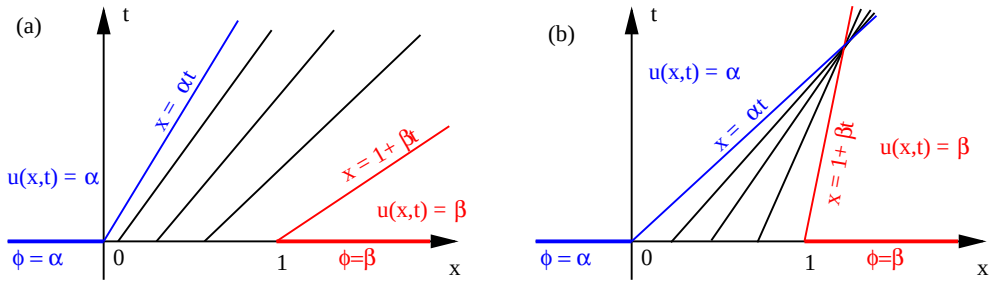

Figure 84: Characteristic lines of the Burger's equation (exercise 4.8). **(a)** $\alpha \leq \beta$, **(b)** $\alpha > \beta$.

Assume that $u(S(t;x_0),t) = \text{Constant}$ for a curve $x = S(t;x_0)$ with $S(0,x_0) = x_0$. Then, $u_t + \dot{S}(t;x_0)\, u_x = 0$. Hence,

$$\dot{S}(t;x_0) = u$$

and the characteristic curves assume the form of straight lines,

$$S(t;x_0) = x_0 + u(S(t;x_0),t)t = x_0 + u(S(0;x_0),0)t = x_0 + u(x_0,0)t$$

(b) Solution of the initial value problem
Case $x < \alpha t$: then $u(x,t) \equiv \alpha$ (see Fig. 84).
Case $x > 1 + \beta t$: then $u(x,t) \equiv \beta$.

This observation is a first hint, that something terrible must happen if $\alpha > \beta$: in this case, there is a region where $u(x,t)$ should be simultaneously α and β.

Case $\alpha t < x < 1 + \beta t$:
In this case, the characteristic originates at the interval $[0,1]$, where $\phi(x;\alpha,\beta)$ is linearly increasing. Hence,

$$S(t;x_0) = x_0 + \phi(x_0;\alpha,\beta)t = x_0 + [\alpha + (\beta - \alpha x_0]t$$

and hence

$$x_0 = x_0(S,t) = \frac{S - \alpha t}{1 + (\beta - \alpha)t}.$$

From this information we are able to derive $u(S,t)$,

$$u(S,t) = \phi(x_0(S,t);\alpha,\beta) = \alpha + (\beta - \alpha)\frac{S - \alpha t}{1 + (\beta - \alpha)t}.$$

It is simple to check that this function satisfies the PDE $u_t(x,t) + u(x,t)u_x(x,t) = 0$.

The solution exists as long as the term $(x - \alpha t)/(1 + (\beta - \alpha)t)$ dopes not blow up. I.e., the solution exist globally for $\beta \geq \alpha$. If $\alpha > \beta$, characteristic lines will intersect and the definition of a classical solution is not applicable any more.

Remark: There are (at least) two ways to proceed and to continuate the solution over the point of this singularity.

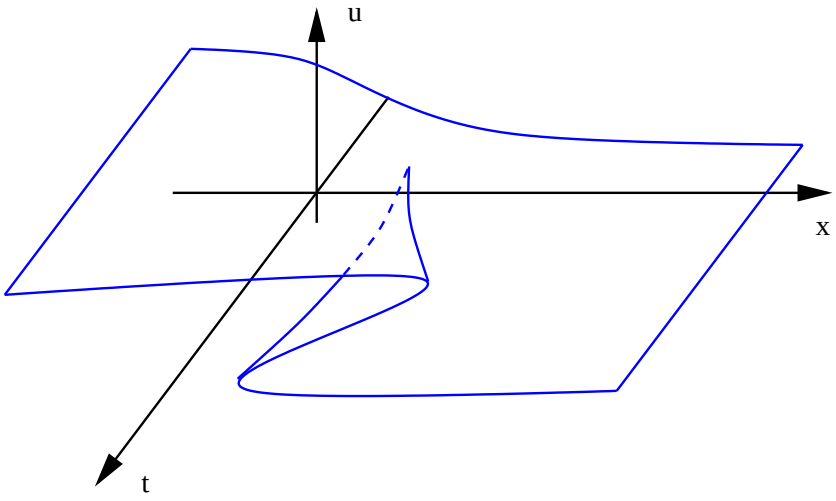

Figure 85: Continuation of the solution of the Burger's equation over the singularity (exercise 4.8).

First, one may not expect a function $u(x,t)$ as solution, but a two-dimensional manifold, embedded in the three dimensional space (spanned by x, t and u, see Fig. 85). This equation may be described by

$$F(x,t,u) = 0,$$

The step from the partial differential equation for u to the implicit representation by $F(.,.,.) = 0$ is called Jacobi-transformation. In general, assume that we consider a quasi-linear PDE of first order,

$$f(x,t,u)u_x + g(x,y,u)u_t - h(x,y,u) = 0.$$

Then, the function $F(x,t,u)$ that satisfies

$$f(x,t,u)F_x(x,t,u) + g(x,t,u)F_t(x,t,u) + h(x,t,u)F_u(x,t,u) = 0$$

has the property that the function $u(x,t)$, implicitly and locally defined by $F(x,t,u(x,t)) = 0$ obeys (if well defined) the original differential equation. We can conclude this directly by

$$F(x,t,u(x,t)) = 0 \quad \Rightarrow \quad F_x + F_u u_x = 0, \quad F_t + F_u u_t = 0$$

and hence we derive

$$f(x,t,u)(-F_u u_x) + g(x,t,u)(-F_u u_t) + h(x,t,u)F_u = 0$$

which implies the original PDE for u.
In case that the solution of the Burger's equation becomes singular, we obtain a manifold shown in Fig. 85: There is a region, where $u(t,x)$ cannot be represented by a function on (x,t), since the manifold has three layers at these points.

The second possibility is to allow for a line at which the solution becomes discontinuous (it jimps form α to β). Especially, if one remembers that this equation is used to model traffic and traffic jam, this solution has the appealing property to reflect the sudden jump in the density of cars at the end of a traffic jam. However, the line along that this discontinuity develops has to be determined in a unique way. The idea/one ideas to get a criterion where this discontinuity is located, one demands that also for the discontinuous solution the law of mass conservation is valid (no cars dissappear or are created in a traffic jam). These solutions lead to shock waves. Find more in the book of Smoller [58].

Solution of Exercise 4.9 : We consider the equation

$$u_t = Du_{xx} + \alpha u, \qquad u|_{x=0} = u|_{x)L} = 0.$$

Using the ansatz $u(x,t) = e^{\lambda t}v(x)$, we find

$$v'' = \frac{\lambda - \alpha}{D}v, \qquad v(0) = v(L) = 0.$$

Hence,

$$v(x) = A\sin(\omega x) + B\cos(\omega x).$$

The boundary conditions imply $B = 0$ and

$$\omega = \omega_n = \frac{\pi}{L}n, \qquad n \in \mathbb{N}.$$

Thus,

$$\frac{\lambda - \alpha}{D} = \omega_n^2,$$

i.e.

$$\lambda\lambda_1 == \alpha - D\omega_n^2 = \alpha - \frac{\pi n}{L}D.$$

We find the stabilizing effect of diffusion (in connection with the Dirichlet boundary conditions): By the diffusion, mass is transported to the boundary of the region. There it is (by the boundary conditions) destroyed. Thus, diffusion has a stabilizing effect on the trivial solution $u \equiv 0$. Even if $\alpha > 0$, i.e. in the case that the trivial solution is not stable in the case without spatial structure (i.e., $D = 0$), we may be able to stabilize the trivial solution in choosing D large enough (s.t. enough mass will be destroyed at the boundary). To be more precise, we need for the persistence of the population that at least λ_1 is positive, i.e.

$$L > \pi\sqrt{\frac{D}{\alpha}}.$$

Solution of Exercise 4.10 : (a) Boundary conditions: outside the region, the environment is hostile. I.e., all particles die at once if they leave the region. Thus, no particles will enter the region from outside. We find the model for the correlated random walk

$$\partial_t u^+ + \gamma\partial_x u^+ = -\mu u^+ + \mu u^- + \frac{1}{2}\alpha(u^+ + u^-), \qquad u^+|_{x=0} = 0.$$

$$\partial_t u^- - \gamma\partial_x u^- = \ \mu u^+ - \mu u^- + \frac{1}{2}\alpha(u^+ + u^-), \qquad u^-|_{x=L} = 0.$$

(b) We aim at the critical value for L, i.e. the value where we find a stationary solution. Hence,

$$\frac{d}{dx}\begin{pmatrix} \gamma u^+ \\ -\gamma u^- \end{pmatrix} = \frac{1}{\gamma}\begin{pmatrix} -(\mu-\alpha/2) & \mu+\alpha/2 \\ -(\mu+\alpha/2) & \mu-\alpha/2 \end{pmatrix}\begin{pmatrix} u^+ \\ u^- \end{pmatrix}, \qquad u^+|_{x=0}=0, \quad u^-|_{x=L}=0,$$

i.e $(u^+,u^-)T = (1/\gamma)A(u^+,u^-)T$ with

$$A = \begin{pmatrix} -(\mu-\alpha/2) & \mu+\alpha/2 \\ -(\mu+\alpha/2) & \mu-\alpha/2 \end{pmatrix}.$$

The eigenvalues of this matrix are ($\mathrm{tr}(A)=0$)

$$\lambda_\pm = \pm i\omega$$

with

$$\omega = \frac{1}{2}(\mathrm{tr}(A) + \sqrt{\mathrm{tr}(A)^2 4\det(A)}) = \sqrt{2\mu\alpha}.$$

In order to obtain a general form of the solution of this ODE, we are interested in vectors that satisfy

$$A\begin{pmatrix} u_1^+ \\ u_1^- \end{pmatrix} = -\frac{\omega}{\gamma}\begin{pmatrix} u_2^+ \\ u_2^- \end{pmatrix}, \quad A\begin{pmatrix} u_2^+ \\ u_2^- \end{pmatrix} = \frac{\omega}{\gamma}\begin{pmatrix} u_1^+ \\ u_1^- \end{pmatrix},$$

i.e. we represent A as a rotational matrix. We find that these two vectors are the complex- resp. real part of the complex eigenvector for the eigenvalue $i\omega$, i.e.

$$\begin{pmatrix} u_1^+ \\ u_1^- \end{pmatrix} = \begin{pmatrix} \mu+\alpha/2 \\ -(\mu-\alpha/2) \end{pmatrix}, \qquad \begin{pmatrix} u_2^+ \\ u_2^- \end{pmatrix} = 2\sqrt{\alpha\mu}\begin{pmatrix} 0 \\ 1 \end{pmatrix}.$$

Hence, the solution reads

$$\begin{pmatrix} u^+ \\ u^- \end{pmatrix} = a\begin{pmatrix} \mu+\alpha/2 \\ \mu-\alpha/2 \end{pmatrix}\cos(\omega x/\gamma) + b\begin{pmatrix} 0 \\ 1 \end{pmatrix}\sin(\omega x/\gamma).$$

The boundary conditions superimpose conditions on the parameters. $u^+(0)=0$ implies $a=0$, and the consequence of $u^-(L)=0$ is

$$\sin(\sqrt{4\mu\alpha/\gamma^2}L) = 0.$$

If we define (like in the parabolic limit) $D=\gamma^2/(2\mu)$, we obtain exactly the same threshold like in the parabolic case,

$$L = \pi\sqrt{D/\alpha}.$$

There is a deeper reason behind this (non-obvious) result: The limit $t\to\infty$ ensures a well mixed population. I.e., the limit in t is in some sense like the limit of μ and γ (with parabolic scaling). Thus, both results necessarily agree.

Solution of Exercise 4.11 : The first condition is that the eigenvalues of the matrix

$$A_0 = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

have negative real part, i.e.

$$\Re(\lambda_\pm) = \frac{1}{2}((a+c) \pm \Re(\sqrt{(a-c)^2 - 4bc})) \leq 0.$$

Thus,

$$\mathrm{tr}(A_0) = a + b \leq 0, \qquad \det(A_0) = ab - bc \geq 0.$$

The second condition is that diffusion should destabilize the trivial solution. We may show this in looking for at least one eigenfunction of the r.h.s. of the PDE (diffusion included) that has an eigenvalue with real part larger than zero. Inspired by exercises 4.9 and 4.10, we use the ansatz

$$u(x) = \begin{pmatrix} A \\ B \end{pmatrix} \sin(kx).$$

The boundary conditions are satisfied for

$$k = (2n+1)\pi/L, \qquad n \in \mathbb{N}$$

and the condition that we have an eigenfunction for the r.h.s. of the PDE yields

$$A_k \begin{pmatrix} A \\ B \end{pmatrix} = \lambda \begin{pmatrix} A \\ B \end{pmatrix}$$

with

$$A_k = \begin{pmatrix} -D_1 k^2 + a & b \\ c & -D_2 k^2 + d \end{pmatrix}.$$

In order to find that the trivial solution is destabilized, we need $\Re(\lambda) > 0$, i.e.

$$\begin{aligned} \mathrm{tr}(A_k) &= a + d - D_1 k^2 - D_2 k^2 = \det(A_0) - (D_1 + D_2)k^2 > 0 \\ \text{or} \quad \det(A_k) &= (a - D_1 k^2)(d - D_2 k^2) - bc = \det(A_0) - (D_1 d + D_2 a)k^2 + D_1 D_2 k^4 < 0 \end{aligned}$$

Since D_1, D_2 and k^2 are nonnegative, we always find $\mathrm{tr}(A_k) < 0$. Thus, only the second condition can be satisfied. If $D_1 = D_2$, we find that

$$(D_1 d + D_2 a) = D_1(a + d) = D_1 \mathrm{tr}(A_0) < 0.$$

Also in he case $a, d < 0$ we find

$$(D_1 d + D_2 a) < 0.$$

and hence in these two cases, again

$$\det(A_0) - (D_1 d + D_2 a)k^2 + D_1 D_2 k^4 > \det(A_0) > 0.$$

The only chance to find eigenvalues with positive real part is $D_1 \neq D_2$ and $a\,d > 0$, and then to choose D_1, D_2 s.t. $(D_1 d + D_2 a) \gg 0$. Indeed, let without restriction $a > 0 > d$. Choose $D_2 > 0$. In this case, we find for k given that

$$\begin{aligned} \lim D_1 \to \infty \det(A_k) &= \lim D_1 \to \infty \det(A_0) - (D_1 d + D_2 a)k^2 + D_1\, D_2 k^4 \\ &= \lim D_1 \to \infty D_1 k^2(|d| - D_2 k^2) > 0 \end{aligned}$$

for $k \leq \sqrt{|d|/D_2}$. Thus, for L appropriate chosen (s.t. there is $n \in \mathbb{N}$ with $k = (2n+1)\pi/L$ is element of the instable modes) we find that diffusion (where booth components must have different diffusion coefficients) leads to a destabilization of the trivial solution. If $D_1 = D_2$, we always find a stabilization of the trivial solution by diffusion.

Solution of Exercise 5.1 : (a) Consider $y_n = \beta x_n$. Then,

$$y_{n+1} = \beta x_{n+1} = \beta\alpha x_n e^{-\beta x_n} = \alpha y_n e^{-y_n}.$$

(b) *Stationary points:* $y = 0$ or $\alpha e^y = 1$, i.e.

$$y \in \{0, \ln(\alpha)\}.$$

Stability: The stability is given by the magnitude of the derivative at the stationary points. Let $\tilde{g}(y) = \alpha y e^{-y}$. Then, $\tilde{g}'(y) = \alpha e^{-y} - \alpha y e^{-y}$ and

$$\tilde{g}'(0) = \alpha, \qquad \tilde{g}'(\ln(\alpha)) = 1 - \ln(\alpha).$$

Trivial stationary state $y = 0$:
The trivial stationary state is locally stable for $\alpha < 1$. It becomes then unstable. At the same time, a (locally) stable non-trivial stationary point ($y = \ln(\alpha)$) appears in the positive axis.
Non-trivial stationary state $y = \ln(\alpha)$:
If $0 < \alpha < 1$, we find

$$1 - \ln(\alpha) > 1,$$

i.e. this stationary point is unstable. If $\alpha < e^2$ we have

$$\alpha < e^2 \quad \Rightarrow \quad \ln(\alpha) < 2 \quad \Rightarrow \quad 1 - \ln(\alpha) > -1.$$

Thus, at $\alpha = e^2$ a period doubling bifurcation happens (strictly spoken, we have to prove that this bifurcation is not degenerated).

Solution of Exercise 5.2 : (a) If we let formally $N \to \infty$, then we find the Galton-Watson process with $\mathrm{Geom}(q_0)$ as the distribution of children. Denote with Y_n the population size in step n of this linear process.

(b) The parameter $q(k)$ can be written as

$$q(k) = q_0 e^{-\alpha k/N}.$$

We show that for a finite time interval $n \in [0, T]$, $T \in \mathbb{N}$, booth processes agree if $N \to \infty$.
Step 1: We reformulate the process that generates the number of the offspring.
Let $\hat{C} = \text{Geom}(q(k))$, $\hat{C} = \text{Geom}(q_0)$. The random variables C, $\hat{C}$ can be defined on the same random space via the following process:
(1) Choose $u = U(\omega)$ a realization of a random variable distributed according to the uniform distribution between $[0, 1]$.
(2) Define $c = C(\omega)$ as the number $c \in \mathbb{N}$, s.t.

$$\sum_{i=0}^{c-1} P(C = i) \leq u < \sum_{i=0}^{c-1} P(C = i).$$

Similarly, $\hat{c} = \hat{C}(\omega)$ is defined as

$$\sum_{i=0}^{\hat{c}-1} P(\hat{C} = i) \leq u < \sum_{i=0}^{\hat{c}-1} P(C = i).$$

(3) Define the random variable Δ (the distribution of Δ depends on k) by

$$\Delta(\omega) = \hat{C}(\omega) - C(\omega).$$

The random variable Δ is non-negative (since $q_0 \geq q(k)$) and assumes the values in $\mathbb{N}$. According to the construction above, we find

$$C = \hat{C} + \Delta.$$

Step 2: Finite number of births, finite population size.
Let B_T be the number of newborns for the linear process, i.e.

$$B_T = \sum_{n=0}^{T} Y_t$$

and let N_T denote the maximal population size up to this point,

$$N_T = \max_{n \in \{0,..,T\}} Y_n.$$

We show that B_T, N_T is finite a.s. First of all, we have $N_T \leq B_T + 1$ (if we start with one individual), i.e. we only have to consider B_T. Since we only consider a finite number of steps, we may construct a Galton-Watson process with population size $\tilde{Y}_n$, s.t. $\tilde{Y}_n(\omega) \geq B_n(\omega)$. All we have to do is to define for this process the number of children to follow the random variable $\tilde{C} = 1 + C$. In this case, the parent o a child "survives" necessarily. Since the population size of a Galton-Watson process is finite after a finite number of steps with probability one, also B_T is finite with probability one.
Step 3: The lionear and nonlinear process agree for $N \to \infty$.
We show that $\Delta = 0$ a.s. for $n \leq T$ and $N \to \infty$. We find for k bounded, that

$$P(\Delta \neq 0) \to 0 \qquad N \to \infty$$

since $q(k) \to q_0$ for $N \to \infty$. For one realization $\omega \in \Omega$, we determine only a number of $B(\omega)$ realizations of Δ, $\Delta_1, .., \Delta_{B_T}$. Since $k \leq N_T$, we find

$$\lim_{N\to\infty} \Delta_i(\omega) = 0.$$

Thus, if $B(\omega) < \infty$ (which is ta.s true), we find that

$$\lim_{N\to\infty} \sum_{i=0}^{B(\omega)} \Delta_i(\omega) = 0 \quad \Rightarrow \quad \lim_{N\to\infty} Y_i(\omega) = X_i(\omega),$$

the linear and te nonlinear process agree on the finite time interval.

If q_0 is small enough, s.t. $E(\hat{C}) < 1$, then the linear process dies out a.s. In his case, the number of all births $B(\omega)$ is finite just because this fact, without restriction of the time. Then, the ressult follows immediately without restrictions on T.

Solution of Exercise 5.3 : (a) We have *a priori* that $0 \leq X_t \leq N$. Thus

$$\begin{aligned}
P(X_{t+\Delta t} = 0 | X_t = k) &\geq P(\text{no births due to } k\text{individuals in } [t, t+\Delta t] \text{ and } k \text{ individuals die}) \\
&= \Big[P(\text{no births due to one individual in } [t, t+\Delta t]) \\
&\qquad\qquad P(\text{one individual dies in } [t, t+\Delta t]) \Big]^k \\
&= \Big[(1 - \beta\Delta t + \mathfrak{o}(\Delta t))(\mu\Delta t + \mathfrak{o}(\Delta t)) \Big]^k \\
&= \tilde{\epsilon}(\Delta t)^k
\end{aligned}$$

If Δt is sufficiently small, we find $1 > \tilde{\epsilon}(\Delta t) > 0$, s.t.

$$P(X_{t+\Delta t} = 0 | X_t = k) \geq \tilde{\epsilon}(\Delta t)^k \geq \tilde{\epsilon}(\Delta t)^N =: \epsilon.$$

(b) Let

$$p_l =: P(\text{Population extinct at time } t = l\Delta t).$$

Then,

$$\begin{aligned}
p_l &\geq P(X_{l\Delta} = 0 \,|\, X_{(l-1)\Delta} > 0)\; P(X_{(l-1)\Delta} > 0) + P(X_{l\Delta} = 0 \,|\, X_{(l-1)\Delta} = 0)\; P(X_{(l-1)\Delta} = 0) \\
&= P(\text{Pop. goes extinct in } [(l-1)\Delta t, l\Delta t]) P(\text{Pop. not extinct at } t = (l-1)\Delta t) \\
&\qquad + P(\text{Pop. extinct at } t = (l-1)\Delta t) \\
&\geq \epsilon(1 - p_{l-1}) + p_{l-1} = \epsilon + (1-\epsilon)p_{l-1}.
\end{aligned}$$

Now define the recursion

$$\tilde{p}_l = \epsilon + (1-\epsilon)\tilde{p}_{l-1}).$$

and $\tilde{p}_0 = p_0 = 1$. Since

$$(p_l - \tilde{p}_l) \geq (1-\epsilon)(p_{l-1} - \tilde{p}_{l-1})$$

we find from $p_0 - \tilde{p}_0 \geq 0$ per induction that $p_l - \tilde{p}_l \geq 0$, i.e.

$$p_l \geq \tilde{p}_l.$$

(c) In the last step, we show that $\tilde{p}_l \to 1$ for $l \to \infty$. Since the function $f(x) = \epsilon + (1-\epsilon)x$ maps the interval $[0,1]$ into itself,

$$f([0,1]) \subset [0,1]$$

and $f'(x) < 1$ (i.e. $f(x)$ is a contraction), the iteration tends to a fixed point. The only fixed point of $f(x)$ is $x = 1$. Thus,

$$\tilde{p}_l \to 1 \qquad \text{for} \quad l \to \infty$$

and since $\tilde{p}_l \leq p_l \leq 1$, we also have

$$p_l \to 1 \qquad \text{for} \quad l \to \infty$$

Solution of Exercise 5.4 : With the notation introduced in definition 5.17, we find

$$\sum_{z' \in \Gamma} G(z, z') = K$$

for all $z \in \Gamma$ (the number of neighbors is independent of the site). In the case of $\Gamma = \mathbb{Z}$ and the nearest neighbors neighborhood, we find $K = 2$. This is almost the only thing needed:

$$\begin{aligned} \sum_{x \in E} [X, A] &= \sum_{x \in E} \sum_{z, z' \in \Gamma} \chi_{\phi(z),x} \chi_{\phi(z'),A} G(z, z') \\ &= \sum_{z, z' \in \Gamma} \left(\sum_{x \in E} \chi_{\phi(z),x} \right) \chi_{\phi(z'),A} G(z, z') \\ &= \sum_{z \in \Gamma} \chi_{\phi(z'),A} \sum_{z' \in \Gamma} G(z, z') = K \sum_{z \in \Gamma} \chi_{\phi(z'),A} = K[A]. \end{aligned}$$

Thus,

$$[A] = \sum_{x \in E} [X, A]/K.$$

Solution of Exercise 5.5 : (a) In this case, the incidence matrix G becomes non-symmetric,

$$G(i,j) = \begin{cases} 1 & \text{for} \quad j = i+1 \\ 0 & \text{else} \end{cases}$$

Thus, it is not obvious that $[0,1] = [1,0]$. Let

$$N_+ = \{i \mid \phi(i) = 0, \ \ \phi(i+1) = 1\} = [0,1], \qquad N_- = \{i \mid \phi(i) = 1, \ \ \phi(i+1) = 0\} = [1,0]$$

(where we always work modulo n, if we are on a torus of size n). We show that $N_+ = N_-$.

Case 1: $N_+ = 0$.
In this case, the state of all cells is either identical one or identical zero, and thus $N_+ = N_- = 0$.
Case 2: $N_+ > 0$.
Thus, there is $l_0, l_1 \in T_n$, s.t. $\phi(l_0) = 0$, $\phi(l1) = 1$. Hence, every pair $[0,1]$ starts a block of cells with state 1. I.e., if $i_0 \in N_+$, then $\phi(i_0) = 0$, $\phi(i_0+1) = 1$. There is a finite $k = k(i_0)$ s.t.

$$\phi(i_0) = 0, \;\; \phi(i_0+1) = \phi(i_0+2) = \cdots \phi(i_0+k) = 1, \;\; \phi(i_0+k+1) = 0.$$

Thus, $i_0 + k \in N_-$. In this way, we are able to define a one-to-one map $\Phi : N_+ \to N_-$, $i \mapsto k(i)$. Hence, $|N_+| = |N_-|$.

(b) This part of the exercise only recalls the definition of $[0,0]$,

$$[0,0] = \sum z, z' \in \Gamma \chi_{\phi(z),0} \chi_{\phi(z'),0} G(z,z') = \sum i \in \Gamma \chi_{\phi(i),0} \chi_{\phi(i+1),0}.$$

Solution of Exercise 5.6 : In order to derive the mean field, we first consider possible events. An event consist of the change of the state of one cell. Since we are only interested in the mean field, and every cell is only influenced by its left neighbor, all we have to consider are pairs: the cell that changes its state and its left neighbor.

Event			Rate	Effect on ([0],[1])
$[0,0]$	$\to$	$[0,1]$	0	(-1,1)
$[1,0]$	$\to$	$[1,1]$	β	(-1,1)
$[0,1]$	$\to$	$[0,0]$	μ	(1,-1)
$[1,1]$	$\to$	$[1,0]$	μ	(1,-1)

Furthermore, we find

$$K = \sum_i G(i,j) = 1$$

and hence, with the result of exercise 5.4,

$$[0] = [0,0] + [0,1], \qquad [1] = [1,0] + [1,1].$$

Hence,

$$\begin{aligned} \frac{d}{dt}|[0]| &= \mu\left(|[0,1]| + |[1,1]|\right) - \beta|[1,0]| \\ &= \mu|[1]| - \beta|[1,0]|. \end{aligned}$$

In order to obtain the mean field equation, we close this equation by the approximation

$$|[1,0]| \approx \frac{|[0]|\,|[1]|}{|\Gamma|},$$

i.e.

$$\frac{d}{dt}|[0]| \approx -\frac{\beta}{|\Gamma|}\ |[0]|\,|[1]| + \mu|[1]|$$

We find $|[1]|$ by

$$|[1]| = |\Gamma| - |[0]|.$$

Thus, the mean field does not changed by the somewhat strange choice of the neighborhood.

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