
Computational Models For Complex Systems (6 cfu) 23-24

Notes

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M.Sc. in Computer Science

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Chapter 1

Introduction

1.1 What is a Model of a System?

A model is a simplified and approximate representation of a system, that allows reasoning on the systems properties. **So we construct models in order to understand some aspect of that system.** We include in the model only the aspect of the system that we consider essential, omitting details that would only complicate the analysis.

1.1.1 Understanding the model

After designing our model, then in order to acquire new knowledge, we have to **analyze the model** (like a child play with a toy to understand what it does), then we have to apply some **reasoning** regarding the result given during the analysis.

1.1.2 Errors

All the three steps listed above (Modelling, Analysis, and Reasoning), **can be sources of errors.** The model can be too abstract; the analysis can be too inaccurate; or the interpretation itself could be wrong. **Recall that the result that you get are showing you only something about the real system, you need to generalise what the result means.**

1.1.3 Examples of Models

Planimetries/project and scale models

In architecture planimetries and scale models are used to assest structural properties at design time, in order to evaluate the result in advance.

Life Science

In biology rats (in-vivo model) or a cell culture (in-vitro model) are used as model for the human being.

In Silico Models

In biology there are also computer-based techniques are usually faster and cheaper than in vivo e in vitro models. They simulate the interaction between proteins.

1.1.4 Mathematical Models

Mathematics provides tools for building abstract models of almost everything like **geometry** for Architecture or **differential equations** for Weather. Mathematical models have two advantages:

- They are formal model specification languages, meaning it is not an ambiguous model.
- there are a lot of analytical and numerical methods to analyze model of this type.

1.1.5 Computational Models

Computational Models is similar to Mathematical Models. A Computational Model is a mathematical representation of a dynamical system (systems which evolves over time) taking a computer-executable form.

in Computational Model we are restricting the class of systems of interest to dynamical systems (systems which evolve over time).

Dynamical Systems

Dynamical systems are systems that **evolve** by changing their state over time. Typically the state of a dynamical system is represented by a finite set of variables called **state variables**. In addition we will have some some law/rules/equations that describe how the state variables will vary over time. Our focus will be in prediction or analyze how the state of a dynamic system changes.

There are different types of dynamical systems depending on how the values of the variables change in either a discrete or a continuous way (or both).

Note: time can be interpreted as a discrete or continuous entity.

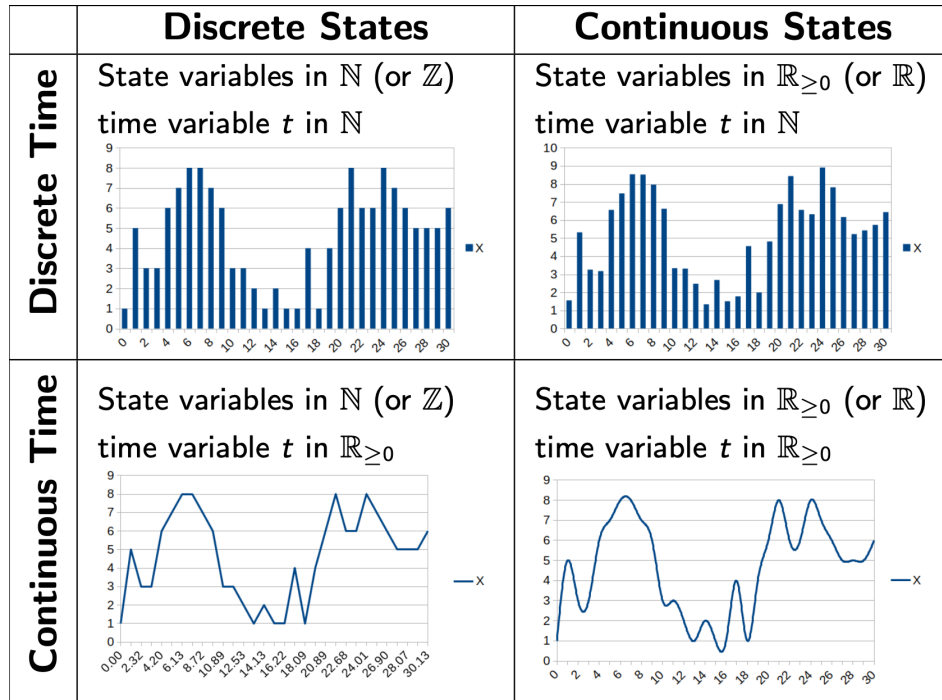


Figure 1.1: All possible types of dynamical systems.

1.1.6 Case of application

What kind of analysis could we do with models of dynamical systems?

- **Reachability of states:** predict the future state of the dynamical system.
- **Behavioral patterns:** the sequence of state that I pass through over time.
- **Effects of perturbations/ control strategies:** once I have a model of a system and I can simulate it, I can try to study how it will behave if I modify it.

1.1.7 How to build a computational models?

There are multiple ways

The Data-driven way

The Data-driven way (e.g. machine learning) consist in starting from the data of the system you want to model and then you apply some machine learning/optimization/whatever method to infer the model automatically. The generated model takes a form suitable for the inference method used. If enough data is available, it often works very well (good predictions), however inferred models are often very difficult to

be interpreted (meaning that we can do good prediction, but we can't explain why they are correct).

The Knowledge-driven way

(also called mechanistic models) consist in trying to reproduce through a mathematical model the internal mechanism of the system in order to reproduce the behaviour and to understand the internals of the systems. It requires limited data, but a good knowledge about the system functioning. Model construction usually requires some effort, and often predictions suffer from approximations but the method generated works also when few data are available; the model is interpretable: it contributes to understanding why a system behaves as observed; modelling allows validation hypotheses on the system functioning.

1.2 What is a complex system?

A complex system is a system consisting of many components (typically with a simple individual behaviours) interacting with each other, from these interaction emerges the global behaviour of the system.

Complex Networks

Complex Networks is a graph with complex structural properties. The dynamics of these networks and its evolution is a field of study (complex networks theory).

1.2.1 Modeling notations for complex systems

Many modeling languages are available for complex systems:

- **mathematics:** Recurrence relations and differential equations.
- **concurrency theory:** we can apply methods seen in the study of concurrent system like Petri nets. Rewrite rules (Multiset rewriting) that describe the different events that happens in a complex systems as rules.
- **artificial life:** approaches proposed to try to reproduce behaviour seen in life. Cellular automata that describe the population as a grid; agents based model in which you explicit as an agent (e.g. an algorithm or set of functions/procedures) and then you can put the agent in a virtual environment to see how they behave together.

1.3 Analyze the model

Modeling languages allow the modeler to express relationships between the state variables of a system and the rules/laws that determine the change of their values over time. The dynamics (or behaviour) of the systems (the actual sequences of states reached by the system over time) can be computed according to the semantics of the modeling language.

1.4 Analyze the behaviour

After the model has been specified, then there are multiple way to analyze the model.

1.4.1 Simulation

You can try to apply some simulation algorithm in order to try to execute that model to have a possible evolution of the system. If the system is deterministic you have only one possible evolution, instead if the system is stochastic-probabilistic you will repeat the simulation several time and get different behaviour of the system. **So simulations can give you only some possible behaviour, not all.** Instead of running simulations to construct some description of the overall behaviour of the systems, it can be done by using **transition systems**.

Transition system

A transition system is a graph (possible infinite) that describe the possible behaviour of a system. A possible transition system is the *Makov chain*

1.4.2 Model Checking

It is an approach that determine whether the whole transition system satisfies a given dynamical property.

1.5 Modeling vs programming

The approach that we will follow to analyze dynamical systems is similar to the approach used to analyze programs

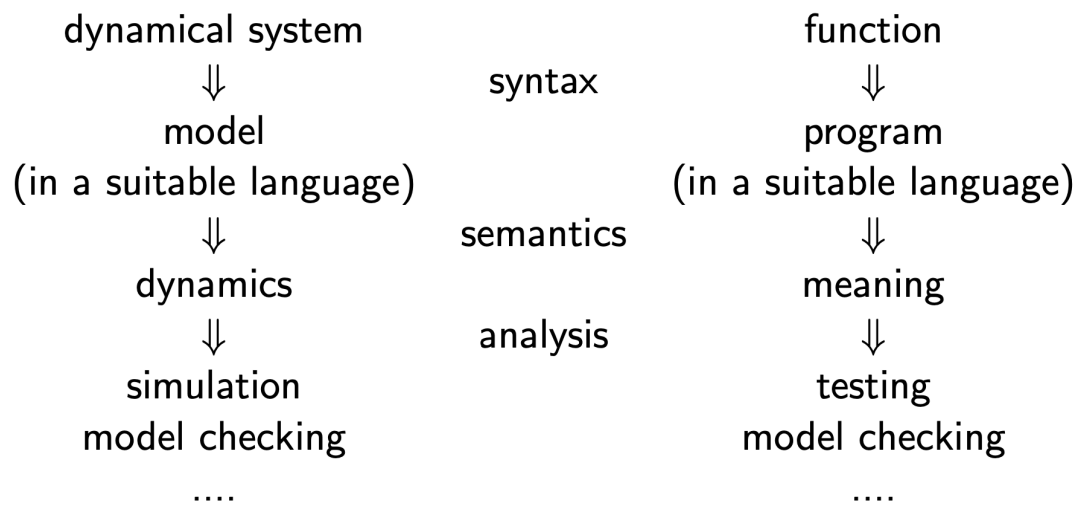


Figure 1.2: Modeling vs programming.

Chapter 2

Discrete Dynamical Systems

They are systems where the evolution is performed using discrete steps, in which the variables describing the state of the system are updated.

2.1 Recurrence relations (Difference equations)

Relations that tell you how from the current state of the discrete systems you obtain the next state of the systems, that is how from the original values they go to the new ones.

In this schema we will consider a generic system that is considered as a **population** (birth/death of individuals). Even the simplest form of interaction between individuals can lead to the emergence of **complex behaviors** (chaotic behavior) in the population.

2.2 Linear Birth Model

The linear birth model is the simplest model describing a recurrence relation.

Given a population, each individual is **indistinguishable** from each other. We denote with $N(t)$ the **density of some population** at a time t , that is the variable that describes the number of individuals that are part of the population at time t .

Given this description we want to predict what will happen to the density of the same population at a future time $t' = t + \Delta t$ assuming that:

- all individuals are indistinguishable from each other.
- there is enough food and space for every individual.
- each individual has λ children every σ time units.

- there is no death occurring in the interval $[t, t + \Delta t)$.
- children do not start reproducing in the interval $[t, t + \Delta t)$.

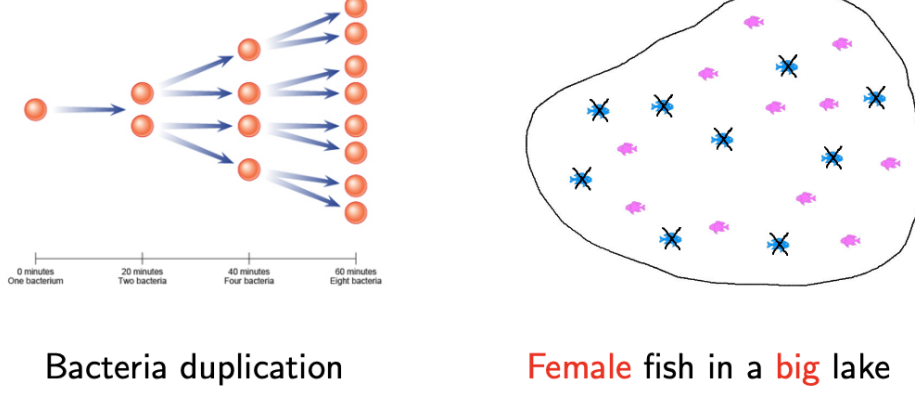


Figure 2.1: Example of populations satisfying the assumption. In the bacteria example in order to assume the no children duplication we set $\Delta t \leq 20 \text{ minutes}$

2.2.1 Describing the birth process as a relation

The idea is that the size of the population at time $N(t + \Delta t)$ will be \geq than $N(t)$ since we assume **that there is no death occurring in the interval $[t, t + \Delta t]$** . Additionally we know from our assumption that each *adult* individual has λ children every σ time units.

Then, the number of individuals at time $t + \Delta t$ corresponds to the number of individuals at time t , plus the number of newborns at time Δt :

$$N(t + \Delta t) = N(t) + \lambda \frac{\Delta t}{\sigma} N(t)$$

if we group for $N(t)$ then the equation can be rewritten as follows:

$$N(t + \Delta t) = N(t) * (1 + \lambda \frac{\Delta t}{\sigma})$$

Where $\frac{\Delta t}{\sigma}$ describes the birth moments for every *adult* individual in the interval $[t, t + \Delta t]$.

2.3 Constructing our algorithm

Defined our equation we can derive a discrete model from it.

We choose a **time step** (discretization step) that describe an update of the population, in our case **the time necessary for a newborns to be considered an adult so that it can reproduce**, and we set it as Δt .

Instead of representing the equation fully we rewrite it using the **notation of sequence theory** by instead of using the actual value of the time Δt , we just count the steps. Thus we obtain:

$$N_{t+1} = r_d N_t$$

where r stands for *rate*; d stands for *discrete*; r_d represents the **constant birth rate** s.t. $r_d = \lambda \frac{\Delta t}{\sigma}$.

2.3.1 Defining the general term of our equation

Given the recurrence relation we can *sometimes* calculate the **general term**, that is the solution of the recurrence relation. In the case of our linear birth model it is a **non-recursive definition of N_t** .

To do so we first calculate the first terms of N_t : N_1, N_2, N_3, \dots

$$N_1 = r_d N_0$$

$$N_2 = r_d N_1 = r_d^2 N_0$$

$$N_3 = r_d N_2 = r_d^3 N_0$$

We notice how *it seems* that $N_t = r_d^t N_0$, **but we have to prove it**. To prove the formula, since we are in the realms of the natural numbers, we can use **mathematical induction**:

Base Case ($t = 0$): $N_0 = r_d^0 N_0$ which is true.

Induction Case ($t = k + 1$): we assume that the formula is correct for $t = 0$ to $t = k$ and check if it is true for $t = k + 1$. We know from assumption that N_{k+1} will be a summation between the previous value for $t = k$ and the newborns in the current step. $N_{k+1} = r_d N_k$ and we know from **induction hypothesis** that $N_k = r_d^k N_0$, thus we can rewrite N_{k+1} as $N_{k+1} = r_d(r_d^k N_0) = r_d^{k+1} N_0$ proving the thesis.

Now having the general term $N_t = r_d^t N_0$ we can compute the solution of our model.

Phase portrait

A way to represent recurrence relations graphically is through **phase portrait**. It consists in putting in the *Cartesian plane*:

- **x-axis**: N_t
- **y-axis**: N_{t+1}

Then in the plane we plot the recurrent relation. First you draw the bisector and you draw the recurrence relation as a function, then by starting from point (N_0, N_0) on the bisector, the other point can be obtained by "bouncing" on the curve of the recurrence relation. **You can see how fast the quantity increases (or decreases) over time.**

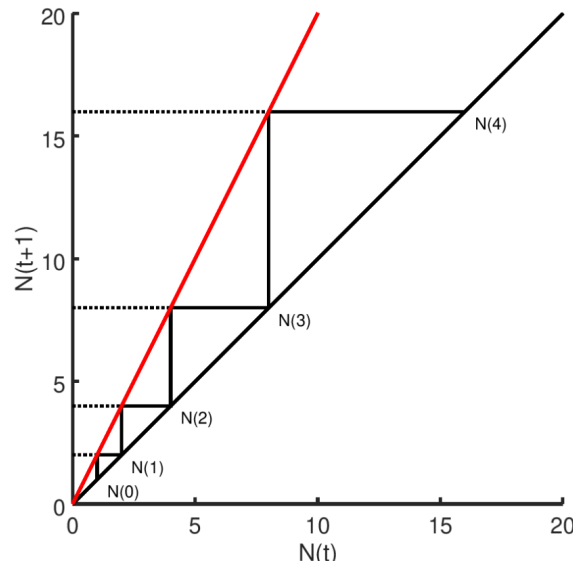


Figure 2.2:

Above an example of phase portrait in our linear birth model.

In **red** we draw the recurrence equation $N_{t+1} = 2N_t$. in **black** the bisector $N_{t+1} = N_t$.

2.4 Introducing death in our model

We complicate our recurrence relation by considering also deaths, so we are adding a negative term that decrease the number of individuals of our population over time.

Assume that, a constant fraction s_d **of adults that die in every time step δt** . Then our recurrence relation now is:

$$N_{t+1} = r_d N_t - s_d N_t$$

By grouping for N_t we can rewrite the equation as:

$$N_{t+1} = (r_d - s_d) N_t$$

Note: since the number of individuals which die cannot be greater than the whole population, then $0 \leq s_d \leq 1$

Since r_d and s_d are two constant, one positive and one negative, we can group them together in one single constant $\alpha_d = (r_d - s_d)$. We call α_d the **net growth rate**, that is the rate where you discard the individuals who dies. We can rewrite our equations as:

$$N_{t+1} = \alpha_d N_t$$

The difference in respect of the previous case is that α_d will be in general greater than 0, but not necessarily greater than 1.

General trend of our model

There could be many possible cases depending on the value of the constant α_d :

- $\alpha_d > 1$: the overall behaviour of the population is the same as before, **since the population at every steps will increase**.
- $\alpha_d = 1$: the population remains constant, **since the number of newborns always is equal to the number of dead ones**.
- $\alpha_d < 1$: if for instance we assume we have less newborns than the death of old individuals, **then at every step the population reduces**.

2.5 Introducing migration in our model

Independently from the size of the population, **we assume a fixed number of individuals arrive in our region**. We only consider people that arrives, so we model the migration using a constant and positive parameter declared as β .

Then our equation becomes:

$$N_{t+1} = \alpha_d N_t + \beta$$

with $\beta \geq 0$ representing the number of individuals entering the population every Δt time units.

By **mathematical induction** we can prove the general term is:

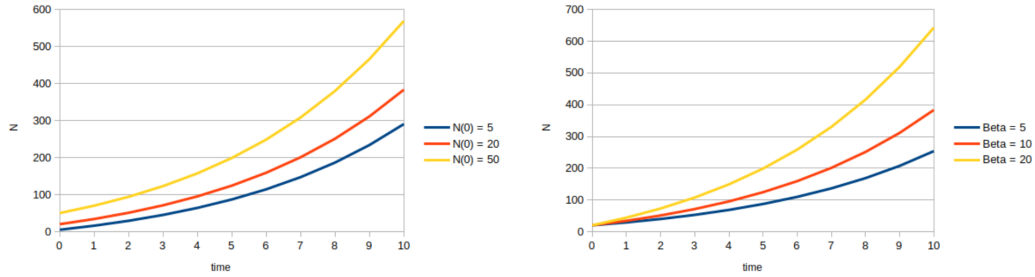
$$N_t = \alpha_d^t N_0 + \sum_{i=0}^{t-1} \alpha_d^i \beta$$

where $\sum_{i=0}^{t-1} \alpha_d^i \beta$ accumulates the β individuals that arrived in the previous step (from 0 to $t - 1$) and the children produced by them at every step.

2.5.1 Simulating the migration

Having our general term, we can see what happens by varying α_d , N_0 and β :

Case $\alpha_d > 1$

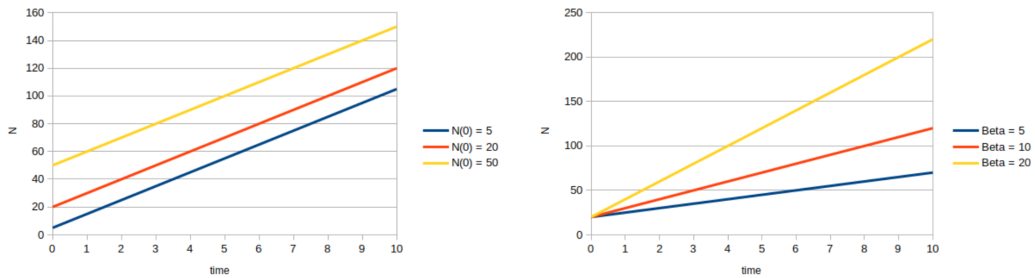


$$N_0 = 5, 20, 50 \quad \beta = 10$$

$$N_0 = 20 \quad \beta = 5, 10, 20$$

Figure 2.3: The dynamics is dominated by the birth process (exponential growth).

Case $\alpha_d = 1$

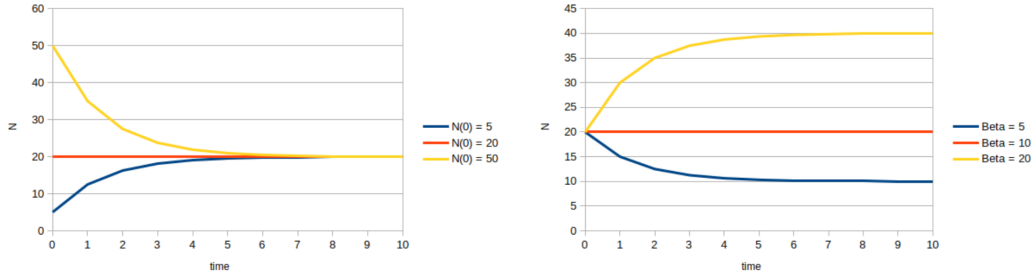


$$N_0 = 5, 20, 50 \quad \beta = 10$$

$$N_0 = 20 \quad \beta = 5, 10, 20$$

Figure 2.4: The dynamics is dominated by the migration process (linear growth).

Case $\alpha_d < 1$



$$N_0 = 5, 20, 50 \quad \beta = 10$$

$$N_0 = 20 \quad \beta = 5, 10, 20$$

Figure 2.5: The population reaches a dynamic equilibrium: a stable state in which opposite phenomena compensate each other (migration compensates deaths). Note that it is independent from N_0

2.5.2 Computing the equilibrium point

The equilibrium point (also called saturation point) is defined as the moment $t = k + 1$ where the computed size of the population is the same as the previous step, that is:

$$N_{t-1} = N_t$$

Knowing that $N_t = \alpha_d N_t + \beta$ we solve the equation in regards to N_t and obtain:

$$N_t = \frac{\beta}{1 - \alpha_d}$$

2.5.3 Non-linear models

So far we have described a population where each individual behaves autonomously, which do not fit the definition of complex system (many components with very simple individual behaviour **that interact with each other and the environment**). Introducing interaction between the individuals **requires a non-linear model** (previously we used a linear one). In our (Non-linear) Birth Model now the environment has limited resources such as food and place, thus requiring that the individuals compete (**a form in interaction**) for survival.

2.6 Rewriting our equation

For simplicity assume we are in a closed environment (no migration), then we define K as the **carrying capacity of the environment**, meaning that in the environment there is enough food and space for K individuals.

The population is still governed by the birth rate, but now death is no more a constant, instead is negatively influenced by K :

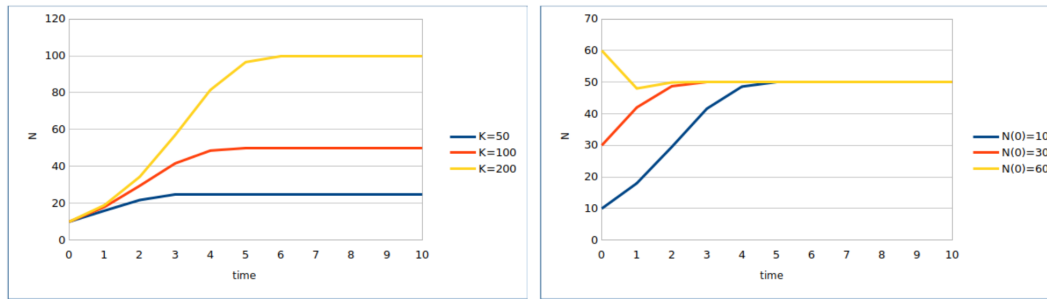
$$N_{t+1} = r_d N_t \left(1 - \frac{N_t}{K}\right)$$

Note: this non-linear equation is called **logistic equation** (it is an alternative formulation)

So now the birth rate is modulated by the ratio of occupancy on the environment $\frac{N_t}{K}$:

- N_t close to 0 : we have a simple birth process with rate r_d (exponential growth).
- N_t increases: the growth tends to stop.

Eventually the population reaches a **dynamic equilibrium** representing the situation in which environment resources are fully exploited (**saturation**)



$N_0 = 10 \quad K = 50, 100, 200$

$N_0 = 10, 30, 60 \quad K = 100$

Figure 2.6: The first graph shows a case where the equilibrium point depends on K . The second graph shows me that the equilibrium point is independent from the initial number of individuals.

2.7 Removing homogeneity

For now we have considered an homogeneous population, but in realistic case we have different individuals with different features and we want to consider each group of individuals. In the system point of view this requires not just a single recurrence equation, but a **system of recurrence equations**.

consider a population of fishes that live in a pond. Each individual can either be a male fish, modelled as M_t or a female fish, modelled as F_t . We consider that a small part of males dies because of fights among them (death rate s_d).

then we construct a system of recurrence equations:

$$\begin{cases} F_{t+1} = r_d F_t (1 - \frac{F_t + M_t}{K}) \\ M_{t+1} = r_d F_t (1 - \frac{F_t + M_t}{K}) - s_d M_t \end{cases}$$

where:

- $r_d F_t$ represent the number of child born, note that they are generated by females.
- $F_t + M_t$ describes the whole population size (to be related with the carrying capacity K).

2.8 Limitation of discrete dynamical models

Discretization of the system dynamics may introduce inaccuracies: recurrence equations assume that nothing happens during the Δt time that occurs between N_t and N_{t+1} . Adjusting Δt to be smaller usually correspond to more accurate approximations, more precisely we should let Δt tend to 0.

Chapter 3

Continuous Dynamical Systems

3.1 Recap - Why we need to introduce ODEs

As we said in the previous chapter, using a discrete representation for the steps in our model can lead us to lose all the informations that happens between the step N_t and the step $N_t + 1$.

The simplest solution is to make the distance in time Δt between the to step very small (≈ 0), but it is not enough.

3.2 Reconsidering the population model

Recall in our population model that with $N(t)$ we denote the **density of some population** at time t . Our goal is to construct a mathematical model able to predict the density of the same population at a time $t' = t + \Delta t$.

3.2.1 Introducing the Ordinary Differential Equation

Given our equation which is based the model:

$$N(t + \Delta t) = N(t) + \lambda \frac{\Delta t}{\sigma} N(t)$$

And the corresponding **recurrence equation**:

$$N_{t+1} = r_d N_t$$

where $r_d = \frac{\Delta t}{\sigma}$ consider the case where $\Delta t \rightarrow 0$. This case cannot be done using discretization, because it can lead to inaccuracies.

To handle the case $\Delta t \rightarrow 0$ we make some transformation to our equation:

$$N(t + \Delta t) = N(t) + \lambda \frac{\Delta t}{\sigma} N(t) \rightarrow \frac{N(t + \Delta t) - N(t)}{\Delta t}$$

then by simplifying we get:

$$\frac{N(t + \Delta t) - N(t)}{\Delta t} = \frac{\lambda}{\sigma} N(t)$$

We can recognize that the left hand side can be traced back as the **difference quotient** $\frac{f(x+h)-f(x)}{h}$, **which when taken to the limit as h approaches 0 gives the derivative of the function f.**

Let's consider our equation for $\Delta t \rightarrow 0$:

$$\lim_{\Delta t \rightarrow 0} \frac{N(t + \Delta t) - N(t)}{\Delta t} = \lim_{\Delta t \rightarrow 0} r_c N(t)$$

with $r_c = \frac{\lambda}{\sigma}$

Note that on the right hand side Δt doesn't appear, thus we can remove the limit; the term on the left hand side is the derivative of $N(t)$, indicated as simply $\dot{N}(t)$. Thus we simplify the equation as follows:

$$\dot{N}(t) = r_c N(t)$$

We have defined the dynamics of the system as the derivative equal to a constant multiplied by the value of the function at time t .

This equation is known as Ordinary Differential Equation (ODE).

An ODE has the following properties:

- it relates the function N with its derivative \dot{N}
- $t \in \mathbb{R}$, **so time is continuous**

We would like to use the Ordinary Differential Equation to run some simulation or to compute a general solution (like we did for the recurrence relation).

3.2.2 Using the ODE

In some very simple case, like our linear birth model, we can find the general solution by finding a closed-form definition of $N(t)$ satisfying the equation. **A closed-form definition is one that depends only on t and some constant.**

for the linear growth model a solution can be found analytically.

Recall our equation:

$$\dot{N}(t) = r_c N(t)$$

Now let's move $N(t)$ from the right to the left hand-side of the equation:

$$\frac{\dot{N}(t)}{N(t)} = r_c$$

Recall that $\frac{\dot{N}(t)}{N(t)} = \ln N(t)$ and r_c is the derivative of $r_c t + c$ for any constant c , obtaining:

$$\ln N(t) = r_c t + c$$

By resolving our equation in regards to $N(t)$ we finally get:

$$N(t) = C e^{r_c t + c}$$

where $C = e^c$ (typically C is set to be equal to $N(0)$)

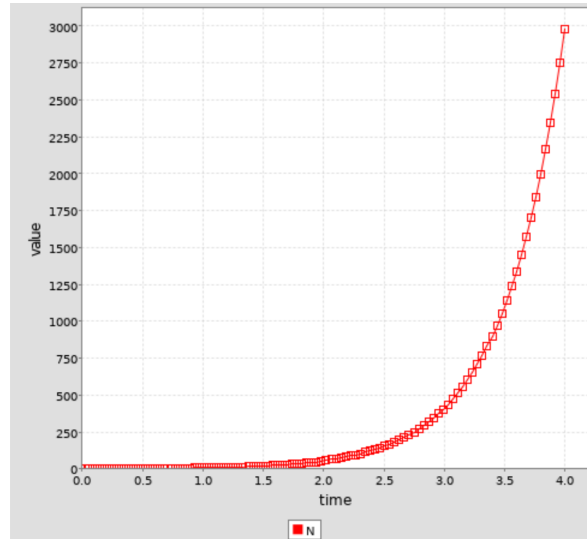


Figure 3.1: This graphs shows us that by setting in our population model $r_c = 2$ and $C = N(0) = 1$ then the population shows an exponential growth over time.

Differences between discrete and continuous model

This behaviour is qualitatively the same as for the discrete model, both showing exponential growth. **What changes is the meaning of the equation:**

- the recurrence relation tells you how to update the variable.
- in our new equation it defines the derivative, **meaning how fast it's changing**.

Note how both equations show $\text{rate} \geq 1$ only if the birth rate $\frac{\lambda}{\sigma}$ is ≥ 1 .

3.3 Example - Radioactive decay

We move from the example of the population model we have seen so far to another one.

Radioactive decay is a process where we have a negative evolution of the population. The idea is that **each molecule decays at a constant rate**, so the whole mass decreases with a rate which is proportional to the mass itself.

We can describe this model by using the following Ordinary Differential Equation:

$$\dot{N}(t) = -d_c N(t)$$

then if we solve it in regards to $N(t)$ we get:

$$N(t) = N(0)e^{-d_c t}$$

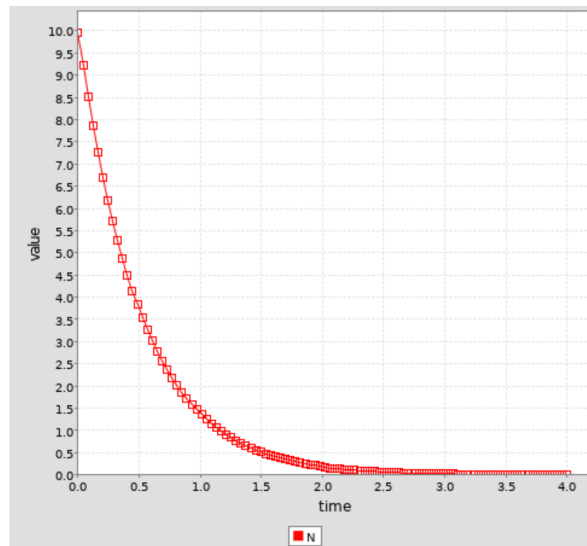


Figure 3.2: Example of applying the ODE of the radioactive decay. Note that by setting $d_c = 2$ and $C = N(0) = 10$ we get $N(t)$ to tend to zero. This is caused by the negative exponent in the ODE.

3.4 Continuous version of the logistic equation

Given the non-linear logistic equation, we can define as follows its continuous version:

$$\dot{N}(t) = r_c N(t) \left(1 - \frac{N(t)}{K}\right)$$

where:

- r_c is the **continuous growth rate**.

- K is the **carrying capacity** of the environment.

Resolving the ODE in regards to $N(t)$ we get:

$$N(t) = \frac{K}{1 + (\frac{K}{N(0)} - 1)e^{-r_c t}}$$

We notice that when $N(t) \rightarrow K$ the **population converges to the carrying capacity of the environment**.

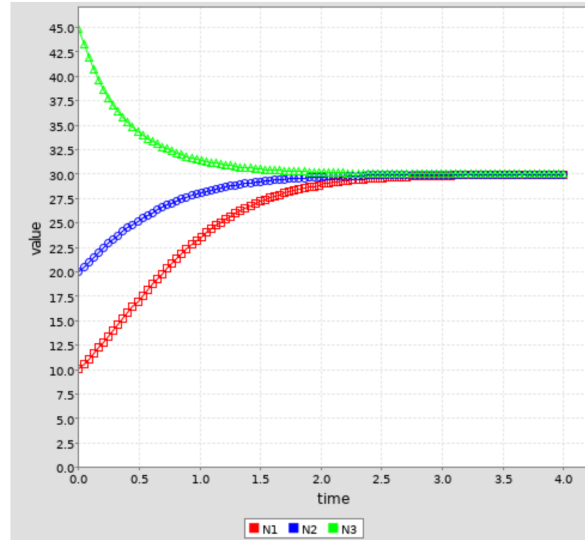


Figure 3.3: Example of the continuous logistic equation. Note how by putting $r_c = 2$, $N(0) = 10$, $K = 30$, the population will eventually converge to the carrying capacity of the environment.

The trend is the same as for the discrete case.

3.5 Systems of ODE

Now let's consider a population of males, indicated as $M(t)$, and females, indicated as $F(t)$. Assume that males fight with each other, so a small part of them dies because of it with a death rate of s_c .

Thus we have to expand our model considering a system of ODEs:

$$\begin{cases} \dot{F}_t = r_c F_t (1 - \frac{F_t + M_t}{K}) \\ \dot{M}_t = r_c F_t (1 - \frac{F_t + M_t}{K}) - s_c M_t \end{cases}$$

where:

- $r_c F(t)$ is used for both genders, **since both are generated by females**.

- $F(t) + M(t)$ describes the whole population size.

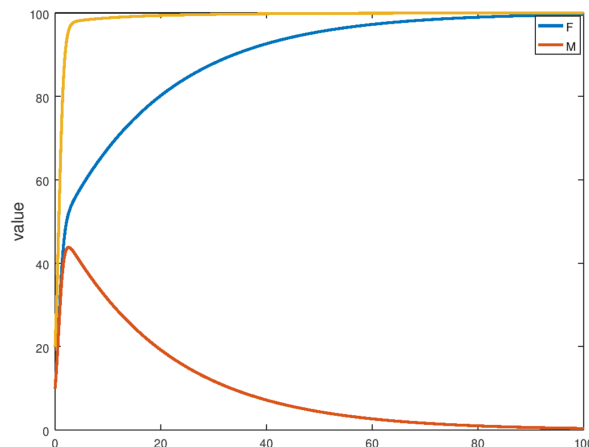


Figure 3.4: Example of the system of ODEs.

What happens in this scenario, after some times you have only females in the population. This shows a completely different behaviour from the discrete case, **because the meaning of their equations is different**:

- The recurrence relations indicates us the size of the population.
- The system of ODEs describes how fast is changing.

3.6 Numerical Solution of ODEs

Recall that we said that computing the solution of an ODE is not always possible. For this reason we prefer working using an approximation of the solution, indicated as **numerical solver** (or numerical simulator). This approximation doesn't compute the general function, **instead it solves the initial value problem, also called Cauchy problem**.

Initial Value Problem

Given an ODE in the form $\dot{N}(t) = f(N(t))$ and an initial value N_0 s.t. $N(0) = N_0$, compute a function $F(t)$ that is a solution of the ODE and s.t. $F(0) = N_0$.

In our case we are interested only in studying the values of $F(t)$ where $t \geq 0$, **hence we perform a numerical simulation starting at $t = 0$** .

3.7 The Euler method

The Euler method is the simplest numerical simulation method available. The main concept behind this approach is to approximate the given continuous system with a recurrence relation specifically designed to approximate the continuous differential equation. **The idea is that, since we know the derivative, we use it as it was the function.**

It is based on the idea of discretizing the dynamics of differential equations by time steps of constant length $\tau = \Delta t$.

Given an Ordinary Differential Equation in the form:

$$\dot{N}(t) = f(N(t))$$

this corresponds to approximating its solution with the following recurrence relation (assuming $N_0 = N(0)$)

$$N_{k+1} = N_k + \tau f(N_k)$$

where $N_k \approx N(\tau k)$

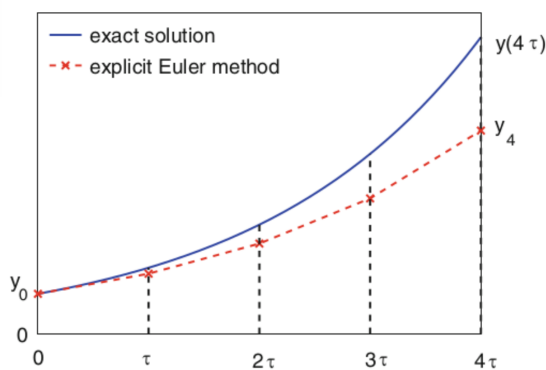


Figure 3.5: A graph showing the correct solution compared to the approximation generated by the Euler method.

3.7.1 Errors in the Euler method

By approximating in each step the Euler method makes local errors that will contribute to a global error at the end of the whole simulation.

The local discretization error is computed as $|N(\tau) - N_1|$ and it is in the order of $O(\tau^2)$ (the motivation is because we truncate the Taylor Series at the first step).

The Global discretization error is obtained by accumulate all the local discretization errors after k steps, namely at time $t = k\tau$. The global error is computes as $|N(k\tau) - N_k|$ and is in the order $O(k\tau^2) = O(\tau)$ since $k\tau = t$ is constant.

3.8 Other numerical simulation methods

A linear error of $O(\tau)$ is quite annoying, requiring us to set $\tau \approx 0$ in order to have something acceptable, making the computation very slow (it requires a lot of steps).

To overcome this other methods have been proposed, having a global discretization error of a higher order (e.g. $O(\tau^p)$ for some p) which is better as long as $\tau \rightarrow 0$ (hence $\tau < 1$). To work these method use more than one point to approximate the value of the function, making a single step require more time, but maintain the error inside some defined boundaries.

A few examples of such methods are:

- **Runge-Kutta methods:** $p = 2$ in the original formulation, but can be higher
- **Multistep methods (e.g. Adams methods):** extrapolate the value of the next step from the values of the previous k steps obtaining $p \approx k$.

State-of-art methods can also:

- self-determine the step size τ based on thresholds on local and global discretization errors.
- dynamically adjust the step size τ during their executing (e.g. Adaptive Runge-Kutta)

3.9 Instability and stiff systems

There is another problem that could arise: if you have a derivative which cause the value of a variable in a very fast way, if τ is not small enough you not only pay some error but you could have that your computed solution is unstable.

What we mean for unstable is that we lose informations and your points start to oscillate creating chaos.

This kind of problematic systems are called **stiff systems**. There is no clear definition of stiffness: intuitively contains a very fast term that cannot be captured by our method, worse if we have in our systems also slow terms to take into account.

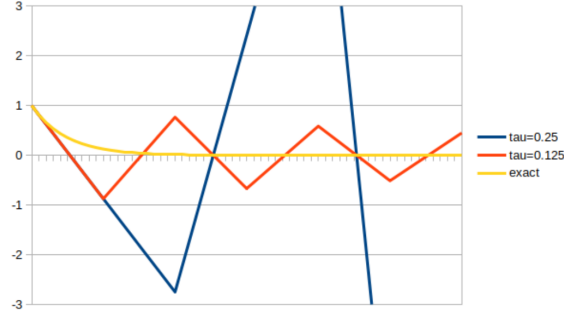


Figure 3.6: An example of a stiff system. In orange is shown the real solution, while in red and blue the one obtained by setting τ to different values

In this cases you need to consider alternative numerical simulation methods called **implicit numerical simulation methods**. All the methods we have seen so far have and implicit version, which requires more computation time for step.

3.10 Implicit Euler method

The idea of the implicit version of the Euler method is that, like the previous version we approximate the function by using its derivative, **but the derivative is not computed on the value N at step k , but at the step $k + 1$.**

By using this approach we are no longer defining N_{k+1} in terms of N_k , but as an equation where N_{k+1} is in both sides:

$$N_{k+1} = N_k + \tau f(N_{k+1})$$

where $N_k \approx N(k\tau)$.

There are methods from numerical analysis that are able to solve these type of equations. This method requires more effort for computing a single step, but **often** the local discretization error is smaller permitting us to use greater values of τ .

3.11 Other implicit methods

Implementations of implicit methods that use more than one variables require the modeler to provide the **Jacobian matrix** (partial derivatives) of the function f . Most are able to compute the Jacobian matrix autonomously by doing some approximation.

There exist methods that are able to automatically switch from explicit to implicit methods by determining if the system is stiff.

Chapter 4

Relevant Examples of ODEs

4.1 Changing the notation

In the ODEs that follows we will omit any explicit reference to the time variable t :

- $X(t)$ will be just called X
- $\dot{X}(t)$ will be just called \dot{X}
- X_0 will be just called $X(0)$

4.2 The Lotka-Volterra model of prey-predator interaction

These are two independent model that resulted to be equivalent:

- *Lotka* designed in 1925 as a description of an hypothetical biochemical oscillator.
- *Volterra* designed in 1926 as a description of two interacting populations.

4.2.1 Introduction

Volterra's model was made to explain a strange phenomenon observed in the Adriatic sea after World War 1. During the war there was a increasing demand of fish, so ecologist and fisherman predicted that the overall population of fish would decrease. To everyone surprise after the Wold War ended, they observed an increase in population for some species.

Volterra's idea was that prey and predator have different (**but related**) dynamics. **The main intuition was that preys proliferate in the absence of predators.**

4.2.2 Making the model

First we abstract the prey population and predator population in the following variables that uses absolute numbers:

- **V**: describes the size (also called density) of the population of preys.
- **B**: describes the size (also called density) of the population of predators.

We then make some basic observation regarding the inner dynamics of preys and predators **when they are isolated from each other**:

- When there are no predators, preys can grow without any limitation.
- When there are no preys, predators die of starvation.

We design a preliminary system of ODEs for describing these observations:

- $\dot{V} = rV$ where r is the **growth rate of preys**.
- $\dot{P} = -sP$ where s is the **death rate of predators**.

Digression

When you construct a model you can follow two approaches:

- Try to model all the possible details in the most accurate way you can. This will lead you to a very complicated model, but if you are able to take all the aspect of the system into account by measuring correctly the parameters introduced, then you should be able to replicate the reality. **So you can make quantitatively prediction about that model.** However this can make the analysis difficult because if you want to explain a certain dynamics, it may be hidden behind all the parameters you have.
- Try having a minimal model when you put only the details you think are necessary to understand the trend you want to predict. Then although quantitative prediction are wrong, you will have a more clear observation of the trend.

Volterra's model follow the second approach.

4.2.3 Interaction between the two species

We have developed a system of ODEs in the case when the two species are separated from each other, but what about when both species are present in the environment? **We observe that the predators hunt the preys.** How can I model hunting in a minimal way?

Assuming that a prey and a predator meet, then the predator eats the prey and increases the change of growth of its population. Assuming that the meeting between individuals of both species is random, then to model it we add one term in each of the ODEs in our system:

- In the predator ODE it has a positive sign because by eating the prey it increases the chance of survival of its population
- in the prey ODE it has a negative sign because by being eaten it decreases the chance of survival of its population

The first intuition was that predation is proportional to the quantity of prey and predators. The rate of predations should be proportional to the quantity of meetings between individuals of the two species (**namely it is proportional to the product $V * P$**). Note that the **meeting between individuals is random**.

When a prey and a predator meet, it could happen that the predator eats the prey, **but not always**.

- So we declare a as the portion of meetings resulting in huntings (the predator eats the prey).

As the predators eat, their chance of survival increases and they start to reproduce.

- So we declare b as the number of offsprings produced for each hunting.

4.2.4 Putting all together

By inserting in our system of ODEs the considerations we have made we obtain:

$$\begin{cases} \dot{V} = rV - aVP \\ \dot{P} = -sP + abVP \end{cases}$$

- **First ODE:** it tells us that prey decrease by the **hunting rate aVP** .
- **Second ODE:** it tells us that predators increase by a **hunting and reproduction rate $abVP$** .

We have modelled predation as a direct form of interaction, **it is not mediated by the environment**

4.3 Steady State

A steady state is a combination of values for the variables that remains unchanged over time. **In a steady state, all differential equations are equal to zero.**

4.4 Example - The SIR epidemic models

Epidemic phenomena deals with the spread of infectious diseases. To study them there are used SIR models.

4.4.1 Introduction

SIR stands for the three types of individuals in our population:

- **Susceptible:** individuals that can be infected.
- **Infected:** infected individuals that can spread the disease to susceptible individuals.
- **Recovered:** infected individuals who passed the infection phase and cannot spread the disease anymore.

There are several variants of the SIR model, some being developed during the COVID pandemic.

4.4.2 Making the model

We design a Ordinary Differential Equation for each type of individual in our population, each ODE describes the ratios of each class of individual:

- **S:** ODE for the Susceptible type.
- **I:** ODE for the Infected type.
- **R:** ODE for the Recovered type.

We make the following assumption:

- The size of the population is constant in time and normalized to 1: $S + I + R = 1$.
- Infected people can only transmit the infection, meaning they **cannot** reproduce, die, migrate and so on.
- A infected person can transmit the disease only to susceptible people through personal contact between the two (horizontal transmission).
- The contact between individuals is random, meaning the number of infections is proportional to both I and S.
- After being Infected a person will recover become resistant to that disease.

Following these assumption we can represent the model as the following system of equations:

$$\begin{cases} \dot{S} = -\beta SI \\ \dot{I} = \beta SI - \gamma I \\ \dot{R} = \gamma I \end{cases}$$

where:

- β : is the **infection coefficient** describing probability of infection after the contact between a susceptible individual and an infected one.
- γ : is the **recovery coefficient** describing the rate of recovery of each infected individual.

Dynamic between S and R

S and R have a very intuitive dynamic: S having only a negative sign will inevitably decrease, while R having only a positive sign will increase.

In the case of I, its behaviour strictly depends on the value of β and γ , more precisely:

- if $\beta < \gamma$: then I will decrease (since $S \leq 1$)
- if $\beta > \gamma$: then the behaviour of I depends on S. If $S > \frac{\gamma}{\beta}$ then I will increase its value.

4.4.3 Extending the model - Vaccination

The SIR model can be used to study the effects of vaccinations: considering if its convenient or not to introduce mandatory vaccination for some diseases.

To better study vaccinations you need to consider the model for several years. For instance if you vaccinates newborns, you will see the result of your choice only after they will become the main part of your population. By considering a long time span **births and deaths cannot be ignored**, so we need to extend our SIR model.

idea: we add a positive terms to represents births and add a negative terms to represent death. To make this work we will use the following assumptions:

- **the population size is still constant over time** (not too wrong: the size of the population of a country does not change significantly over 10-20 years).
- No vertical transmission of the disease (meaning from parent to children).
- Newborns are considered Susceptible from the get go.

To make the population constant we introduce the coefficient μ for both birth and death. Consider that the population size is normalized to 1. We declare with N the population size s.t. $N = S + I + R$ and $\dot{N} = \mu - \mu N$.

Made these assumption we can extend the model obtaining the following system of ODEs:

$$\begin{cases} \dot{S} = \mu - \beta SI \\ \dot{I} = \beta SI - \gamma I \\ \dot{R} = \gamma I \end{cases}$$

Remember: we are assuming that all type of people could reproduce, but the newborns are always Susceptible, since we are not considering vertical transmission. Thus in the ODE of S we put μ alone to represent the number of people born during the current time unit.

4.4.4 Introducing death

As we have stated multiple times, the population size is assumed to be constant and normalized to 1. So having newborns in our model could lead us to an increase of the population, which is wrong. The solution is to introduce death in order to maintain the size.

The death is introduced by using the same parameter as the birth μ , only with a negative sign. The obtained model will be:

$$\begin{cases} \dot{S} = \mu - \beta SI - \mu S \\ \dot{I} = \beta SI - \gamma I - \mu I \\ \dot{R} = \gamma I - \mu R \end{cases}$$

The dynamics of the model is governed by the ration between the positive and negative coefficients in the equation of I:

- $\beta < (\mu + \gamma)$: I can only decrease (since $S \leq 1$).
- $\beta > (\mu + \gamma)$: the behaviour of I depends on S. It increases if $S > \frac{(\mu + \gamma)}{\beta}$.

Note how compared to the previous case where S could only decrease, **now this is no longer true because the births could maintain S above $\frac{\mu + \gamma}{\beta}$.**

4.4.5 Introducing vaccination

Now let's consider the case where we can fight the disease by using vaccination.

We consider to vaccinate the newborns, the model can tell us if this will help us and the fraction of newborns p are needed to be vaccinated to do so.

We consider that if a newborn is vaccinated, then it has type Recovered.

The model we get is the following:

$$\begin{cases} \dot{S} = (1 - p)\mu - \beta SI - \mu S \\ \dot{I} = \beta SI - \gamma I - \mu I \\ \dot{R} = p\gamma I - \mu R \end{cases}$$

4.4.6 Determining the vaccination threshold

We declare with p_c the threshold value of vaccinations needed, that is the ratio of newborns that should be vaccinated in order to eradicate the disease.

There are two ways to compute p_c :

- The value can be determined by simply performing numerical simulation varying the value of p
- The value of p_c can be computed analytically.

By considering the second option we obtain the following formula to compute the ratio:

$$p_c = 1 - \frac{\mu + \gamma}{\beta}$$

4.5 Limitation of continuous dynamical models

The main limitation of this approach is that they are deterministic: once you define the ODE and you fix an initial value for the variables you obtain **THE** only possible dynamics of the system.

In many cases there are aspects you did not model and there are events that can happen with some probabilistic distribution that you have not modelled here. To overcome this limitation we need to use a different modelling technique that introduce probability distribution in our model.

Chapter 5

The Chemical Reaction Metaphor

Chemical reactions are illustrative examples of complex systems, they exhibit complex dynamics out of very simple interactions. Also chemical reaction are much easier to write than ODEs, so we will use them as a modelling language. **Chemical Reaction are used as a metaphor to describing interactions.**

5.1 What is a chemical reaction?

A chemical reaction is an interaction between molecules in a chemical solution that cause a transformation of these molecules. We categorize as:

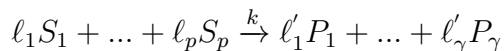
- **reactants:** the group of molecules that participate in the reaction.
- **products:** the group of molecules (it could be a different quantities that the reactants) that are obtained after the transformation.

We abstract molecules as symbols, **it does not matter what they are in the reality**. Molecules are assumed to be in a **chemical solution**, that is a fluid medium where they float. While in these solution they can meet and start a chemical reaction.

In order to represent the quantity of molecules is usually expressed in terms of **concentrations** (number of molecules per unit).

Given the molecule A, $[A]$ denotes the concentration of that molecule, usually expressed in $\frac{mol}{L}$.

Usually the notation for chemical reactions is some sort of rule between the reactants and the products:



where:

- S_i are **reactants**.
- P_i are **products**.
- $\ell_1, \ell'_i \in \mathbb{N}$. are **stoichiometric coefficients**. They express the number of reactants/products of each type that are consumed/produced in the reaction
- $k \in \mathbb{N}_{\geq 0}$ is the **kinetic constant**. It express the rate of occurrence of reaction in a chemical solution.

Note: when we omit the l_i , it means that its value is 1.

5.1.1 Types of Chemical Reactions

There are several types of chemical reactions:

- **Synthesis:** $\xrightarrow{k} P$
- **Degradation:** $S \xrightarrow{k}$
- **Transformation:** $S \xrightarrow{k} P$
- **Binding:** $S_1 + S_2 \xrightarrow{k} P$
- **Unbinding:** $S \xrightarrow{k} P$
- **Catalysis:** $E + S \xrightarrow{k} E + P$

and many more

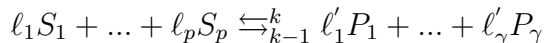
Complex types as aggregation of simpler type

Complex chemical reaction can be redefined as a sequence of simpler chemical reactions. Take for example the Catalysis ($E + S \xrightarrow{k} E + P$), it can be reinterpreted as a sequence of:

- Binding: $E + S \xrightarrow{k} M$
- Transformation: $M \xrightarrow{k} N$
- Unbinding: $N \xrightarrow{k} E + P$

5.1.2 Reversibility of Chemical Reactions

Often chemical reactions can occur in both directions. To indicate formulas that are reversible we will use the symbol $\xrightleftharpoons[k_{-1}]{k}$:



where k_{-1} is the kinetic constant of the inverse reaction, transforming products P_i into reactants S_i .

In reality all chemical reactions are reversible, only one of the two directions is so unlikely that it is not considered possible.

5.1.3 The mass action kinetics of chemical reactions

The dynamics of chemical reactions is based on the assumption that **molecules float in a well-stirred fluid medium** (e.g. water). In this scenario they are free to move and randomly meet each other. When two molecules meet, they can react.

The dynamics of chemical solution is modeled by the **law of mass action**

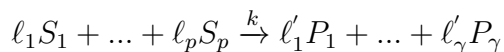
Law of mass action

The **rate** of a chemical reaction expresses the number of occurrences of such a reaction in a given chemical solution in a time unit.

The law of **mass action** is an empirical law for the computation of the rate of chemical reaction:

The rate of a chemical reaction is proportional to the product of the concentrations of its reactants.

Given the following chemical reaction:



Then the rate of a reaction is defined as follows:

$$k[S_1]^{\ell_1} \dots [S_p]^{\ell_p}$$

The rate of its inverse reaction (from right-to-left) is:

$$k_{-1}[P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma}$$

5.1.4 Understanding the kinetic constant

What is the measure unit of a kinetic constant k ? It depends on the number of reactants:

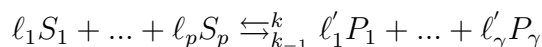
- The measure unit of **concentrations** is $\frac{mol}{L}$
- The measure unit of the **reaction rate** is $\frac{mol}{(L \times sec)}$ (it is the concentration of each product produced in one unit of time).

Note: some kinetic constants have to be changed if you change the measure unit of concentrations (e.g. μmol) or the time unit (e.g. hours).

5.1.5 Dynamic equilibrium

Given an initial concentration we can have an idea about which is the faster reaction that will take place among the one we have. Something we can compute is an equilibrium point for our reversible reactions.

Given a generic reversible reaction:



A dynamic equilibrium is **reached when the two rates are equal**:

$$k[S_1]^{\ell_1} \dots [S_p]^{\ell_p} = k_{-1}[P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma}$$

Then it is easy to compute the equilibrium using the following formula:

$$\frac{k}{k_{-1}} = \frac{[P_1]^{\ell'_1} \dots [P_\gamma]^{\ell'_\gamma}}{[S_1]^{\ell_1} \dots [S_p]^{\ell_p}}$$

5.2 From chemical reactions to Ordinary Differential Equations

We can use reaction rates to be able not only to compute point-wise rates and equilibrium point, but **to be able to analyse the dynamics of a system any time**.

Since rates are frequencies, **so some sort of derivative**, we can use them to define ODEs.

We will consider every molecule of the reaction as a variable of our system of differential equation. Each molecule will have its own differential equation and then in each of these equations we will add positive and negative terms according to the reaction in which these molecules participates:

- for every reaction where the molecule we are considering is a reactant, that is **it will be consumed to generate a product**, then its ODE will contain a negative term: $-\ell r$
- for every reaction where the molecule we are considering is a product, that is **it will be produced**, then its ODE will contain a positive term: $+r$

where:

- ℓ : is a **stoichiometric coefficient** of a product S in R.
- r : is the rate of R.

5.3 Reverse engineering ODEs

As we have proved, starting from a system of chemical reaction we can exploit the law of mass actions to translate it into a system of polynomial ODEs.

Let us now consider the opposite: starting from a system of ODEs and finding a way to translate it into a system of chemical reactions. As we will see, **this works often, but not always**.

Notation

We begin from ODEs by omitting the $[\]$ brackets representing concentrations. The idea is to **start from a generic system of ODEs**, not one that refers to chemical reactions.

Let us consider the following system of ODE as an example:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

We can translate it back to a system of chemical reactions by constructing one reaction for each term of each equation by matching each term with the pattern:

$$\ell_i k [S_1]^{\ell_1} \dots [S_p]^{\ell_p}$$

For example $6X$ in the equation of X tells us:

- there is a reaction producing X (since the sign of the term is positive)
- the reaction has X as its only reactant

- $\ell_i k = 6$ where ℓ_i is the number of new X to be produced.
- There is a reaction producing Y from X (since the sign of the term is negative).
- to be precise we are only sure that X will not be produced, so we select Y since its not X.
- the reaction has X and Y as its reactant.
- $\ell_i k = 0.2$ where $k = 2$ sincere there are no X to be produced.

Lets translate the whole system:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Will be the following reactions:

- $X \xrightarrow{6} 2X$
- $X + Y \xrightarrow{0.2} Y$
- $X + Y \xrightarrow{0.4} X + 2Y$
- $Y \xrightarrow{2}$

5.3.1 Counterexample

Consider the following example:

$$\begin{cases} \frac{dX}{dt} = 6X - 0.2XY - Y \\ \frac{dY}{dt} = 0.4XY - 2Y \end{cases}$$

Now no reaction can reduce the concentration of X without having X among its reactants.

From this counterexample we derive the following conjecture:

The translation should work for all systems of polynomial ODEs in which each negative term contains all the variable of its equation

5.4 Reverse engineering the Lotka-Volterra model

Let us see how to transform the Lotka-Volterra model into a system of chemical reactions.

Given the system of ODEs:

$$\begin{cases} \dot{V} = rV - aVP \\ \dot{P} = -sP + abVP \end{cases}$$

- **V**: denotes preys
- **P**: denotes predators.
- **a**: denotes the portion of eetings resulting in hunting.
- **b**: denotes the number of offsprings produced for each hunting.

By applying the steps we have stated, we obtain:

- $V \xrightarrow{r} 2V$
- $P \xrightarrow{s}$
- $V + P \xrightarrow{a} (1 + b)P$

5.5 Reverse engineering the SIR model

Let us see how to transform the SIR model into a system of chemical reactions.

Given the system of ODEs:

$$\begin{cases} \dot{S} = (1 - p)\mu - \beta SI - \mu S \\ \dot{I} = \beta SI - \gamma I - \mu I \\ \dot{R} = p\gamma I - \mu R \end{cases}$$

- **S**: denotes susceptible people
- **I**: denotes infected people
- **R**: denotes recovered people
- β : denotes the infection coefficient
- γ : denotes the recovery coefficient

- μ : denotes the birth and death coefficient

By applying the steps we have stated, we obtain:

- $\xrightarrow{\mu} S$
- $S \xrightarrow{\mu}$
- $I \xrightarrow{\mu}$
- $R \xrightarrow{\mu}$
- $S + I \xrightarrow{\beta} 2I$
- $I \xrightarrow{\gamma} R$

5.6 Reverse engineering the logistic equation

Recall the form of the logistic equation:

$$\dot{N} = r_c N \left(1 - \frac{N}{K}\right)$$

where:

- r_c : is the **birth rate**
- **K**: is the **carrying capacity** of the environment

First we rewrite the equation as:

$$\dot{N} = r_c N - \frac{r_c}{K} N^2$$

By applying the steps we have stated, we obtain:

- $N \xrightarrow{r_c} 2N$
- $2N \xrightarrow{\frac{r_c}{K}} N$

Chapter 6

Stochastic Simulation of Chemical Reactions

Recall that a Ordinary Differential Equations is continuous and deterministic, while in contrast chemical reactions can manifest themselves randomly. This will lead us to the definition of stochastic simulation algorithm for chemical reactions.

6.1 Introducing randomness in chemical reactions

Chemical reactions are not deterministic. Given for example to single molecules in a chemical solution, it is difficult to predict in advance when they react. Doing it would require to know the angle and speed of the molecules, to take into account the molecules that compose the solution they are in and so on. Thus we abstract the time of the occurrence of the reaction using a **continuous probability distribution**.

So taking into account these information, using ODEs to represent chemical reaction seems wrong now. This is true, but if we take into account a chemical solution with an high concentrations of reactants, **the law of large numbers allow us to ignore the random aspect of our chemical reaction**. So the rule is:

- **If there are a lot of molecules:** random aspects can be ignored, permitting us to use ODEs to represent the reaction.
- **If there are a small number of molecules:** random aspects become crucial, requiring necessary the use of **discrete variables**.

6.2 Gillespie's Stochastic Simulation Algorithm (SSA)

The Gillespie's Stochastic Simulation Algorithm is an exact procedure for simulating the time evolution of a chemical reacting system by taking proper account of the randomness inherent in such a system.

Consider a set of reactions $\mathcal{R} = \{R_1, \dots, R_n\}$, then the SSA:

- Assumes a stochastic reaction constant c_μ for each chemical reaction $R_\mu \in \mathcal{R}$.
- Given an infinitesimal time interval dt , then $c_\mu dt$ is the probability that a particular combination of reactants of R_μ react during the interval.

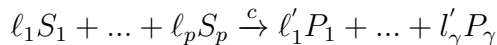
6.2.1 Explaining c_μ

The constant c_μ is used to compute the **propensity** (also called stochastic rate) of R_μ to occur in the whole chemical solution a_μ as follows:

$$a_\mu = h_\mu c_\mu$$

where h_μ is the number of distinct molecular reactant combinations.

Defined R_μ as:



The number of distinct reactant combinations of R_μ in a solution with X_i molecules of S_i with $1 \leq i \leq \rho$ is:

$$h_\mu = \prod_{i=1}^{\rho} \binom{X_i}{\ell_i}$$

Note: you can interpret the propensity as the rate of stochastic equations: **the higher is the propensity, the more often the reaction will take place.**

6.2.2 Using propensity as a stochastic rate

Propensity a_μ is used in Gillespie's as a stochastic rate. It is a parameter of a probability distribution used to describe the time of every reaction s.t on average I obtain a frequency which is the same as I got in the differential equation. To do so I will use the propensity in an exponential probability distribution to compute the time between subsequent occurrences of reaction R_μ . The obtained probability distribution will tell me when the next occurrence of the reaction we have model will take place.

6.2.3 What is an exponential distribution

An exponential distribution is a continuous probability distribution that takes place in $[0, \infty]$ describing the **timing between events** in a Poisson process, namely a process in which events occur continuously and independently at a constant average rate. The constant average rate is a parameter.

The exponential distribution is described by a negative probability density function f and by a cumulative distribution function. Both are using the parameter λ as follows:

The probability density function $f(x)$ will tell you how likely the event will take place over time. Obviously in our case we will set $\lambda = a_\mu$ (the propensity). Below the formula:

$$f(x) = \begin{cases} \lambda e^{-\lambda x} & x \geq 0 \\ 0 & x < 0 \end{cases}$$

The cumulative distribution function that tell you the probability that the event will happen from 0 to x .

$$F(x) = \begin{cases} 1 - e^{-x} & x \geq 0 \\ 0 & x < 0 \end{cases}$$

Note: the mean of an exponentially distributed variable with parameter λ is $\frac{1}{\lambda}$.

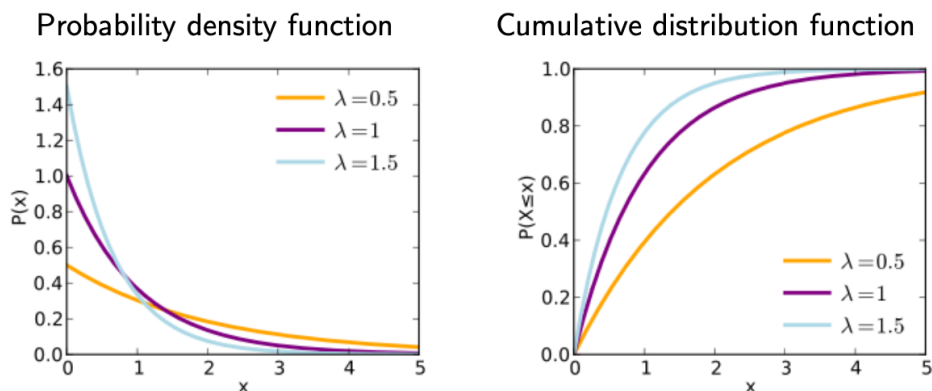


Figure 6.1: example of a graph for a Density Function and a Cumulative Function

For every reaction in the set of reaction I am considering I have a propensity that is associated to a probability distribution. We can interpret reaction as parallel processes that happen recursively and the frequency of the occurrence are computed by exponential distribution

Properties of exponential distribution

There are two important properties of the exponential distribution:

- **The exponential distribution is memoryless:**

$$P(X > t + s | X > s) = P(X > t)$$

This allows a simulation algorithm in which the exponential distribution is used to forget about the history of the simulation.

- Let X_1, \dots, X_n be some independent exponentially distributed random variables with parameters $\lambda_1, \dots, \lambda_n$, then the equation:

$$X = \min(X_1, \dots, X_n)$$

is also exponentially distributed. We set $\lambda = \lambda_1 + \dots + \lambda_n$. This allows a simulation algorithm to use a unique exponential distribution for the whole set of reactions to be simulated.

6.2.4 Introducing the algorithm

Given:

- A set of molecular species $\{S_1, \dots, S_n\}$.
- an initial numbers of molecules of each species $\{X_1, \dots, X_n\}$ with $X_i \in \mathbb{N}$.
- a set of chemical reactions $\{R_1, \dots, R_M\}$.

Gillespie's algorithm computes a possible evolution of the system.

The **state** of the simulation:

- is a vector representing the multiset of molecules in a chemical solution (at the start it is initialized as $[X_1, \dots, X_n]$).
- a real variable t representing the simulation time (at the start it is initialized as $t = 0$).

Then the algorithm iterates the following steps until it reaches a final value indicated as t_{stop} :

- The time $t + \tau$ at which the next reaction will take place. The time is randomly chosen with τ exponentially distributed with parameter $a_0 = \sum_{v=1}^m a_v$
- The reaction R_μ that has to occur at time $t + \tau$ is randomly chosen with probability $\frac{a_\mu}{\sum_{v=1}^M a_v}$

At each step t is incremented by τ and the multiset representing the chemical solution is updated by subtracting reactants and adding products.

6.2.5 Implementation details

Generation of τ

Recall that τ is randomly chosen at each step. A random number with any probability distribution can be computed from a random number with uniform distribution by applying the **inversion sampling method**. The idea is to use the inverse of the cumulative distribution function.

Given a cumulative distribution function F of a probability distribution $dist$ and a uniformly distributed random variable U , the variable $X = F^{-1}(U)$ is a random variable with distribution $dist$.

In the case of the exponential distribution, the cumulative distribution function for $x \geq 0$ is $F(x) = 1 - e^{-\lambda x}$. Let us now invert the function:

$$\begin{aligned} F(X) = 1 - e^{-\lambda x} &\Rightarrow 1 - F(x) = e^{-\lambda x} \Rightarrow \ln(1 - F(x)) = -\lambda x \\ &\Rightarrow -\frac{1}{\lambda} \ln(1 - F(x)) = x \Rightarrow \frac{1}{\lambda} \ln \frac{1}{1 - F(x)} = x \end{aligned}$$

So we obtain:

$$F^{-1}(Y) = \frac{1}{\lambda} \ln \left(\frac{1}{1 - Y} \right)$$

Since Y is uniformly distributed, also $1 - Y$ is uniformly distributed. This allows us to simplify the definition of F^{-1} as:

$$F^{-1}(Y) = \frac{1}{\lambda} \ln \left(\frac{1}{Y} \right)$$

where:

- τ is exponentially distributed with parameter a_0 can be computed as $\tau = \frac{1}{a_0 \ln(\frac{1}{Y})}$ with Y obtained from a standard random number generator.

Choice of reaction R_μ

Recall that R_μ is the reaction we randomly choose to take action at the step τ . First of all R_μ will be chosen with probability $\frac{a_\mu}{a_0}$.

We do this by following these steps:

- We generate a random number N uniformly distributed in $[0, a_0]$, that is $N = n * a_0$ with $n \in [0, 1)$ obtained by using a standard number generation.
- we start summing a_1, a_2, \dots

- as soon as the sum becomes greater than N , the number of completed iterations gives you μ

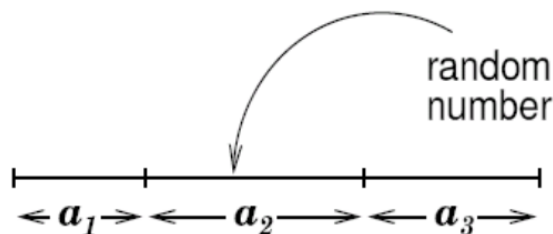


Figure 6.2: Choosing the random number

Note: μ is the smallest integer k satisfying $\sum_{i=1}^k a_i > na_0$ with n uniformly distributed in $[0, 1)$

6.2.6 Computational cost of Gillespie's algorithm

The problem of this stochastic approach is the computational cost: because I am executing reaction one by one, I have to repeat the simulation sever time to explore as many behaviour as possible, wasting a lot of time. In the case of large models this may become extremely high, like for example:

- when there are large number of molecules
- kinetic constant are high

In respect to ODEs, this is the only disadvantage.

6.2.7 Variants

To solve the computational drawback, several variants of Gillespie's algorithm have been introduces.

Exact approaches

Exact approaches are variants that improve the computation cost without introducing any approximation:

- Gibson and Bruck proposed the use indexed binary tree priority queue to improve the choice of the reaction R_μ for each step.

- Cao et al. and McCollum et al. proposed dynamical ordering strategies for reaction propensities a_1, \dots in order to probabilistically reduce the time needed to choose R_μ at each step.

Approximate approaches

Approximate approaches aims to reduce the computational cost by reducing the number of steps of the overall computation:

- Gillespie proposed the τ -leaping method: the idea is to allow several reactions to take place in a single longer time step, under the condition that reaction rates do not change too much during that time.
- Gillespie et al. proposed the slow-scale Stochastic Simulation Algorithm ssSSA which separates fast reactions from slow reactions. At each step fast reactions are dealt with by assuming that they reach a dynamic equilibrium, so only their steady state is computed. Slow reactions are simulated one by one in the standard SSA.
- Hybrid simulation is a technique which combines ODEs with stochastic simulation: ODEs are applied to molecules occurring in big numbers, stochastic simulation to molecules occurring in small number.

Note: the τ -leaping method is the most common.

Bibliography