Systems Biology: Mathematics for Biologists

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Wiskunde achtergrond?

Voordat we beginnen:
Wat is jullie wiskunde achtergrond:
A Wiskunde A
B Wiskunde B
C Wiskunde D
D MLS
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Differential equations of one variable

Contents

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  - Why use them?
  - Simple examples with their solution.
- Qualitative analysis.
  - Phase portrait.
  - Stable and unstable equilibria.
  - Basins of attraction.
- Parameters and bifurcations.

Differential equations and their solutions

Differential equation:

$$\frac{dx}{dt} = ...$$

describes **change of variable** x **over time**

Solution:

$$x(t) = ...$$

describes **the size of variable** x **as a function of time**

Use of variables and parameters in differential equations

Variable:
something for which we want to know the change over time

Example: the number of rabbits in a country

Parameter:
describes the *unspecified* rate of a process affecting the variable

constant for a particular situation, differences reflect different conditions

Example: the birth rate of rabbits may differ between countries

Why are differential equations used

What would the differential equation for the number of individuals in a population in which birth and death processes occur look like?

A $\frac{dN}{dt} = b - dN$
B $\frac{dN}{dt} = bN - dN$
C $\frac{dN}{dt} = b - d$
D $\frac{dN}{dt} = bN - d$

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Why are differential equations used

Often easy to write down equations for the change of a variable over time, as a function of the processes causing changes:

$$\frac{dN}{dt} = bN - dN = (b - d)N = rN$$

Often hard to write down equations for its size as a function of time, in terms of these same processes:

$$N(t) = N_0 e^{(b-d)t} = N_0 e^{rt}$$

Needs to be obtained by solving differential equation!

Why are differential equations used (2)

Once we have a differential equation we can use it to:

- Find out about the **long term behaviour of the variable**:
  - does it increase to ∞? (a plague)
  - does it decrease to 0? (extinction)
  - does it reach a steady state? (constant population size)
  - will it oscillate? (variable population size)
- Find out how this depends on the **initial values** of variables, and on the particular conditions (i.e. the **parameter settings** of the system).

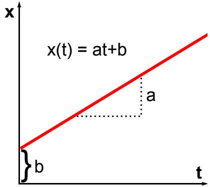
Examples:

- In a forest with rabbits and foxes, do they coexist? Or do the foxes die out and will the rabbit population explode? Or do both populations die out?
- How much fish can we catch before the fish die out?

Simple differential equations and their solution

Simplest possible equation: $dx/\,dt = a$
e.g. position change of a car travelling at constant *speed a*.

$$\frac{dx}{dt} = a$$



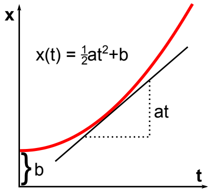
General solution: $x(t) = at + b$, with $x(0) = b$

Solution of initial value problem:
given $x(0) = 10$ solution is $x(t) = at + 10$

Simple differential equations and their solution (2)

A slightly less simple equation: $dx/\,dt = at$
e.g. position change of a car travelling at constant *accelleration* a.

$$\frac{dx}{dt} = at$$



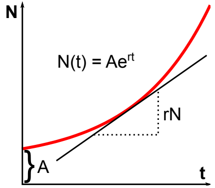
General solution: $x(t) = \frac{1}{2}at^2 + b$, with $x(0) = b$

Solution of initial value problem:
given $x(0) = 30$ solution is $x(t) = \frac{1}{2}at^2 + 30$

Simple differential equations and their solution (3)

A simple biological equation:
a population that changes size due to birth and death processes

$$\frac{dN}{dt} = bN - dN = (b-d)N = rN$$



General solution: (less easy to find)
$N(t) = Ae^{rt}$, with $N(0) = A$: exponential growth

Solution of initial value problem:
given $N(0) = 30$ solution is $N(t) = 30e^{rt}$

Doubling time:
time in which a 2-fold change of variable occurs: $\tau = \frac{\ln 2}{r}$

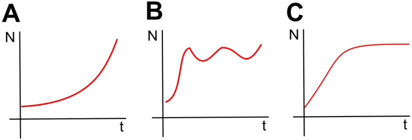
An example of exponential growth

- The birth rate b is 0.4 and the death rate d is 0.2 per rabbit per month.
- The net population growth rate r is $0.4 - 0.2 = 0.2$ per rabbit per month.
- The doubling time is $\tau = \frac{\ln 2}{r} = \frac{0.693}{0.2} = 3.5$ months.
- In 1859, 24 rabbits were released into Australia.
- How many rabbits were there after 6 years?
- In 1865 The actual number was estimated at around 22 million.

Simple differential equations and their solution (4)

Another simple biological equation:
a population that changes size due to immigration and death processes:
$\frac{dN}{dt} = k - dN$

What does the graph of $\frac{dN}{dt}$ look like?



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Simple differential equations and their solution (4)

Another simple biological equation:
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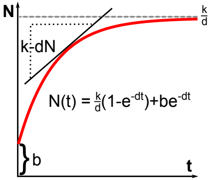
$$\frac{dN}{dt} = k - dN$$



General solution: (less easy to find)
$N(t) = \frac{k}{d}(1 - e^{-dt}) + N(0)e^{-dt}$

Equilibrium:
for $t \to \infty$ we get $e^{-dt} \to 0$ so $N(t) \to \frac{k}{d}$
indeed $dN/dt = k - dN = 0$ gives $N = \frac{k}{d}$

Qualitative analysis

Up until now
understand the dynamics of a differential equation by obtaining solution and determining its behavior for $t \to \infty$.

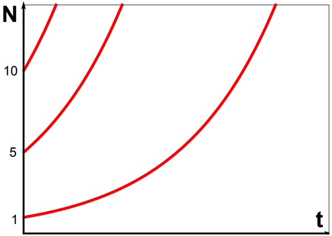
However,
a lot of differential equations cannot be (easily) solved.

Therefore,
use qualitative analysis to understand the dynamics without the need to solve the differential equation.

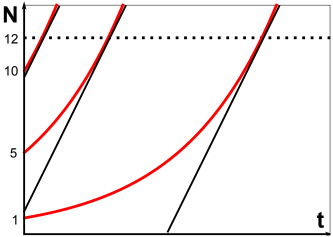
Phase portrait: Different sizes

$$\begin{aligned} \frac{dN}{dt} &= bN - dN = rN \\ N(t) &= N(0)e^{rt} \end{aligned}$$

For $\frac{dN}{dt} = rN$ with $r = 4$ and different $N(0)$ we can draw:



Phase portrait: Same slopes

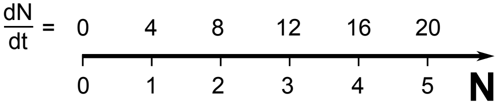


Observations:

- Change in N = slope of $N(t)$ = derivative $N'(t)$.
- The derivative $N'(t)$ is given by $\frac{dN}{dt}$!
- Autonomous equation: $\frac{dN}{dt}$ only depends on N.

Phase portrait: From 2D to 1D representation

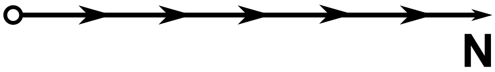
For qualitative overview of dynamics we only need the N-axis!
on which we indicate the size of increase or decrease: value of $\frac{dN}{dt}$



For given $N(t)$ find what is change $\frac{dN}{dt}$ and hence what will be $N(t + \Delta t)$

Phase portrait: From Size to Sign

For qualitative overview of dynamics we can even further simplify!
we can indicate only sign of change $\frac{dN}{dt}$:
$\frac{dN}{dt} > 0$, so increase: $\rightarrow$
$\frac{dN}{dt} < 0$, so decrease: $\leftarrow$
$\frac{dN}{dt} = 0$, so zero change: $\bullet$



We call this representation a **phase portrait**

For given $N(t)$ what is sign of $\frac{dN}{dt}$ and hence whether at $t + \Delta t$ N will have increased, decreased or stayed the same

Phase portrait

Given an equation: $\frac{dx}{dt} = f(x)$
How to draw the phase portrait?

We can find the sign of $\frac{dx}{dt}$ from whether the graph of $f(x)$ lies above or below the x-axis or intersects it!

- If $f(x)$ is above the x-axis $\frac{dx}{dt} > 0$ so draw $\rightarrow$
- If $f(x)$ is below the x-axis $\frac{dx}{dt} < 0$ so draw $\leftarrow$
- If $f(x)$ crosses the x-axis $\frac{dx}{dt} = 0$ so draw $\bullet$

So if you can draw $f(x)$ you can find the phase portrait.
We do not need the solution $x(t)$ of $\frac{dx}{dt} = f(x)$!

Equilibria

What happens if $\frac{dx}{dt} = f(x) = 0$ for $x = x^*$:

- at this point the graph of $f(x)$ crosses the x-axis
- $\frac{dx}{dt} = 0$ means that x does not change over time
- so if $x = x^*$, x remains at x^* (unless perturbed)

We call $x = x^*$ an **equilibrium** point of $\frac{dx}{dt} = f(x)$

Stability of Equilibria

Assume that a differential equation has a single equilibrium.
Also assume that the system is somewhat noisy
What will be the long term value of the variable?

A zero
B the equilibrium value
C infinity
D impossible to tell

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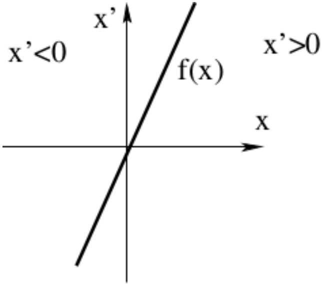
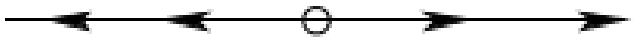
Stability of Equilibria

Consider $\frac{dx}{dt} = 4x$



By solving $4x = 0$ we find equilibrium point $x = 0$

Graph shows decrease left, increase right of equilibrium
Follows naturally from positive slope of $f(x) = 4x$



Stability of Equilibria

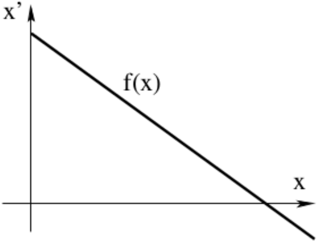
For $\frac{dx}{dt} = 4x$:

- in the equilibrium point slope $f'(x) > 0$
- arrows point away from equilibrium
- perturbation causes divergence from equilibrium
- unstable: system will not stay there

An equilibrium x^* is **unstable** if $f'(x^*) > 0$
Unstable equilibria are called **repellors** of the system

Stability of Equilibria

Consider $\frac{dx}{dt} = 240 - 0.01x$



By solving $240 - 0.01x = 0$ we find equilibrium point $x = 24000$

Graph shows increase left, decrease right of equilibrium
Follows naturally from positive slope of $f(x) = 240 - 0.01x$

Stability of Equilibria

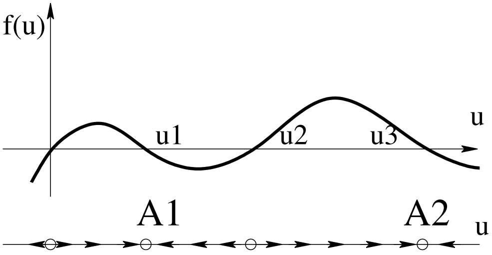
For $\frac{dx}{dt} = 240 - 0.01x$:

- in the equilibrium point slope $f'(x) < 0$
- arrows point towards the equilibrium
- after perturbation, convergence to equilibrium
- stable: system returns there

An equilibrium x^* is **stable** if $f'(x^*) < 0$
Stable equilibria are called **attractors** of the system

Basins of Attraction

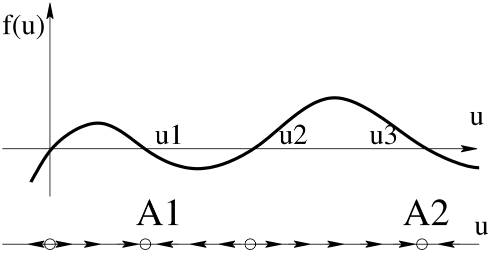
A differential equation can have multiple **stable** equilibria:



Total of 4 eq.: u_0 till u_3
Total of 2 stable eq.: A_1 (u_1) and A_2 (u_3)

When will system go to A_1 and when to A_2?

Basins of Attraction



The **basin of attraction** of an attractor is the range of x-values for which convergence to that equilibrium occurs.

Boundaries are formed by unstable equilibria or end of domain.

For A_1 basin of attraction $[u_0, u2]$
For A_2 basin of attraction $[u_2, \infty]$

Global plan

$$\frac{dx}{dt} = f(x)$$

Global plan of phase portrait analysis:

1. Sketch the graph of $f(x)$.
2. Determine where $f(x) = 0$ and draw equilibria points.
3. Determine where $f(x) > 0$ and draw $\rightarrow$ there.
4. Determine where $f(x) < 0$ and draw $\leftarrow$ there.
5. Determine attractors and their basin of attraction.

Now we can predict the systems long term behaviour as a function of initial conditions.

Parameters and Bifurcations

Consider a population with logistic growth subject to harvesting:

$$\frac{dn}{dt} = rn(1 - \frac{n}{k}) - h$$

r, k and h are all parameters

Different system behaviour for different parameter values?

For given r, k how much can we harvest (h) without extinction?

Parameters and Bifurcations

What happens to $f(n) = rn(1 - \frac{n}{k}) - h$ when increasing h?

A The graph shifts up
B The graph shifts to the left
C The graph shifts to the right
D The graph shifts down

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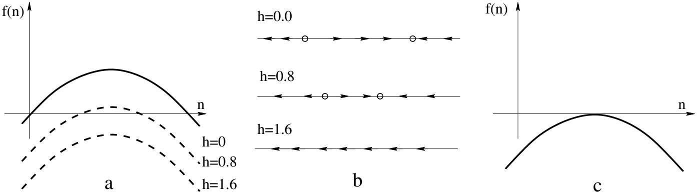
Parameters and Bifurcations

Increasing h shifts down graph



equilibria first converge, then coincide, finally disappear!

A **bifurcation** is a **qualitative change** in system behaviour due to a small change in parameter value.

Summary

- Differential equations: $\frac{dx}{dt} = ...$
- Solution: $x(t) = ...$
- Often the solution is not easy to find.
- Qualitative analysis can tell us long-term behaviour.
- **Phase portrait**: where x increases, decreases, stays constant.
- **Equilibrium**: no change $\Leftrightarrow \frac{dx}{dt} = 0 \Leftrightarrow$
- Equilibria can be stable (attractor) or unstable (repellor).
- **Basin of attraction**: set of inital conditions converging to an attractor.
- Equilibria can gradually shift when parameters change.
- Equilibria can also (dis)appear when parameters change: **bifurcation**.