Models of cellular processes (WS 2019/2020)

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Overview

18.10.2019 - **01. Modelling Introduction**
- Why modelling? Why mathematics? Overview and content?
- general terms, phase space, trajectories

25.10.2019 - **02. Boolean networks**
- attractors, limit cycles & fix points

01.11.2019 - **03. Cellular automata**

08.11.2019 - **04. Finite difference equations**
- stability of maps, fix points

15.11.2019 - **05. Ordinary differential equation models (ODE)**
- 1 dimensional ODE, fix points, growth models, graphical solution, stability, bistability,
- 2 dimensional ODE, nullclines, Jacobi matrix, linear stability analysis, Taylor expansion, Lotka-Volterra system, solve dynamic graphically, predator-prey systems, chaos, Lorenzsystem
- numerical integration (Euler method)

22.11.2019 - **06. Models of metabolism**
- mass-action kinetics, enzyme kinetics, reversible vs. irreversible reactions; thermodynamics; effects of activation and inhibition, Michaelis-Menten equation and derivation, stochiometry

29.11.2019 - **07. Stoichiometric matrix & network reconstruction**

06.12.2019 - **08. Constraint-based analysis (CBA) & flux balance analysis (FBA)**
- stoichiometric matrix, optimality as criterium,

13.12.2019 - **09. Sensitivity & Metabolic control analysis (MCA)**
- sensitivity equations, logarithmic sensitivity

20.12.2019 - **10. Stochastic Processes**
- stochastic model of gene expression
- master equation
- Gillespie algorithm

10.01.2020 - **11. Signaling Pathways**
- typical systems: phosphorylation cycle and two-component system

17.01.2020 - **12. Standard formats (Reproducibility) & Sensitivity Examples**
- SBML

24.01.2020 - **13. Parameter estimation**

31.01.2020 - **14. Biological databases**

07.02.2020 - **15. Course Review**

13-14.02.2020 - Exams

Modelle zellulärer Prozesse

Einführung

Ziel

- Verständnis der Modellierung zellulärer Prozesse

Methode

- Mathematik & Computermodellierung

Themen

- Boolesche Netzwerke
- Differentialgleichungen & dynamische Systeme
- Constraint-based models
- Cellular networks
- Stochastic systems
- Parameter fitting

Anwendungen

- Stoffwechsel
- Signaltransduktion
- Genexpression
- Cell cycle
- Circadiane Oszillationen

Lernziele

- wie modelliert man zelluläre Prozesse
- was ist ein dynamisches System?
- was sind feedback loops?
- was ist Stabilität?

Komplexität biologischer Systeme

- **incomplete knowledge**
- many components
- roles of and interactions between components are often obscure and change over time
- **nonlinearities & feedbacks**
- **multiple spatial scales**: from organism to single molecule
- **different time-scales**: from the human life span down to molecular kinetics, e.g. of enzyme catalysis in a fraction of a second
- build via evolution

⇒ complex processes

- often not explained from first principle
- no understanding of behavior by intuition
- emergent properties (more than the sum of its parts)

⇒ requirement of abstract representation

Was ist ein Model?

A model is an artificial construct in the language of mathematics that represents biological phenomenon.
(Analogy: geographische Karte)

Gute Modelle

- “essentially, all models are wrong, but some are useful” G. Box

- enable **insights into processes/systems** (that we would not be able to gain otherwise)
- **repository of knowledge:** make sense of large number of isolated facts and observations
- allow to make **predictions** and **extrapolations** (which can be tested)
- lead to the **formulation of new hypotheses**

Models can take any form

- model can be intuitive or very abstract
- minimal models vs. whole cell models

Wie konstruiere ich ein Modell?

Abstraction steps

- biological system
- mental model
- model scheme
- process model
- mathematical model
- quantitative analysis

Modellierung ist Kunst

- requires: **technical expertise** and **creativity**
- nicht zu kompliziert/nicht zu einfach → richtiger Abstraktionsgrad
- conceptualizing in modules/components/processes
- subjective and selective procedure
- abhängig von Fragestellung

Modelling cycle, model predictions → experiments (validation) → refining models

Nichtlineare Dynamik

Dynamisches System: a function describes the time-dependence of a point in a state space.

- state: Zustand
- state space: Zustandsraum (all possible states)
- function: rule how state is changing over time (depending on state and possible history)

Zustand:

- discrete / continuous
- single state variable, or more often state vector (i.e. multiple variables define the concrete state, e.g., concentrations of metabolites)

Zustandsraum:

- entsprechend diskret/kontinuierlich
- ein-dimensional / hoch-dimensional

Zeit/time:

- diskret/kontinuierlich

Function/rules:

- deterministisch, stochastisch
- (description as state updates or changes in state over time)

Mögliche Fragen:

- time-evolution of the system (where do I end up depending on the start conditions)?
- steady states (nothing is changing over time any more)?
- which states are visited? periodic states (oscillations)?

- stability & robustness ? (if I change a bit do I get similar results)
- sensitivity (what is the effect of parameter changes and initial condition changes)

Let's build a model

Even simple systems can confuse us

- simple linear chain with and without feedback

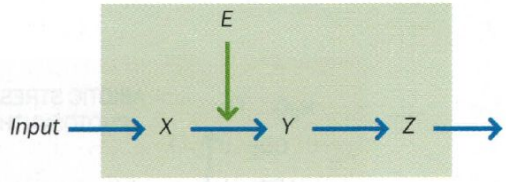

Figure 1.8 The human brain handles linear chains of causes and events very well. In this simple pathway, an external input is converted sequentially into *X*, *Y*, and *Z*, which leaves the system. The conversion of *X* into *Y* is catalyzed by an enzyme *E*. It is easy to imagine that any increase in *Input* will cause the levels of *X*, *Y*, and *Z* to rise.

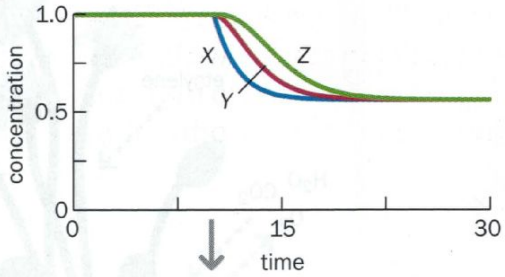

Figure 1.9 Simulations with the system in (1.1) confirm our intuition: *X*, *Y*, and *Z* reflect changes in *Input*. For instance, reducing *Input* in (1.1) to 75% at time 10 (arrow) leads to permanent decreases in *X*, *Y*, and *Z*.

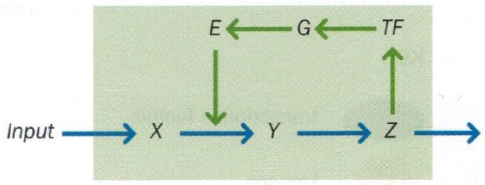

Figure 1.10 Even simple systems may not allow us to make reliable predictions regarding their responses to stimuli. Here, the linear pathway from Figure 1.8 is embedded into a functional loop consisting of a transcription factor *TF* and a gene *G* that codes for enzyme *E*. As described in the text, the responses to changes in *Input* are no longer obvious.

- even if we know these alternative responses are possible, the unaided mind is not equipped to integrate the numerical features of the model in such a way to predict the response for a given set of parameters
- computational model gives answer in a fraction of a second
- cannot rely on our intuition to make predictions
- emergent properties of the system, here oscillations

Literatur

- Herbert Sauro, *Introduction to Pathway Modeling, First Edition*
  Chapter 4, Introduction to modelling
- Olaf Wolkenhauer: Why are human-induced changes in CO2 such a great risk to earth

- Eberhard O. Voit, *A first course in Systems Biology, second edition*
  Chapter 1, Biological systems
  Chapter 2, Introduction to mathematical modelling
- Klipp, Liebermeister, Wierling, Kowald; *Systems Biology - A Textbook, Second Edition*
  Part I, Introduction to Systems Biology

Misc

System and surrounding

- **System** is a defined region of the universe that we wish to study
- The **surroundings** is everything else other than the system
- The **boundary** is the interface between the system and the surroundings

Open, closed and isolated systems

- Isolated: no transfer of energy and matter
- Closed: No transfer of matter
- Open: transfer of matter and energy