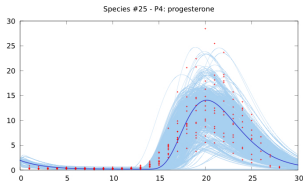


Specification and Uncertainty in Systems Biology Modelling

Dr. Susanna Röblitz

Computational Systems Biology Group
Zuse Institute Berlin (ZIB)

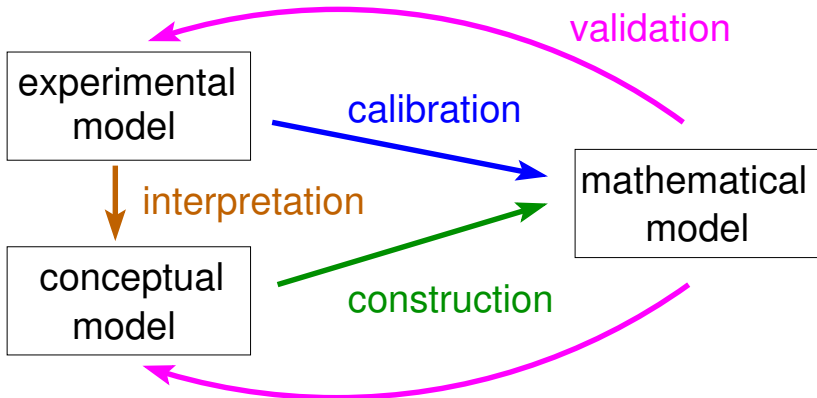
Takustr. 7
14195 Berlin



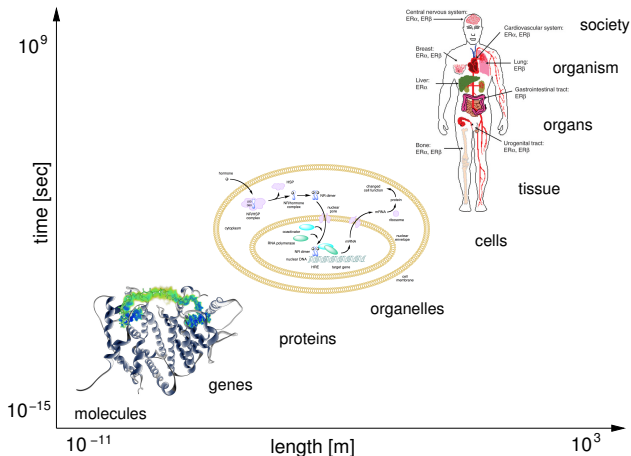
Zuse-Institut Berlin



FU Berlin



Integration of experimental data into a system's understanding at different scales in space and time



**“A (mathematical) model should be as simple as possible,
but not any simpler”**

(A. Einstein)

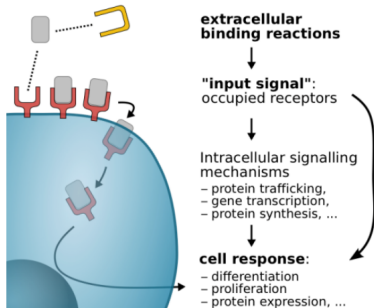
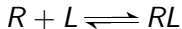
- ▶ increase in model **complexity** is associated with an increase in the number of model parameters, thus an increase in model **uncertainty**
- ▶ too **simple** models loose their **predictive** ability

Studying complex, non-linear systems often requires advanced analytical and numerical **mathematical tools** !

$$y'(t) = f(y(t), u(t), \theta, t), \quad y(t=0) = y_0$$

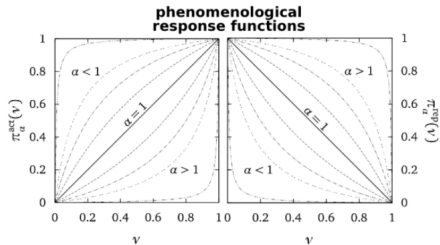
Mass action kinetics

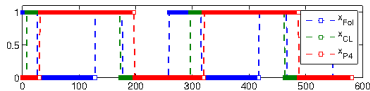
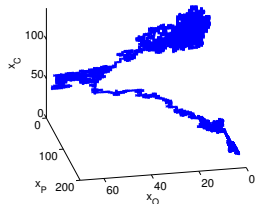
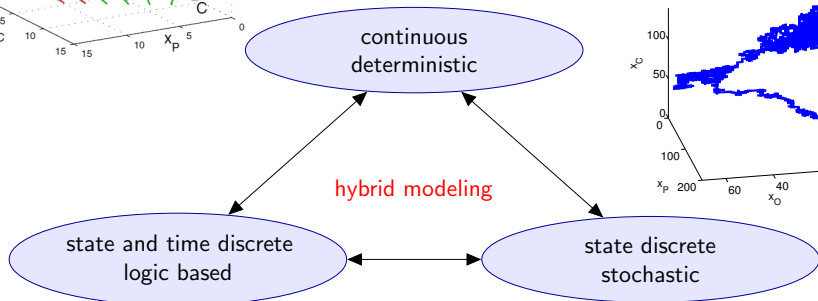
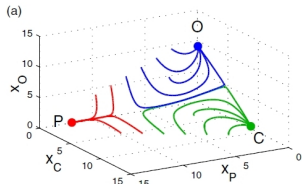
e.g. receptor-ligand interactions



Hill kinetics:

stimulatory/inhibitory effects





Model: $y(t, \theta) = (y_1(t, \theta), \dots, y_n(t, \theta)) \in \mathbb{R}^n$

Parameters: $\theta = (\theta_1, \dots, \theta_q) \in \mathbb{R}^q$

Data: $z_{kl} \approx y_k(t_l, \theta)$, $k = 1, \dots, n$, $l = 1, \dots, m_k$

(i) **direct minimisation** of **least squares error**

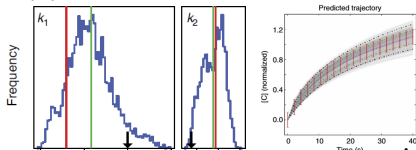
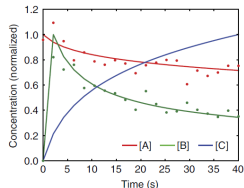
$$\|F(\theta)\|_2^2 = \sum_{k=1}^n \sum_{l=1}^{m_k} \frac{(z_{kl} - y_k(t_l, \theta))^2}{2\sigma_{kl}^2} \xrightarrow{\theta} \min$$

\Rightarrow ill-posed problem

(ii) computation of joint **probability distributions** according to

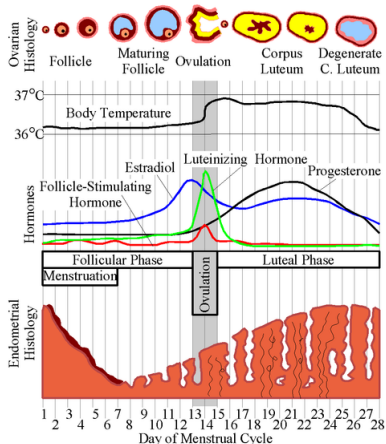
Bayes' theorem $P(\theta|z) \propto P(z|\theta)P(\theta)$ with likelihood

$$P(z|\theta) \propto \exp(-\|F(\theta)\|_2^2)$$

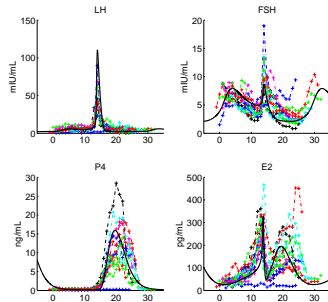


Application: The human menstrual cycle

GynCycle: 33 ODEs, 114 parameters [Röblitz et al., J Theoret Biol 2013]



(Average values. Durations and values may differ between different females or different cycles.)



endocrine disorders → infertility

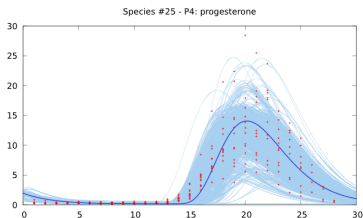
- ▶ clinical success rates: 8-35%
- ▶ limited understanding of variability

→ model-based decision tool

Model specification:

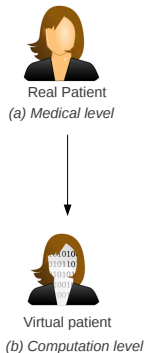
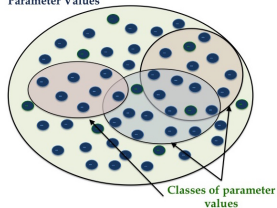
Compute parameter distribution represented by a finite set of biologically admissible parameters [Mancini et al. (2014)]

→ **virtual patients**



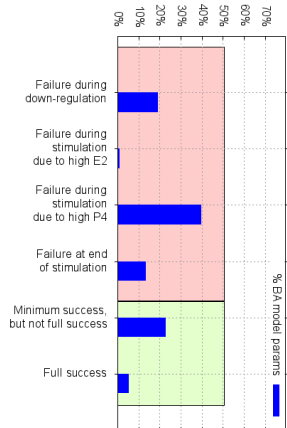
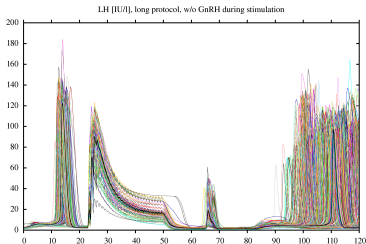
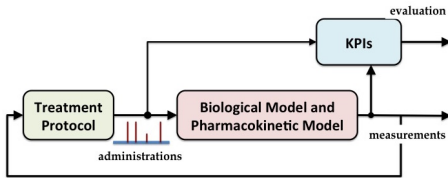
offline

Set of Biologically Admissible
Parameter Values

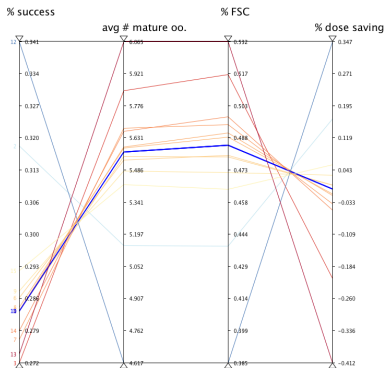
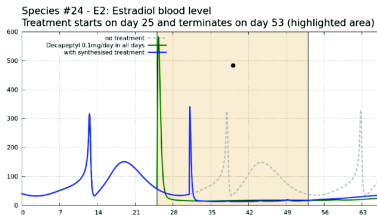
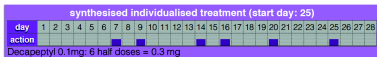
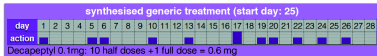
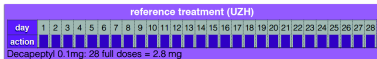


online

Validate treatment outcome wrt. key performance indicators (KPIs): E2 levels, number and size of follicles, total amount of drug → evaluate **success rate**



Find values for treatment parameters (type, dose and time of drug) that **optimize** KPIs



→ set of *Pareto-optimal* treatments, in which at least one performance indicator is better

Mathematical modelling

- ▶ **bridges the gap** between conceptual models and experimental validation
 - ▶ can assist in **formulating hypotheses** and **finding experiments**
 - ▶ helps in quantifying inter- and intra-individual **variability**
 - ▶ enables design of **optimal treatment strategies**
- goes **beyond pure data-based approaches**
- foundation of **Computational Systems Biology**

Computational Systems Biology Group

<http://www.zib.de/numeric/csb>



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