Model-driven data analysis in reproductive medicine

Dr. Susanna Röblitz

Computational Systems Biology Group
Zuse Institute Berlin (ZIB)
Takustr. 7
14195 Berlin

Zuse-Institut Berlin

FU Berlin

Computational Systems Biology

Models

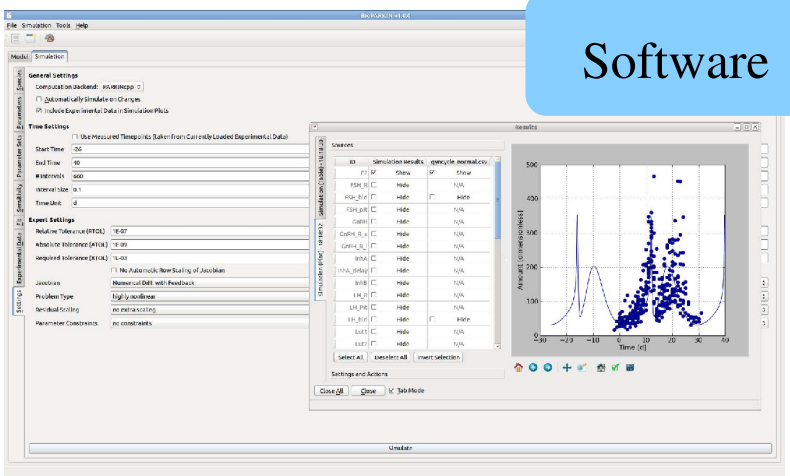
Development of
predictive
mathematical models
for biological and
biochemical systems

Software

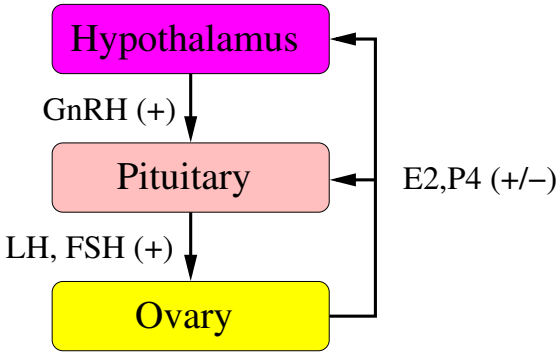
Algorithms

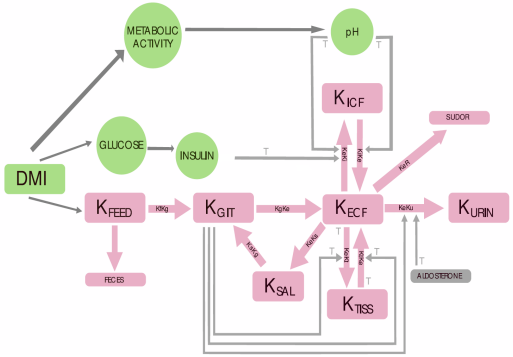
Simulation
Parameter identification
Uncertainty quantification

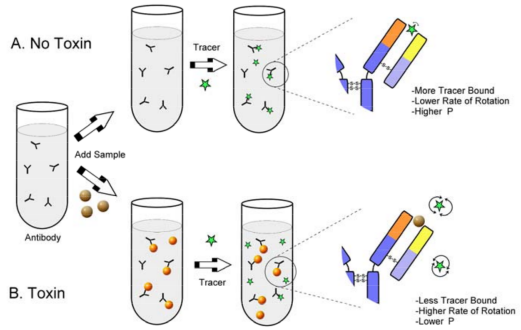
BioPARKIN



Applications & Cooperations







Regulatory Networks

- hormonal regulation and treatment computation in humans (EU project PAEON)
- cellular signalling (FU Biochemistry & Vet. Biochemistry)
- epidemiology

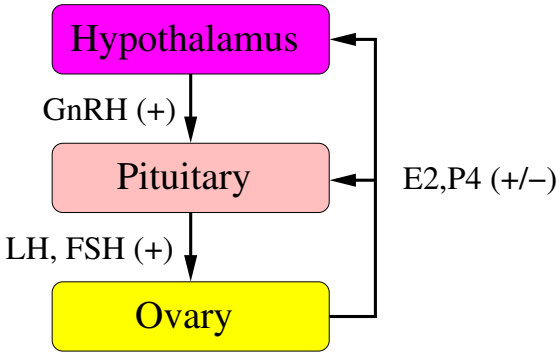
Metabolic Networks

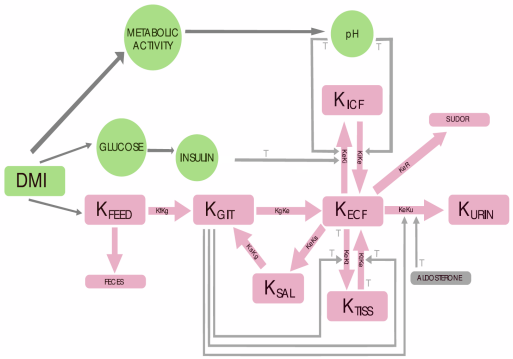
- bovine fertility, milk yield and nutrition (e:Bio JRG BovSys, FU Vet. Medicine)

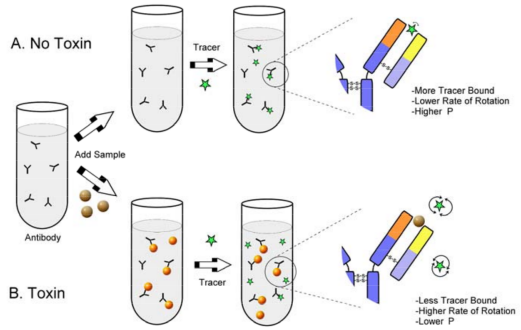
Reaction Kinetics

- biosensors (aokin AG, Fraunhofer IBMT)
- rebinding effects (AG Weber, ZIB)

Applications & Cooperations







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Outline

1. Motivation
2. Experimental data *in vivo*
3. Model development for the human menstrual cycle
4. Results of *in silico* experiments
5. Summary and outlook

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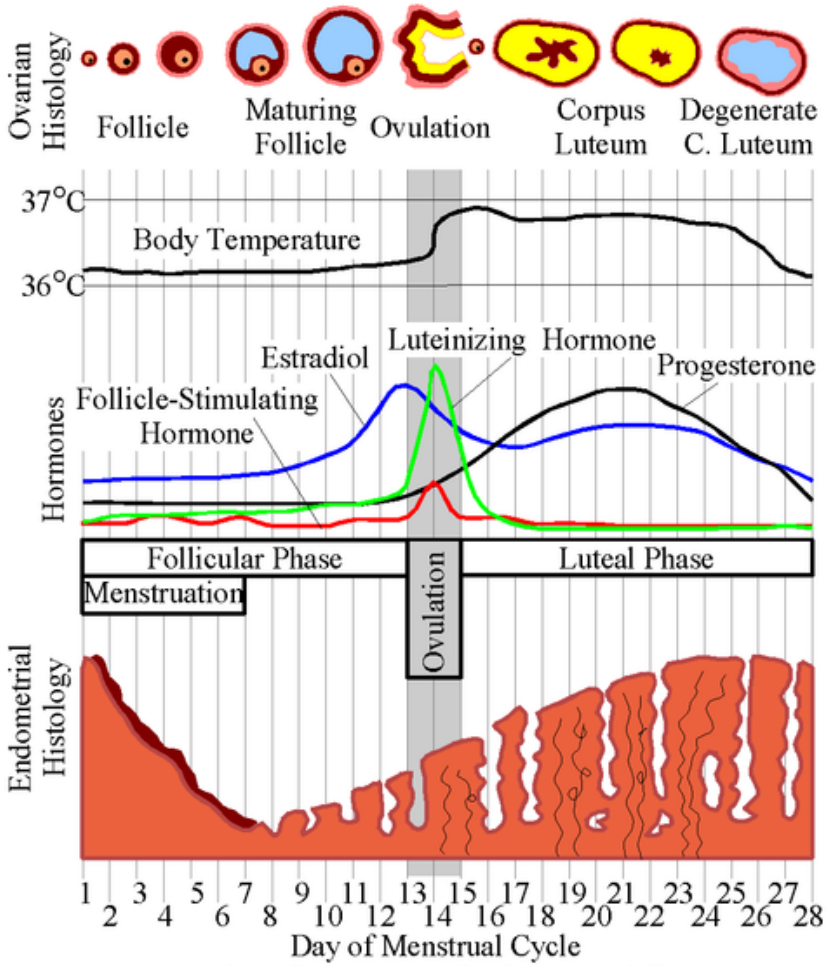
The human menstrual cycle



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

(http://www.websters-online-dictionary.org/definitions/Menstrual Cycle)

Exactly timed interplay of physiological processes

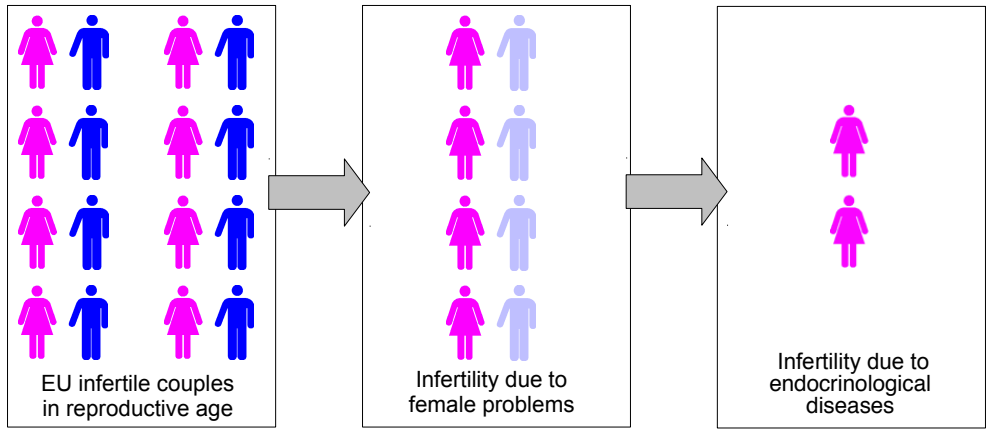
- Follicle development
- Ovulation and fertilization
- Formation of corpus luteum
- embryonic attachment and growth in the uterus

$\Rightarrow$ coordination between neural and endocrine systems

Endocrine disorders

Unwanted childlessness among couples in Europe: 12-15%

Female health problems: 50%, thereof 40% endocrinological diseases



- **PCOS** (Polyzystic Ovarian Syndrom):
  main cause for hyperandrogenism, leading to cycle disorders and infertility (4-12% of women in reproductive age)
- **Endometriosis** (uterine lining outside uterus):
  about 40% of women at reproductive age, thereof 30-50% infertility
- **Hyperprolactinemia** (increased blood levels of prolactin):
  in about 20% of women with reproductive disorders
- **External factors**: smoking, BMI, age

Reproductive medicine

Increased chance for successful pregnancy by modern techniques:

- In-vitro fertilization (IVF)
- Intracytoplasmic sperm injection (ICSI)

Success rates:
8 - 35%, depending on the clinic due to different treatment strategies

Aim: supply of model-based *clinical decision support system* for reproductive endocrinologists

- better understanding of complex processes
- simulation and optimization of treatment strategies *in silico* (cost-saving and efficient)

Virtual hospital

PAEON: Model-Driven Computation of Treatments for Infertility Related Endocrinological Diseases

- input: patient data, treatment protocol
- output: actions to be performed on the patient

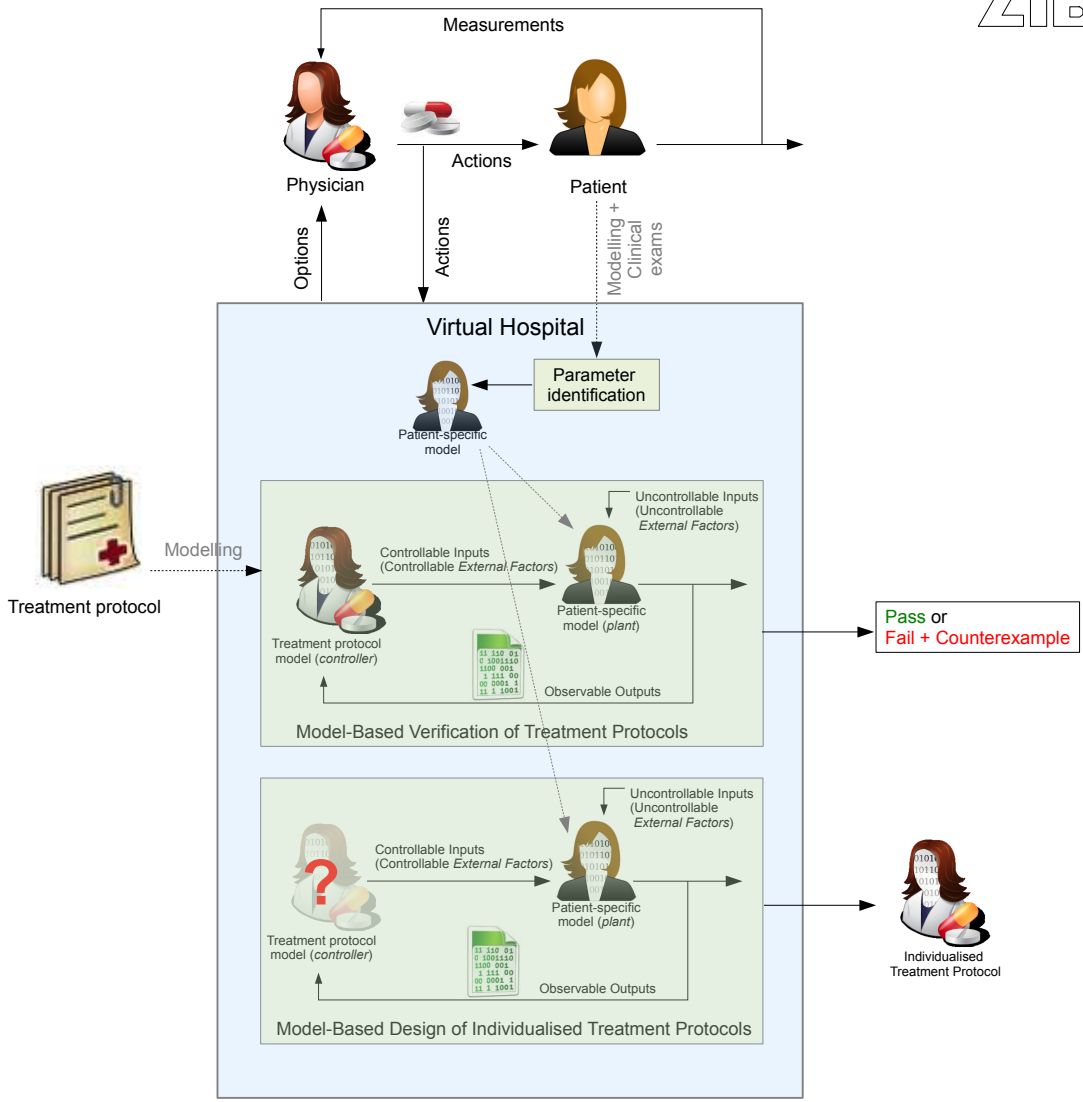
Cooperation partners:

University La Sapienza Rome,

University Lucerne,

University Hospital Zürich,

Hannover Medical School



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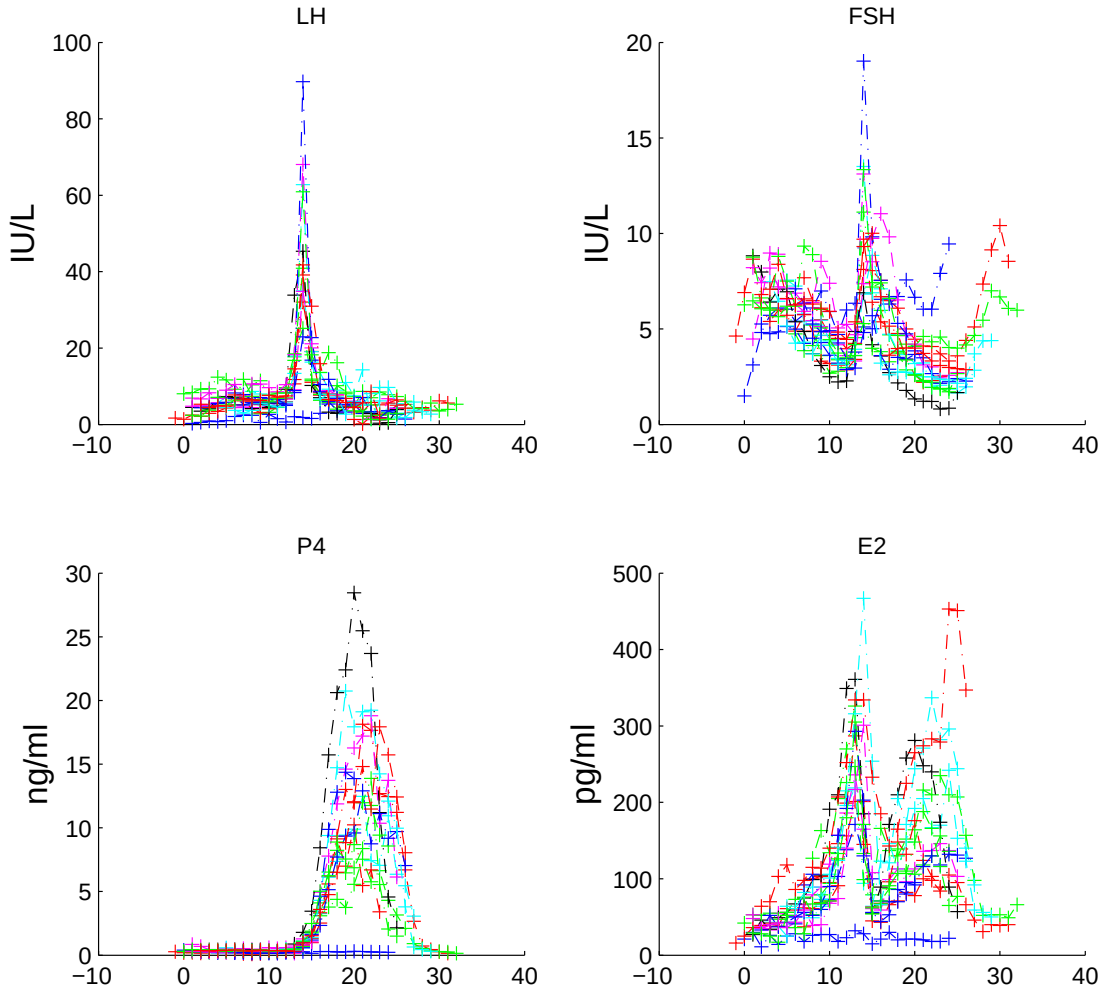
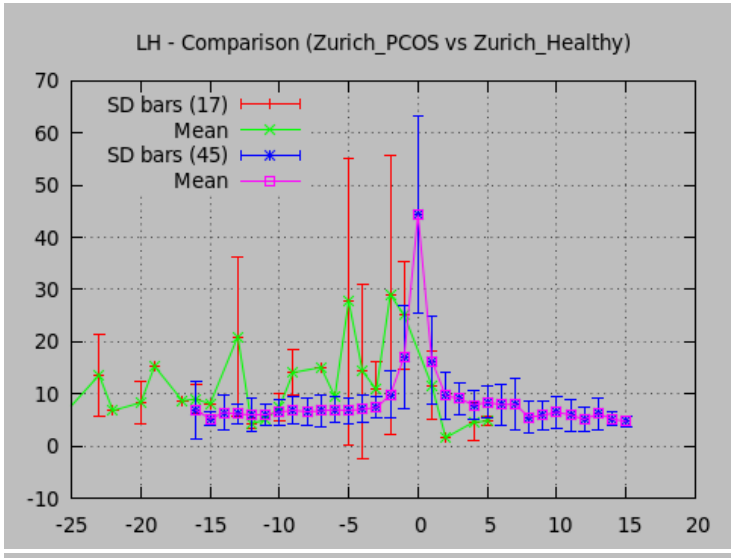
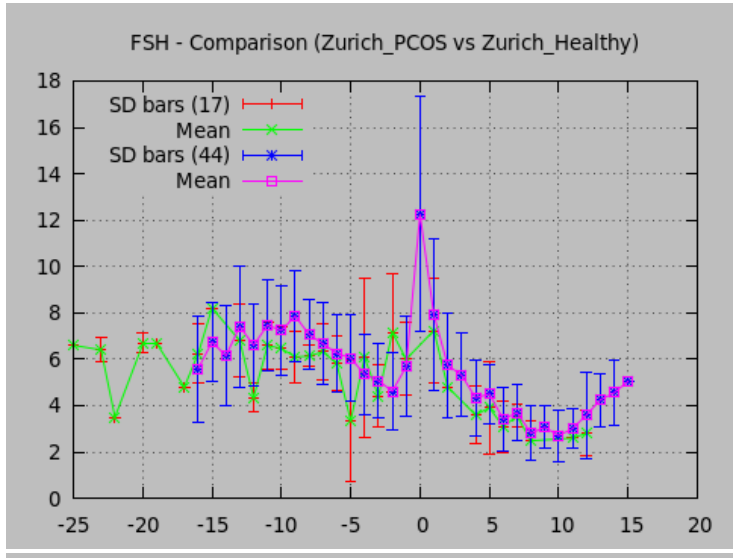
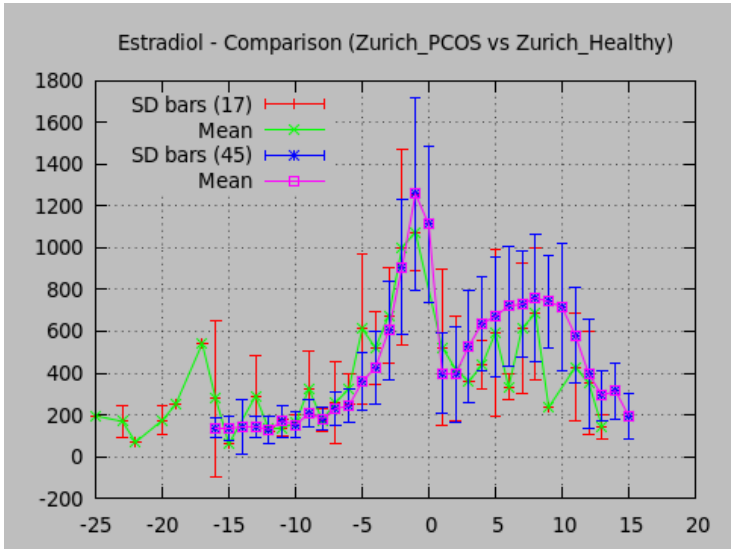
Untreated cycles: healthy women

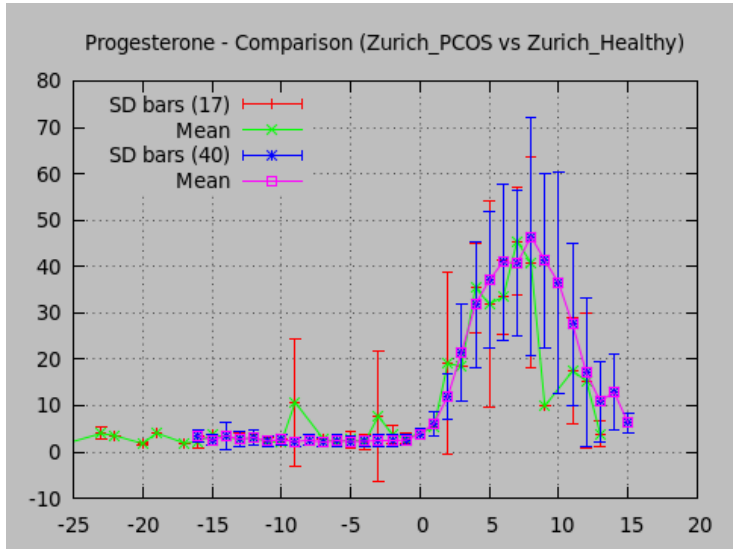


Untreated cycles: women with PCOS

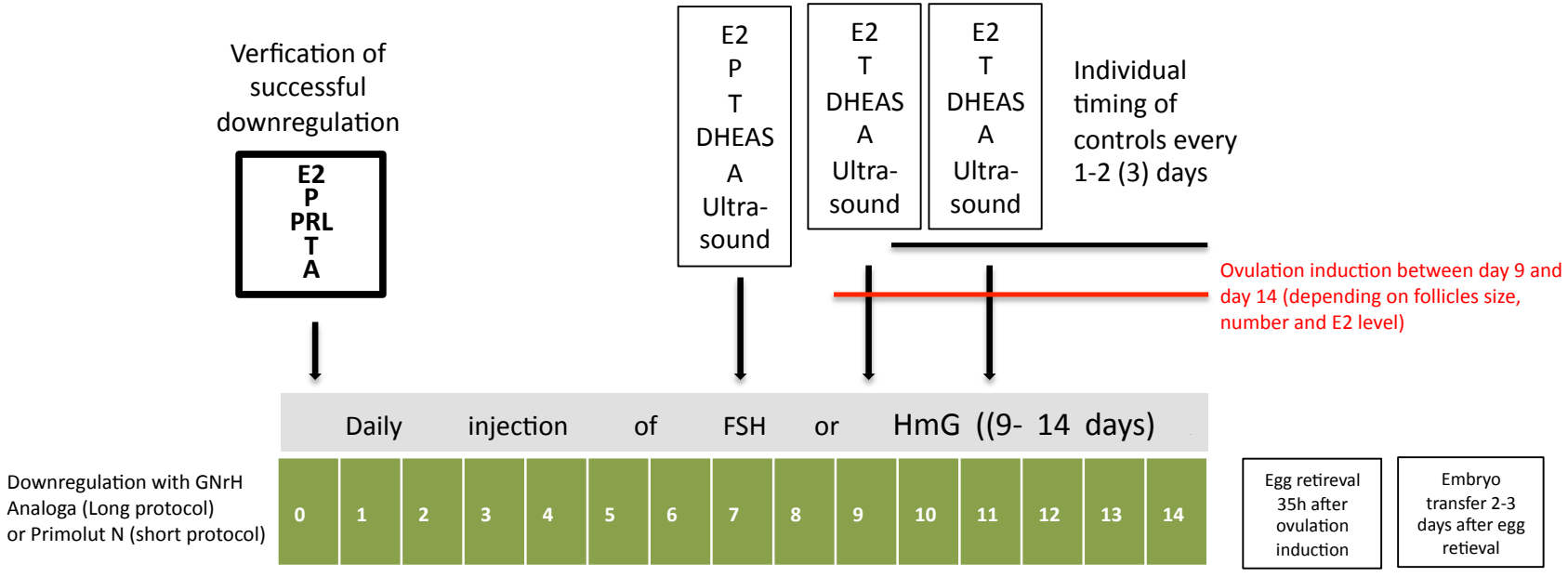








Treatment protocol data



							Ovar rechts							Ovar links						
GnRHa	hMG/ FSH	Tag	Datum	BT	E2 pmol/L	P4 nmol/L	< 10	10 11	12 13	14 15	16 17	18 19	≥ 20	< 10	10 11	12 13	14 15	16 17	18 19	≥ 20
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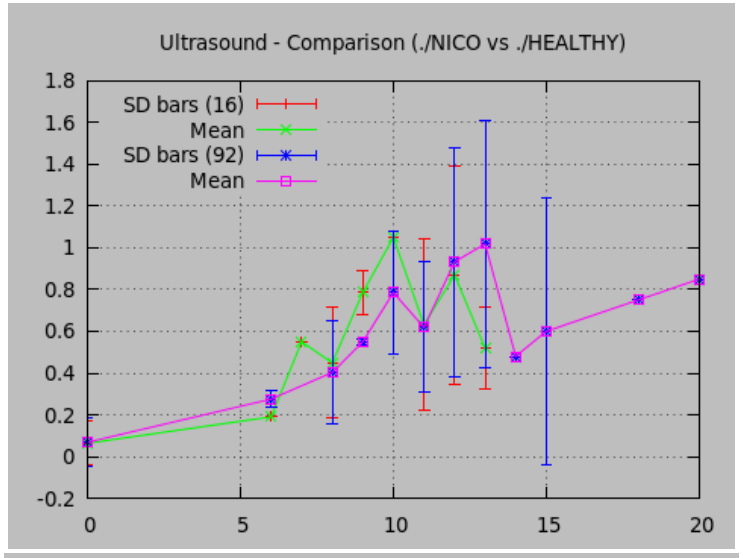
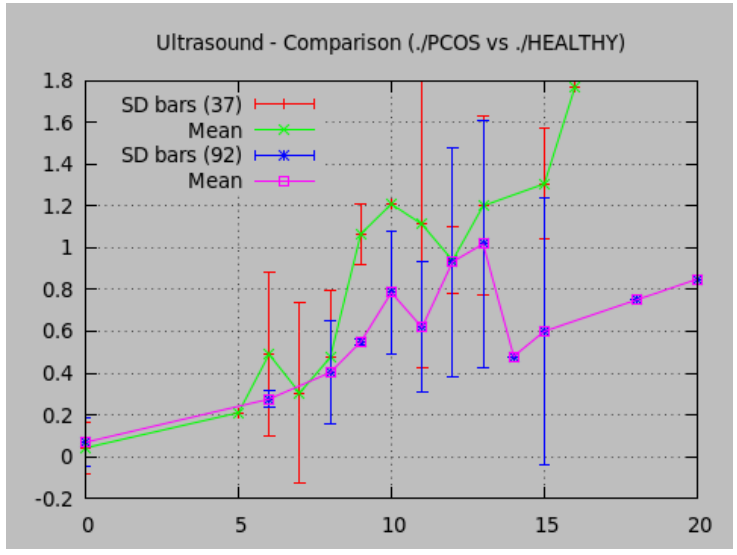
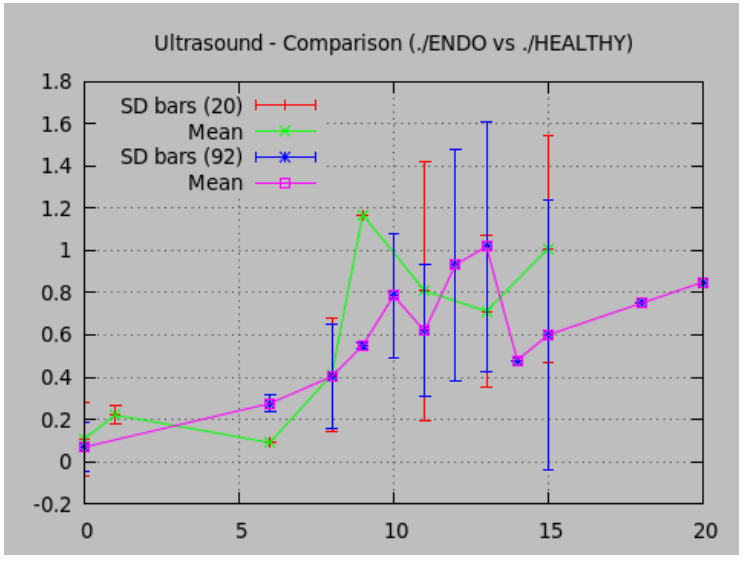
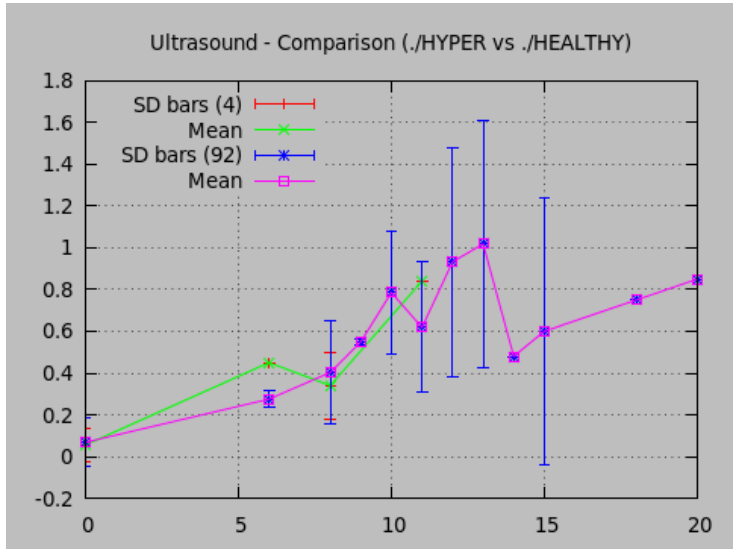
.																				
.																				
1	225	Fr	07.06.13	8	2841		4	1	1					5	1	1				
1	225	Sa	08.06.13	9																
1	225	So	09.06.13	10																
1	225	Mo	10.06.13	11	6062		2		1		1	1		2	3	5	3	3		

Treatment cycle: ultrasound measurements

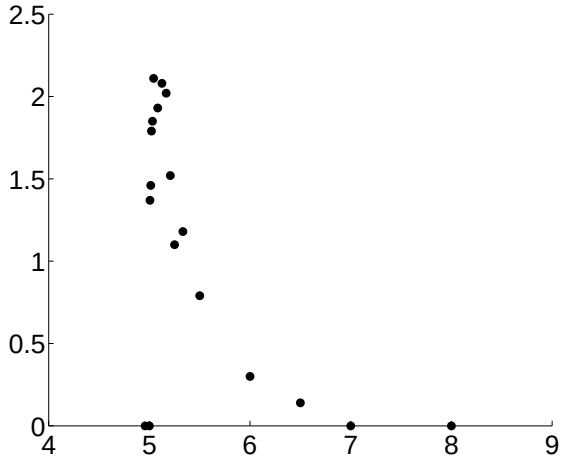




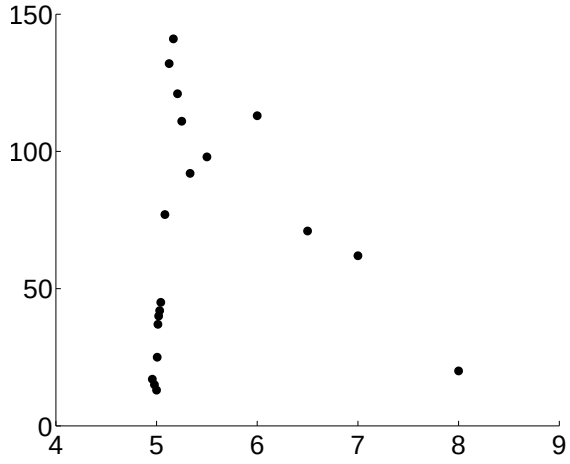




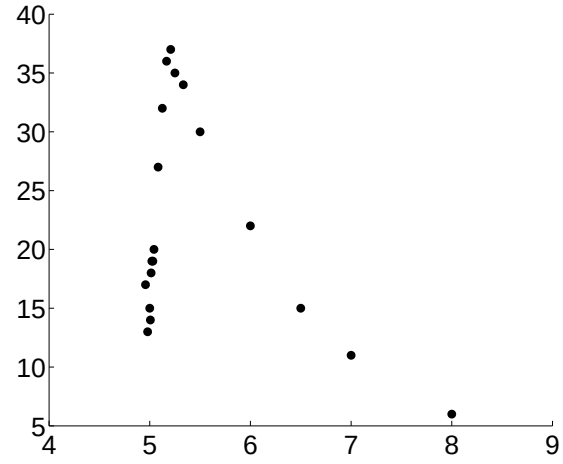
Drug data: single dose nafarelin



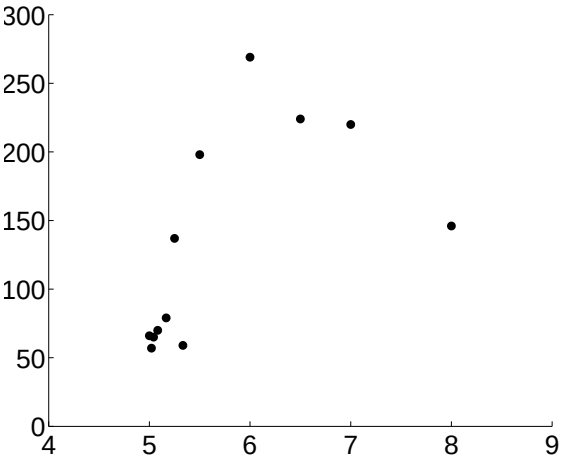
nafarelin



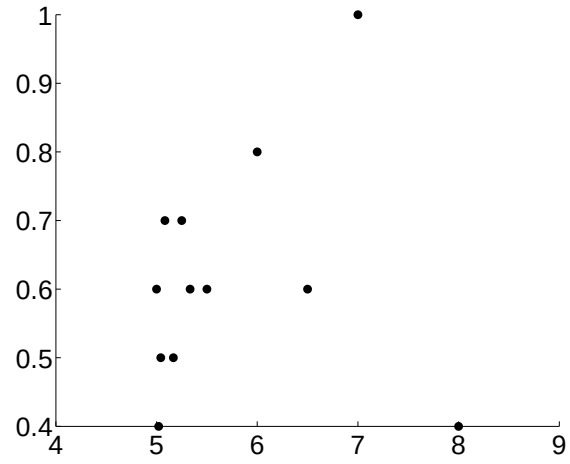
LH



FSH



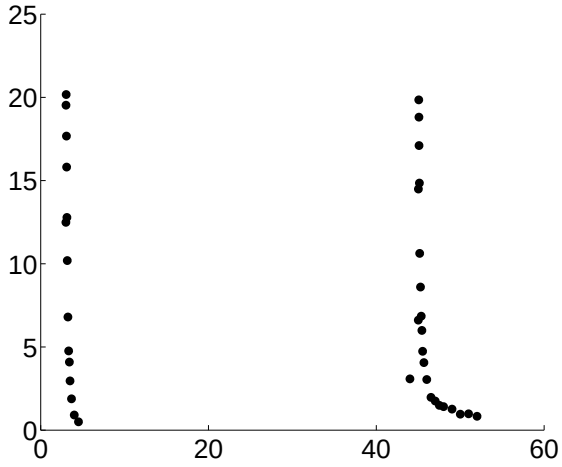
E2



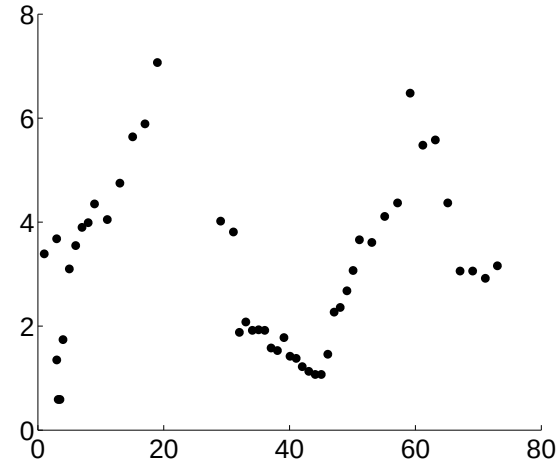
P4

GnRH-Agonist: activation of GnRH receptor resulting in (initially) increased secretion of FSH and LH, followed by a drop in gonadotropin secretion caused by receptor downregulation

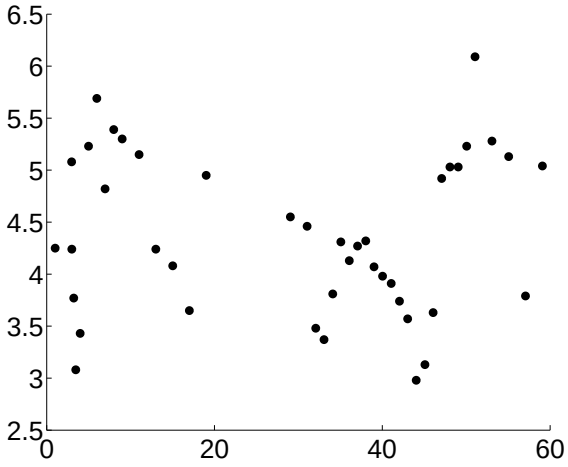
Drug data: single and multiple dose cetrorelix



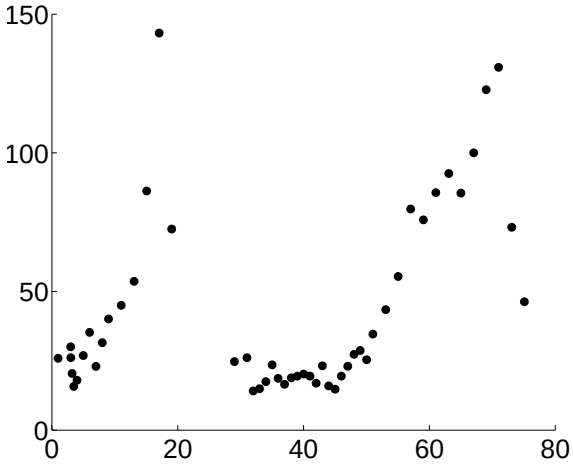
cetrorelix



LH



FSH



E2

GnRH-Antagonist: competitive and reversible binding to GnRH receptors, immediate drop in gonadotropin secretion

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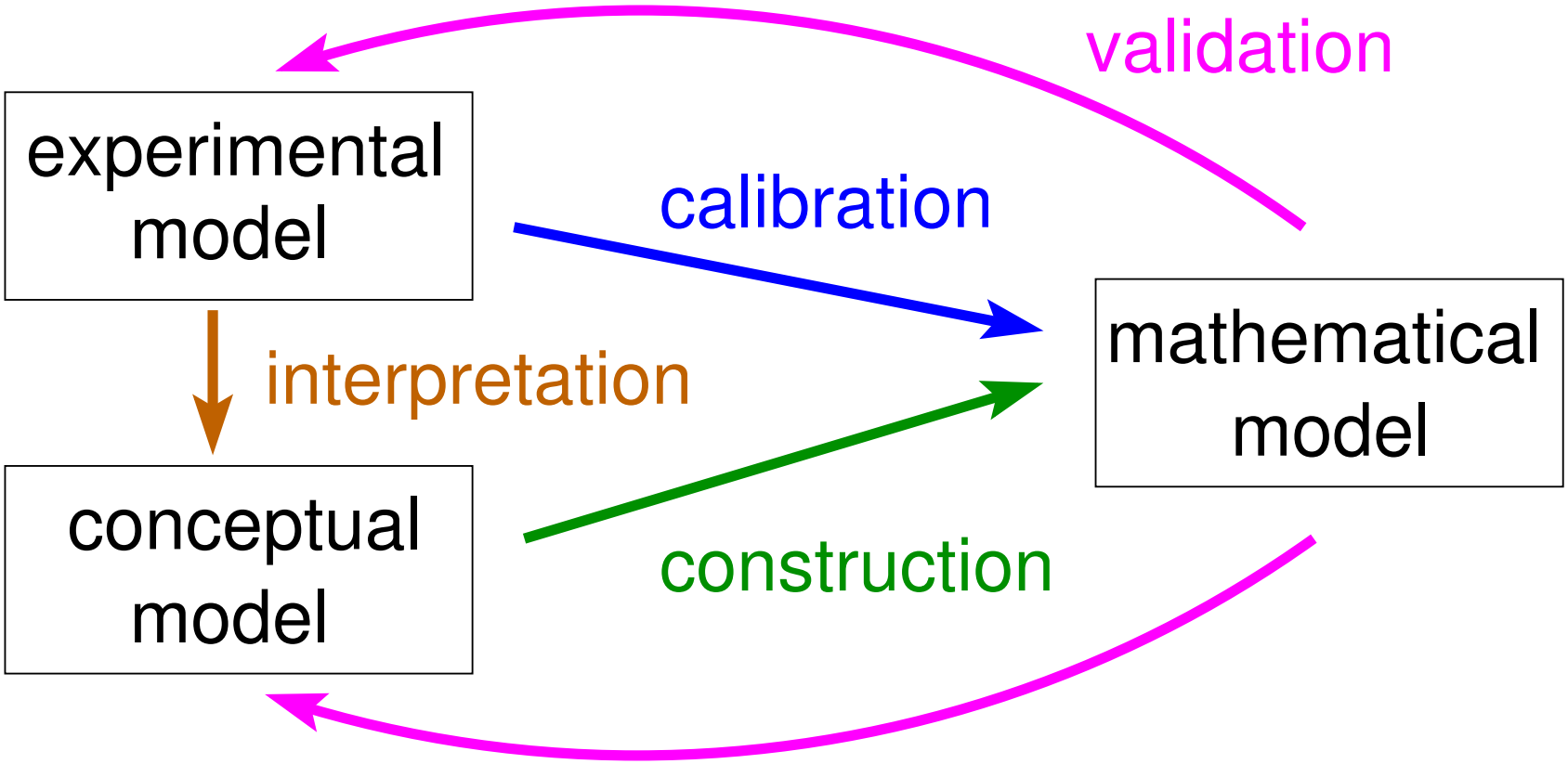
Modelling


validation
experimental model
calibration
mathematical model
interpretation
conceptual model
construction

Difficulties and limitations

"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

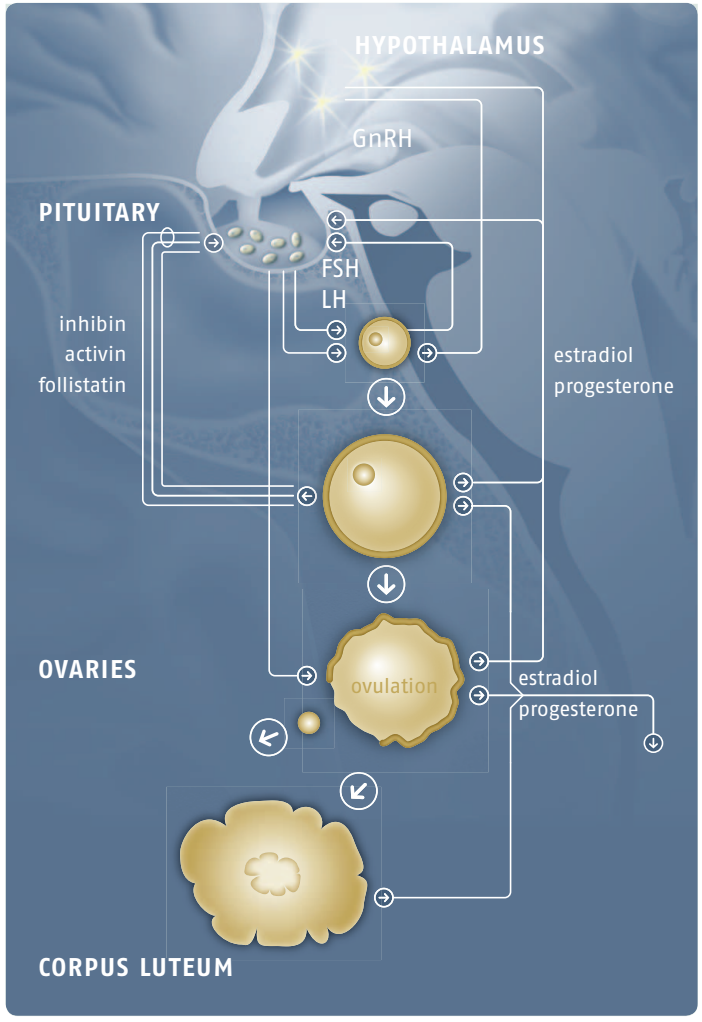
Studying complex, non-linear systems often requires advanced analytical and numerical **mathematical tools** !

Conceptual model

Compartments: blood, ovaries, uterus, pituitary, hypothalamus

Components:

- Estradiol
- Progesterone
- Inhibin A and B
- LH + receptor binding
- FSH + receptor binding
- GnRH + receptor binding
- 6 follicular stages
- 6 luteal stages (corpus luteum)



Mathematical model

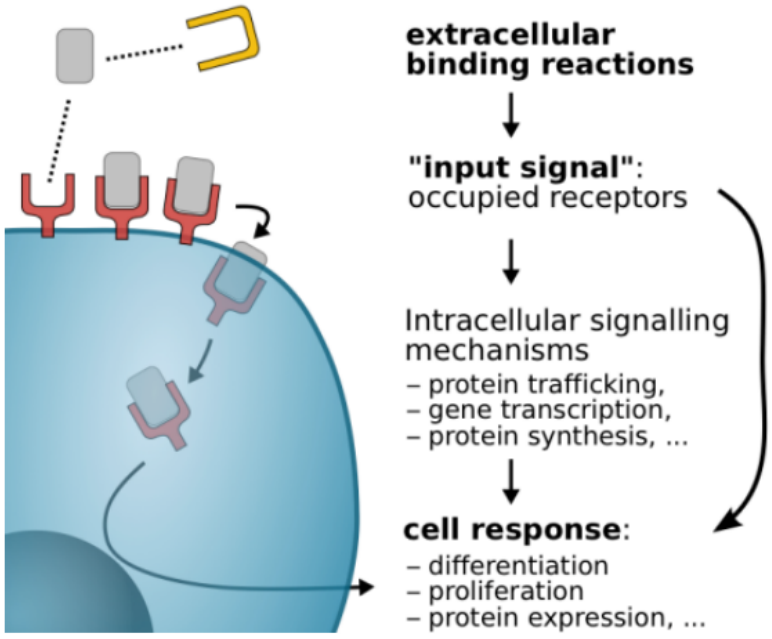
Mass action kinetics

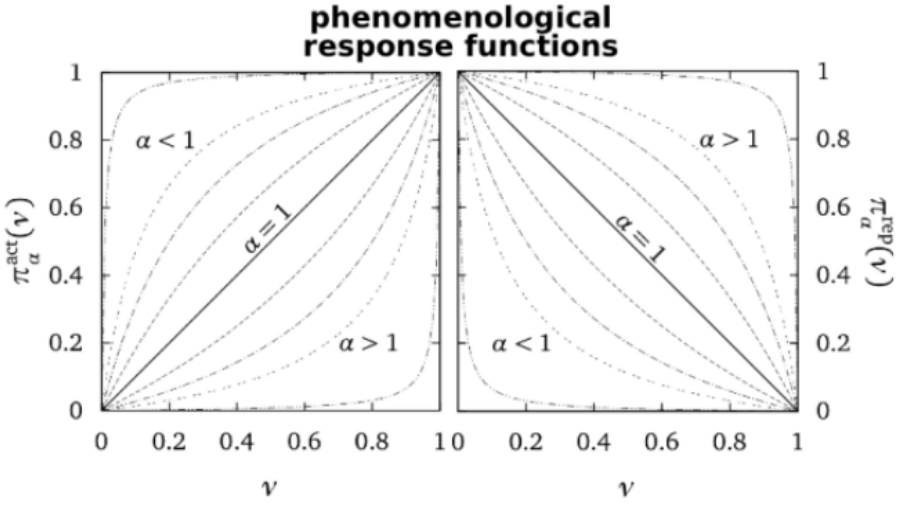
e.g. receptor-ligand interactions

$R + L \rightleftharpoons RL$

Hill kinetics:

stimulatory/inhibitory effects

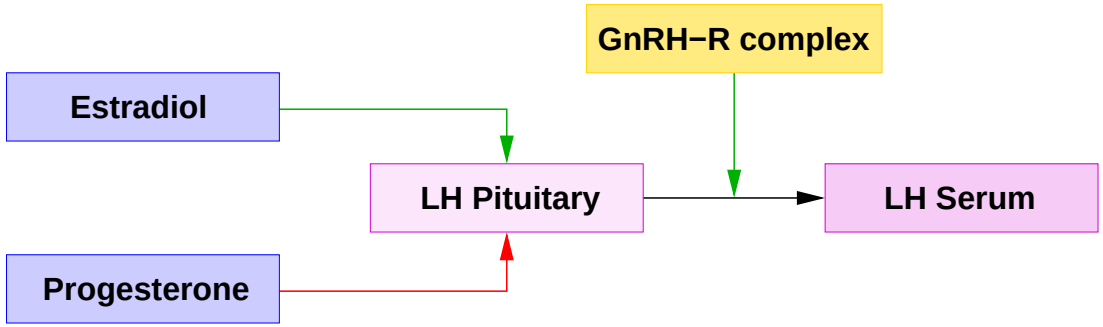




[Pivonka et al., INTECH (2012)]

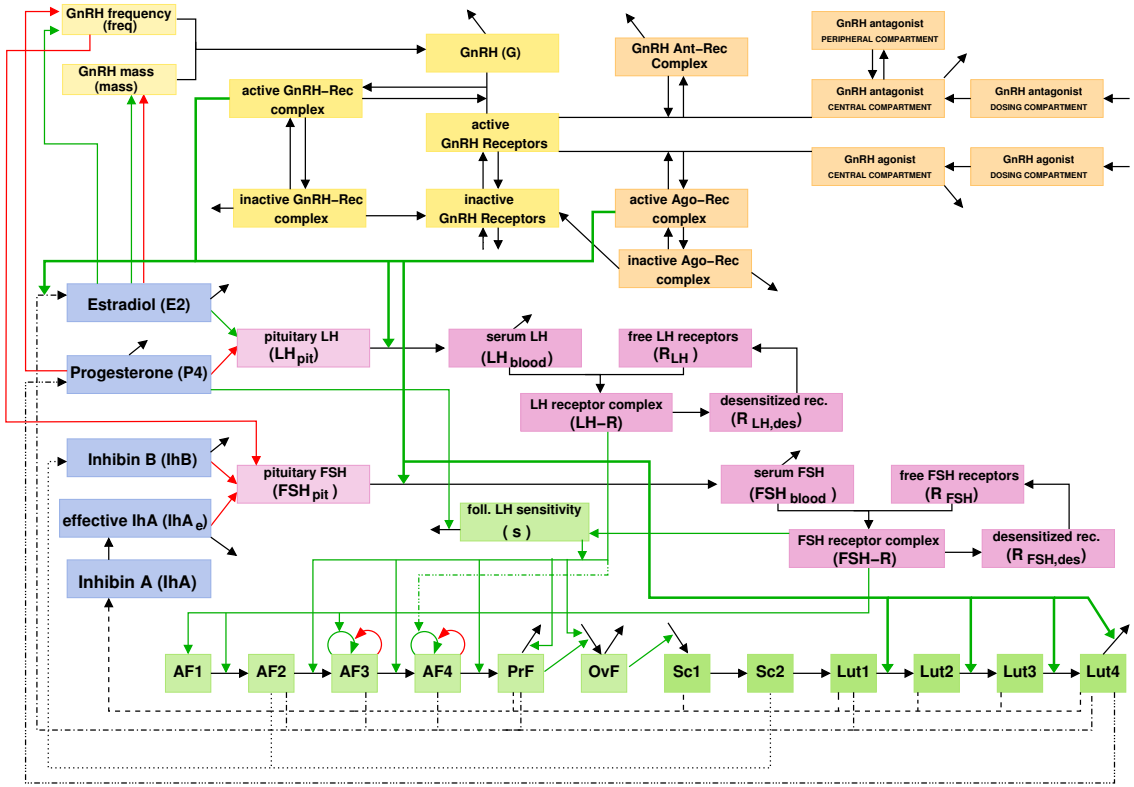
$$y'(t) = f(y(t), u(t), \theta, t), \qquad y(t=0) = y_0$$

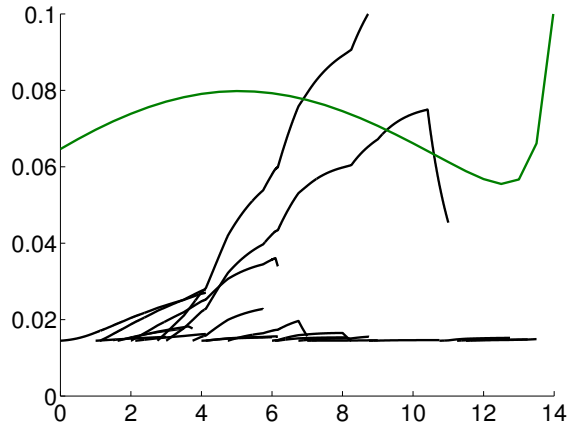
Example: Modelling of LH



$$
\begin{aligned}
Syn_{LH}(t) &= (b_{Syn_{LH}} + m_{E2} \cdot H^{+}(E2, T_{E2}; n_{E2})) \cdot H^{-}(P4, T_{P4}; n_{P4}) \\
Rel_{LH}(t) &= (b_{Rel_{LH}} + m_{GnRH\text{-}R} \cdot H^{+}(GnRH\text{-}R, T_{GnRH\text{-}R}, n_{GnRH\text{-}R})) \cdot LH_{Pit}(t) \\
\frac{d}{dt} LH_{Pit}(t) &= Syn_{LH}(t) - Rel_{LH}(t) \\
\frac{d}{dt} LH_{blood}(t) &= \frac{1}{V_{blood}} Rel_{LH}(t) - k_{on} \cdot LH_{blood} \cdot R_{LH} - c \cdot LH_{blood}
\end{aligned}
$$

Current models





GynCycle: 33(+8) ODEs, 114 parameters

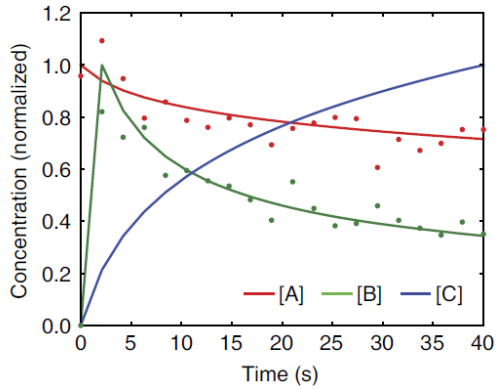
[Röblitz et al. (2013)]

(stochastic) submodel for follicular development

Parameter estimation

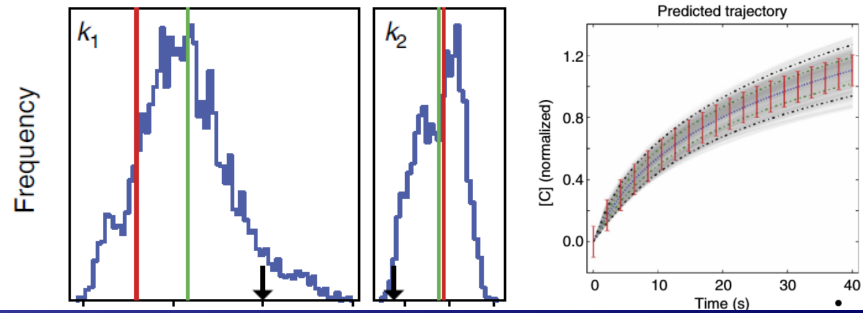
Model: $y(t,\theta) = (y_1(t,\theta), \ldots, y_n(t,\theta)) \in \mathbb{R}^n$
Parameters: $\theta = (\theta_1, ..., \theta_q) \in \mathbb{R}^q$
Data: $z_{kl} \approx y_k(t_l,\theta),\ k = 1, \ldots, n,\ l = 1, \ldots, m_k$
(i) **direct minimisation** of least squares error

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



$\Rightarrow$ ill-posed problem
(ii) computation of joint **probability distributions** according to Bayes' theorem $P(\theta|z) \propto P(z|\theta)P(\theta)$ with likelihood

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



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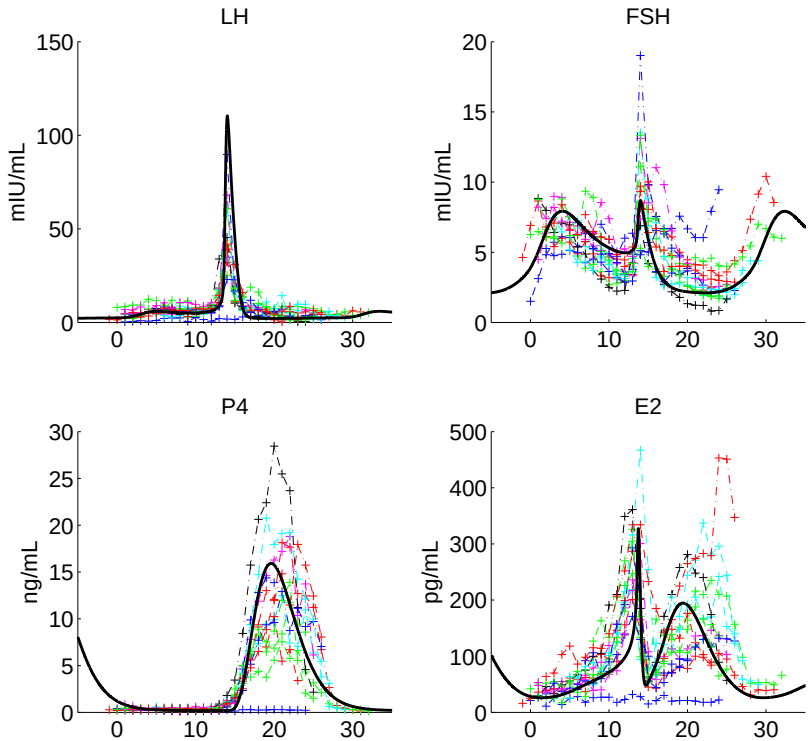
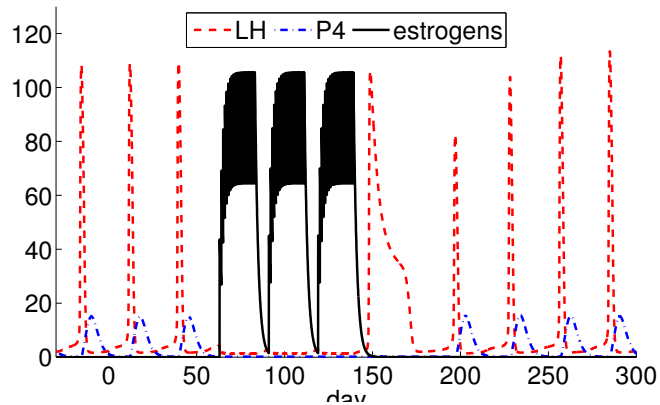
Generic model for normal cycles

Single parametrization from **real patient normal cycle data**.

- normal cycle simulation



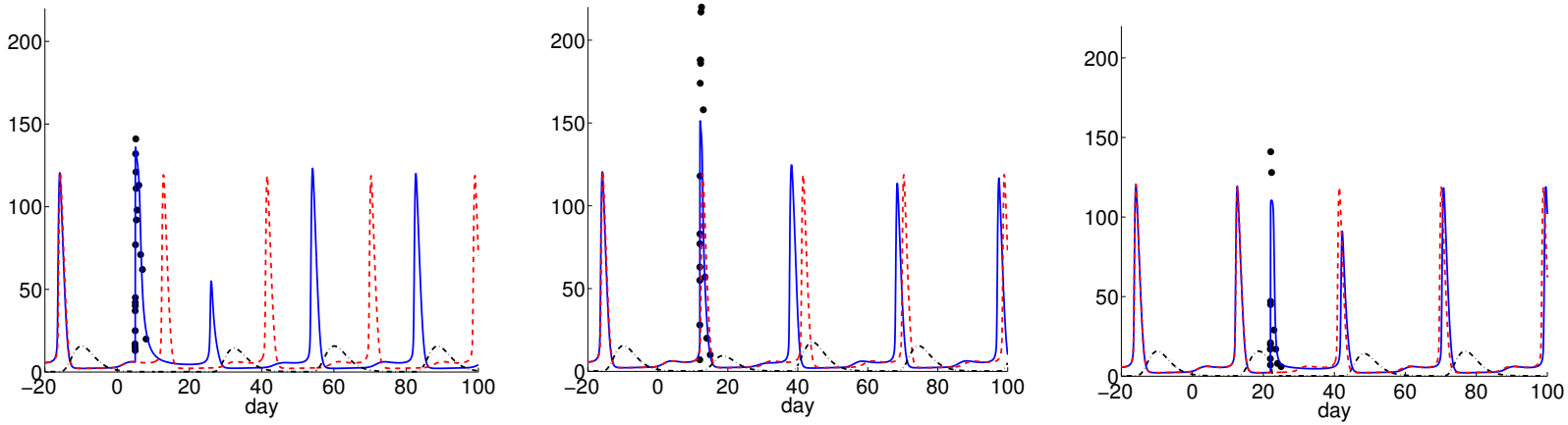
- simulating the effect of birth control pills



Validation of generic model

Validate generic model with **real patient treatment data**.

- single dose agonist (nafarelin)



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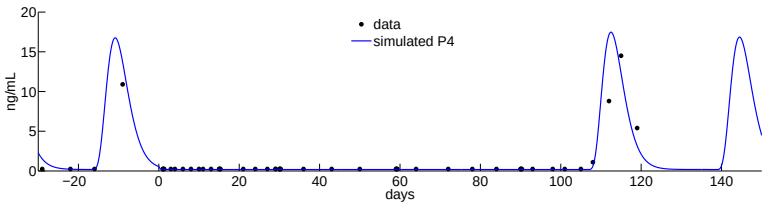
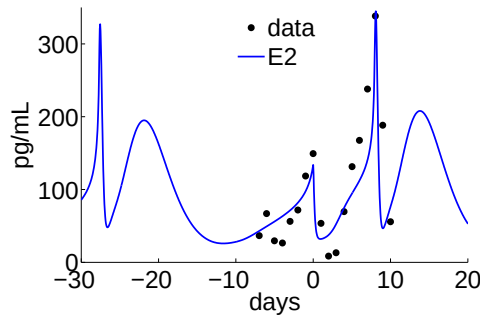


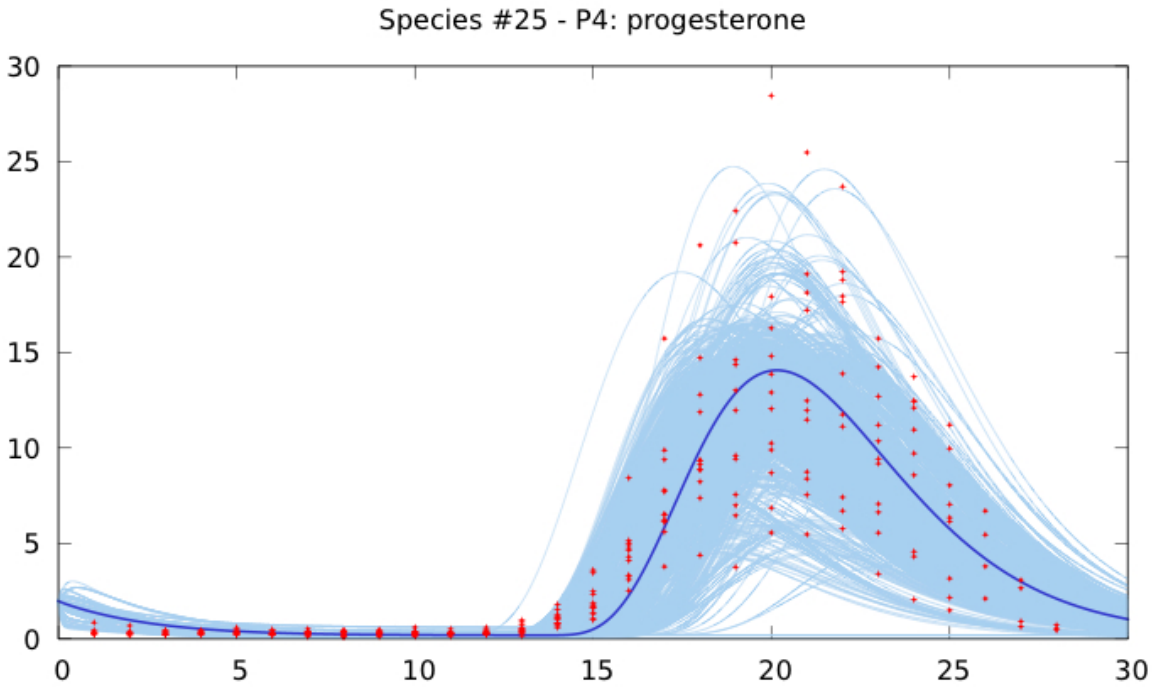
[Röblitz et al. (2013)]

- single dose antagonist (cetrorelix)



Virtual patients

Generate model instances (parametrizations) compatible with **real patient data** for the normal cycle [Mancini et al. (2014)].



Real Patient

(a) Medical level

Virtual patient

(b) Computation level

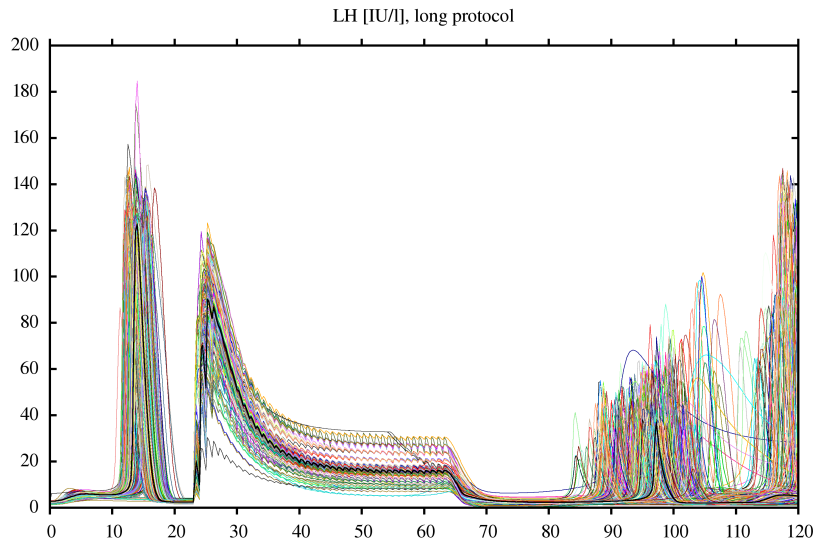
finite set of biologically admissable parameter sets

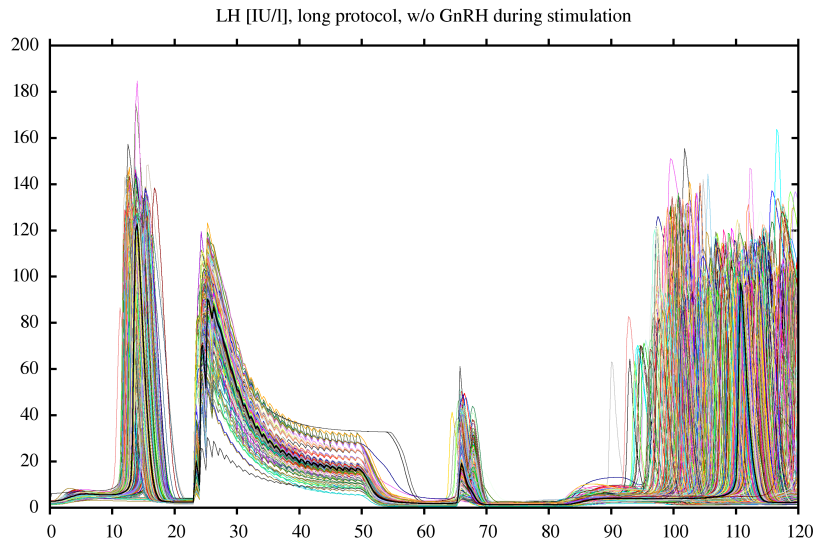
offline $\longrightarrow$ *online*

Virtual patients

Validate virtual patient models with **real patient data** from treatment cycles.

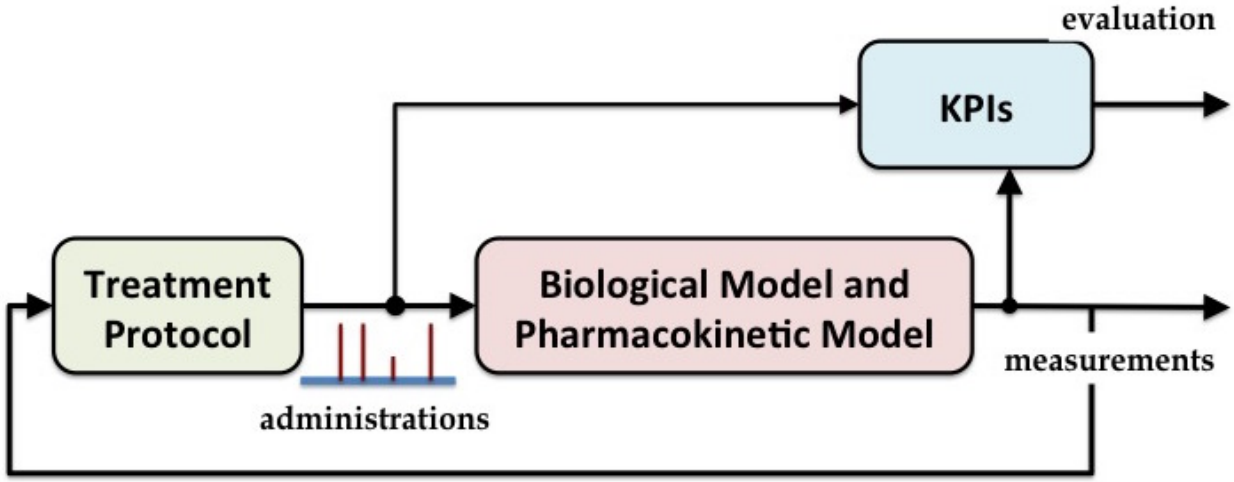
Long protocol: downregulation cycle days 23 to 50 with Triptoreline, then 14 days stimulation, finally Ovitrelle (drug database!)





$\longrightarrow$ model refinement $\longrightarrow$

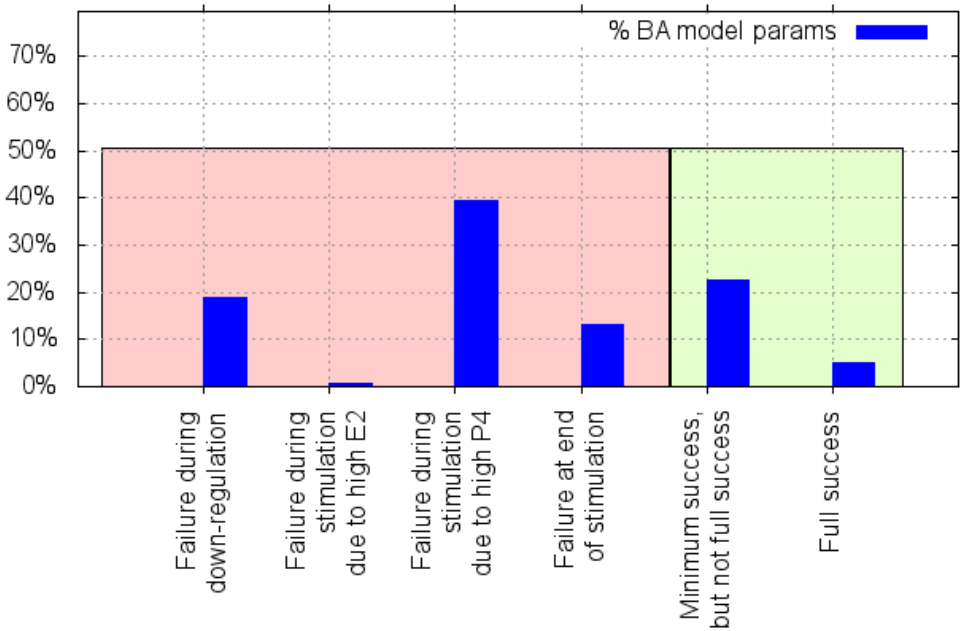
Model-based treatment verification & design

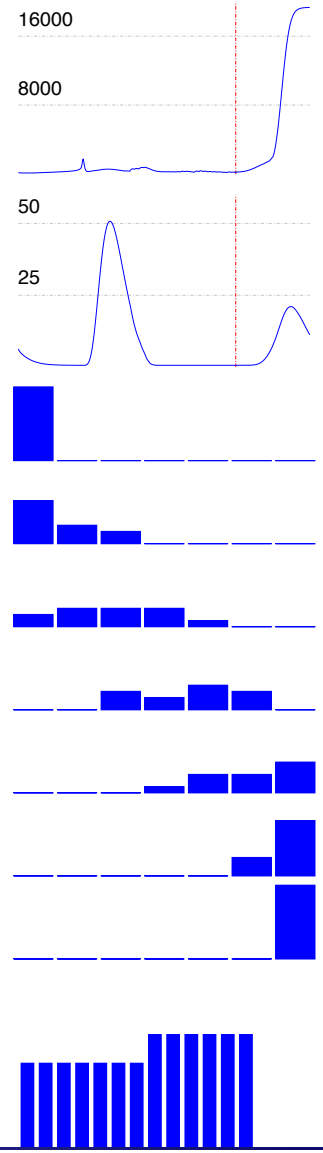


- **treatment verification**
  the treatment model (closed loop system) reaches a state in which some desired property is satisfied (treatment goals)
- **treatment design**
  finding values for treatment parameters (type, dose and time of drug) that optimize some key performance indicators (KPIs): E2 levels, number and size of follicles, total amount of drug

Model-based treatment verification

Verify that a given treatment protocol reaches its goal for the largest possible number of (virtual) patients → evaluate success rate





Model-based treatment design

reference treatment (UZH)

day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
action	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Decapeptyl 0.1mg: 28 full doses = 2.8 mg

synthesised generic treatment (start day: 25)

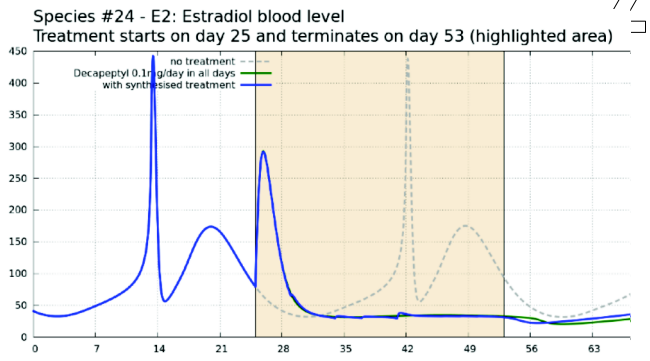
day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
action	■				■	■				■			■				■			■	■			■			■			

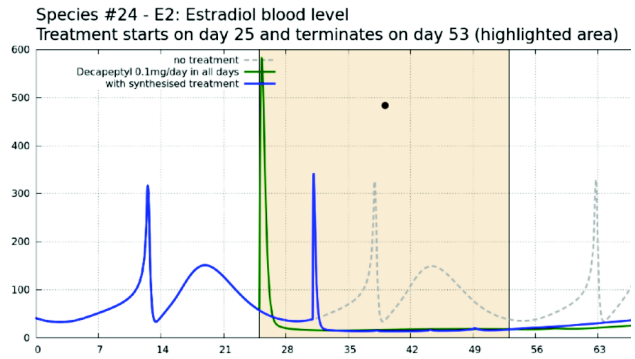
Decapeptyl 0.1mg: 10 half doses +1 full dose = 0.6 mg

synthesised individualised treatment (start day: 25)

day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
action							■		■					■		■				■					■			

Decapeptyl 0.1mg: 6 half doses = 0.3 mg





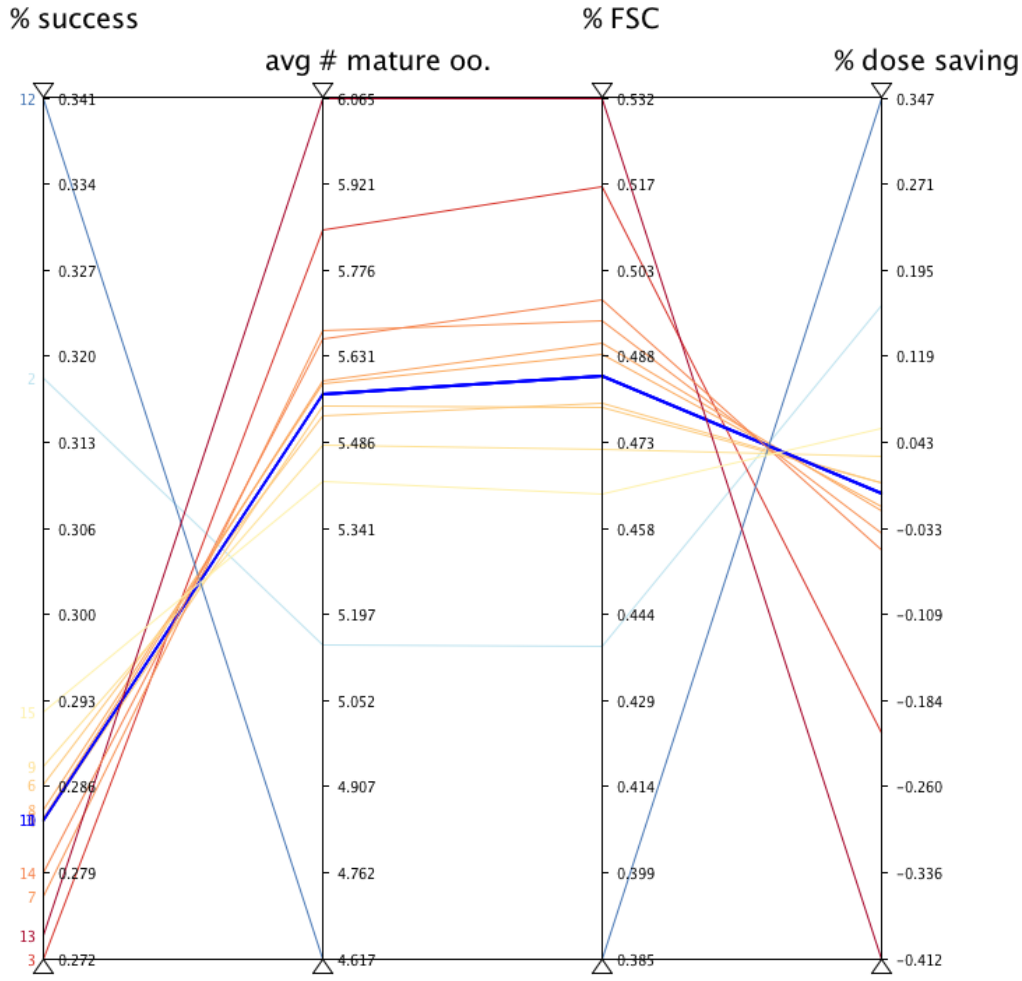
Synthesised generic down-regulation treatments require 40% of the injections and <25% of the overall Decapeptyl amount required by reference treatment. Individualised treatments even lighter, still achieving clinical goals!

Model-based treatment design

incremental change of treatment parameters:

- age class
- AMH level
- AFC class
- dose of stimulation drug

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

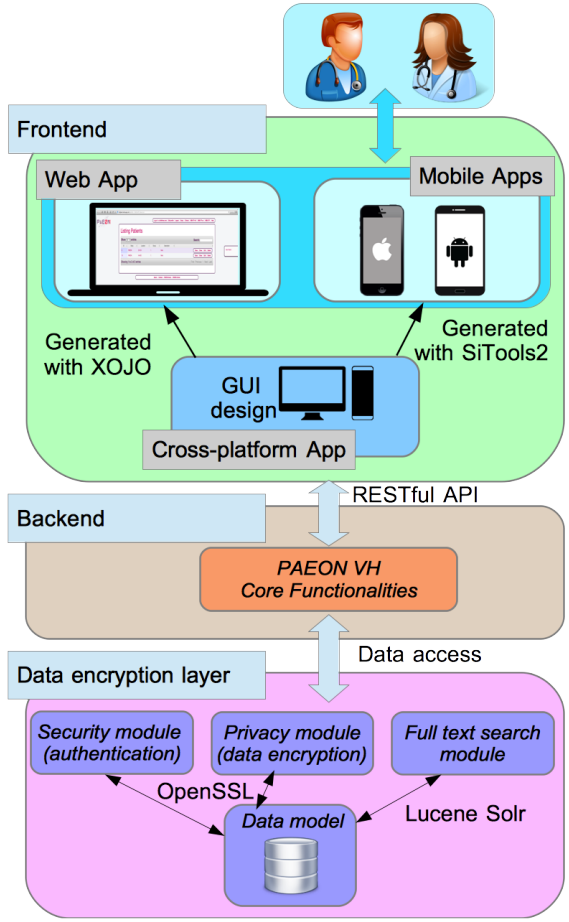


Outline

1. Motivation
2. Experimental data *in vivo*
3. Model development for the human menstrual cycle
4. Results of *in silico* experiments
5. Summary and outlook

Future Work

- improve the model
- improve the mathematical algorithms
- perform model-based comparison of treatment protocols
- extend approach to endocrinological diseases



Take home message

Mathematical modelling

- bridges the gap between conceptual models and experimental validation
- provides new information about potential mechanisms
- can assist in formulating hypotheses and finding experiments
- enables design of optimal treatment strategies in terms of parameter and sensitivity studies

$\rightarrow$ goes **beyond pure data-based approaches**

$\rightarrow$ foundation of **Computational Systems Biology**

Communication and collaboration between experimental and theoretical groups requires mutual understanding of research methodologies!

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Contact: susanna.roeblitz@zib.de

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