# Model-based treatment planning in reproductive medicine


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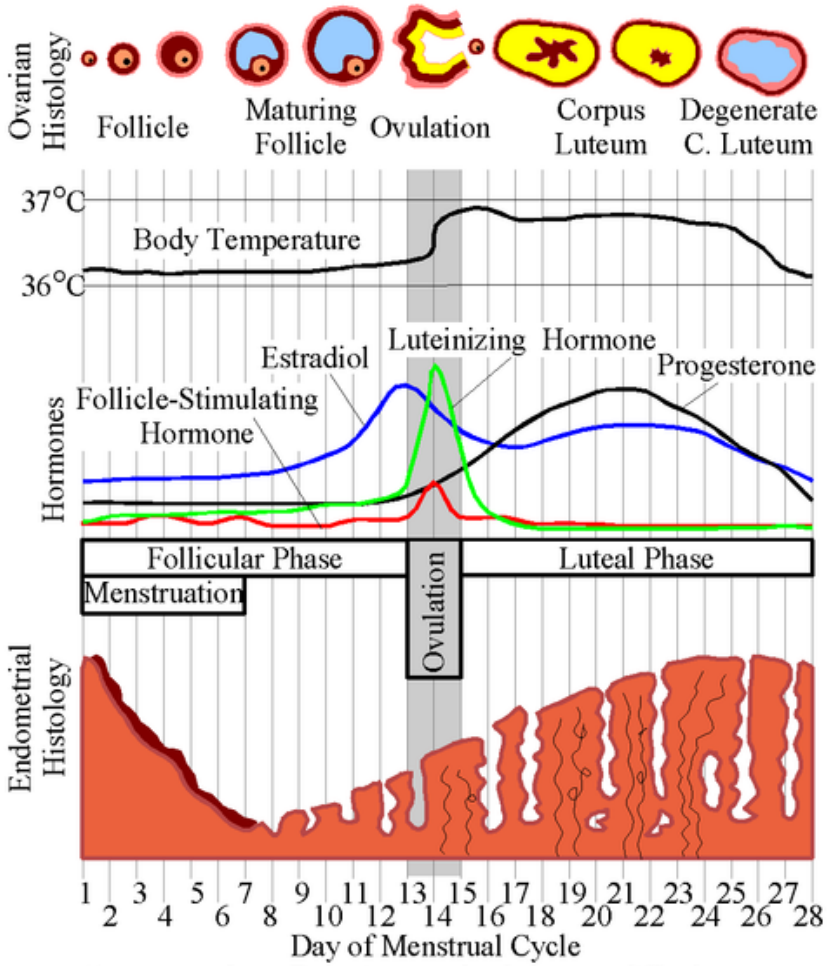
# Motivation

# 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

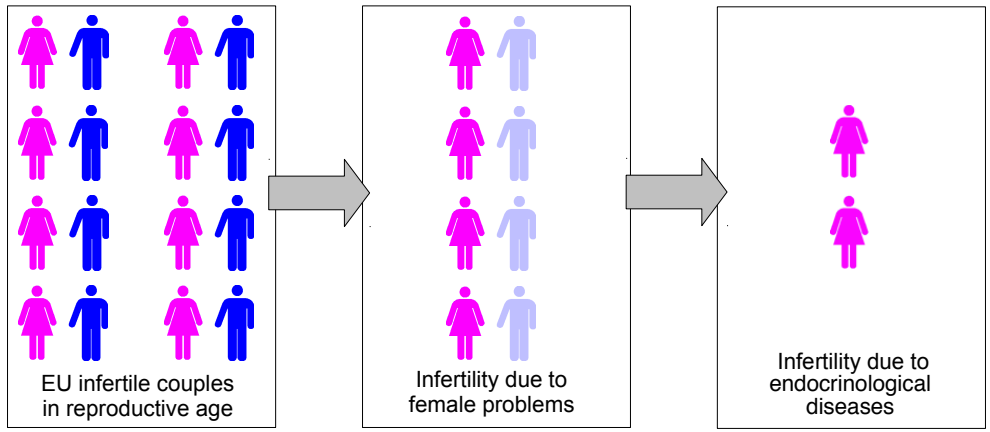
- follicle development
- ovulation and fertilization
- formation of corpus luteum
- embryonic attachment and growth in the uterus

$\Rightarrow$ coordination between neural and endocrine systems

# Endocrine disorders

Unwanted childlessness among couples in Europe: 12-15%

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

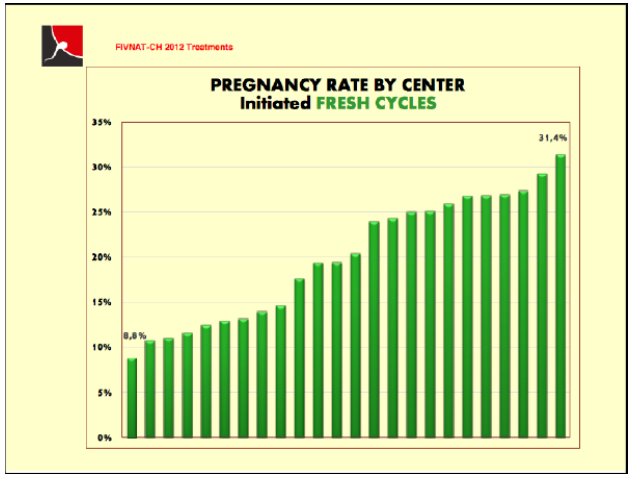



- **PCOS** (Polyzystic Ovarian Syndrom):
  main cause for hyperandrogenism, leading to cycle disorders and infertility (4-12% of women in reproductive age)
- **Endometriosis** (uterine lining outside uterus):
  about 40% of women at reproductive age, thereof 30-50% infertility
- **Hyperprolactinemia**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

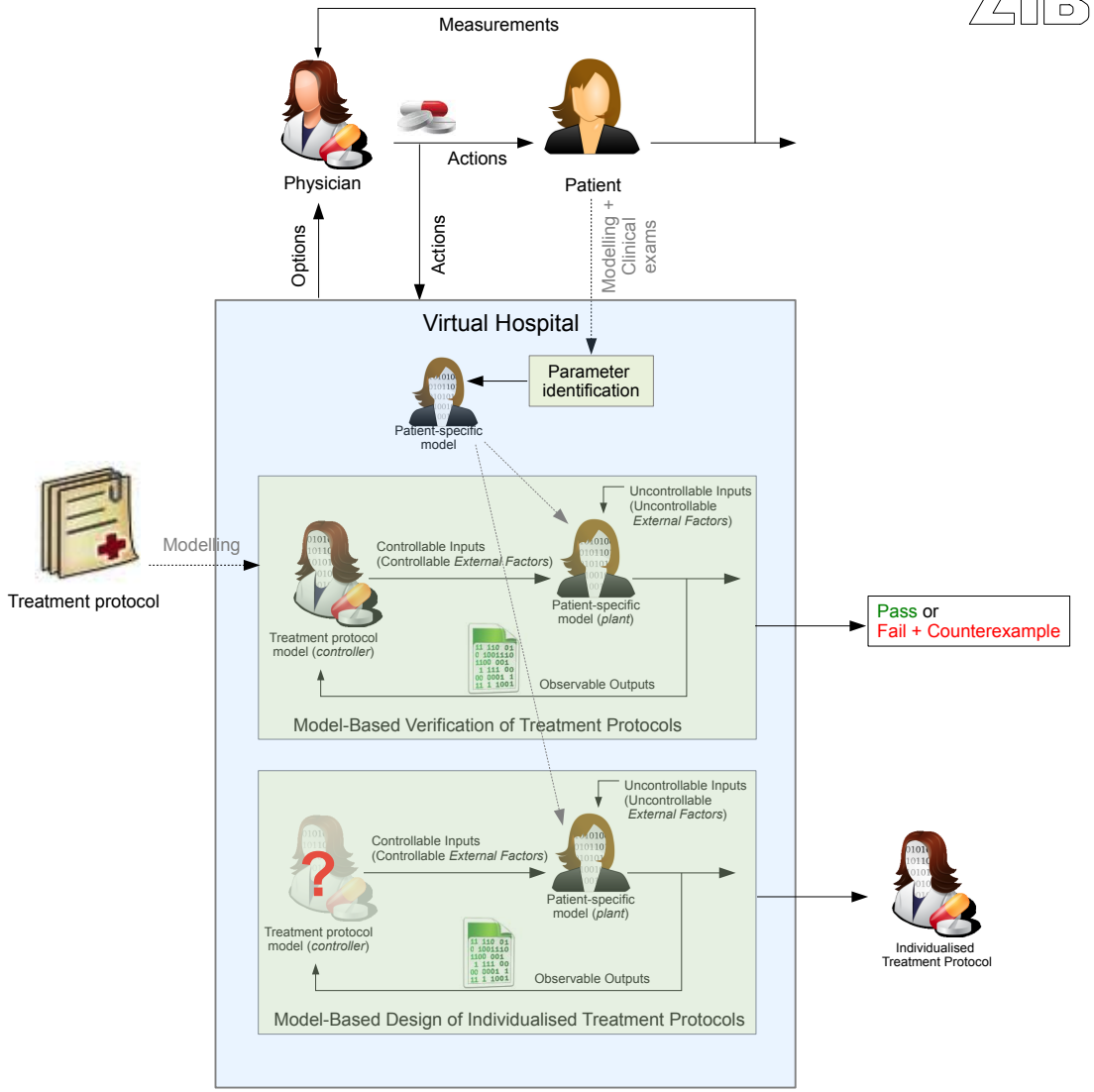
- better understanding of complex processes
- simulation and optimization of treatment strategies *in silico* (cost-saving and efficient)

# Virtual hospital

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

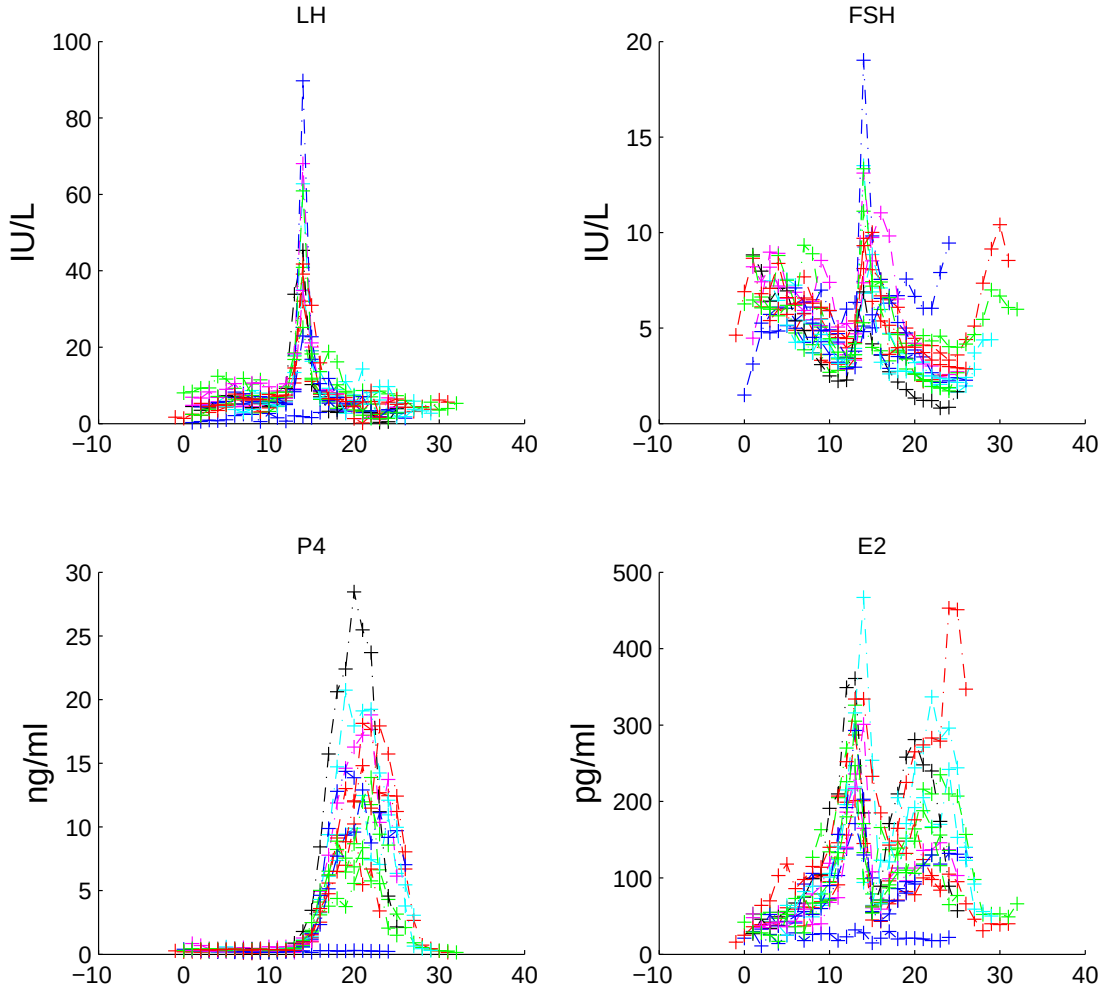
based on

- a population of virtual patients
- a virtual doctor

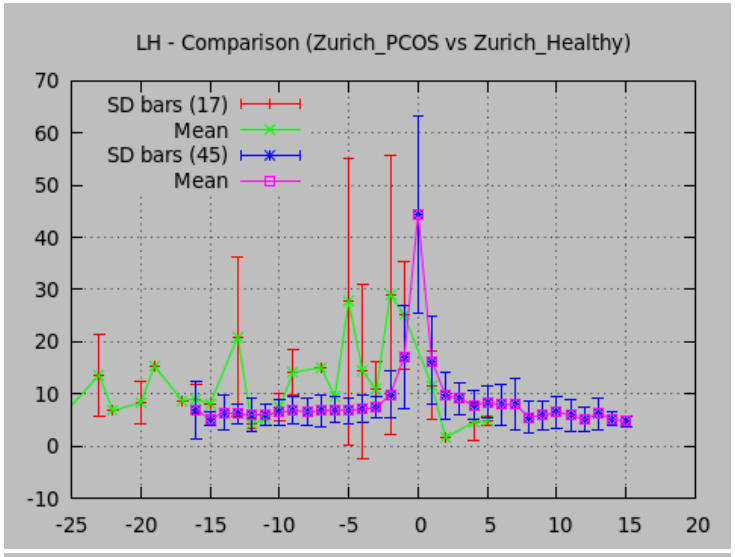


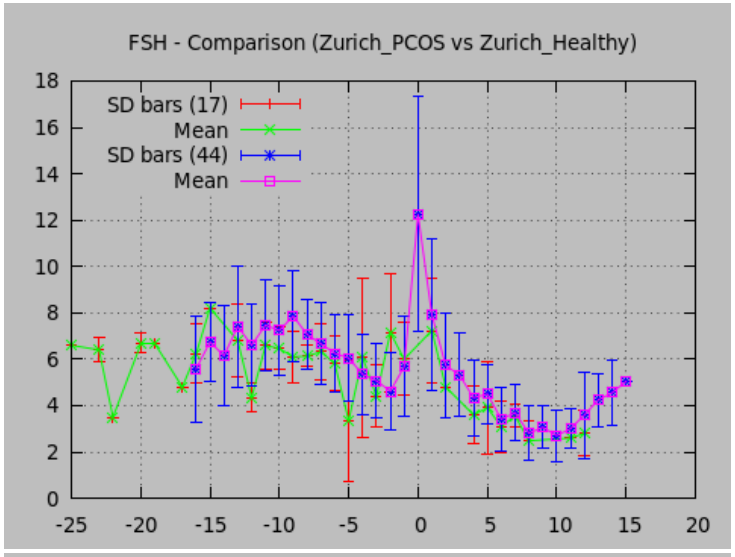
# Experimental data *in vivo*

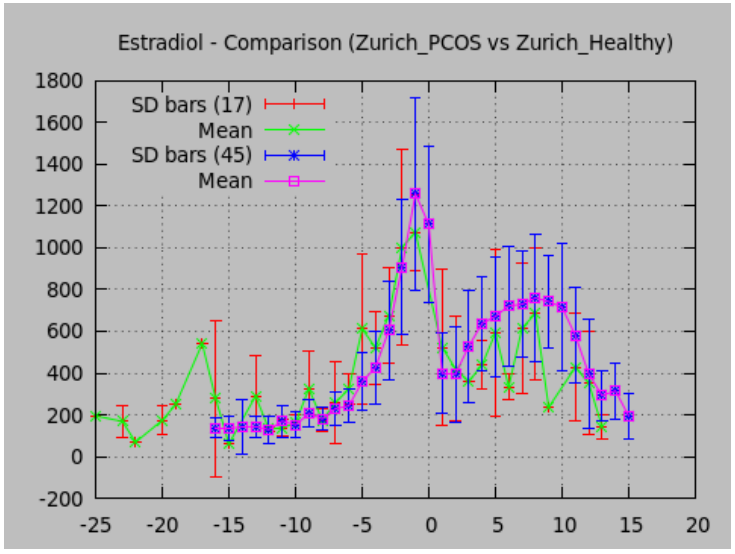
# Untreated cycles: healthy women

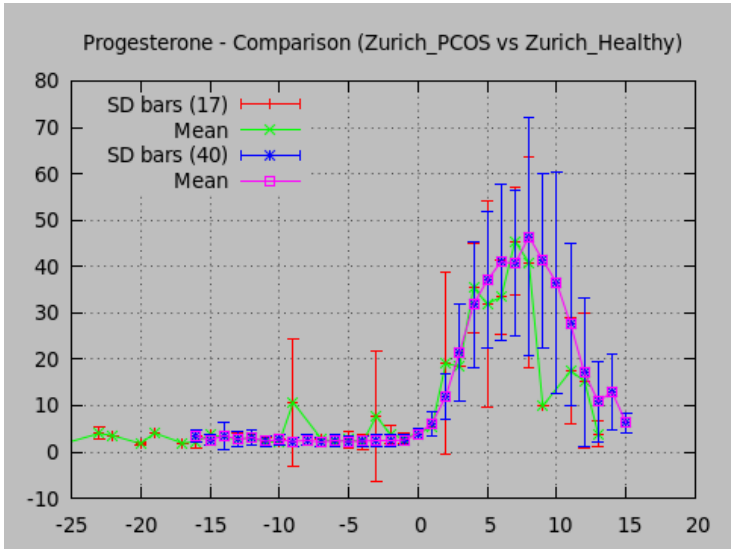


# Untreated cycles: women with PCOS

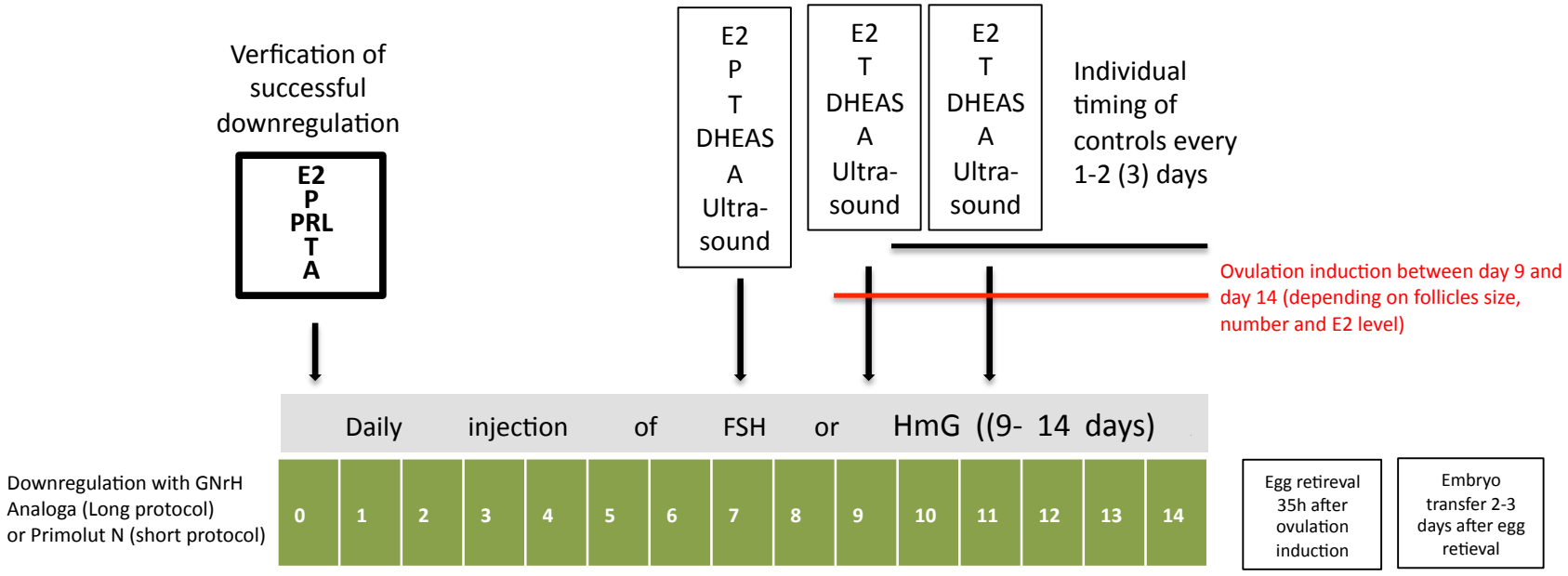


# Treatment protocol data




| | | | | | | | 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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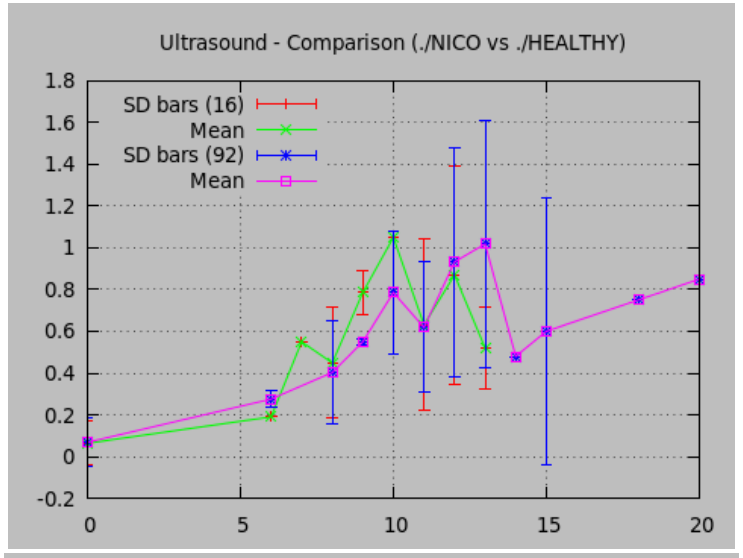
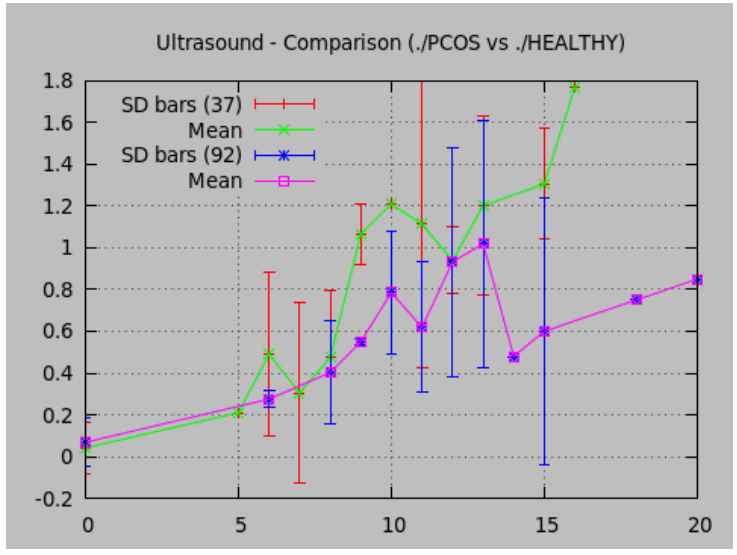
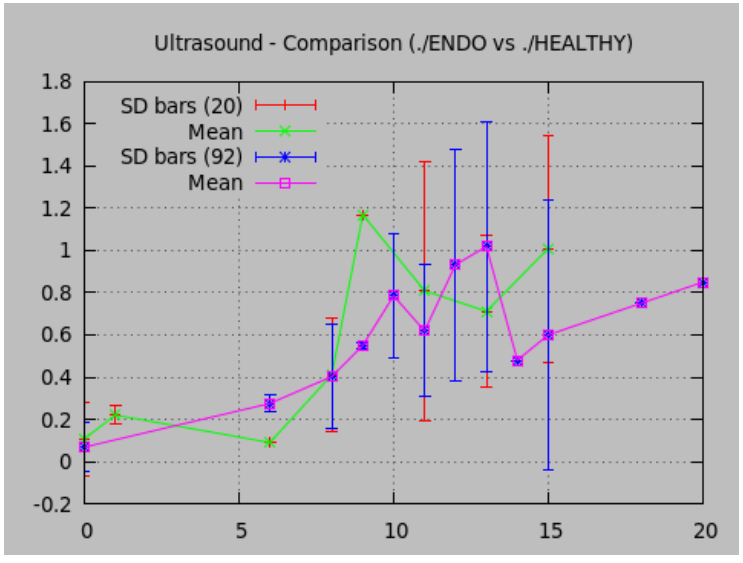
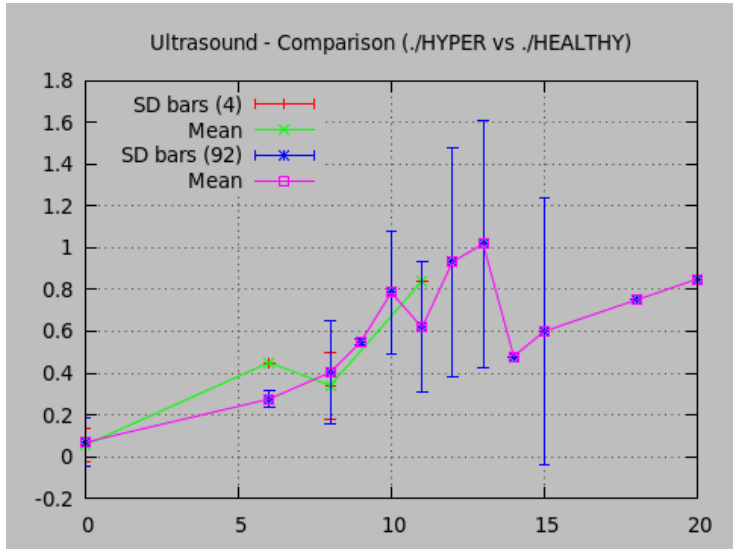
# Treatment cycle: ultrasound measurements



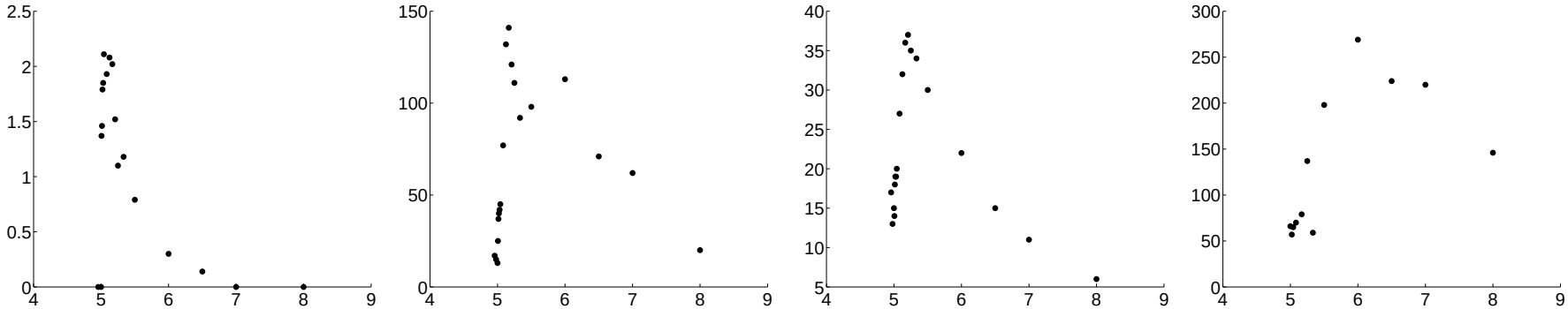



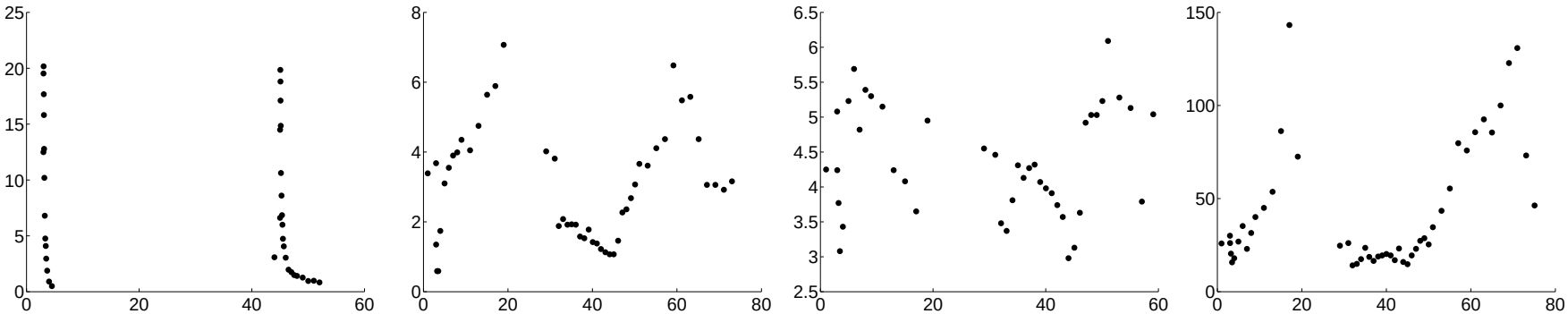



# Drug data

## Single dose Nafarelin (GnRH agonist)



## Single and multiple dose Cetrorelix (GnRH antagonist)



measurements: drug, LH, FSH, E2

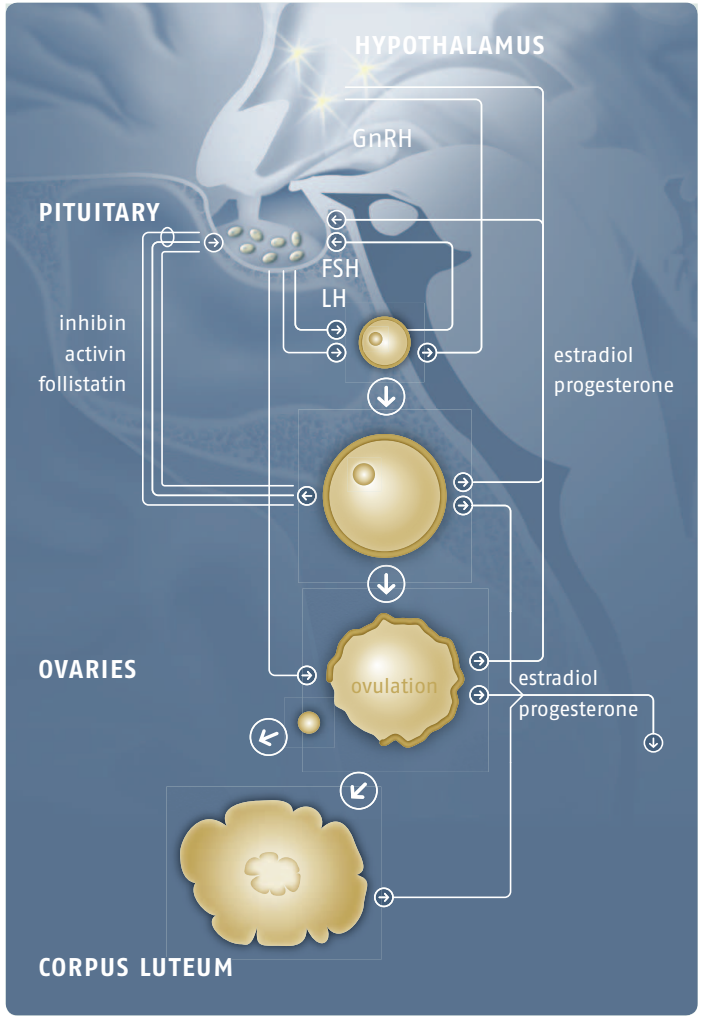
# Model development for the human menstrual cycle

# Conceptual model

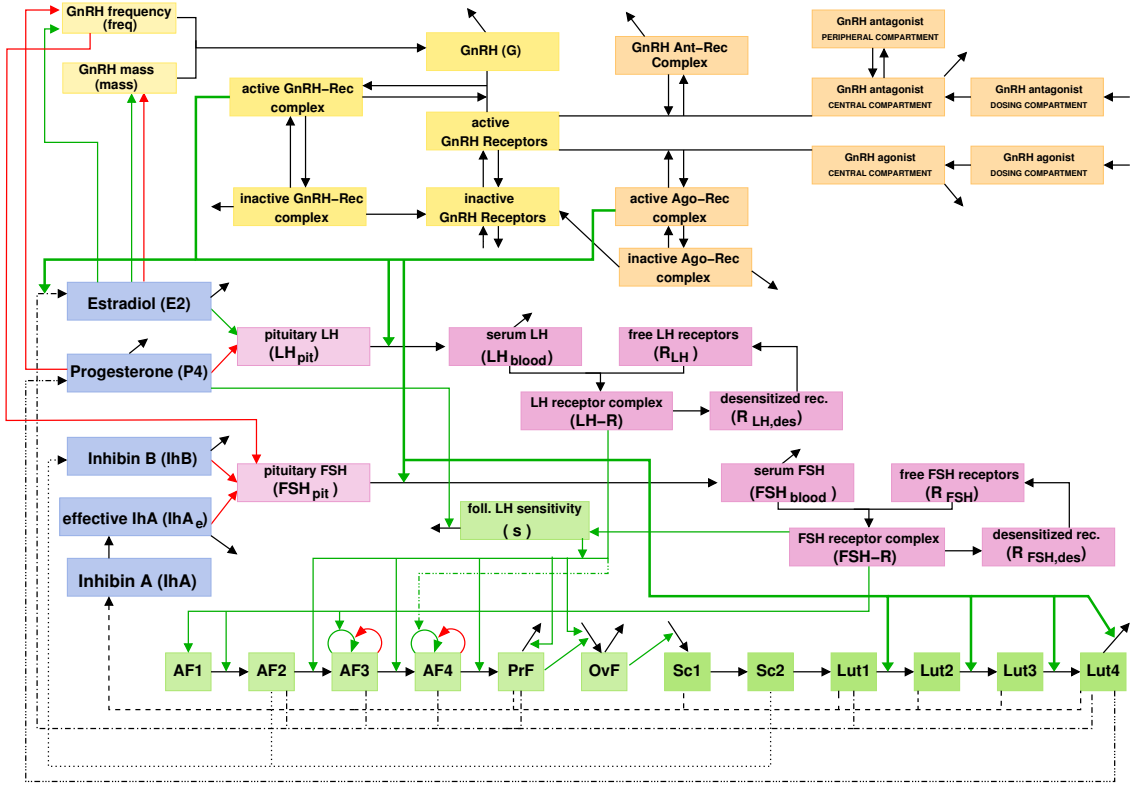
Compartments: blood, ovaries, uterus, pituitary, hypothalamus

Components:

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



# Model GynCycle




GynCycle: 33(+8) ODEs, 114 parameters [Röblitz et al. (2013)]

- a model for the idealized cycle of a healthy woman
- computation of hormone profiles and follicle development over time

# Submodel for follicular development

$x_i$: radius of follicle $i$

$$\frac{dx_i}{dt} = A(G - D), \quad i = 1, \ldots, n$$

$$A := \mu H_i^+(FSH)$$

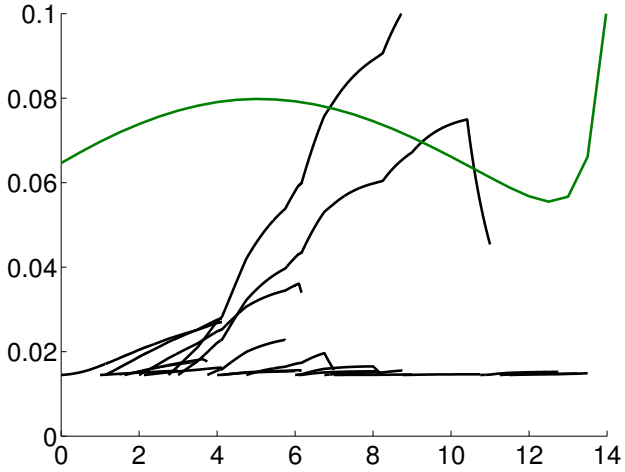
$$G := \left( \nu\kappa H^-(P4) + (\nu + \beta) x_i \sum_{j=1}^{n} x_j \right) x_i$$

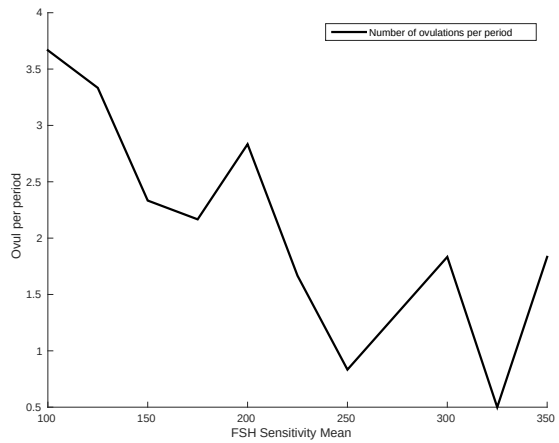
$$D := \left( (\nu\beta + x_i^2) \sum_{j=1}^{n} x_j + \kappa x_i \right) x_i$$

$$H^-(P4) := c \frac{\eta^5}{P4(t)^5 + \eta^5}, \quad H_i^+(FSH) := \frac{FSH(t)^5}{{\delta_i}^5 + FSH(t)^5}$$

initial FSH sensitivity: $\sim \mathcal{N}(\mu, \sigma)$

# follicles created in a fixed time interval: $\sim$ Poisson

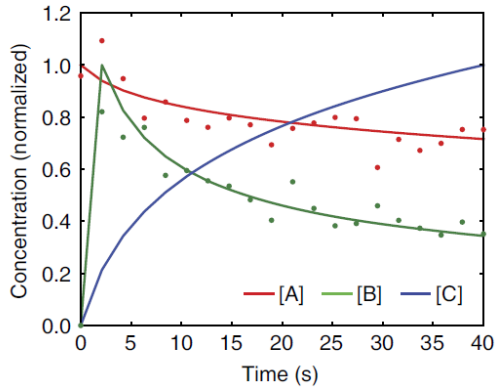


# Parameter estimation

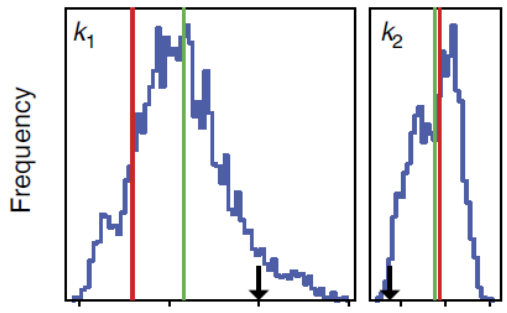
Model: $y(t,\theta) = (y_1(t,\theta), \ldots, y_n(t,\theta)) \in \mathbb{R}^n$
Parameters: $\theta = (\theta_1, ..., \theta_q) \in \mathbb{R}^q$
Data: $z_{kl} \approx y_k(t_l,\theta),\ k = 1, \ldots, n,\ l = 1, \ldots, m_k$
(i) **direct minimisation** of least squares error

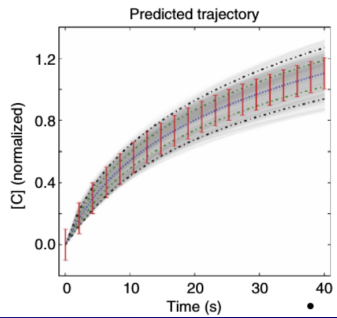
$$\|F(\theta)\|_2^2 = \sum_{k=1}^{n} \sum_{l=1}^{m_k} \frac{(z_{kl} - y_k(t_l,\theta))^2}{2\sigma_{kl}^2} \xrightarrow{\theta} \min$$




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

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



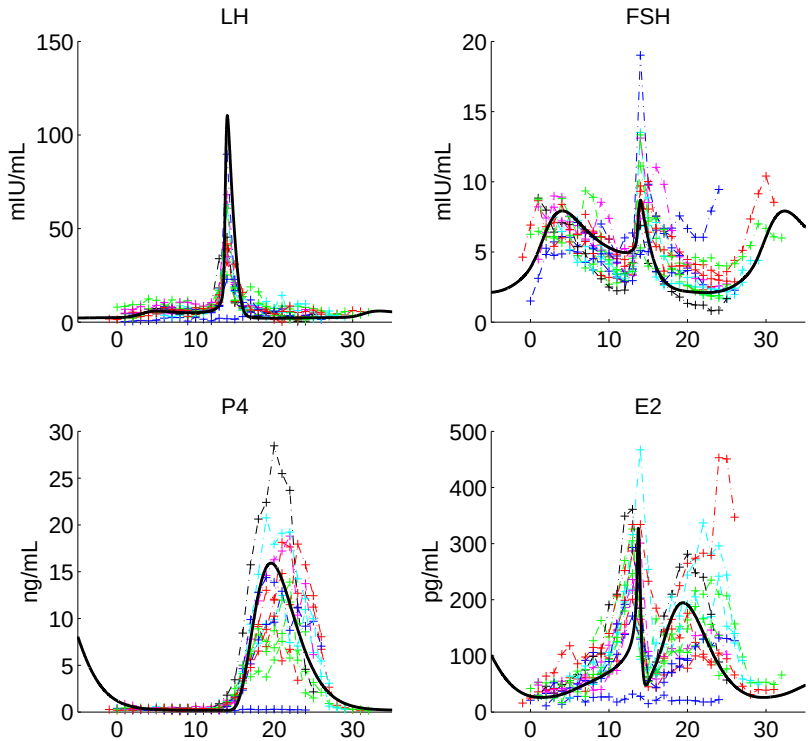



# Results of *in silico* experiments

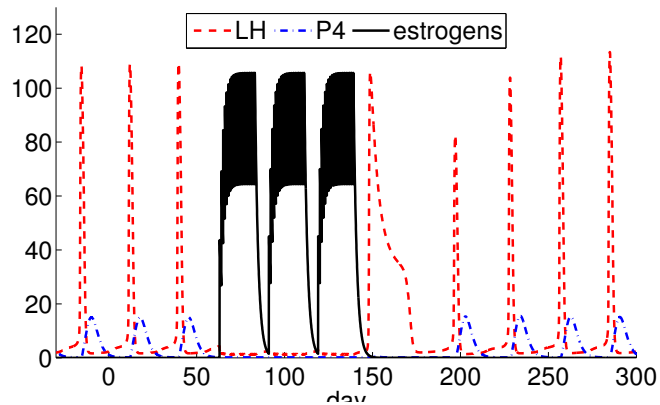
# Generic model for normal cycles

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

- normal cycle simulation



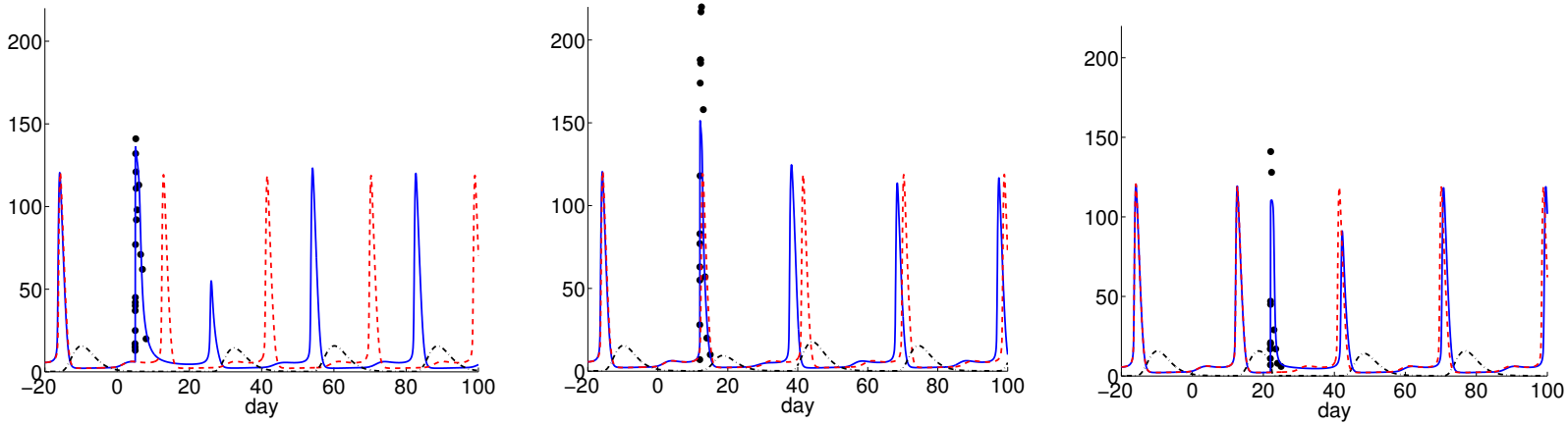

- simulating the effect of birth control pills



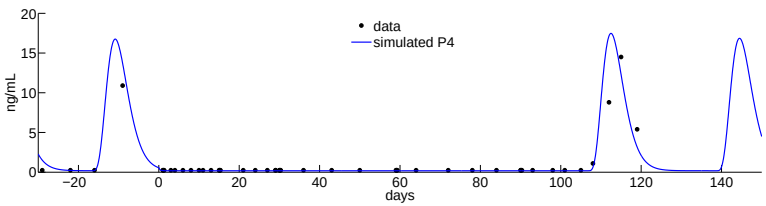
# Validation of generic model

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

- single dose agonist (nafarelin)

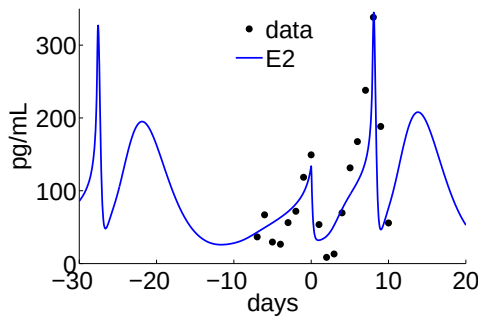



- multiple dose agonist (nafarelin)

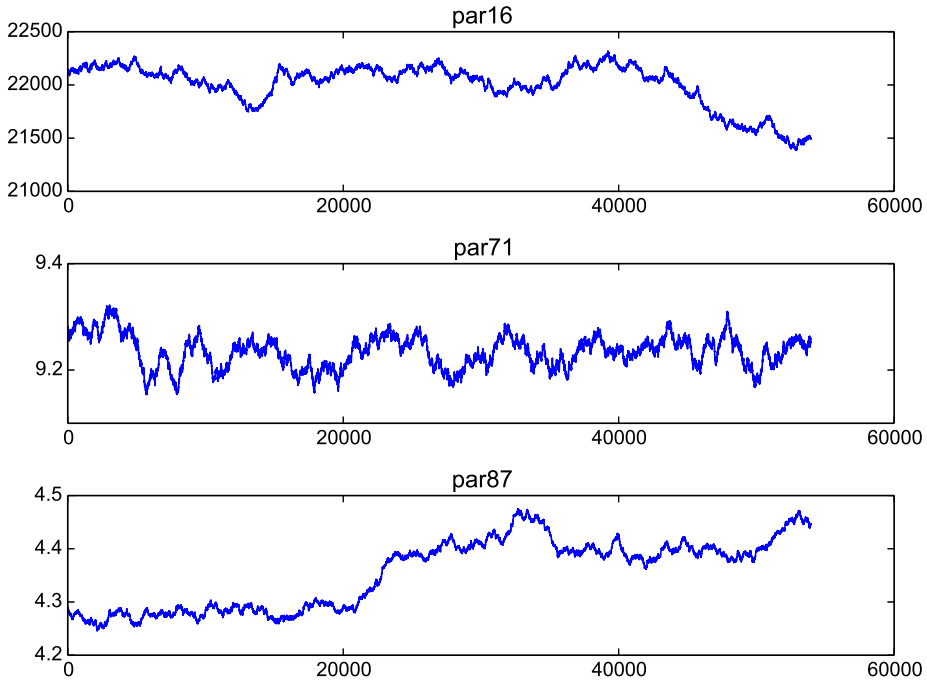


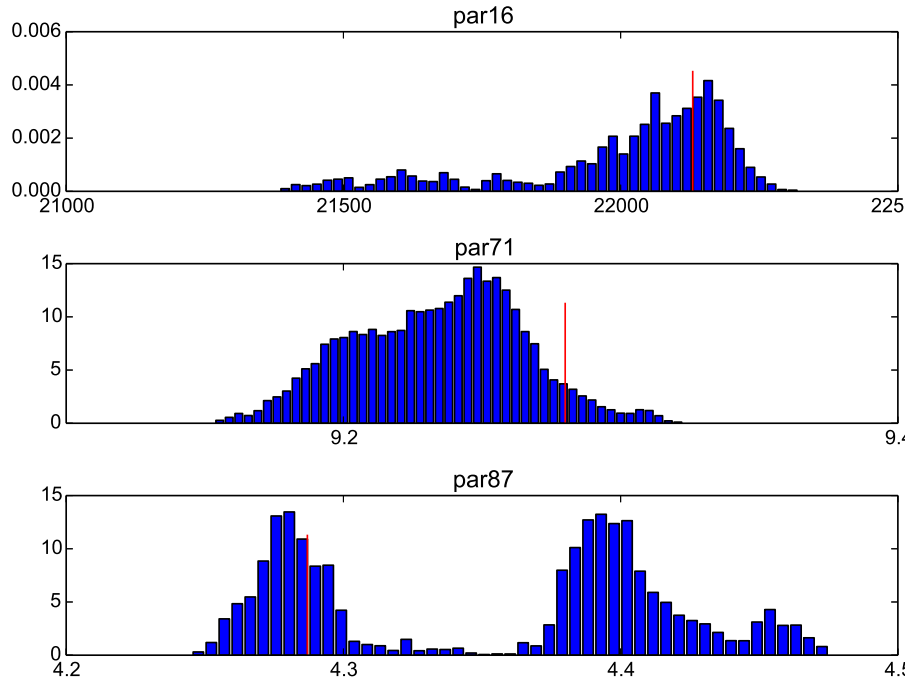

[Röblitz et al. (2013)]

- single dose antagonist (cetrorelix)



# Uncertainty quantification

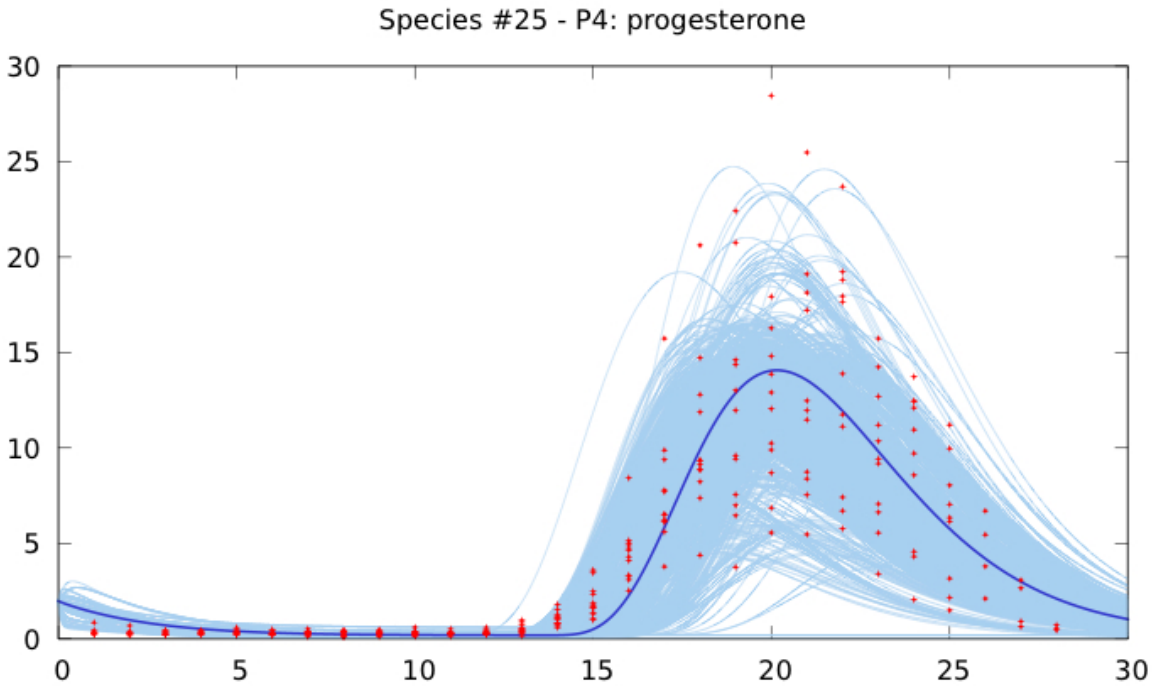



- 82 random variables, uniform prior distribution
- posterior sampling: Metropolis-Hastings algorithm with lognormal proposal distribution
- alignment of LH peaks in each sample; only acceptance of periodic solutions with cycle length 20-50 days

# 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*

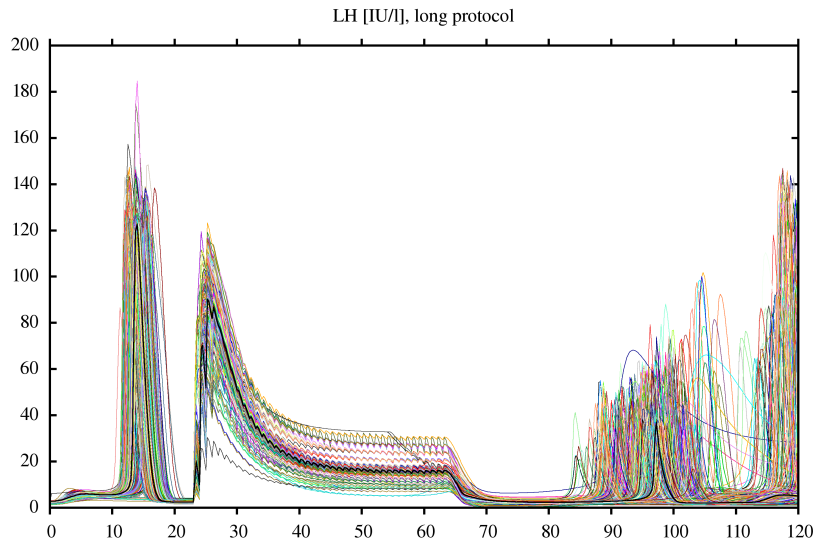
finite set of biologically admissable parameter sets

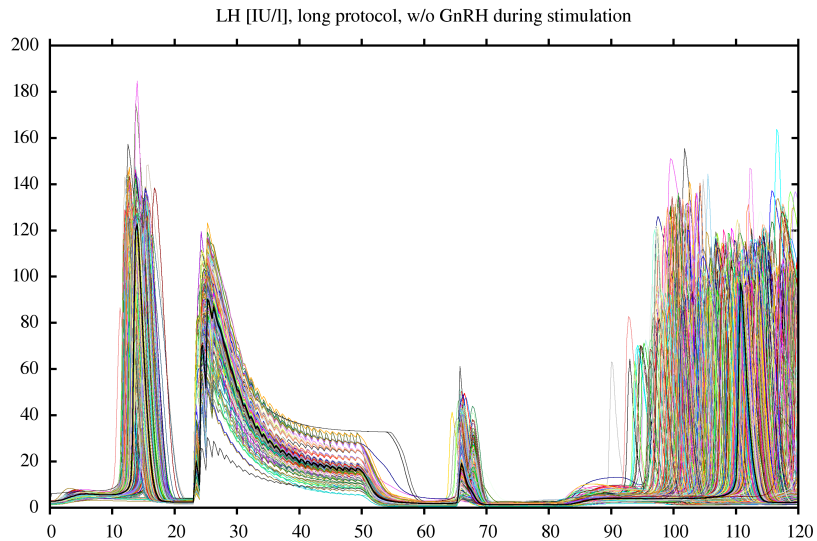
*offline* $\longrightarrow$ *online*

# Virtual patients

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

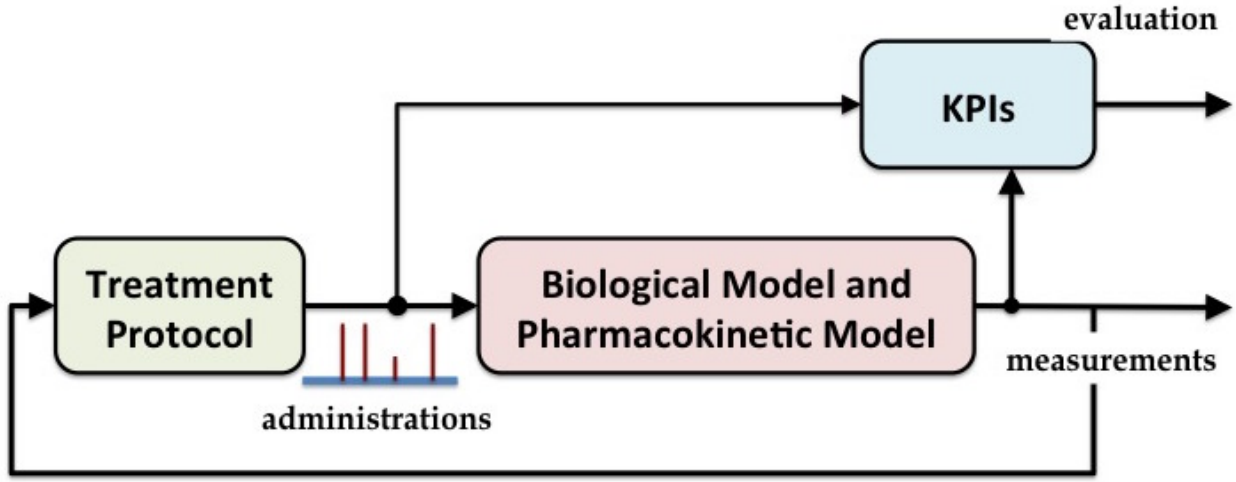
Long protocol: downregulation cycle days 23 to 50 with Triptoreline, then 14 days stimulation, finally Ovitrelle (drug database!)




$\longrightarrow$ model refinement $\longrightarrow$

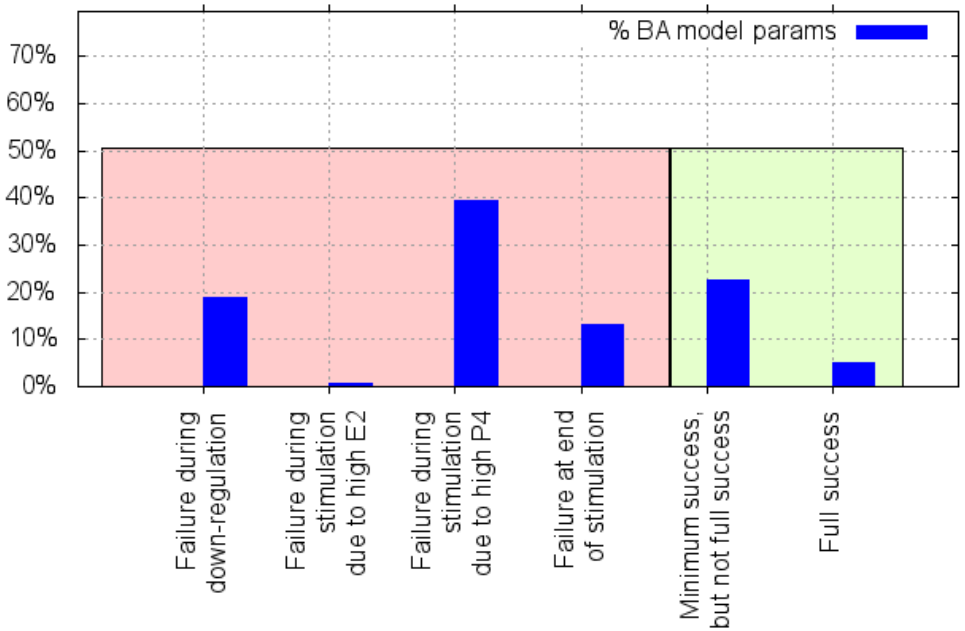
# Model-based treatment verification & design

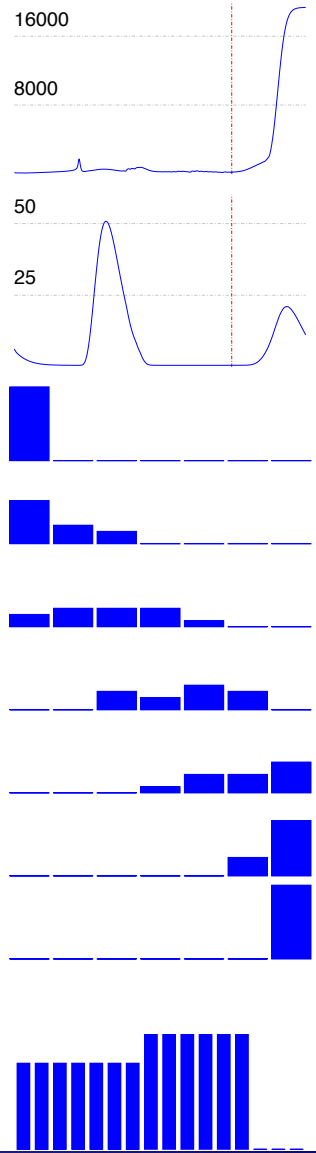



- **treatment verification**
  the treatment model (closed loop system) reaches a state in which some desired property is satisfied (treatment goals)
- **treatment design**
  finding values for treatment parameters (type, dose and time of drug) that optimize some key performance indicators (KPIs): E2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

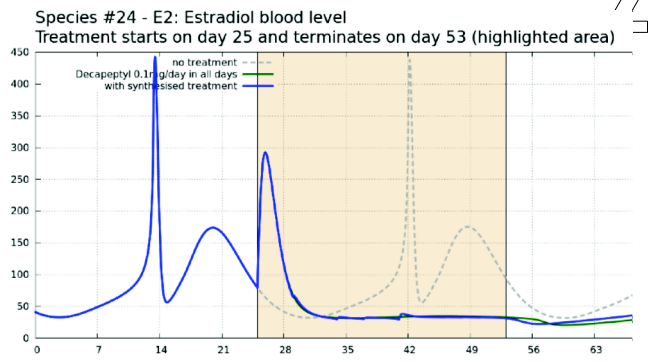
| day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| action | ■ | | | | ■ | ■ | | | | ■ | | | ■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

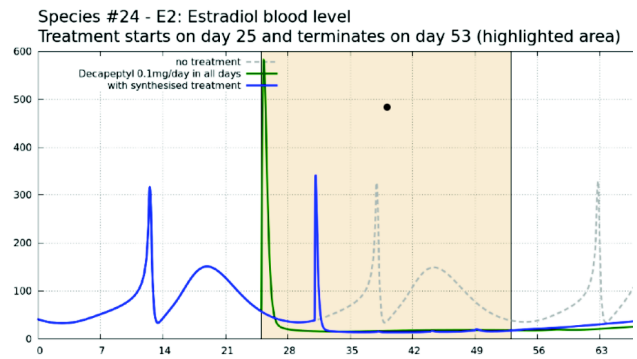
Decapeptyl 0.1mg: 10 half doses +1 full dose = 0.6 mg

**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



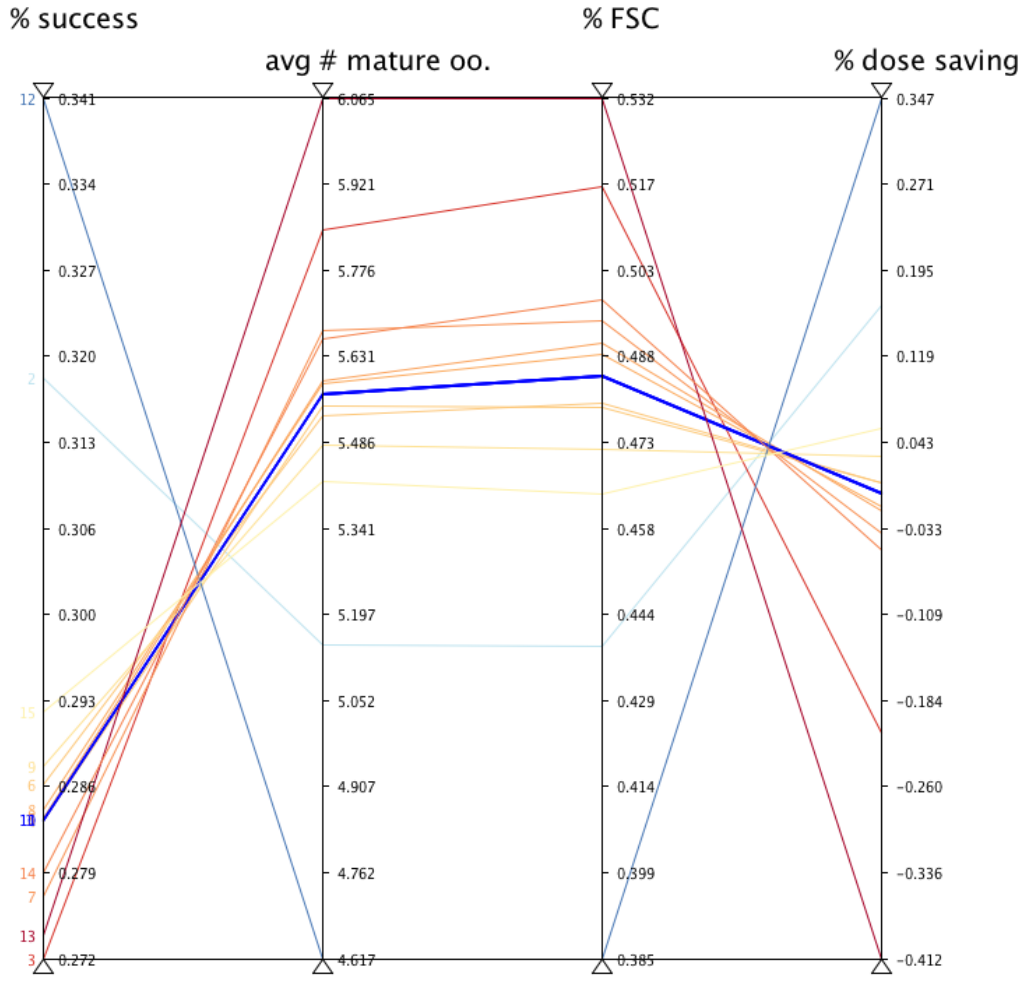

Synthesised generic down-regulation treatments require 40% of the injections and <25% of the overall Decapeptyl amount required by reference treatment. Individualised treatments even lighter, still achieving clinical goals!

# 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



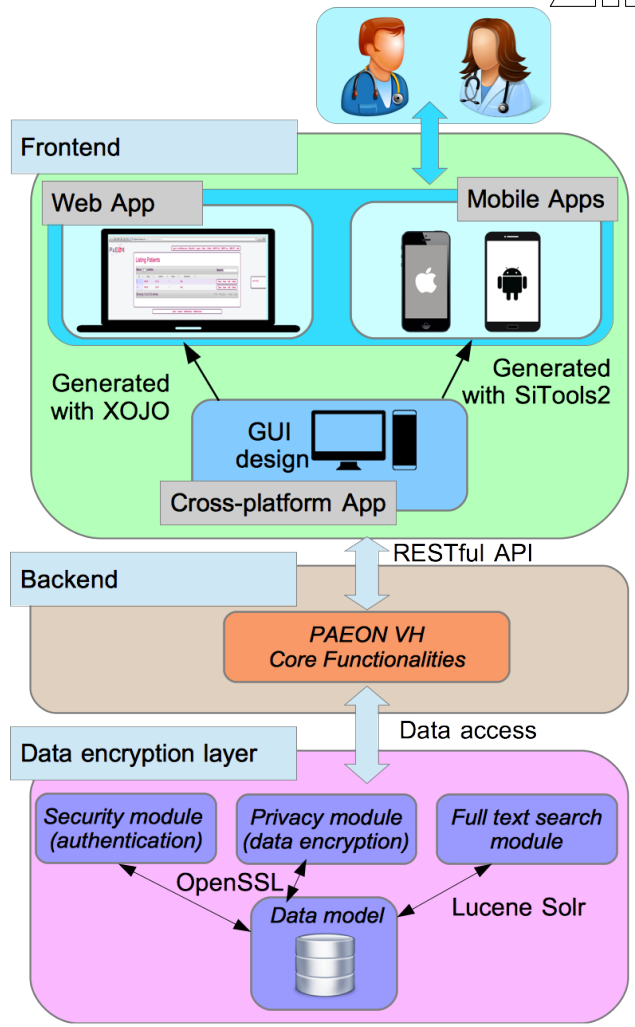
# Conclusion

## Benefit

- the virtual hospital as a training tool for physicians
- suggestions for new clinical studies

## Future work

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



# Acknowledgement

**Computational Systems Biology Group**
http://www.zib.de/numeric/csb

in particular:
Thomas Dierkes, Rainald Ehrig, Stefan Schäfer, Claudia Stötzel

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**Partners in the EU-project PAEON-Model-Driven Computation of Treatments for Infertility Related Endocrinological Diseases**

- Enrico Tronci (La Sapienza Rome)
- Brigitte Leeners (University Hospital Zurich)
- Tillmann Krüger (Hannover Medical School)
- Marcel Egli (University Lucerne)