Mathematical Modelling of Hormonal Regulation

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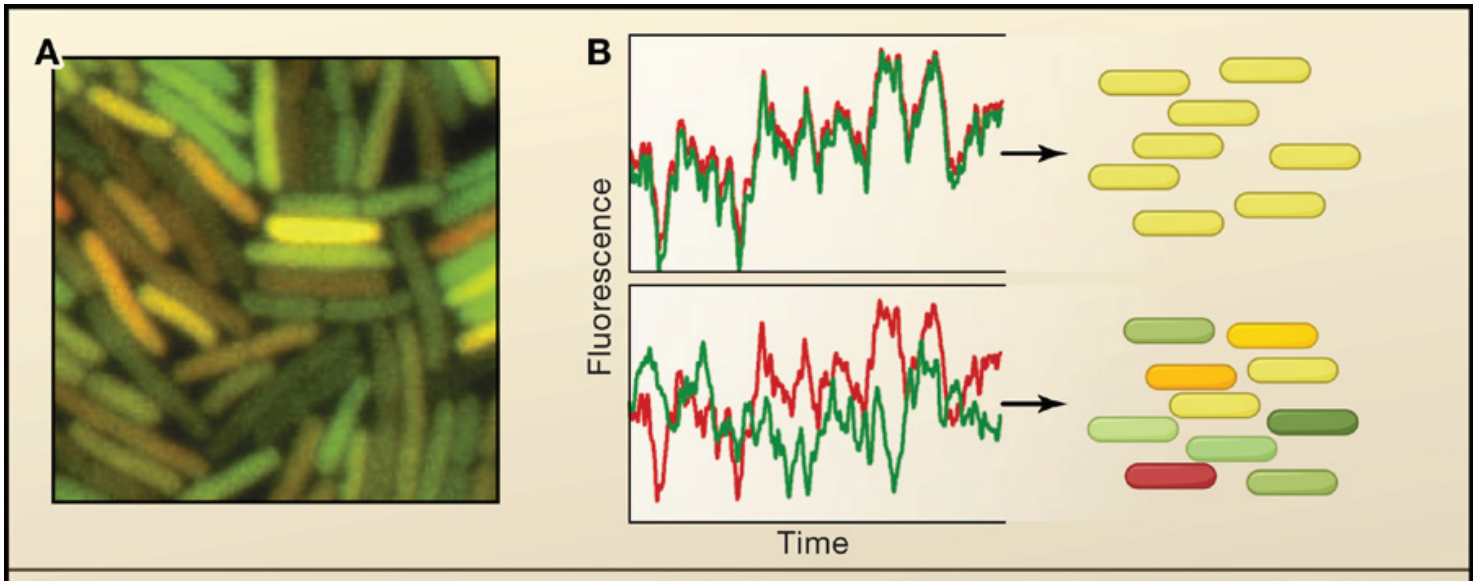
Stochasticity in biological systems



Fluorescence imaging of individual E. coli reveals marked variability in protein expression
[Raj et al. 2008. DOI 10.1016/j.cell.2008.09.050]

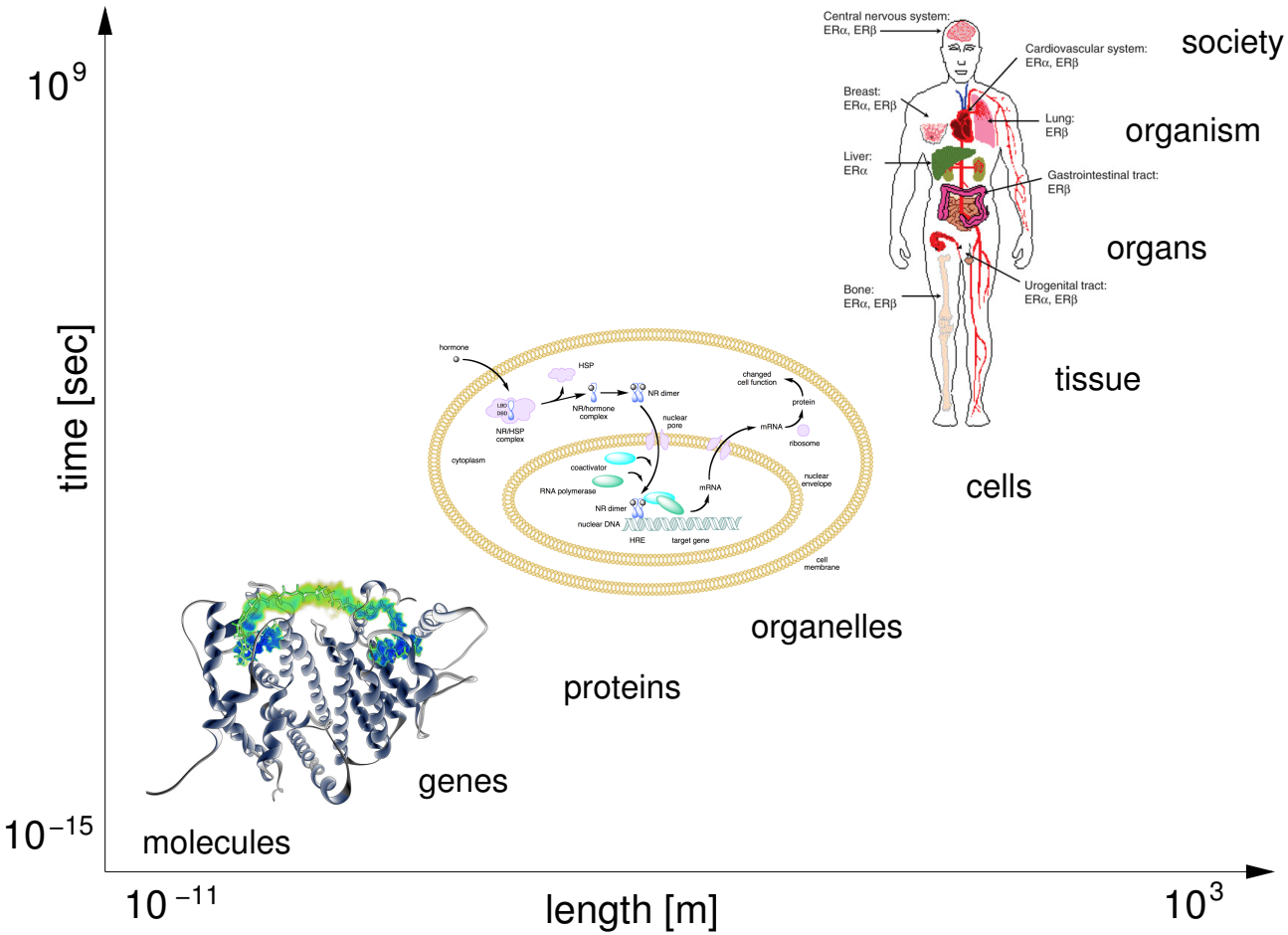
extrinsic noise:
fluctuations in cellular environmental factors

intrinsic noise:
fluctuations arising from low copy numbers (*E.coli*: 10 mRNA molecules per cell)

This presentation focuses on modelling of extrinsic noise!

Challenge

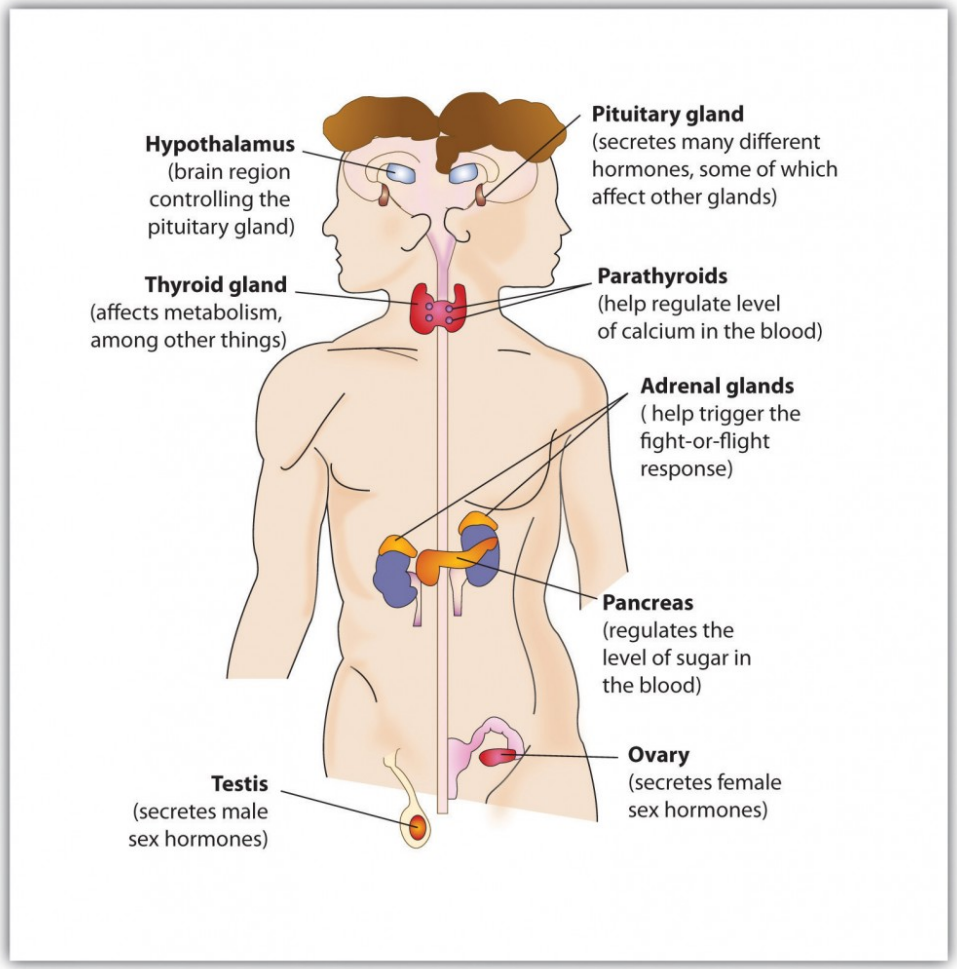
Integration of experimental data (in vitro and in vivo) into a system's understanding at different scales in space and time



Outline

- Why modelling hormonal regulation?
- Physiological background
- Experimental data *in vivo*
- Model development for the human menstrual cycle
- Conclusion and outlook

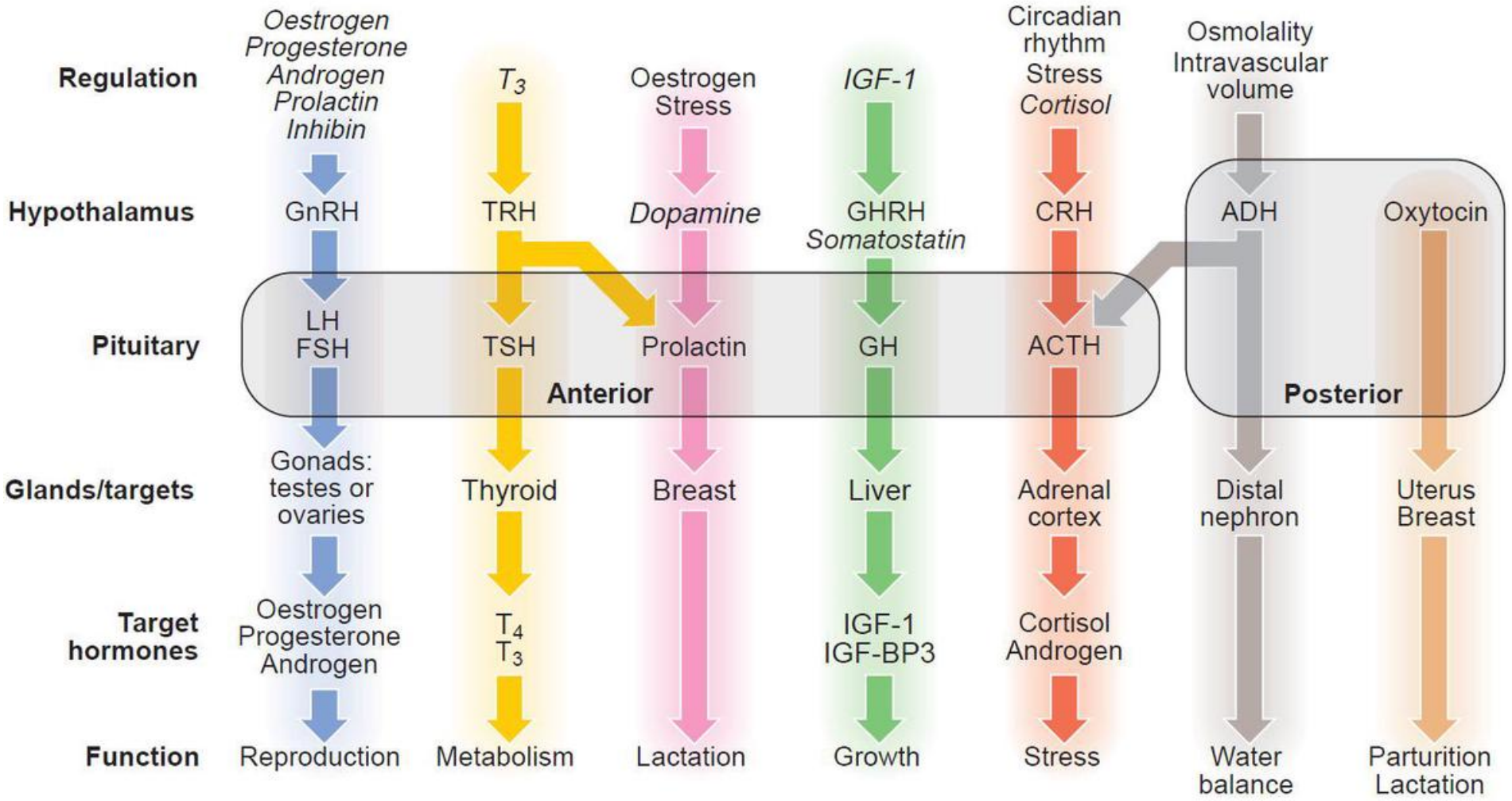
Hormones



- hormones control a lot of functions: sexual reproduction and development, whole-body metabolism, blood glucose levels, plasma calcium concentration, growth,...
- hormones are produced in, and released from, diverse places
- they are carried in the bloodstream and capable of acting on target cells throughout the body

[https://opentextbc.ca/introductiontopsychology/chapter/3-4-putting-it-all-together-the-nervous-system-and-the-endocrine-system/]

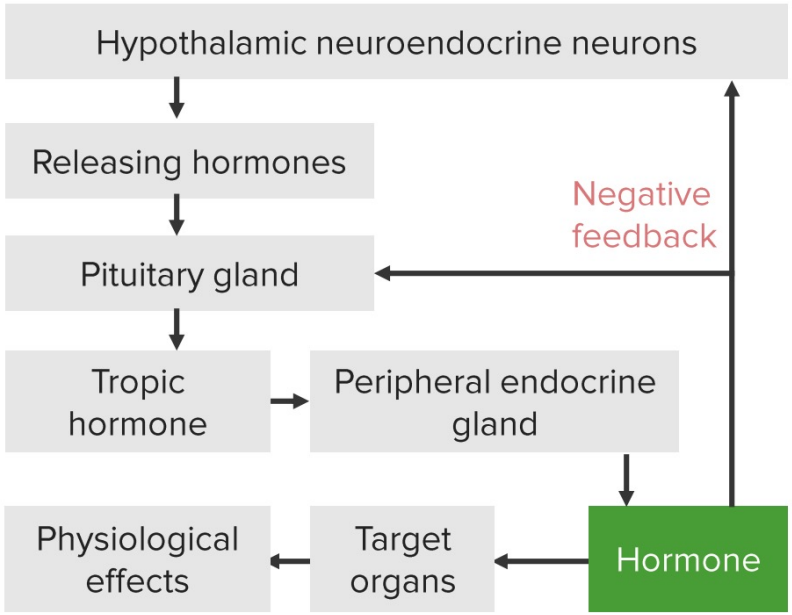
Hormonal axes



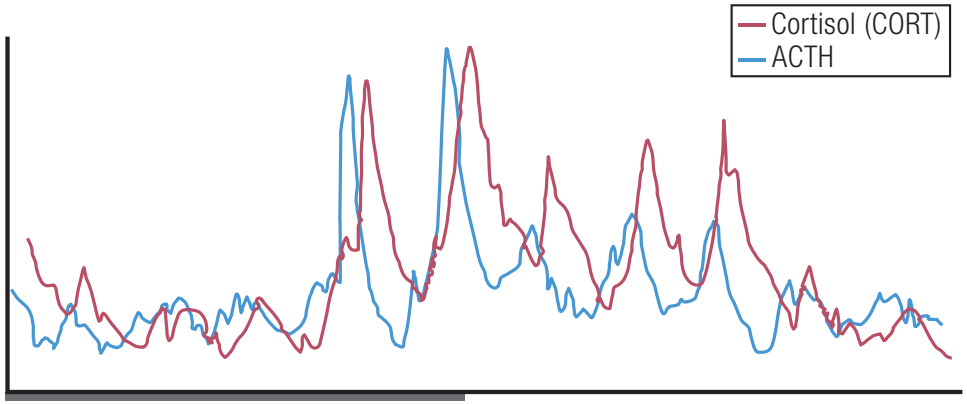
Source: Davidson's Essentials of Medicine, 2nd ed.

Hormonal regulation

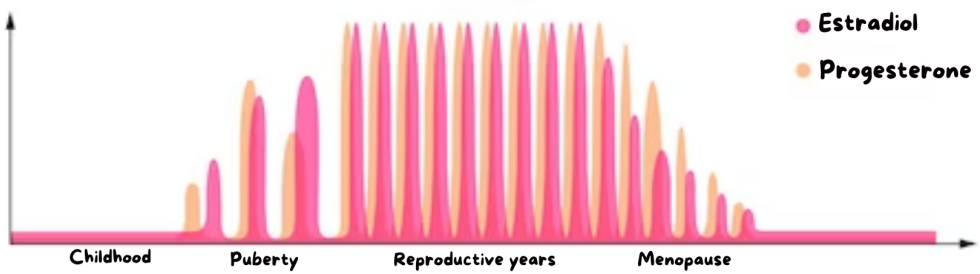
Feedback mechanisms lead to **oscillatory behavior** (milliseconds to days)
$\rightarrow$ significant implications for treatment



[https://www.lecturio.com/concepts/hypothalamic-and-pituitary-hormones/]



[Lightman et al. (2020), doi: 10.1210/endrev/bnaa002]



Why modelling?

- endocrine axes are largely studied in isolation (reductive approach)
- dynamic changes in hormone levels are not captured well by single-point measurements
- challenging to collect longitudinal data on long-time processes like puberty and menopausal transition
- under-representation of women in clinical studies due to (i) potential maternal-fetal liability and (ii) the menstrual cycle as confounding variable

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- provides new information about potential mechanisms and can identify areas of deficient knowledge

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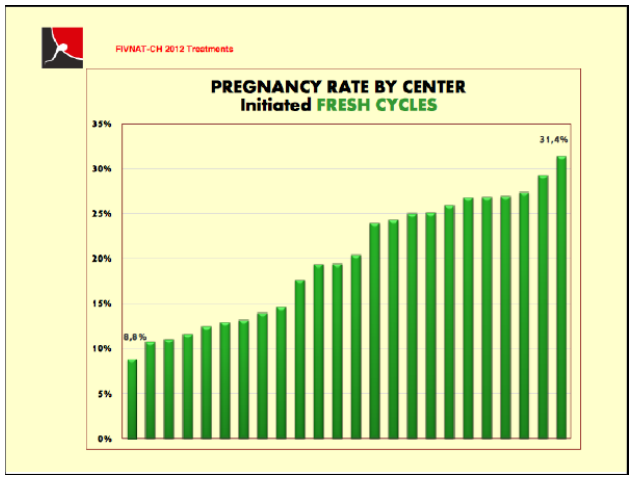
Mathematical modelling...

- allows to formulate and test hypothesis *in-silico* (answer various "what if?" scenarios), including those that are costly, challenging or not feasible in-vitro or in-vivo
- provides new information about potential mechanisms and can identify areas of deficient knowledge
- helps in quantifying inter- and intra-individual variability

Reproductive medicine

Increased chance for successful pregnancy by modern techniques:

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



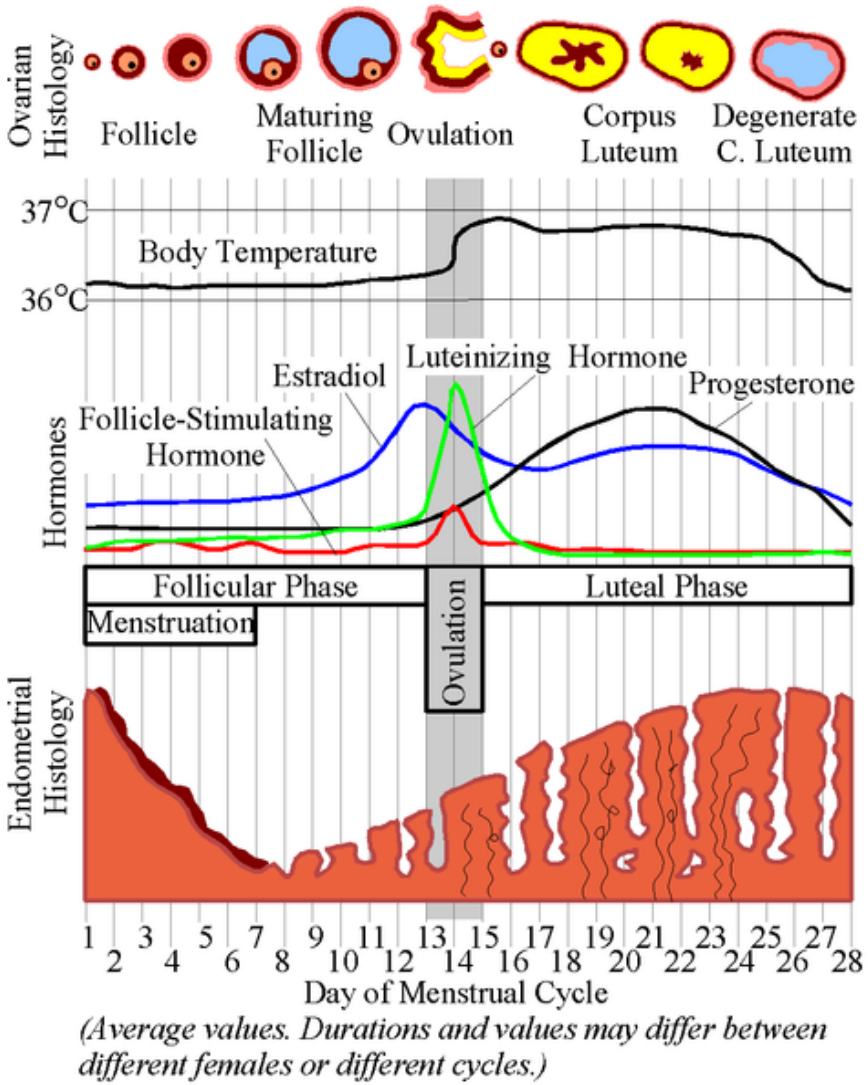
Success rates: 8 - 35%

Depending on the clinic due to different treatment strategies!

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

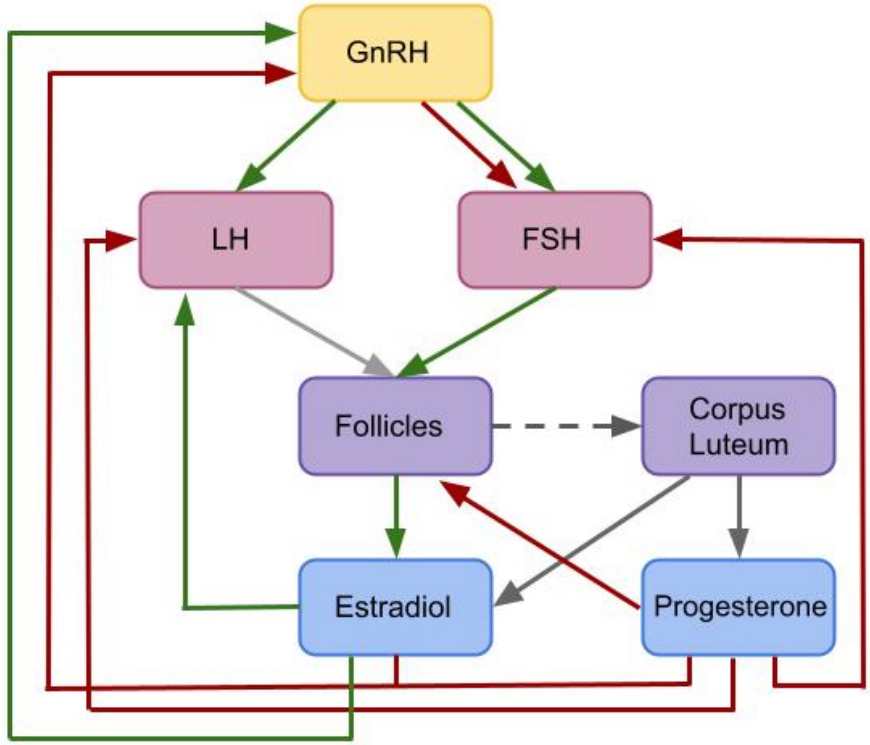
- better understanding of complex processes
- simulation and optimization of treatment strategies *in silico* (cost-saving and efficient)

The human menstrual cycle

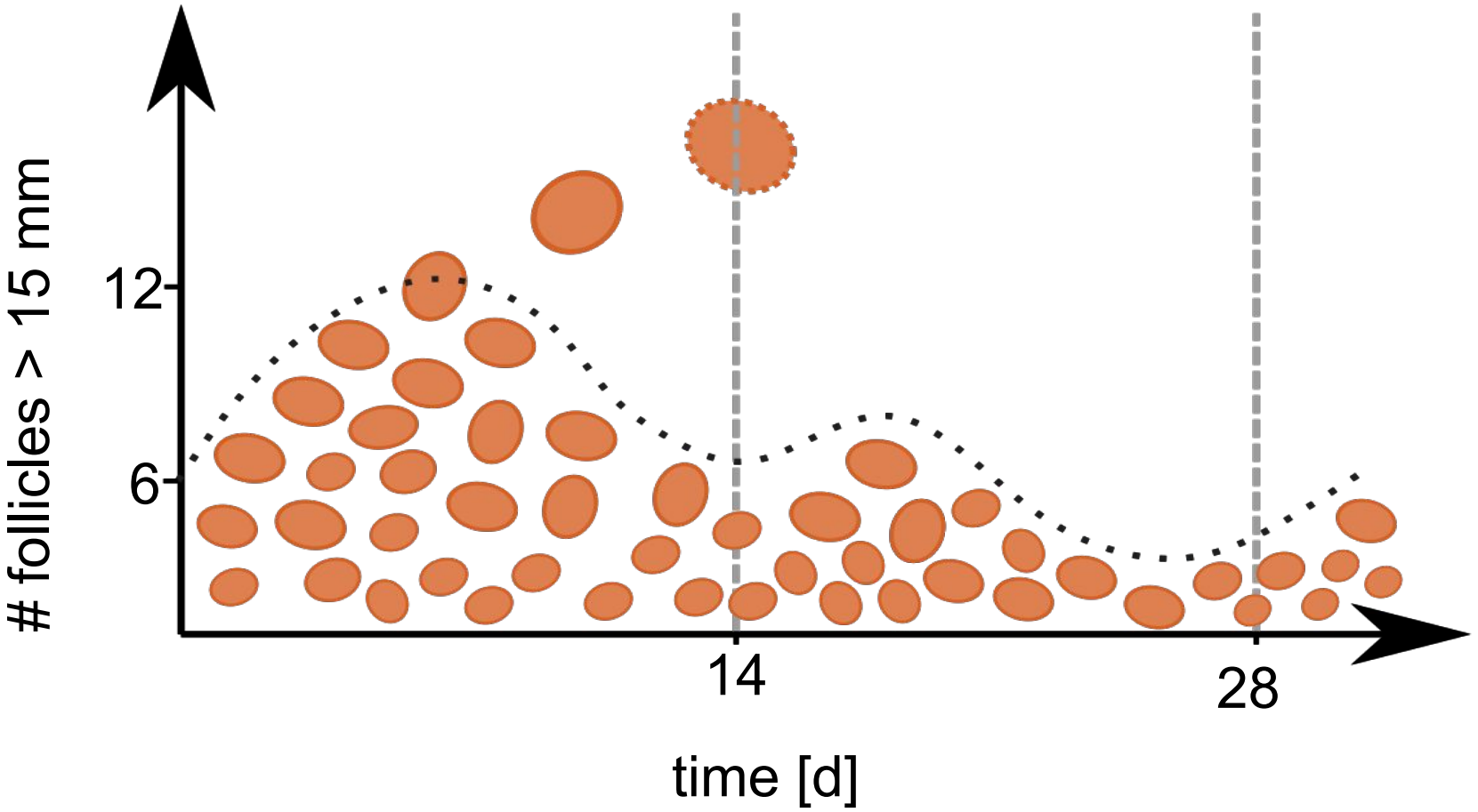


[Chris 73 / Wikimedia Commons]

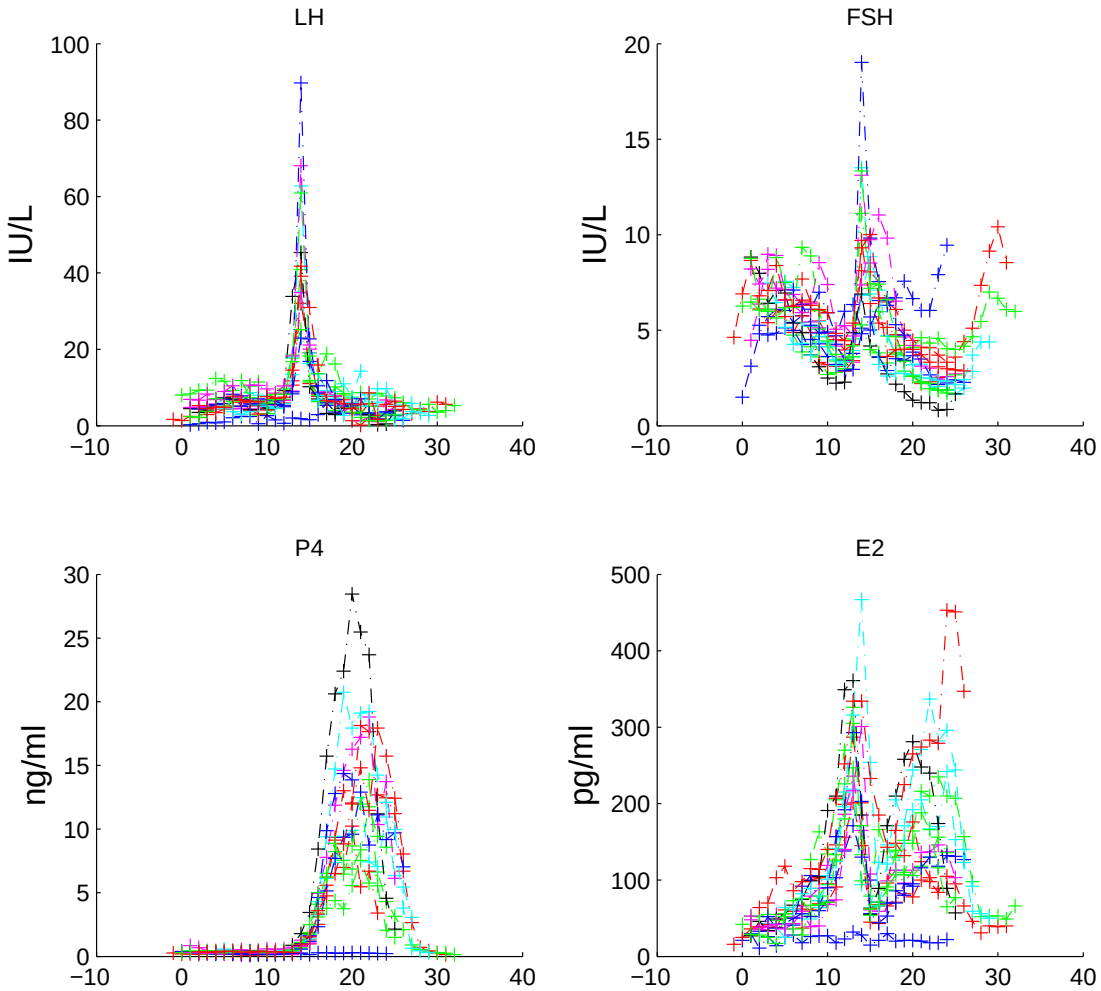
Orchestrated interplay of hormones along the HPG-axis:



Follicular development

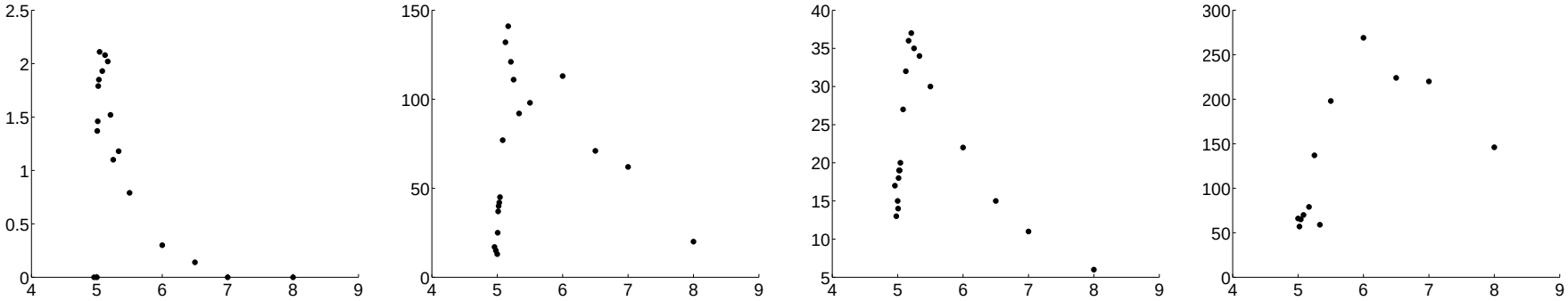


Clinical trials: Hormone blood data from healthy women

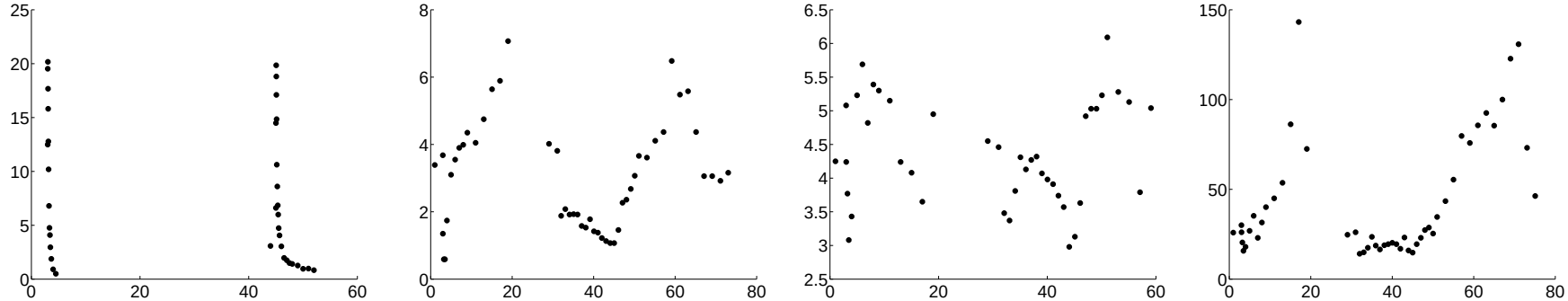


Clinical trials: Pharmacokinetik (PK) data

Single dose Nafarelin (GnRH agonist):

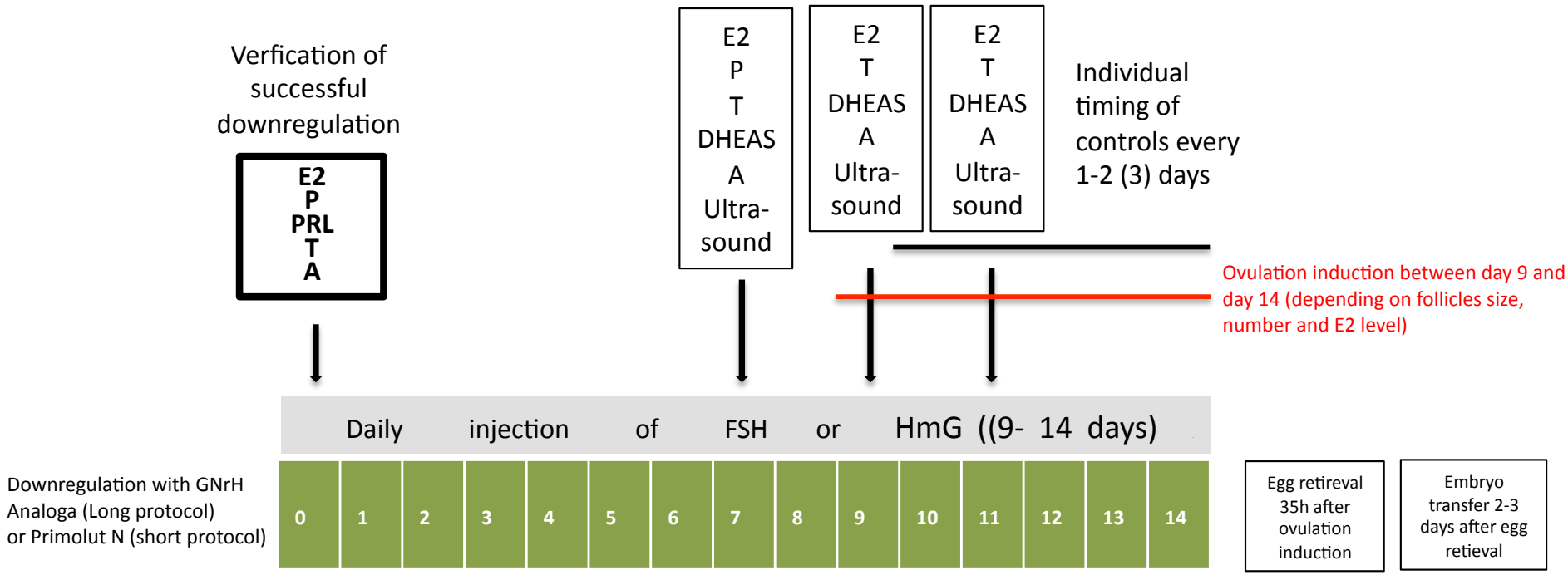


Single and multiple dose Cetrorelix (GnRH antagonist):



measurements: drug, LH, FSH, E2

Ovarian stimulation: Treatment protocol data



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GnRHa	hMG/ FSH	Tag	Datum	BT	E2 pmol/L	P4 nmol/L	$<$ 10	10 11	12 13	14 15	16 17	18 19	$\geq$ 20	$<$ 10	10 11	12 13	14 15	16 17	18 19	$\geq$ 20
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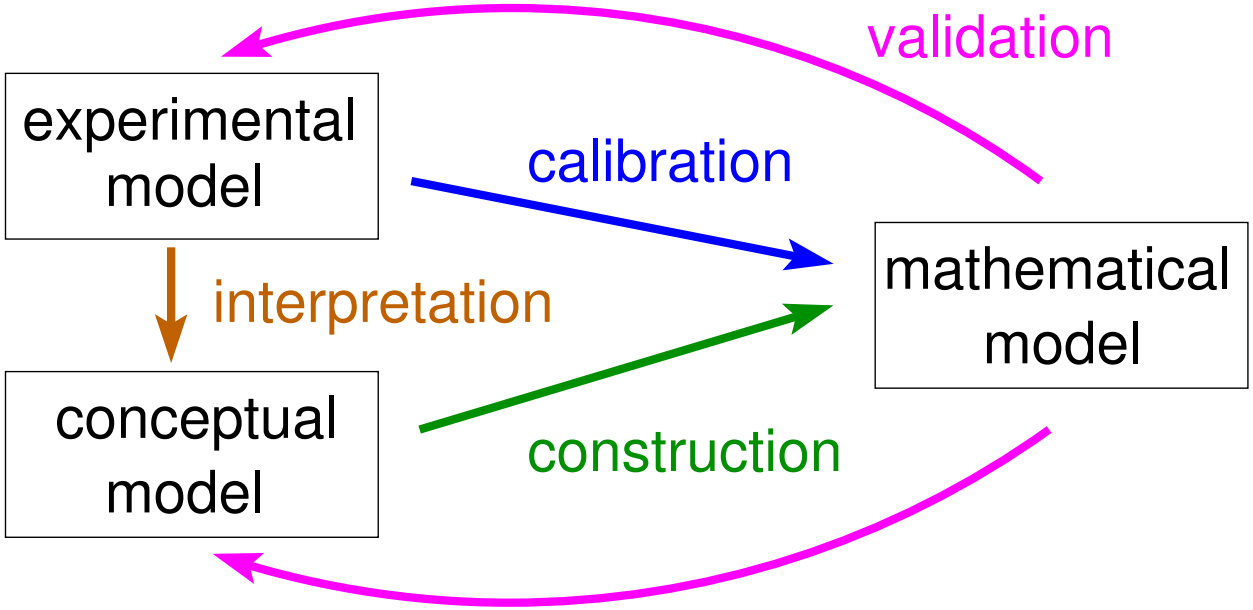
1	225	Mo	10.06.13	11	6062		2		1		1	1		2	3	5	3	3		

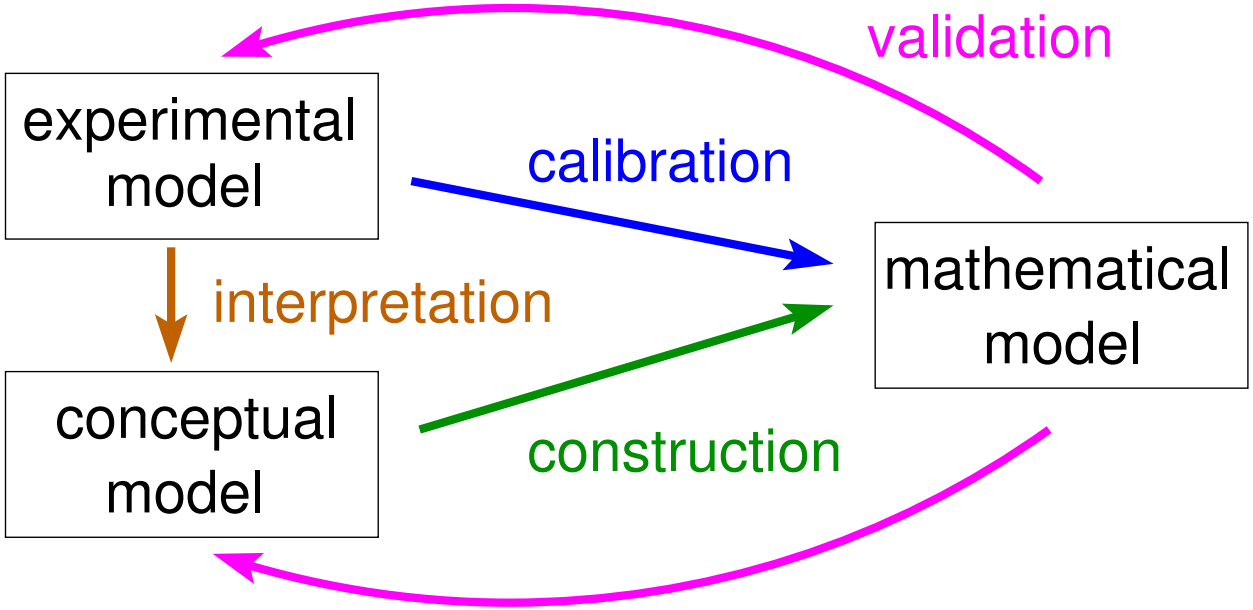
Typical problems

- time series data of a few components
- many patients, but few data points per patient, mostly under treatment
- high inter- and intra-individual variability
- different physical units, sometimes not even convertible
- missing measurement errors
- missing information about the cycle day
- averaged data for women with different cycle length or in different stages of the cycle

Modelling in biology and medicine



Modelling in biology and medicine



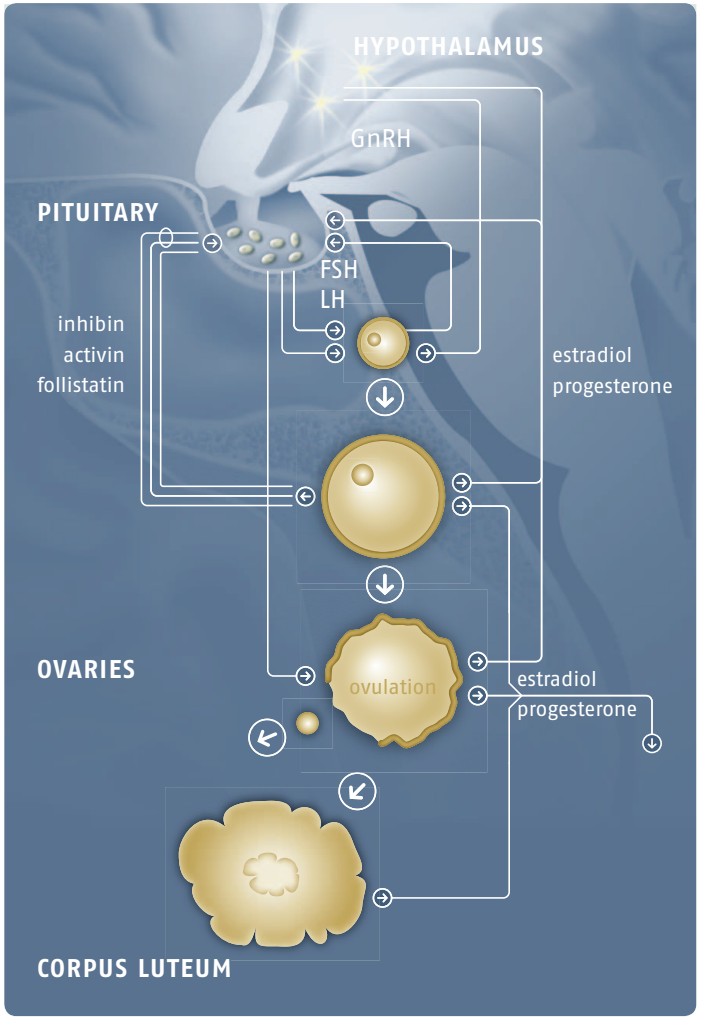
"Essentially, all models are wrong, but some are useful"
(George Box)
"fitness for purpose" rather than being "right or true"

"A (mathematical) model should be as simple as possible, but not any simpler"
(A. Einstein)

Conceptual model

Compartments: blood, ovaries, uterus, pituitary, hypothalamus
Components:

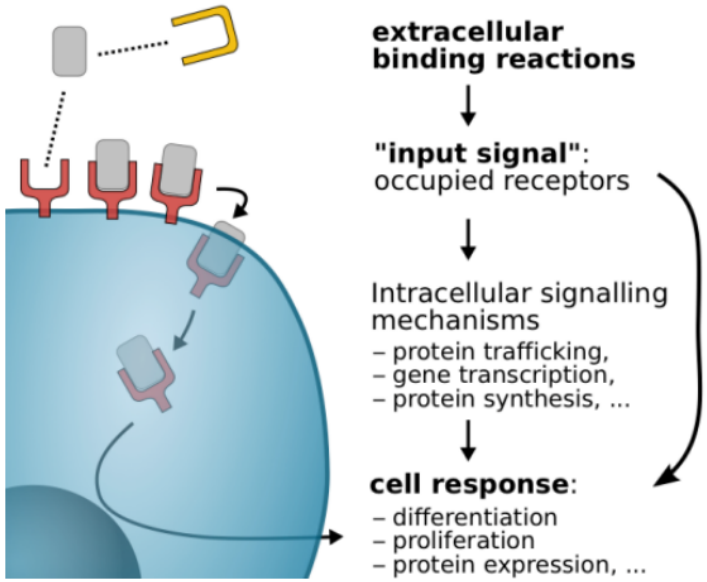
- Estradiol
- Progesterone
- Inhibin A and B
- LH + receptor binding
- FSH + receptor binding
- GnRH + receptor binding
- 6 follicular stages
- 6 luteal stages (corpus luteum)



Mathematical model

Mass action kinetics:

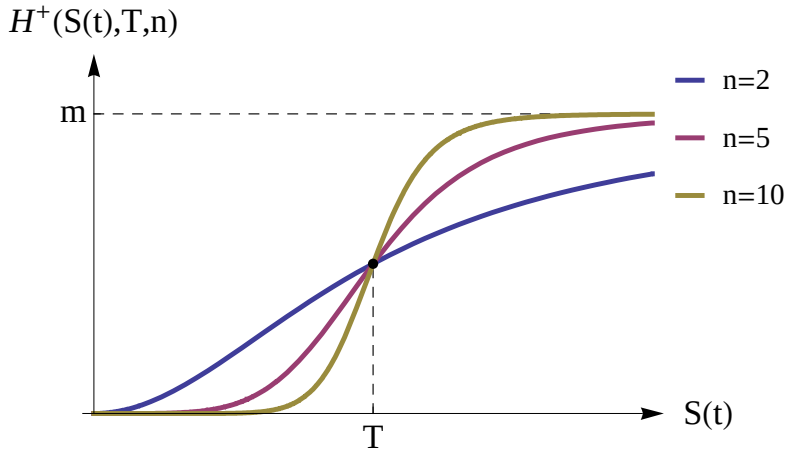
$R + L \leftrightarrow RL$



[Pivonka et al., InTech 2012]

Hill kinetics: stimulatory/inhibitory effects

$$H^+(S(t), T, n) := \frac{S(t)^n}{S(t)^n + T^n}$$



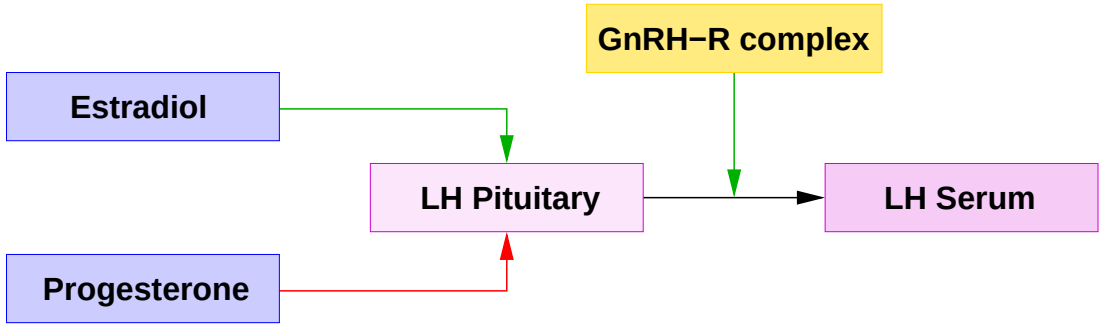
The model: ordinary differential equations (ODEs)

$$x'(t) = f(x(t), u(t), \theta),\ x(0) = x_0$$

Experimental measurements (with additive Gaussian noise):

$$y(t) = h(x) + \epsilon(t), \quad \epsilon(t) \sim \mathcal{N}(0, \sigma^2(t))$$

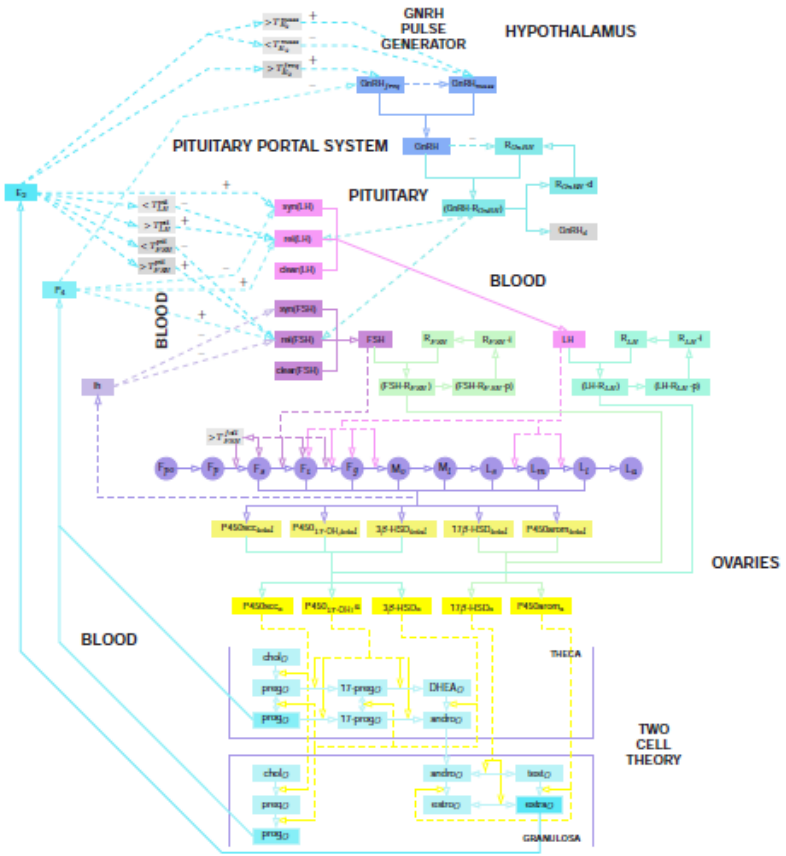
Example: Modelling of LH



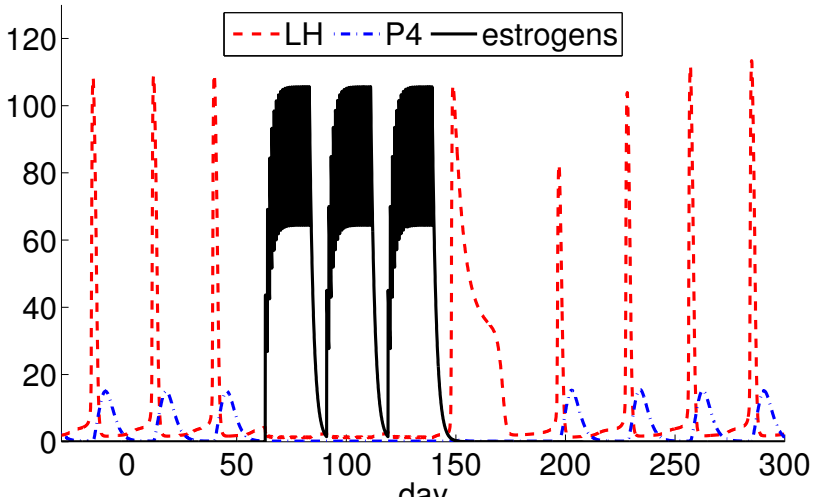
$$
\begin{aligned}
Syn_{LH}(t) &= (b_{Syn_{LH}} + m_{E2} \cdot H^{+}(E2, T_{E2}; n_{E2})) \cdot H^{-}(P4, T_{P4}; n_{P4}) \\
Rel_{LH}(t) &= (b_{Rel_{LH}} + m_{GnRH\text{-}R} \cdot H^{+}(GnRH\text{-}R, T_{GnRH\text{-}R}, n_{GnRH\text{-}R})) \cdot LH_{Pit}(t) \\
\frac{d}{dt} LH_{Pit}(t) &= Syn_{LH}(t)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

The FemCyc model

Purpose: simulate the effect of birth control pill on hormone blood concentrations



49 DDEs, 208 parameters



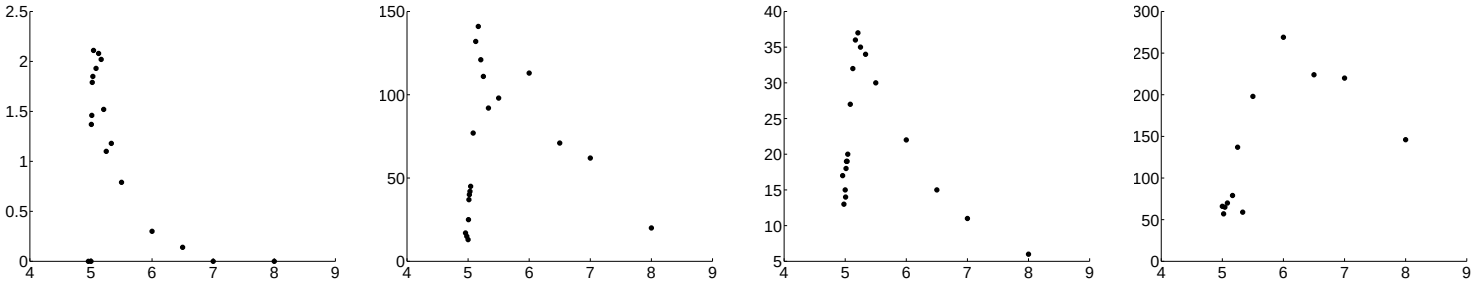
[I. Reinecke, P. Deuflhard. A complex mathematical model of the human menstrual cycle. J Theor Biol. 2007; 247(2):303-30. doi: 10.1016/j.jtbi.2007.03.011]

The GynCycle model

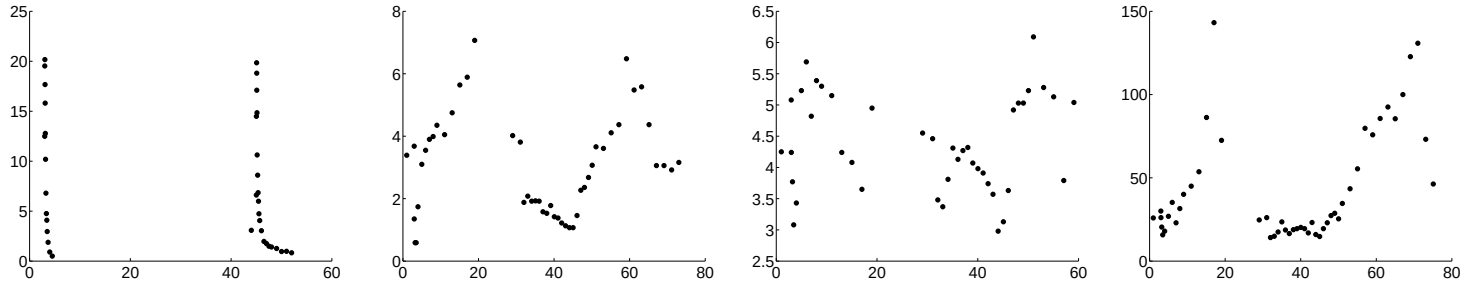
Purpose: development of a pharmacokinetik/pharmacodynamic (PKPD) model for single and multiple dose administration of GnRH analogues (in collaboration with Pfizer UK)

Blood measurements (drug, LH, FSH, E2):

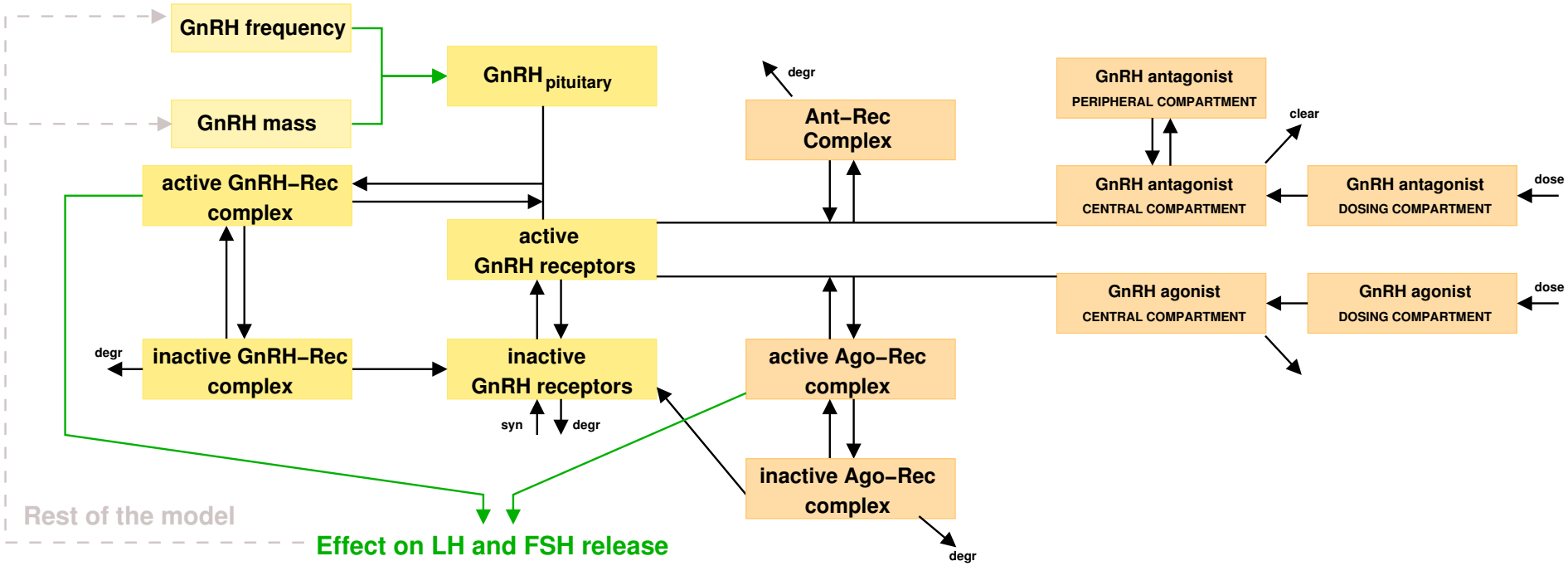
single dose Nafarelin (GnRH agonist)



single and multiple dose Cetrorelix (GnRH antagonist)



PKPD Modelling: GnRH agonists



G protein-coupled receptor (GPCR) model coupled to PK model for GnRH agonists and antagonists

Drug Database

PK description as unique parametrizations of important drugs:

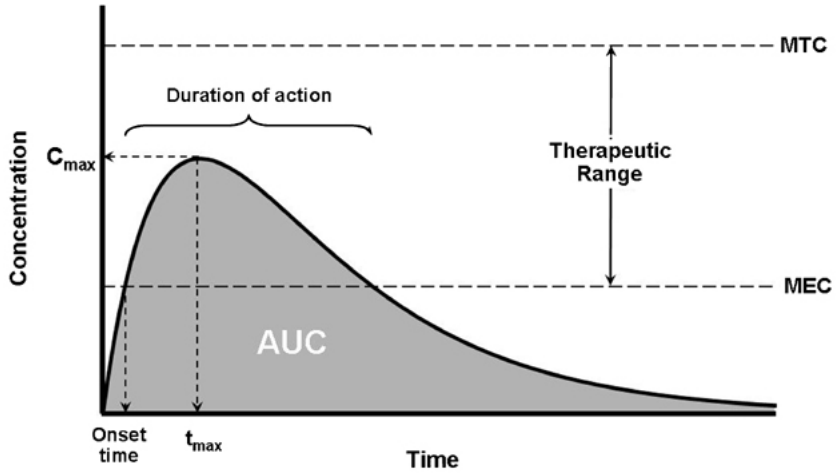
Administered compound	dimension	dose	beta	clearance rate
Triptorelin (Decapeptyl 0.1 mg)	mg	2.5	250.0	6.00
FSH (Merional 75 I.E.)	I.E.	5.347	4.271	0.488
FSH (Menopur 600 I.E.)	I.E.	13.378	9.871	0.417
FSH (Puregon/Gonal-f 600 I.E.)	I.E.	21.387	4.271	0.488
LH (Merional 75 I.E.)	I.E.	0.594	6.041	3.199
LH (Menopur 600 I.E.)	I.E.	5.669	6.041	3.199
LH (Ovitrelle 250)	I.E.	39.632	6.041	3.199
Norethisterone (Primolut N)	mg	27.291	52.324	11.090

http://www.kompendium.ch/home/de

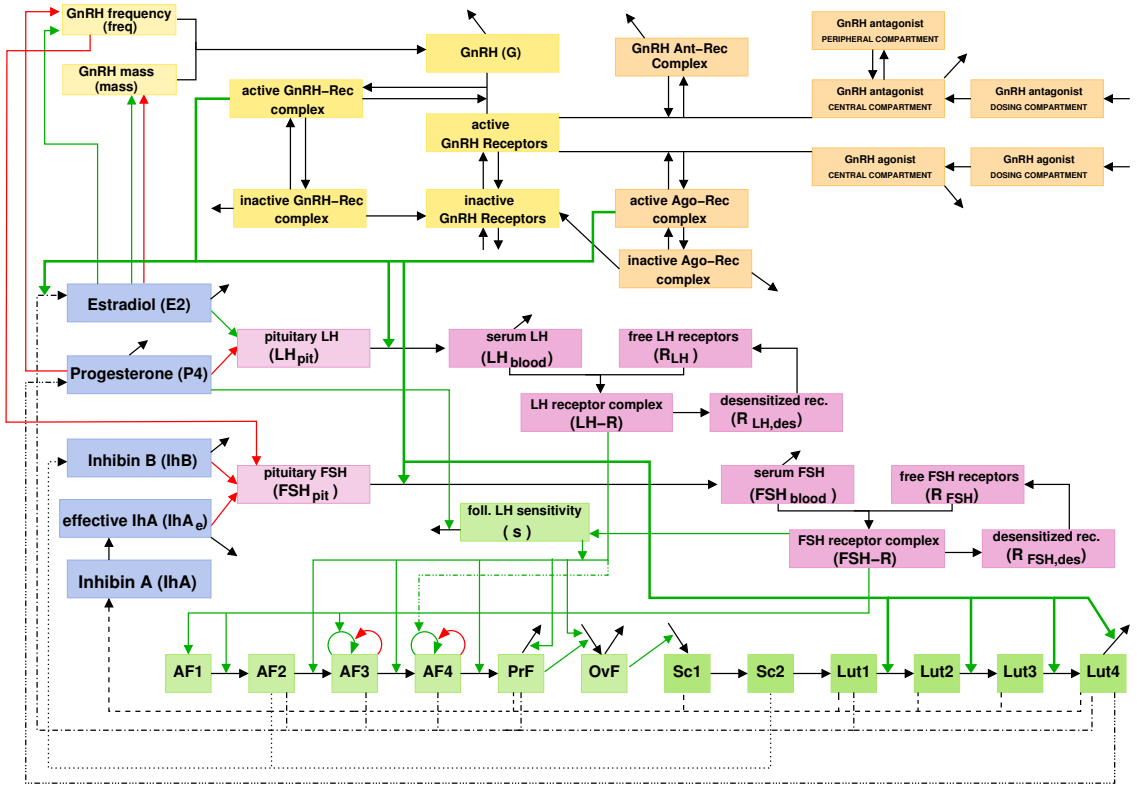
$$\frac{dc_{\text{drug}}(t)}{dt} = D\beta^2 t \exp(-\beta t) - c_L c_{\text{drug}}(t)$$

parameters can be determined via nonlinear equations from PK parameters

$t_{\max}$, $c_{\max}$, $AUC_{0-\infty}$



The GynCycle model



GynCycle: 33(+8) ODEs, 114 parameters

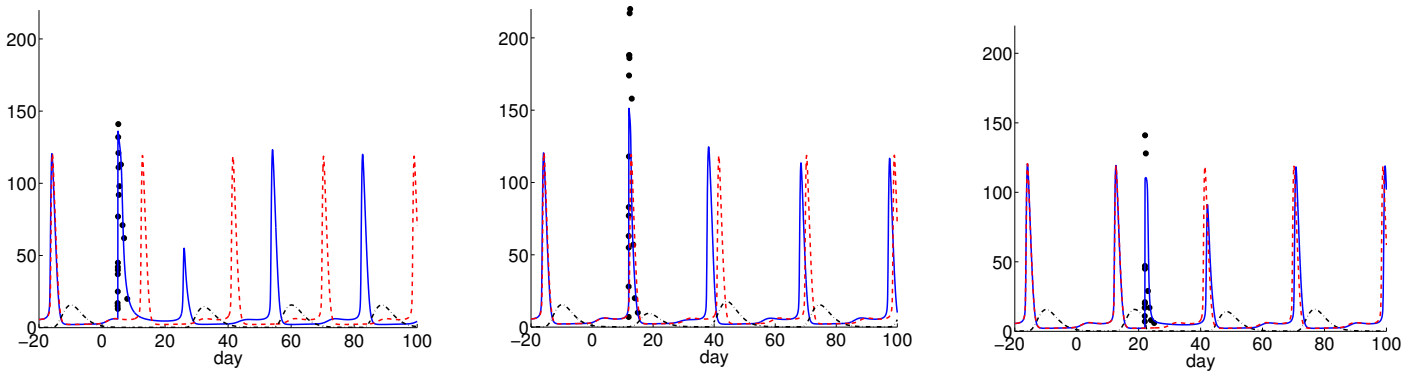
BioModels database: `http://biomodels.caltech.edu/BIOMD0000000494`

[S. Röblitz et al. A mathematical model of the human menstrual cycle for the administration of GnRH analogues. *J. Theoret. Biol.* 321:8–27, 2013. DOI: 10.1016/j.jtbi.2012.11.020]

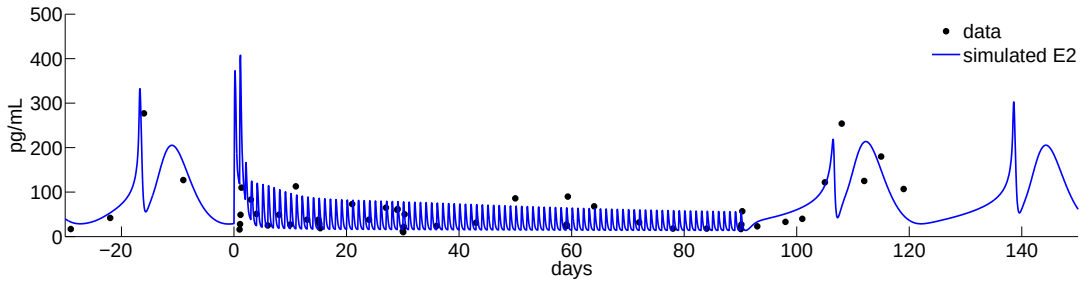
GynCycle: Results

The model **allows to**

- systematically study the influence of **drug, dose and timing of administration** on hormone profiles in a "normal" menstrual cycle



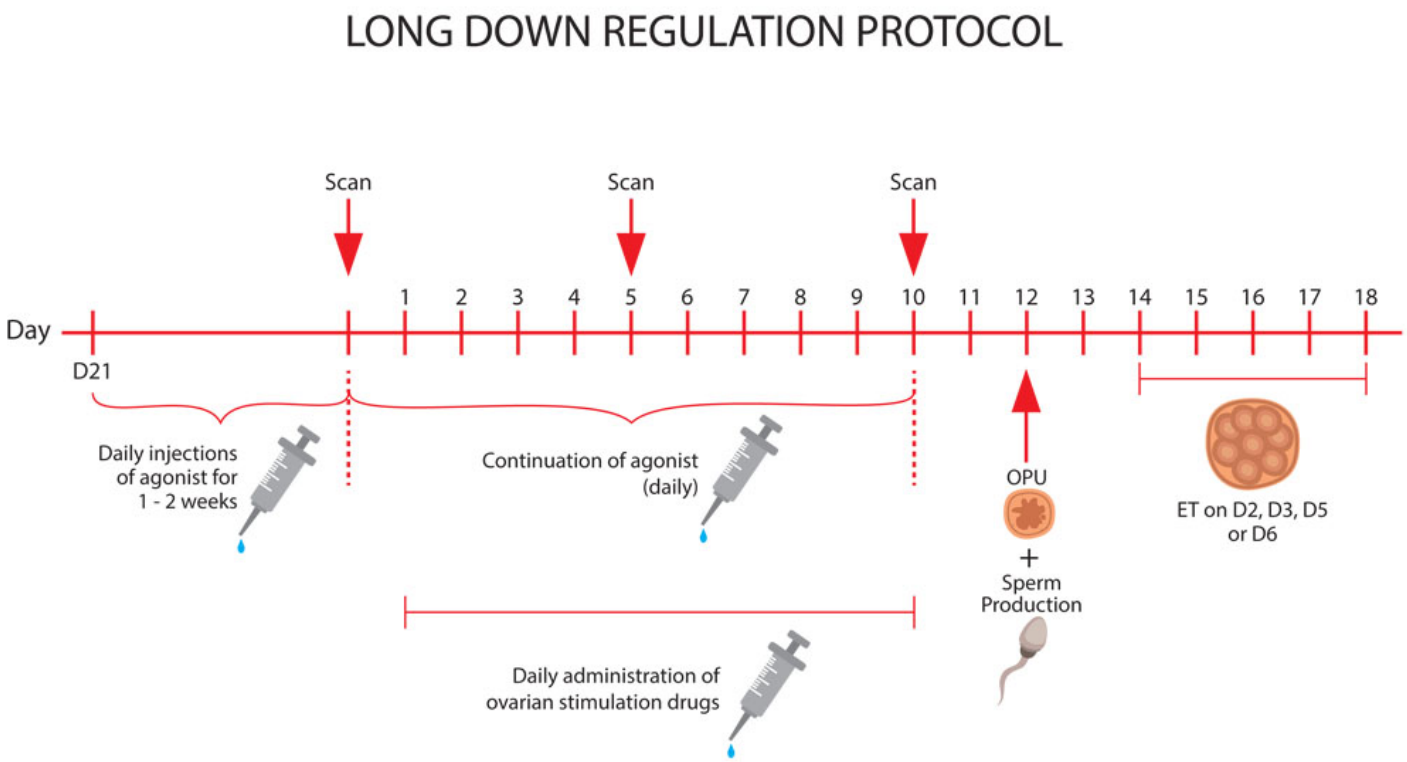
- study **long-time effect** of drug administration under different **compliance** behaviors



The PAEON model

Purpose: Simulation of female fertility treatments

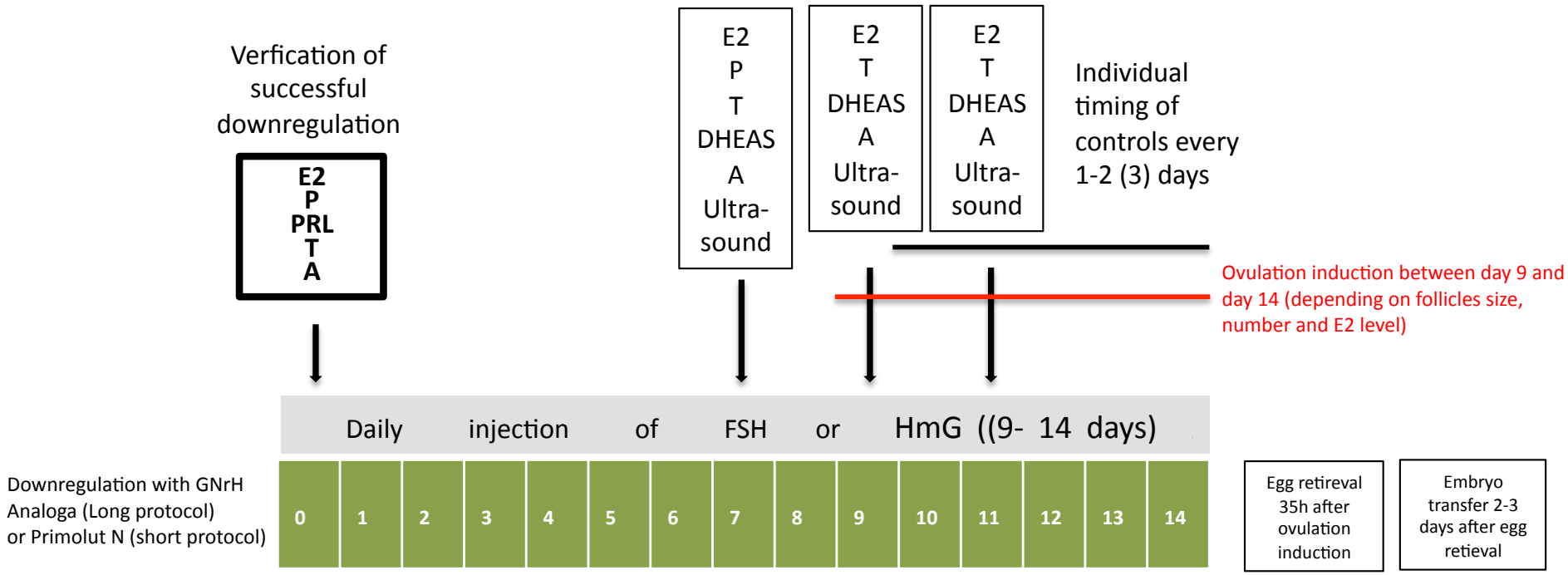
downregulation + stimulation + oocyte retrieval



Aim: between 11 and 15 mature oocytes

Risk: Ovarian hyperstimulation syndrome (OHSS)

Treatment protocol data



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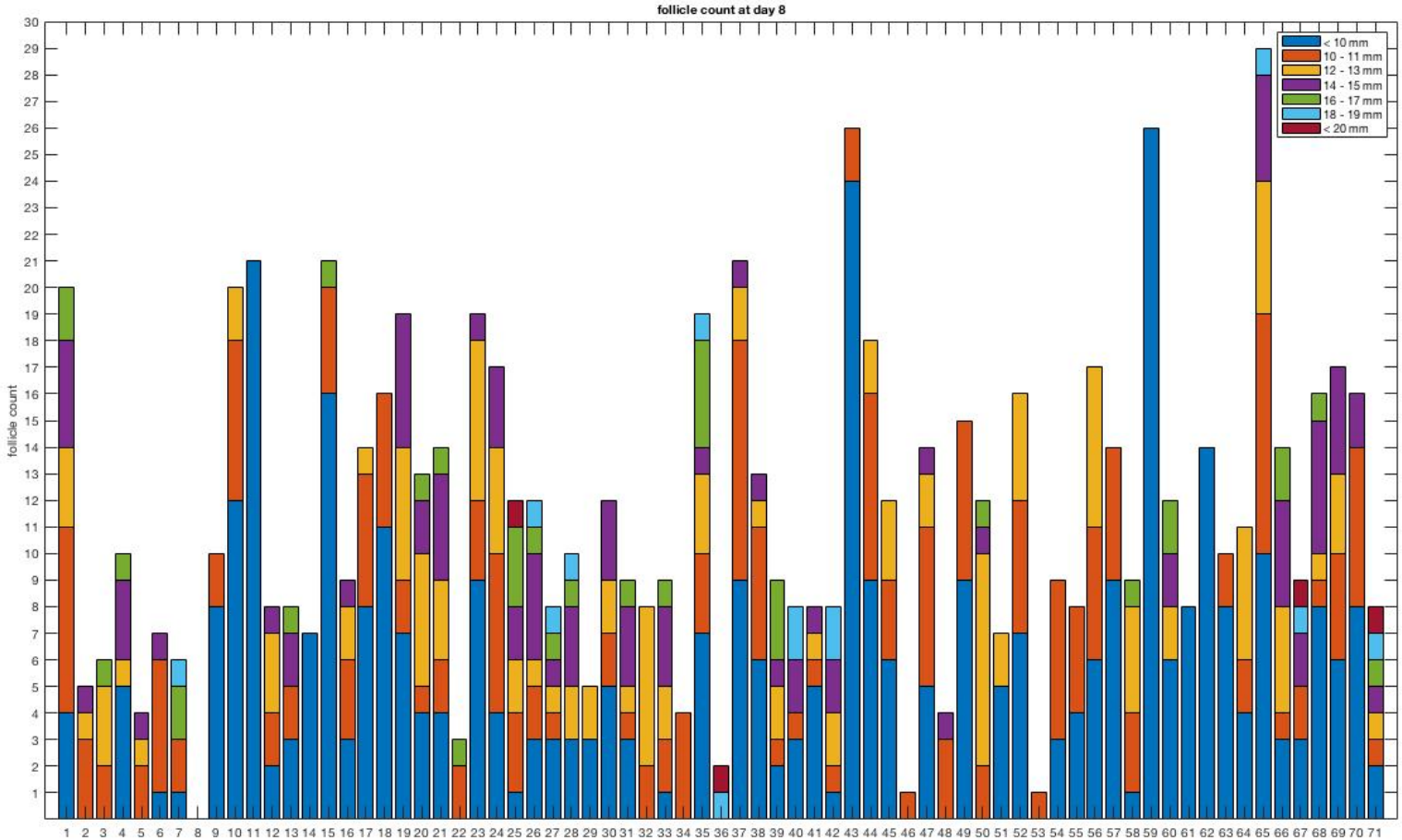
1	225	Mo	10.06.13	11	6062		2		1		1	1		2	3	5	3	3		

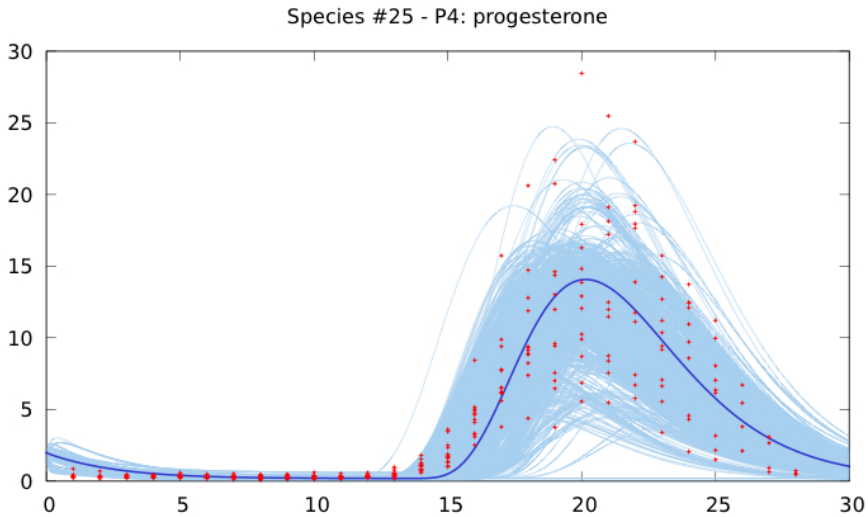
Treatment cycle: ultrasound measurements

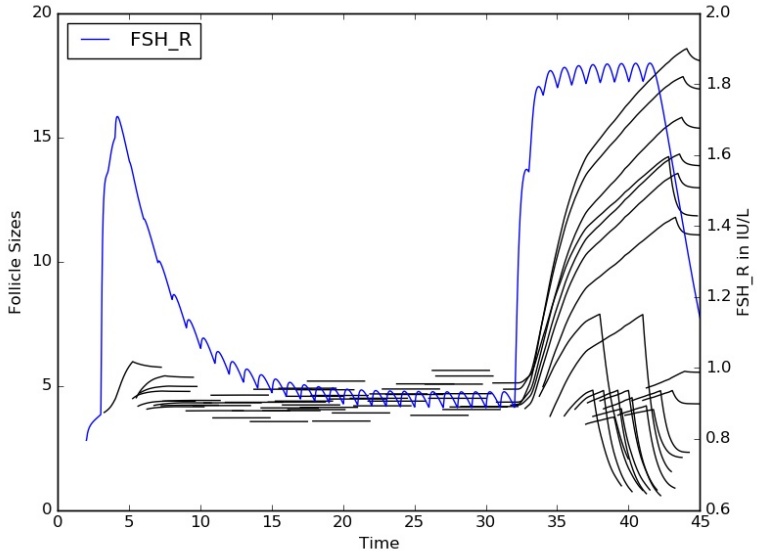


The PAEON model

Tasks:

- create a virtual patient population
- develop a new model for follicular development to simulate the stimulation phase





PAEON project: Model-Driven Computation of Treatments for Infertility Related Endocrinological Diseases (02/13-01/16)

Partners: ZIB, La Sapienza U Rome, U Lucerne, U Hospital Zürich, Hannover Medical School

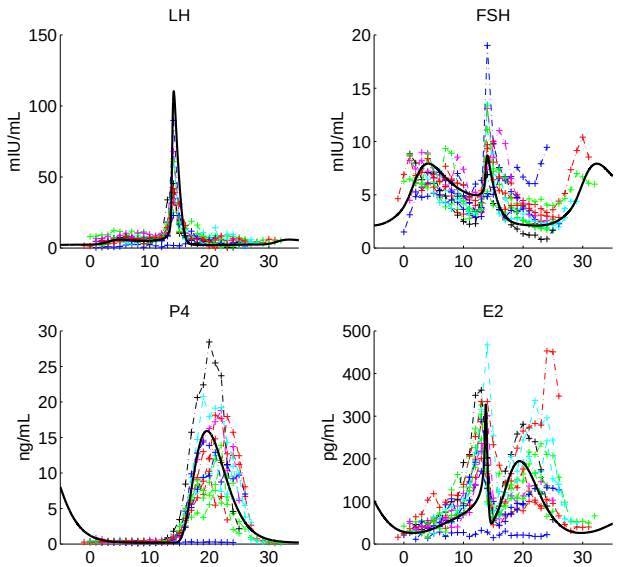
Parameter estimation

Frequentists's approach:

$$\|F(\theta)\|_2^2 \xrightarrow{\theta} \min$$

with sum of least squares errors

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

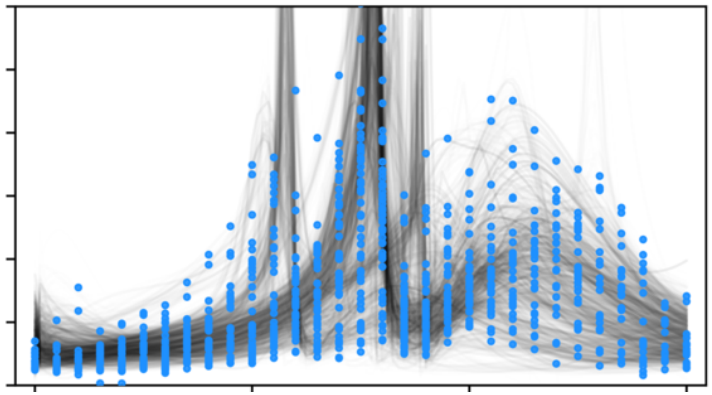


Bayesian approach:
computation of probability distributions according to Bayes' theorem

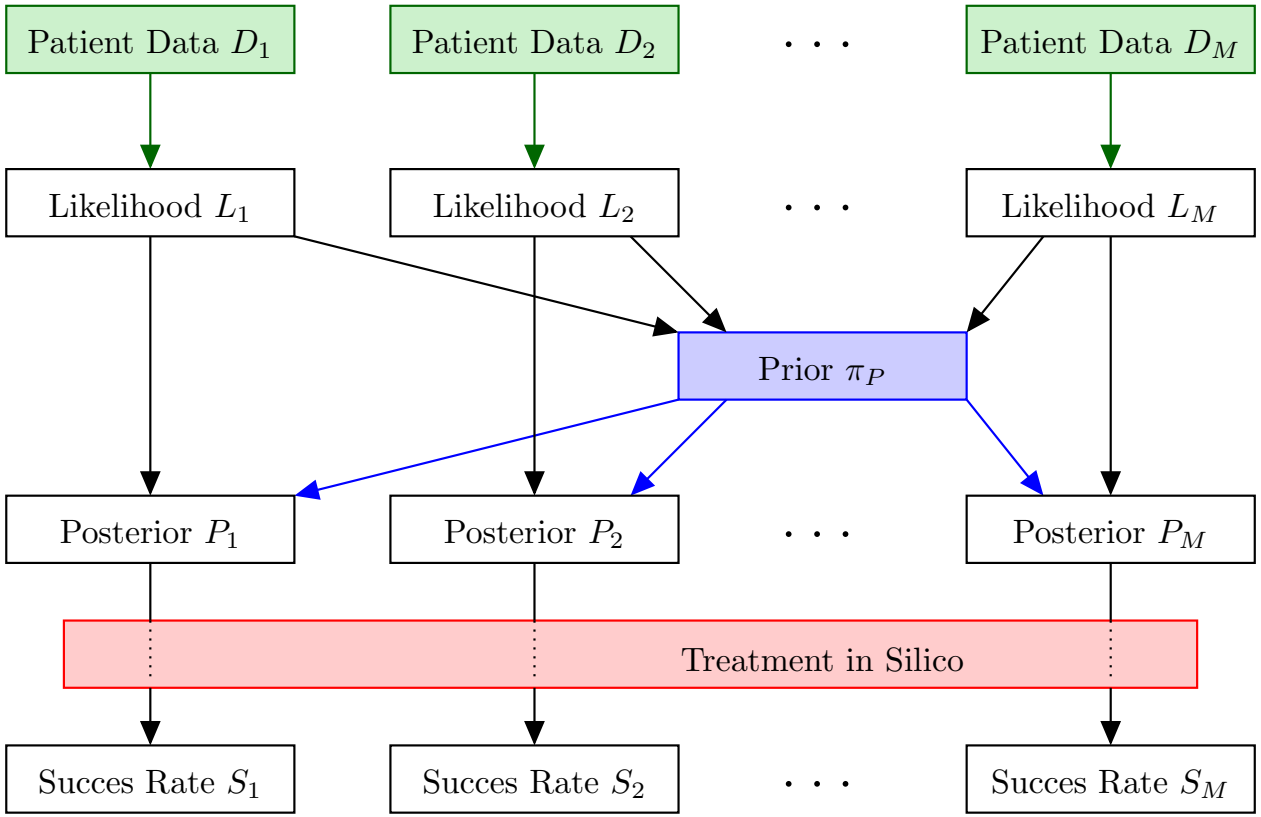
$$P(\theta|z) \propto P(z|\theta)P(\theta)$$

with likelihood

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



Prior estimation

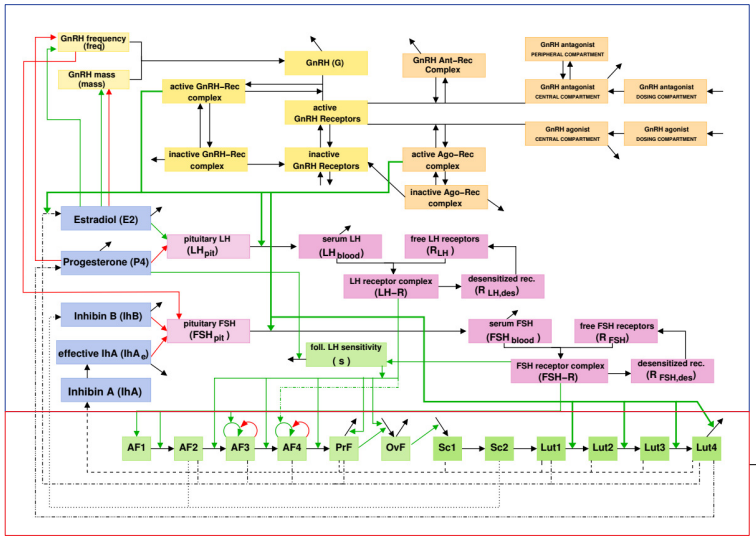


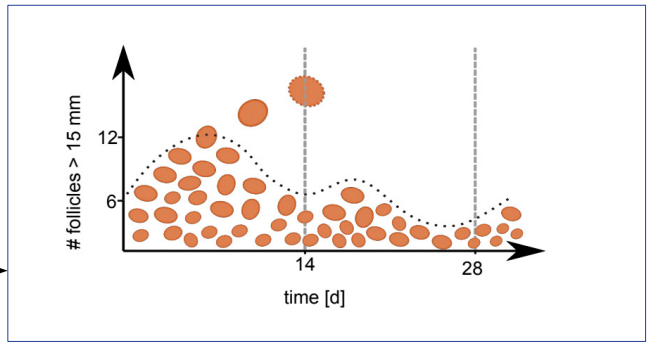
We introduced a nonparametric, transformation-invariant estimator for the prior distribution defined in terms of the missing information.

[Klebanov et al. Objective priors in the empirical Bayes framework. *Scand J Statistics* 48(4), 2021.]

A new follicle model

Replacing the "old" follicle model with a new one...





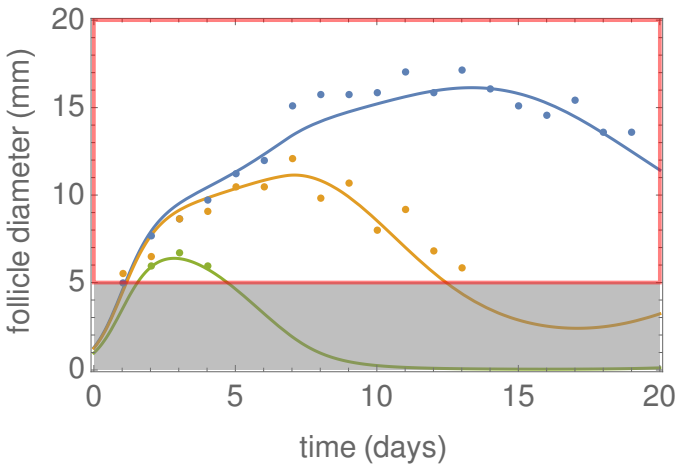
A new follicle model

Purpose: simulate the competitive growth of multiple follicles

$$x_i' = x_i(\xi - x_i)(\gamma - \kappa(\Sigma_j x_j^\nu - \mu x_i^\nu)), \quad x_i(0) \in (0, \xi)$$

$x_i(t)[mm]$: diameter of follicle $i = 1, \ldots, n$
$\xi[mm]$: upper limit for the size of a follicle (usually 20 mm)
$\gamma[1/(mm \cdot d)]$: individual growth rate
$\kappa[1/(mm^3 \cdot d)]$: strength of competition
$\mu \in (0, 1)$: proportion of self-harm
ν: fractal dimension

Fit to bovine ultrasound data:
[S. Cummins et al. *J Dairy Science* 95(7), 2012]



Number of dominant follicles:

$$d = \left[\mu + \frac{\gamma}{\kappa \xi^\nu}\right]$$

[Lange et al. (2019). doi: 10.1007/s00285-018-1284-0]

A hormone-dependent follicle model

Biological knowledge:

- FSH concentrations need to surpass a distinct level to stimulate ovarian follicle growth (FSH threshold concept).
- A limited duration of elevated FSH levels above the threshold is needed for single dominant follicle selection (FSH window concept).
- Progesterone exerts an inhibitory action on follicular development.
- There is follicle-to-follicle variablity in the response to FSH.

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Model assumptions:

- The FSH-receptor complex level regulates growth and selection.
- High system level FSH inhibits competition.
- Progesterone inhibits the follicular growth rate.
- Follicles have individual FSH sensitivity thresholds.

$$\frac{d}{dt}x_i = H^+(FSHR, T_{FSHR}(i), n_{FSHR}) \cdot (\xi - x_i)x_i \left(\gamma - \kappa \left(\sum x^2 - x_i^2\right)\right)$$

$$\kappa = \kappa_0 \cdot H^-(FSH, T^{\kappa}_{FSH}, n^{\kappa}_{FSH})$$

$$\gamma = \gamma_0 \cdot H^-(P4, T^{\gamma}_{P4}, n^{\gamma}_{P4}) \cdot H^+(FSHR, T^{\gamma}_{FSHR}, n^{\gamma}_{FSHR}).$$

A stochastic follicle model

Biological knowledge:

- The higher the FSH blood level, the more follicles are recruited.
- Follicular artresia is irreversible.

A stochastic follicle model

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Model assumption:

- The recruitment of follicles follows a Poisson process. The Poisson parameter λ (expected number of follicles that start growing within a certain time interval) is modulated by the FSH concentration.

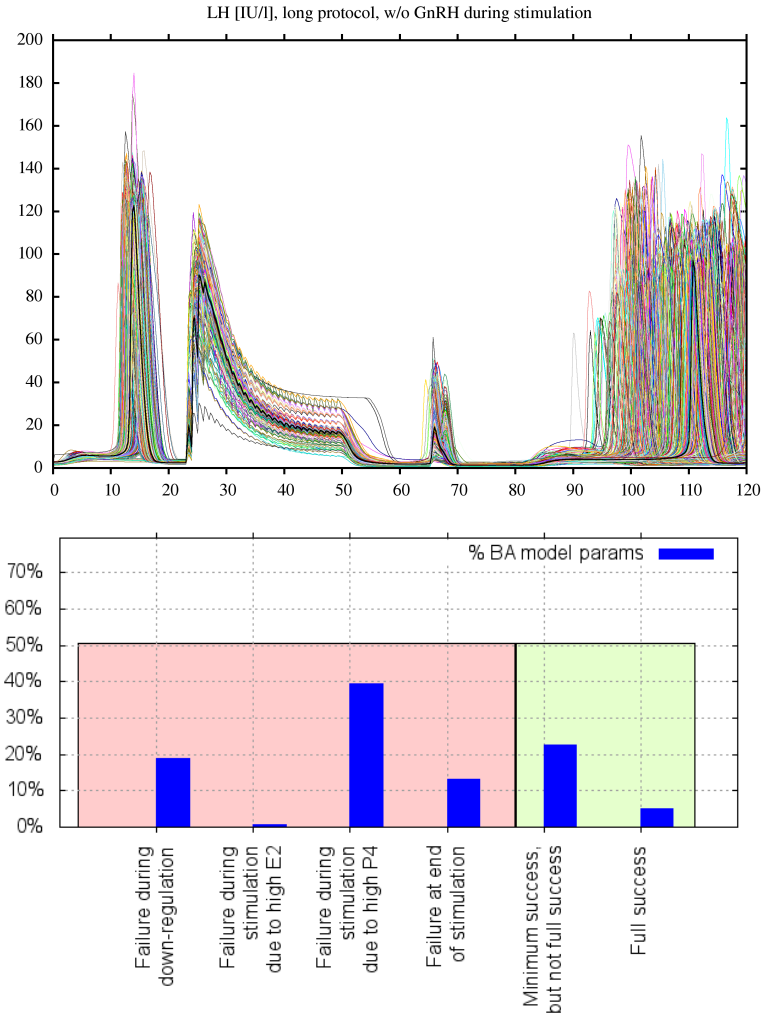
$$\lambda = \lambda_0 \cdot \left(1 + s_{FSH}^{Pois} \cdot H^+(FSH(T), T_{FSH}^{Pois}, n_{FSH}^{Pois})\right)$$

- Four possible follicular destinies:
  - (i) growth ($x_i'(t) \geq 0$)
  - (ii) ovulation ($x_i > 18$mm, $LH \geq T_{LH} = 25$ mIU/mL)
  - (iii) decay ($x_i'(t) < 0$)
  - (iv) large ($x_i > 18$mm) for 2 days, but not ovulating ($LH < T_{LH}$)

  Follicles (ii)-(iv) are removed from the simulation.

The PAEON model: Results

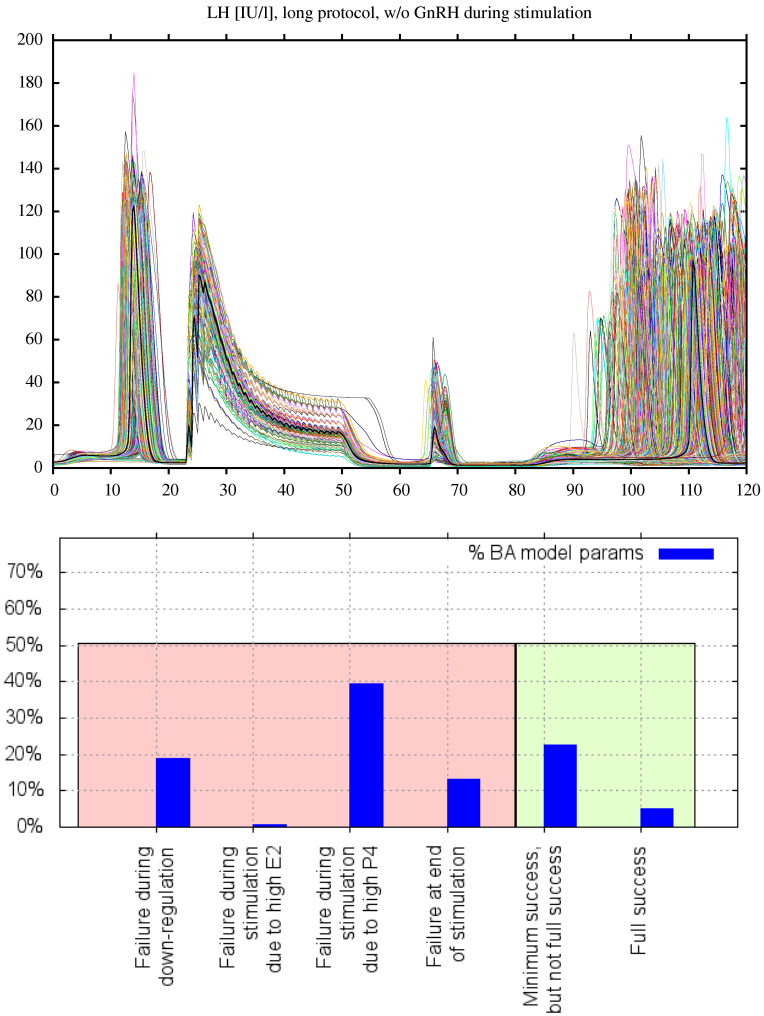
Treatment Verification



[Tronci et al. (2014). doi: 10.1109/FMCAD.2014.6987615] [Mancini et al. (2018). doi: 10.29007/g864]

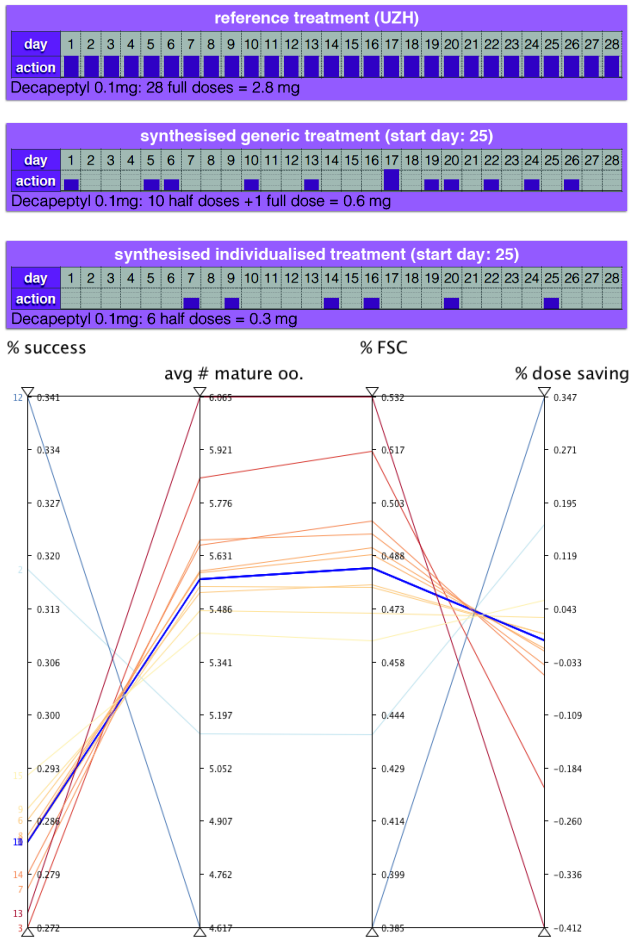
The PAEON model: Results

Treatment Verification



Design & Optimization

w.r.t. efficacy, cost, safety



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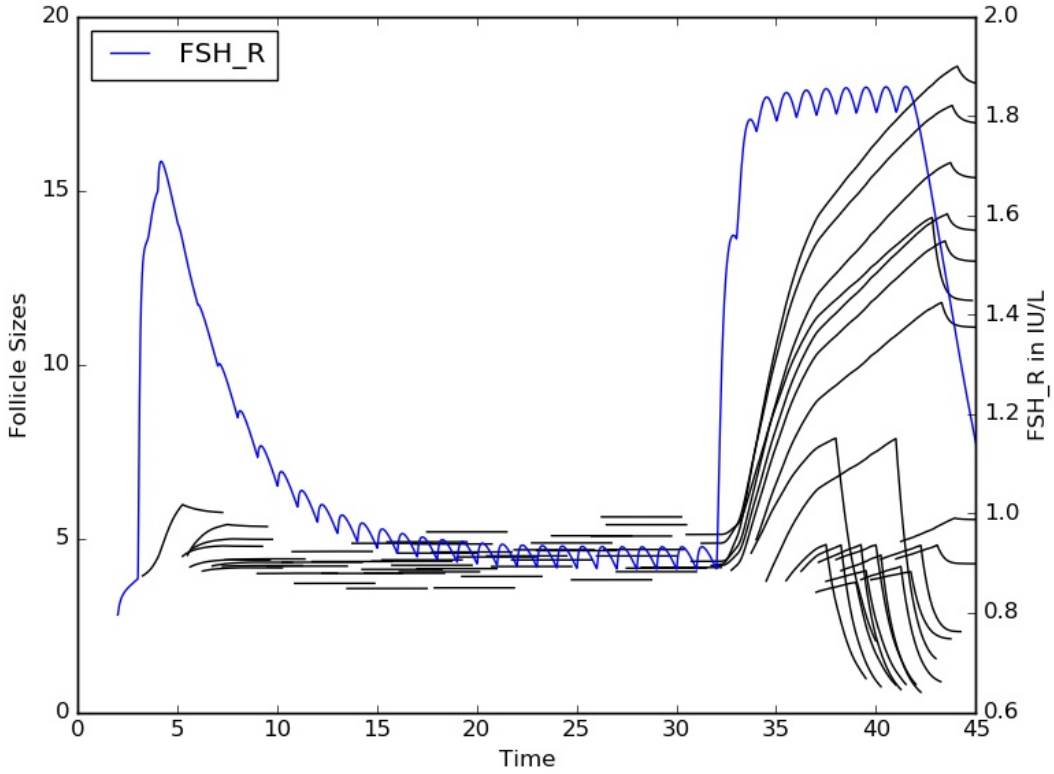
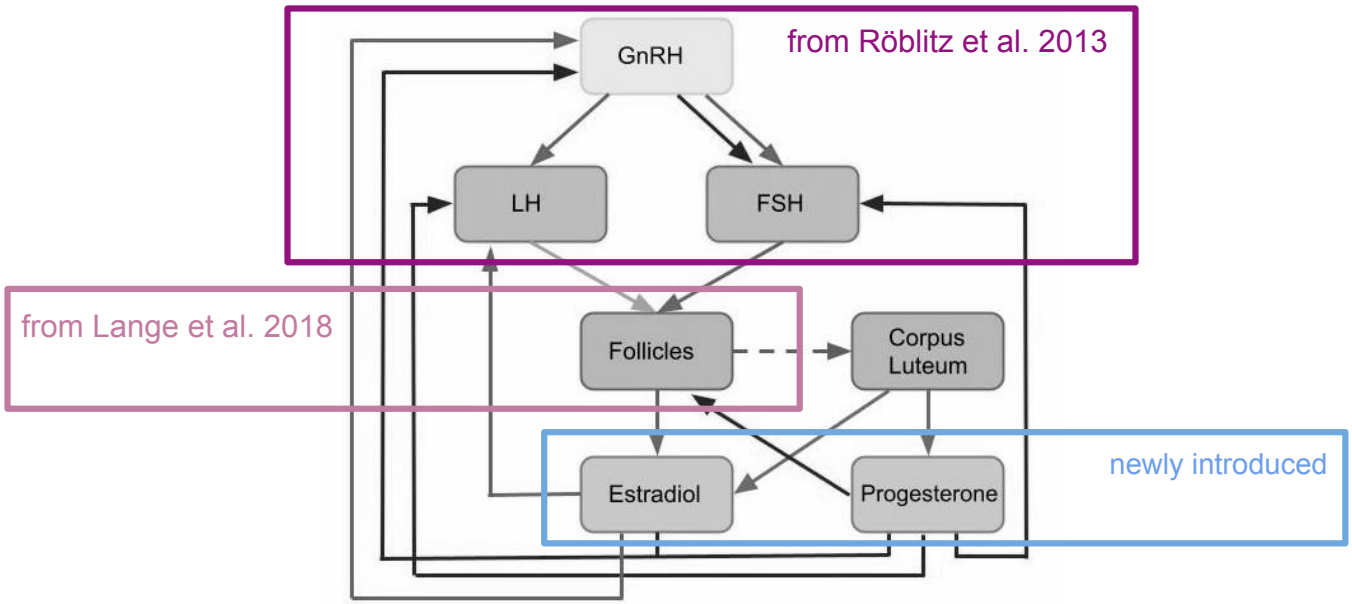
Follicular dynamics under treatment

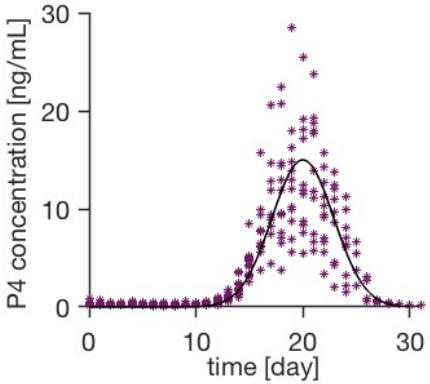


Note! The PAEON model is not fully coupled and can only be usd to simulate follicular growth dynamics under GnRH agonist treament when the feedback loop is interrupted due to GnRH-receptor downregulation n the pituitary.

A fully coupled model

Purpose: Simulation of hormone dynamics and follicular growth throughout consecutive cycles



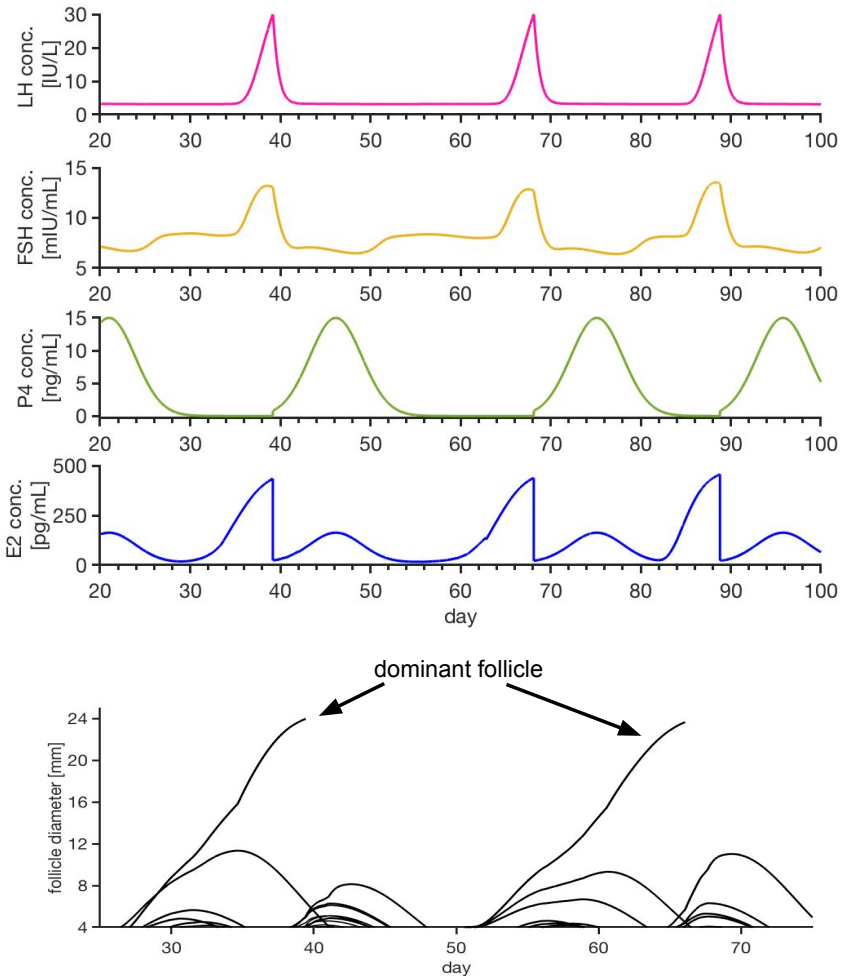


$$FS = \pi \cdot \sum H^{+}(x_i, T_{FS}, n_{FS}) \cdot (x_i)^2$$

$$E2(t) = b_{syn}^{E2} + s_{FS} \cdot FS + h_{E2} \cdot \exp\left(-w_{E2}(t - (T_{Ovu} + \tau))^2\right)$$

$$P4(t) = b_{syn}^{P4} + h_{P4} \cdot \exp\left(-w_{P4}(t - (T_{Ovu} + \tau))^2\right)$$

Unstimulated cycle

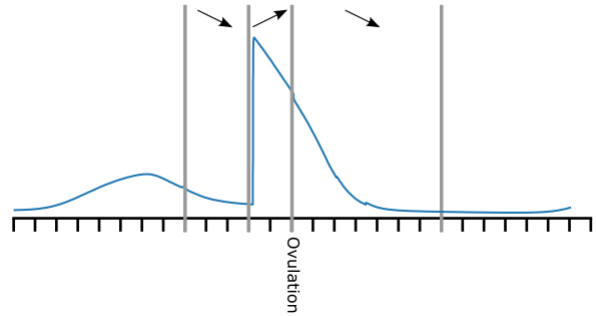


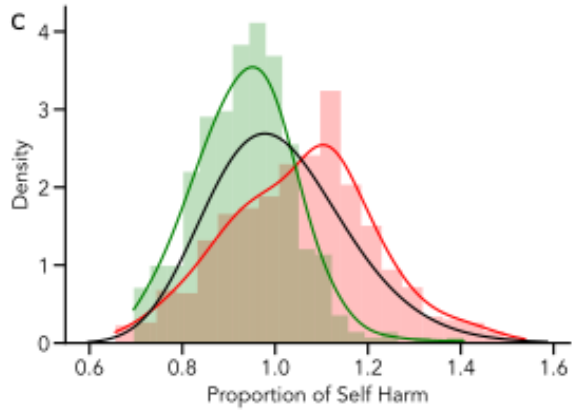
- the model generates quasi-periodic solutions for all four hormones
- wave-like growth behavior of the follicles (not enforced by implementation!)
- ovulation of a dominant follicle 12 h after the LH peak
- variability in cycle length (30.56 ± 7.00) and number of follicles per cycle (16.19 ± 3.08):
- no correlation between cycle length and follicular count

[S. Fischer et al. (2021). DOI: 10.3389/fendo.2021.613048]

Parameter space exploration

- the likelihood $P(z|\theta)$ is difficult to compute for a stochastic model
- $\rightarrow$ Approximate Bayesian Computation (ABC) rejection algorithm with summary statistics and log-normal prior
- acceptance criteria:
  - characteristic FSH profile in $> 80\%$ of the cycles
  - mean cycle lenght and standard deviation within physiological ranges



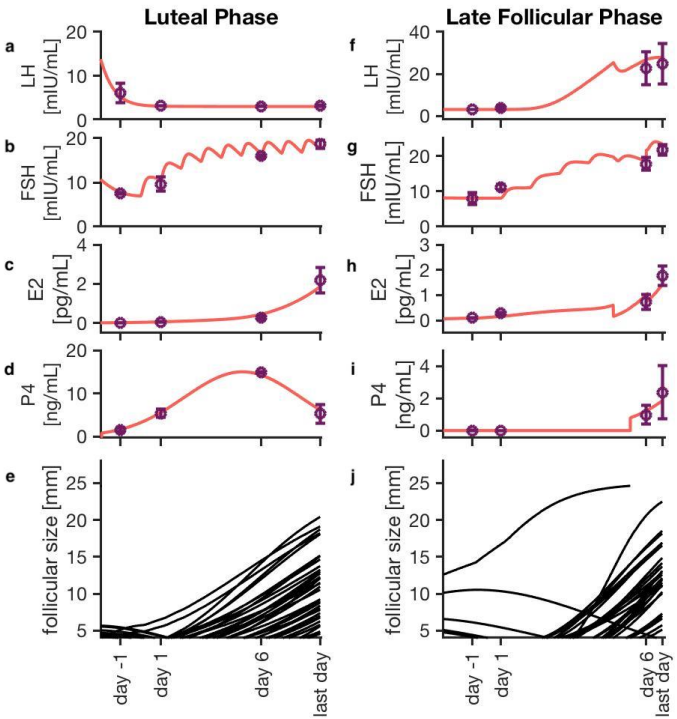


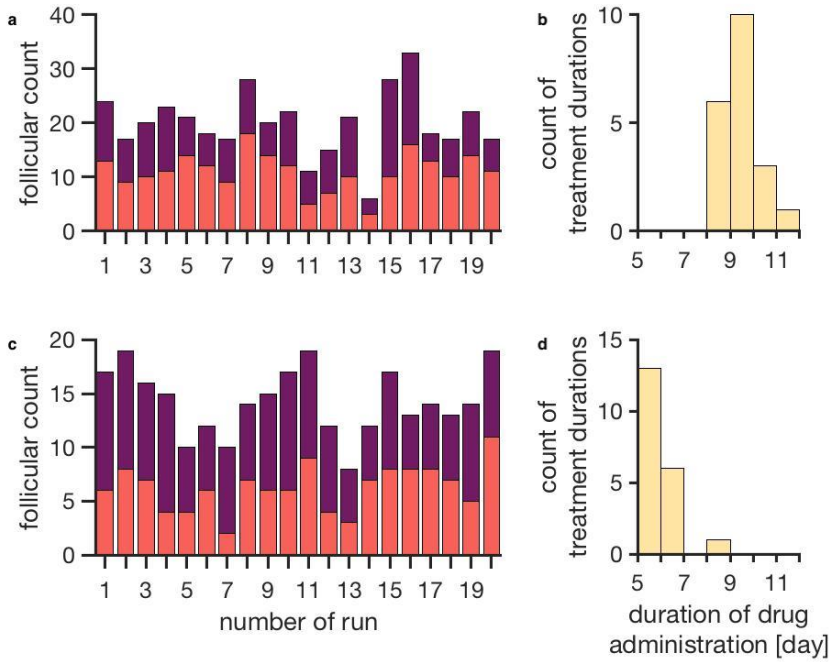
Results:

- μ (proportion of self-harm) is lower in normal cycles and negatively correlated with cycle length

[S. Fischer et al. (2022). DOI: 10. 1016/j.jtbi.2022.111150]

Random start ovarian stimulation





	Luteal Phase Stimulation		Late Follicular Phase Stimulation	
	[Kuang et al.]	Simulation	[Zhu et al.]	Simulation
# follicles 10 - 14 mm	13.9 ± 7.8	11.1 ± 3.5		6.3 ± 2.2
# follicles > 14 mm	11.1 ± 5.5	8.9 ± 3.7	11.7 ± 6.2	8.0 ± 2.2
treatment duration	10.2 ± 1.6	9.4 ± 0.7	10.93 ± 1.66	6.0 ± 0.7

[X. Zhu, Y. Fu. (2019). doi: 10.3389/fendo.2019.00448; Y. Kuang et al. (2014). doi: 0.1016/j.fertnstert.2013.09.007; S. Fischer et al. (2021). DOI: 10.3389/fendo.2021.613048]

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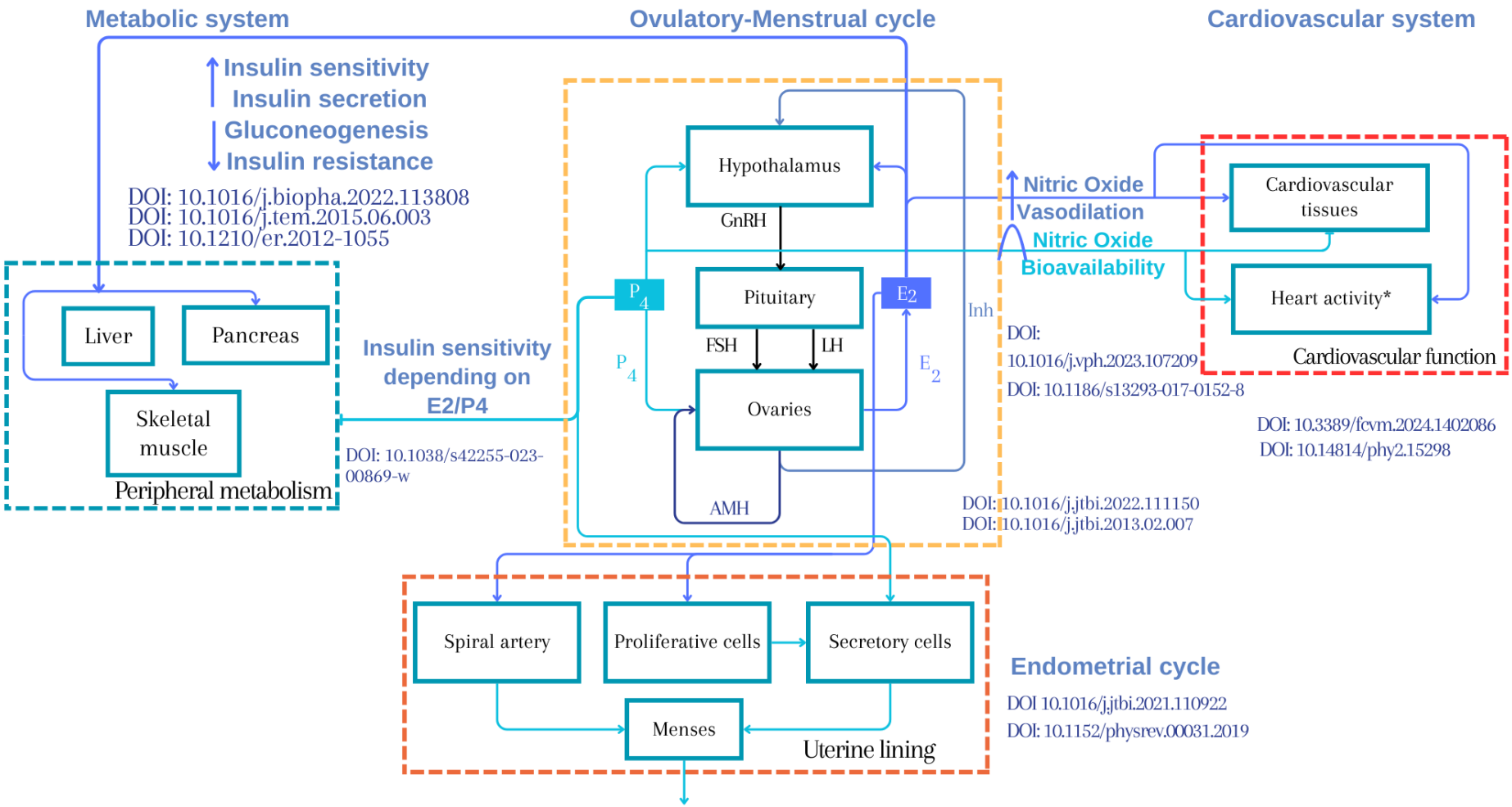
- Model simulations confirm that ovarian hyperstimulation can be started at random time points in the cycle.

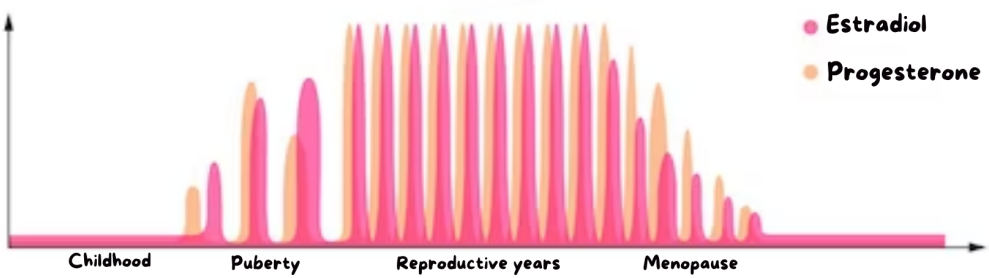
Outlook

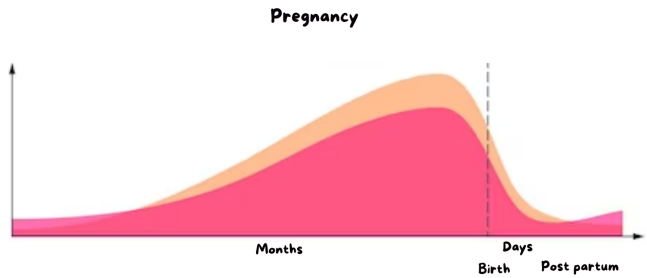


The hypothalamic-pituitary-ovarian axis interacts with other endocrine sub-systems!

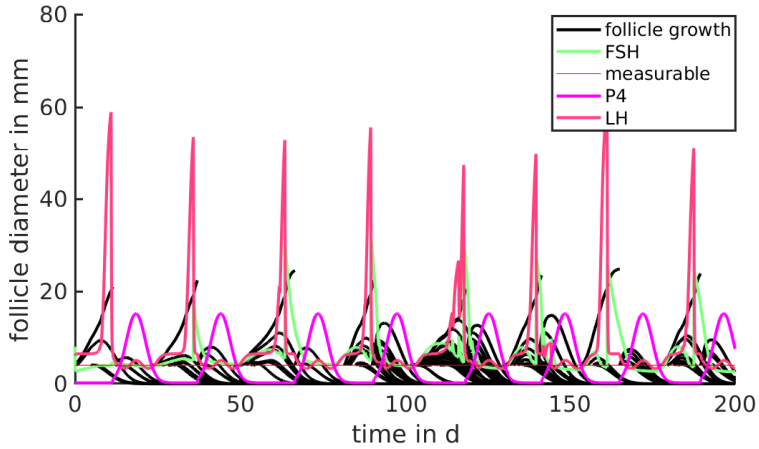
Outlook

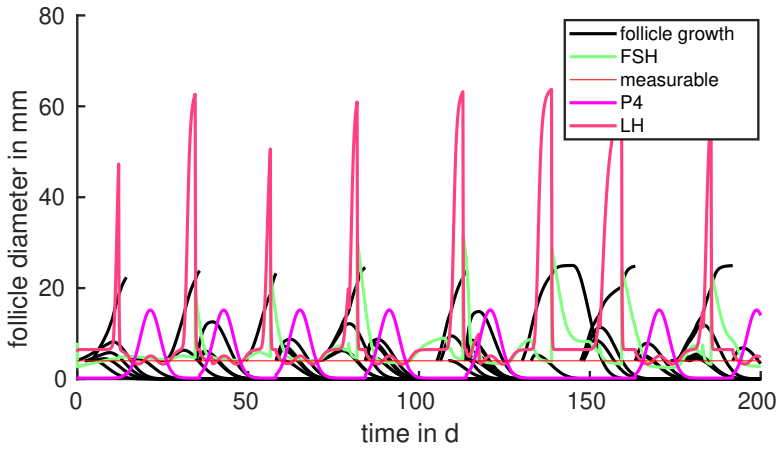
Hormonal rhythms change with age and during pregnancy!





Simulation of menopausal transition by reducing the follicular recruitment rate:





Key publications

- S. Fischer-Holzhausen, S. Röblitz. Hormonal regulation of ovarian follicle growth in humans: Model-based exploration of cycle variability and parameter sensitivities. *Journal of Theoretical Biology* 547:111150, 2022. https://doi.org/10.1016/j.jtbi.2022.111150
- S. Fischer, R. Ehrig, S. Schäfer, E. Tronci, T. Mancini, M. Egli, F. Ille, T. H. C. Krüger, B. Leeners, S. Röblitz. Mathematical Modeling and Simulation Provides Evidence for New Strategies of Ovarian Stimulation. *Frontiers in Endocrinology* 12:613048, 2021. https://doi.org/10.3389/fendo.2021.613048
- A. Lange, R. Schwieger, J. Plöntzke, S. Schäfer and S. Röblitz. Follicular competition in cows: The selection of dominant follicles as a synergistic effect. *Journal of Mathematical Biology* 78(3):579–606, 2019. https://doi.org/10.1007/s00285-018-1284-0
- S. Röblitz, C. Stötzel, P. Deuflhard, H. M. Jones, D.-O. Azulay, P. van der Graaf, and S. W. Martin. A mathematical model of the human menstrual cycle for the administration of GnRH analogues. *J. Theoret. Biol.* 321:8–27, 2013. https://doi.org/10.1016/j.jtbi.2012.11.020.

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Carolina Ramirez Mazo (UNAL/CBU)