

# Endocrinological Networks

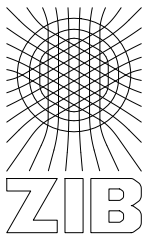
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## From Data to Mathematical Models

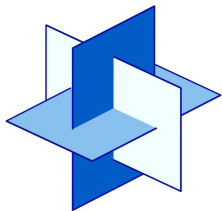
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(Computational Systems Biology Group)

Molecular Interactions  
September 16, 2010

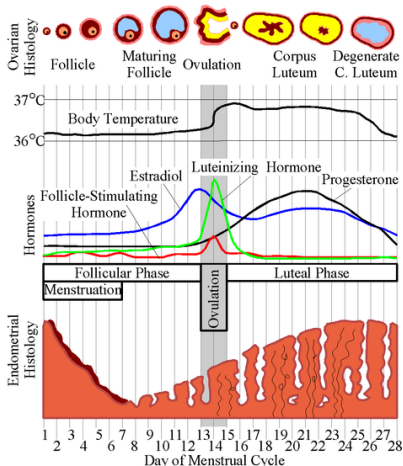


Zuse Institute Berlin



DFG Research Center  
MATHEON

# 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>

## First step

- ▶ a model for the idealized cycle of an idealized woman
- ▶ calculation of hormone profiles and follicle development over time

## What can we use such a model for?

- ▶ find parametrizations for individual women, study of infertility or genetic differences
- ▶ simulation of external effects (administration of drugs, design of hormone therapies)

## Models available before

- ▶ **smaller compartment models**: fewer (though essential) compartments coupled by coarse interactions

[Schlosser/Selgrade 2000, Harris 2001]

- ▶ **small biochemical reaction models** (such as receptor binding): often not fully integrated into total model

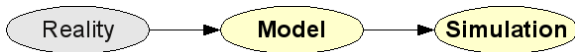
[Clément 2001]

## ZIB Model **GynCycle**

- ▶ **fully integrated compartment model**: containing most relevant couplings, both physiological and biochemical ones
- ▶ modifications for special purposes:
  - ▶ model **reduction** (to focus on specific aspects)
  - ▶ model **expansion** (to catch further effects)

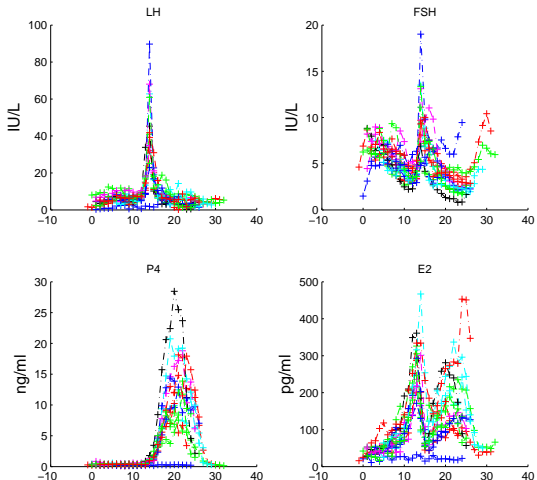
- ▶ see the cycle as a whole system rather than only focusing on individual parts
- ▶ investigate how the components function together
- ▶ find reliable abstraction levels that display the most important mechanisms

## What the Mathematicians do



- ▶ **model development** and **parametrization** such that the simulation results match given data
- ▶ two error sources:
  - ▶ modeling error
  - ▶ data errors (measuring techniques and their interpretation)

# Data



measurement values for 12 women over one cycle

- ▶ 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

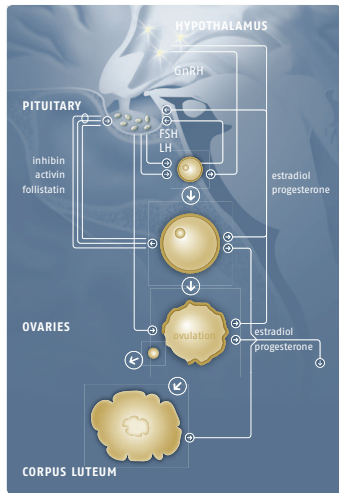
**ideal measurement:** data for a single woman together with the length of her cycle, the stage of the cycle (days since last menses), and measurement errors

# Model Development

**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)



The change of a component over time is modeled as

$$\frac{d}{dt} \textit{Component}(t) = \textit{Production}(t) - \textit{Clearance}(t)$$

or as

$$\frac{d}{dt} \textit{Component}(t) = \textit{Synthesis}(t) - \textit{Release}(t)$$

[Schlosser/Selgrade 2000]

Abstract mathematical formulation:

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

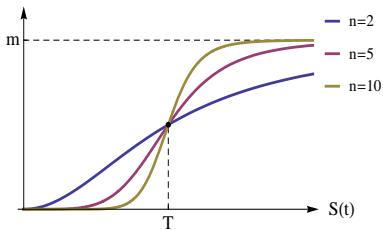
Production, clearance, synthesis and release usually depend on other components. To model **stimulation** or **inhibition** we use **Hill-functions**.

## stimulation

positive Hill function

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

$H^+(S(t), T, n)$

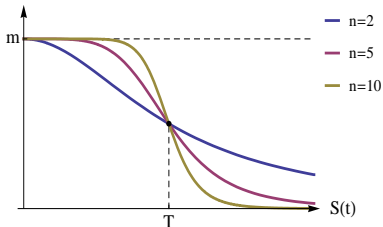


## inhibition

negative Hill function

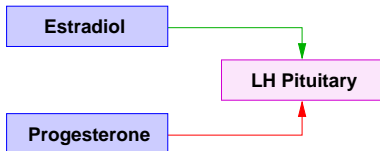
$$H^-(S(t), T, n) := \frac{T^n}{S(t)^n + T^n}$$

$H^-(S(t), T, n)$

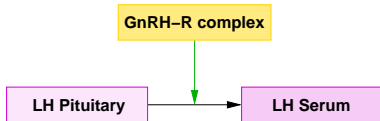


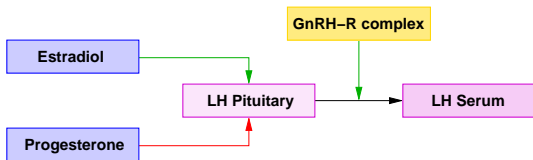
# Example: Model building for LH

LH synthesis in the pituitary is stimulated by estradiol and inhibited by progesterone.



The release of LH into the blood is stimulated by the GnRH-receptor complex if the complex is above a certain threshold.



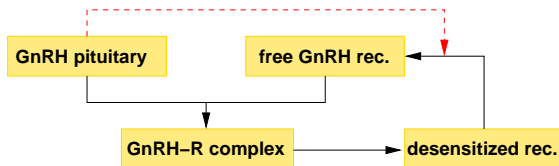


$$Syn_{LH}(t) = (b_{Syn_{LH}} + m_{E2} \cdot H^+(E2, T_{E2}; n_{E2})) \cdot H^-(P4, T_{P4}; n_{P4})(1 - LH_{Pit}/K_{LH_{Pit}})$$

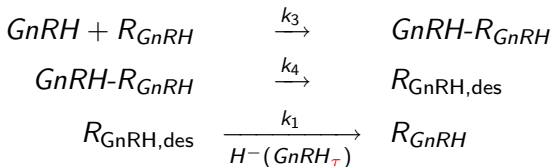
$$Rel_{LH}(t) = (b_{Rel_{LH}} + m_{GnRH-R} \cdot H^+(GnRH-R, T_{GnRH-R}, n_{GnRH-R})) \cdot GnRH-R \cdot LH_{Pit}(t)$$

$$\frac{d}{dt} LH_{Pit}(t) = Syn_{LH}(t) - Rel_{LH}(t)$$

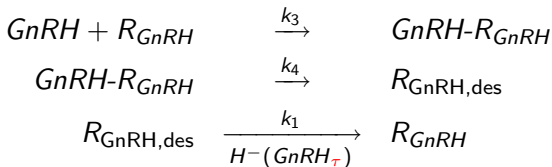
$$\frac{d}{dt} LH_{blood}(t) = \frac{1}{V_{blood}} \frac{1}{c_{nmol/IU}} Rel_{LH}(t) - k \cdot LH_{blood} \cdot R_{LH} - c \cdot LH_{blood}$$



GnRH inhibits the formation of free receptors from the desensitized receptors with a certain **delay**



## Reaction equations



## (Delay) differential equations

$$\begin{aligned}\frac{d}{dt}R_{GnRH} &= k_1 \cdot R_{GnRH,des} \cdot H^-(GnRH_{\tau}, T_{GnRH}; 1) \\&\quad - k_3 \cdot GnRH \cdot R_{GnRH} \\ \frac{d}{dt}GnRH-R_{GnRH} &= k_3 \cdot GnRH \cdot R_{GnRH} - k_4 \cdot GnRH-R_{GnRH} \\ \frac{d}{dt}R_{GnRH,des} &= k_4 \cdot GnRH-R_{GnRH} \\&\quad - k_1 \cdot R_{GnRH,des} \cdot H^-(GnRH_{\tau}, T_{GnRH}; 1)\end{aligned}$$

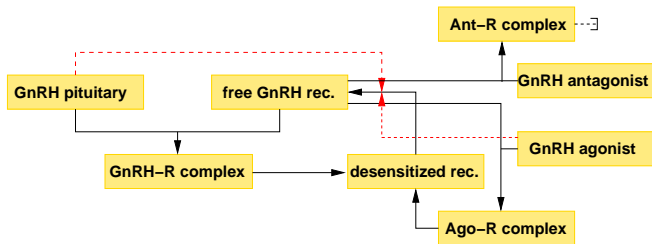
In some equations **time delays** are incorporated to capture the time needed for components to influence each other:

$$y'(t) = f(t, y(t), y(t - \tau_1), \dots, y(t - \tau_m)), \quad \tau_i > 0, i = 1, \dots, m$$

e.g. transportation times in blood, receptor recovery times

Use of special solvers for delay differential equations, e.g. RADAR5

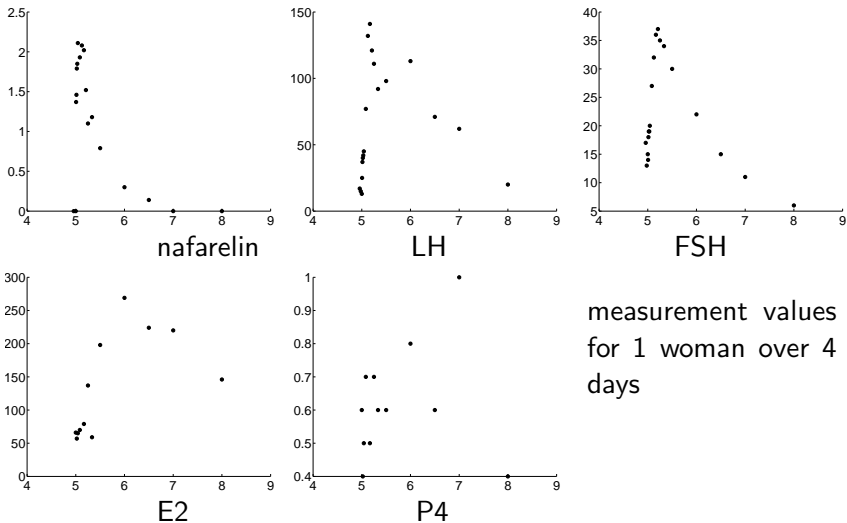
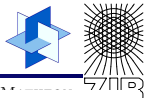
[Guglielmi and Hairer, 2004]

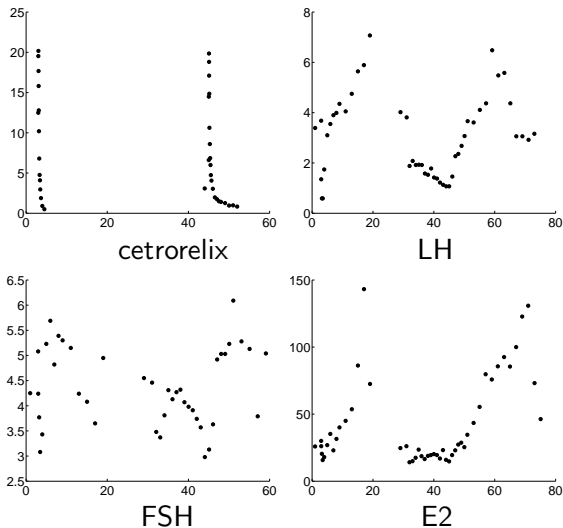


Two types of analogues have to be distinguished

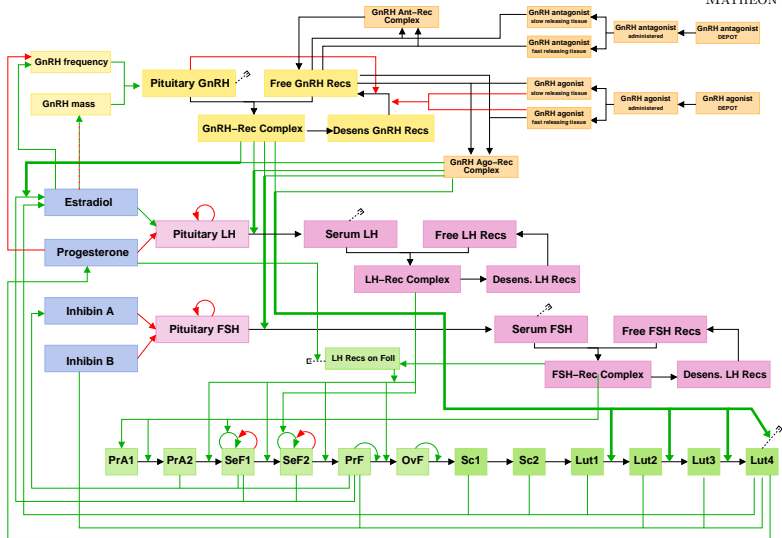
- ▶ **Agonists:** activation of GnRH receptor resulting in (initially) increased secretion of FSH and LH, followed by a drop in gonadotropin secretion caused by receptor downregulation
- ▶ **Antagonists:** competitive and reversible binding to GnRH receptors, resulting in an immediate drop in gonadotropin secretion

# Data for single dose nafarelin





measurement values  
for 1 woman over  
several days



# Parameter Identification

Model  $y(t, p) = (y_1(t, p), \dots, y_n(t, p))$

Parameters  $p = (p_1, \dots, p_q)$

Data  $x = (x_1, \dots, x_m)$ ,  $m \geq q$

mostly  $m \gg q$ , data compression

Least squares formulation:

$$\|F(p)\|_2^2 = \sum_{i=1}^m \left( \frac{x_i - y(t_i, p)}{\delta x_i} \right)^2 \rightarrow \min$$

$\delta x_i$  : measurement accuracy for the  $x_i$  (never forget!)  
**relative** measurement accuracy:

$$\delta x_i = \varepsilon_x x_i$$

$\varepsilon_x$  mostly  $10^{-1}$  to  $10^{-3}$  in experiments

- ▶ solution of the **nonlinear** least squares problem by a global adaptive Gauss-Newton method

$$\|F'(p^{(k)})\Delta p^{(k)} + F(p^{(k)})\|^2 \rightarrow \min$$
$$p^{(k+1)} = p^{(k)} + \lambda_k \Delta p^{(k)}, k = 0, 1, 2, \dots$$

[Deuffhard: Newton Methods for Nonlinear Problems, 2004]

- ▶ sequence of **linear** least squares problems with  $(m \times q)$  Jacobian matrix  $F'(p)$
- ▶  $F'(p)$  gives us some hints whether the current combination of model and data will permit an actual identification of the parameters
- ▶ good **initial guess** required (model decomposition)

## Analysis of the matrix $F'(p)$

- ▶ the rows contain the **sensitivities** of the measured components w. r. t. the parameters  $p = (p_1, \dots, p_q)$

$$F'_{ij}(p) = \frac{\partial}{\partial p_j} y_{k_i}(t_i, p), \quad i = 1, \dots, m, \quad k_i \in \{1, \dots, n\}$$

- ▶ small **column norm** indicates small sensitivity
- ▶ detection of linear dependencies by monitoring the **subcondition** numbers

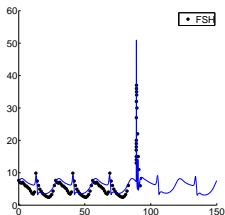
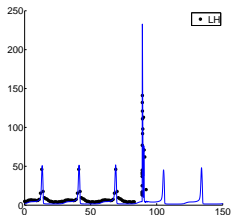
$$F'(p)\Pi = QR, \quad r_{11} \geq r_{22} \geq \dots \geq r_{qq}$$

$$sc_j = r_{11}/r_{jj}$$

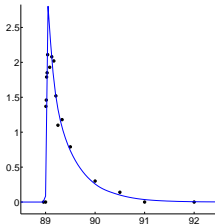
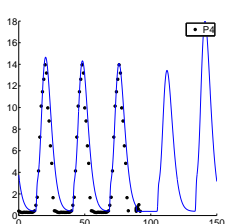
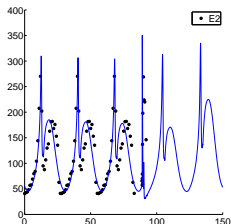
- ▶ identifiable parameters:  $\varepsilon_x sc_j < 1$  [Deuffhard/Sautter 1980]

# Some Simulation Results

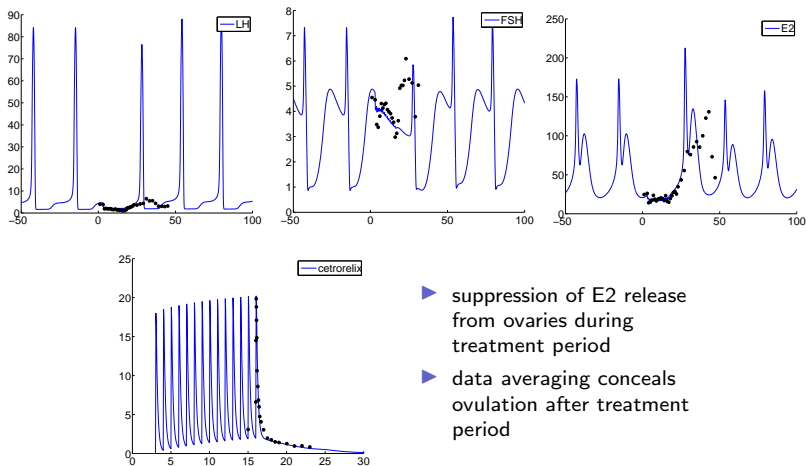
# Agonist: Nafarelin 100mg SD, cycle day 5



- ▶ reference: prolongation of cycle by  $4.6 \pm 1.7$  days (ovulation 15 days after nafarelin administration)
- ▶ actual: prolongation of cycle by 8 days (ovulation 16 days after nafarelin administration)



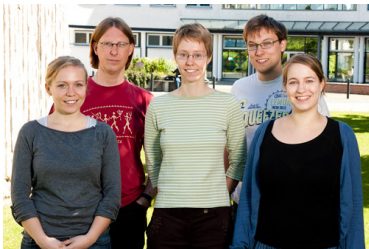
# Antagonist: Cetrorelix 1mg MD, days 3–16



- ▶ suppression of E2 release from ovaries during treatment period
- ▶ data averaging conceals ovulation after treatment period



**Thank you for your attention!**



**Contact:**

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<http://www.zib.de/Numerik/CompSysBio/index.en.html>