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## Motivation

For modelling and simulation of biological models:

**identification of unknown parameter values**  
such as growth and clearance rates of the involved  
substances is crucial

Use of  
**Bayesian methods**  
to recover and analyse  
**the joint probability distributions**  
of the free parameters

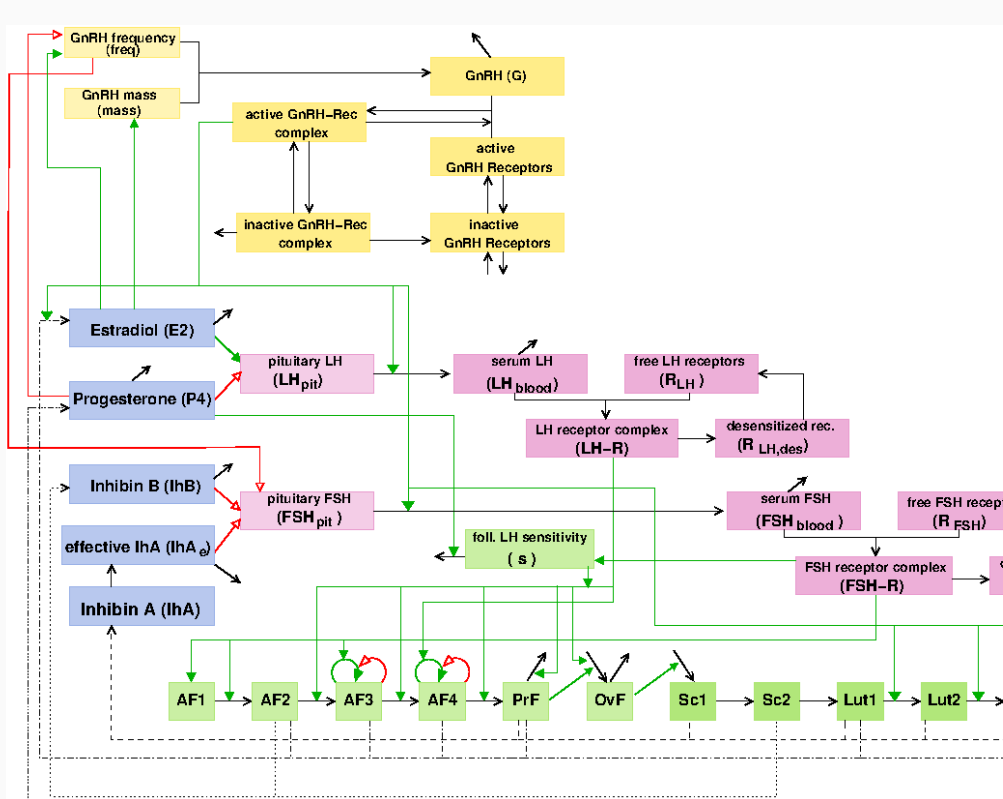
### Analysis of the sampled marginal distributions



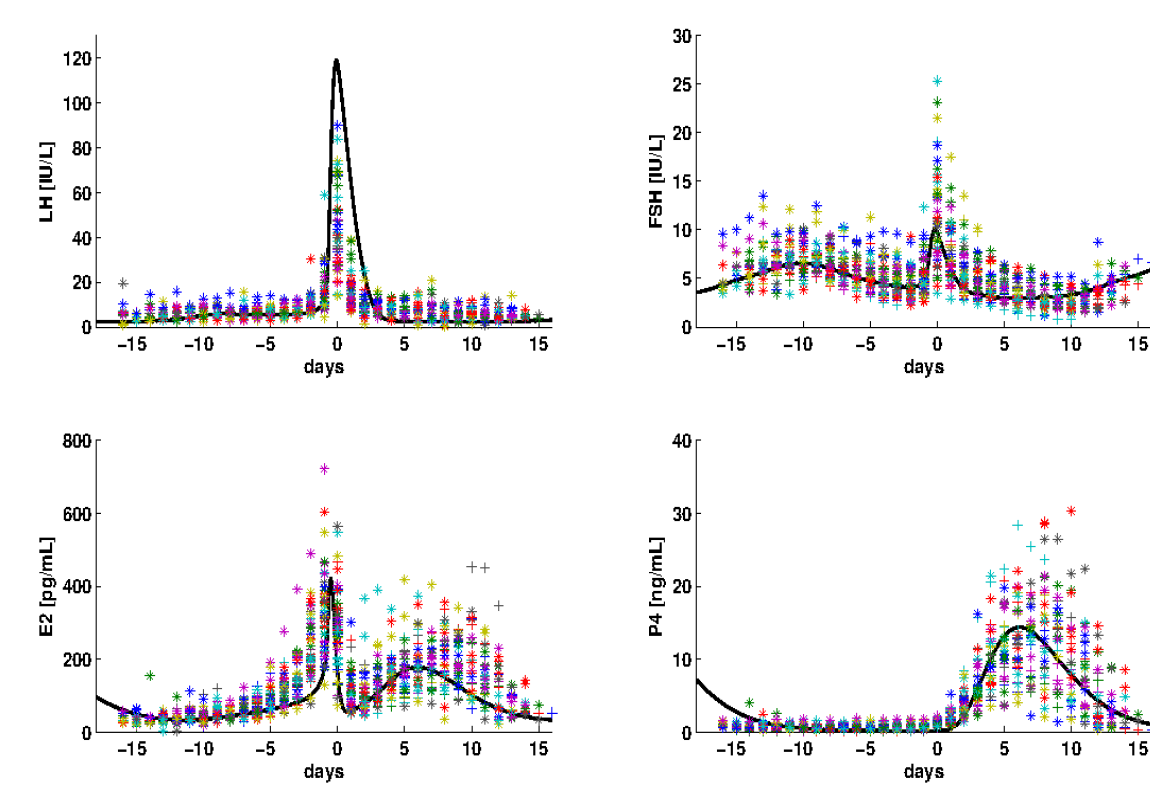
**detect parameter regions which lead to the simulation of pathological situations**

## ODE Model and Simulation

ODE model GynCycle: **33 highly nonlinear ODEs, 114 parameters** (63 identifiable), describes the regulation of the female menstrual cycle

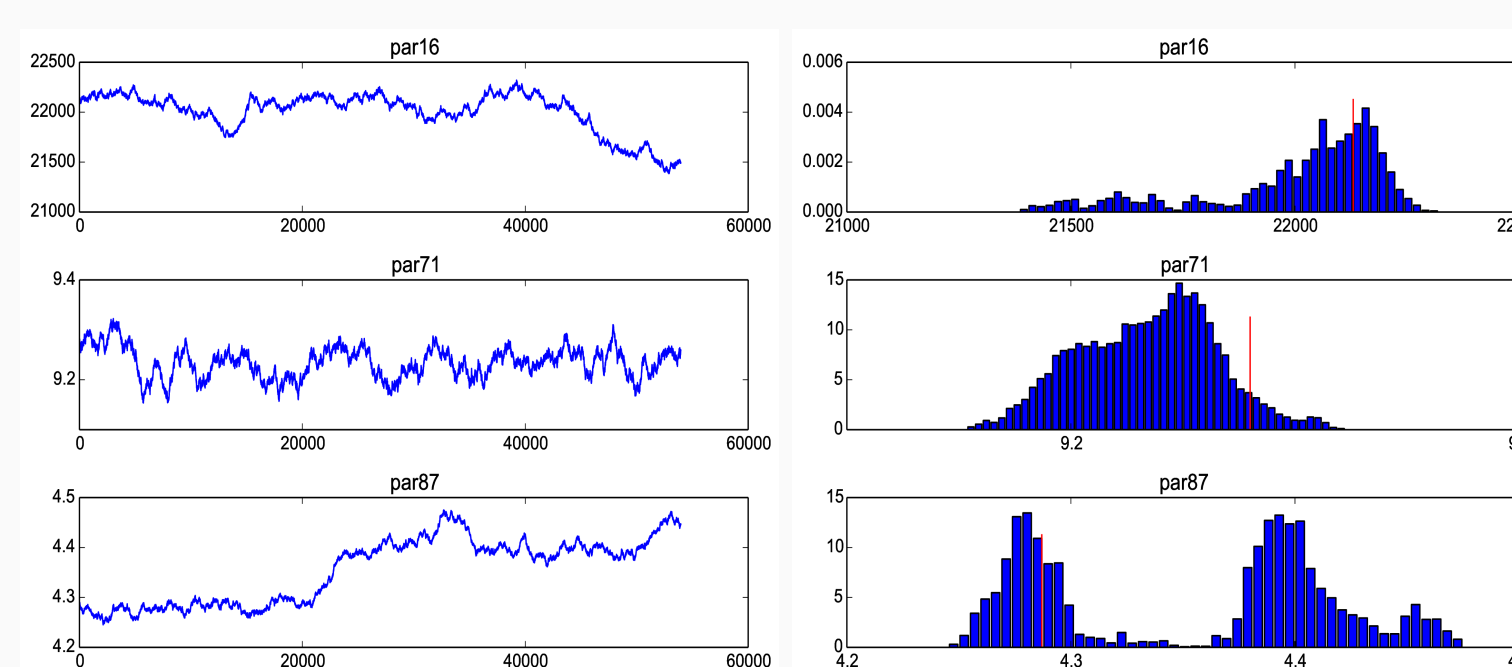


## Mechanisms for regulation of female menstrual cycle



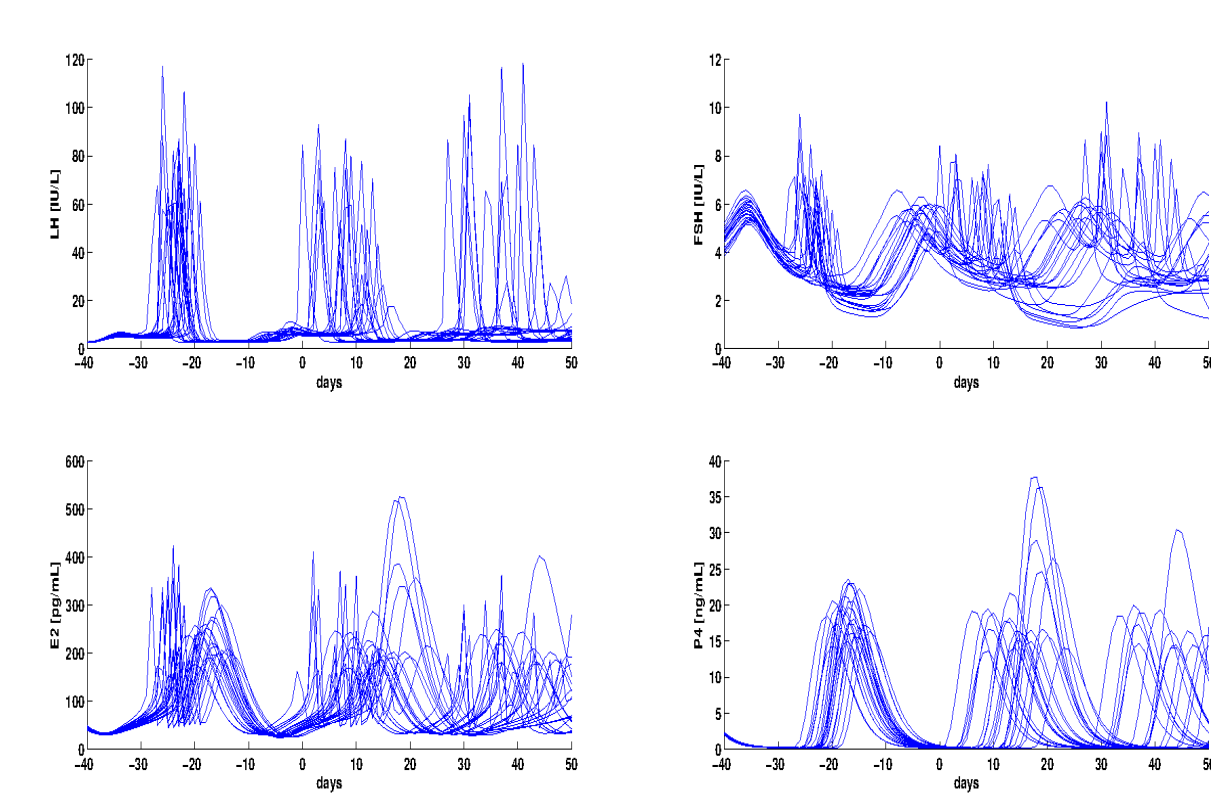
Simulation results with nominal parameter set, together with experimental data of 40 individuals in courtesy of Dorothea Wunder, CHUV, Lausanne, and 12 individuals from a previous collaboration with Pfizer

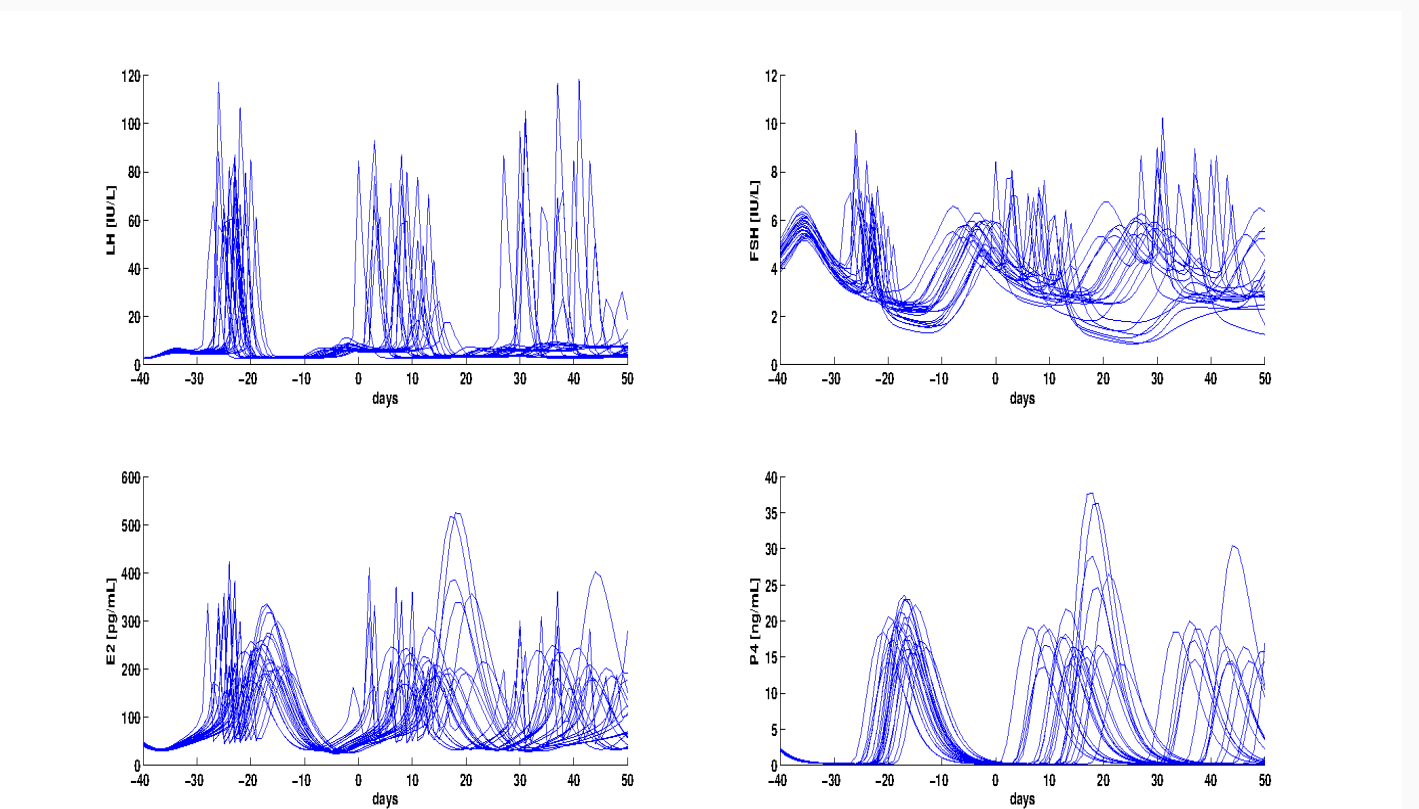
## Markov-Chain-Monte-Carlo Method



## Markov chains and marginal distributions for a selection of parameters

- **Implementation of Metropolis-Hastings in Python**
- **Integration of ODEs in LIMEX (Fortran, connected via f2py) - speed-up (for a simulation of 150 days, Matlab ode23tb: 2.75 secs, numpy lsoda: 1.55 secs, fortran LIMEX called from python: 0.043 secs )**

- After every integration: **shift data** to the corresponding period
  - Accept **only periodic solutions**
  - Sensitivities of the parameters in the nominal set are used as standard deviation of the proposal distribution
  - **Lognormal distribution** for the transition probabilities
  - **Uniform distribution** as priors
  - Sampling from the **joint distribution** accounts for hormone profiles of individual patients
- 
- Simulation results for 3 periods with sampled



### Simulation results for 3 periods with sampled parameter sets

## Parameter Estimation

Wanted  $\theta \in \mathbb{R}^n$  (parameter), given  $z \in \mathbb{R}^m$  (measurements)

$z \approx y(\theta)$        $y$  model  
(e.g. solution of ODE system  $y' = f(y, \theta)$ )

### Least Squares approach

$$argmin_{\theta \in \mathbb{R}^n} \left( \sum_k \sum_l \left( \frac{z_{kl} - y_k(t_l, \theta)}{\sigma_{kl}} \right)^2 \right)$$

Identify the most probable parameter value, assume normal distribution  
Problem: Does not account for dependencies between parameters

### Bayesian approach

$$\pi^z(\theta) = \frac{1}{C} \rho(z - y(\theta)) \pi_0(\theta)$$

|                       |                                                   |
|-----------------------|---------------------------------------------------|
| $\pi^z(\theta)$       | Posterior density for $\theta$ ( $\mu^z$ measure) |
| $\rho(z - y(\theta))$ | Likelihood for $z$                                |
| $\pi_0(\theta)$       | Prior density for $\theta$ ( $\mu^0$ measure)     |

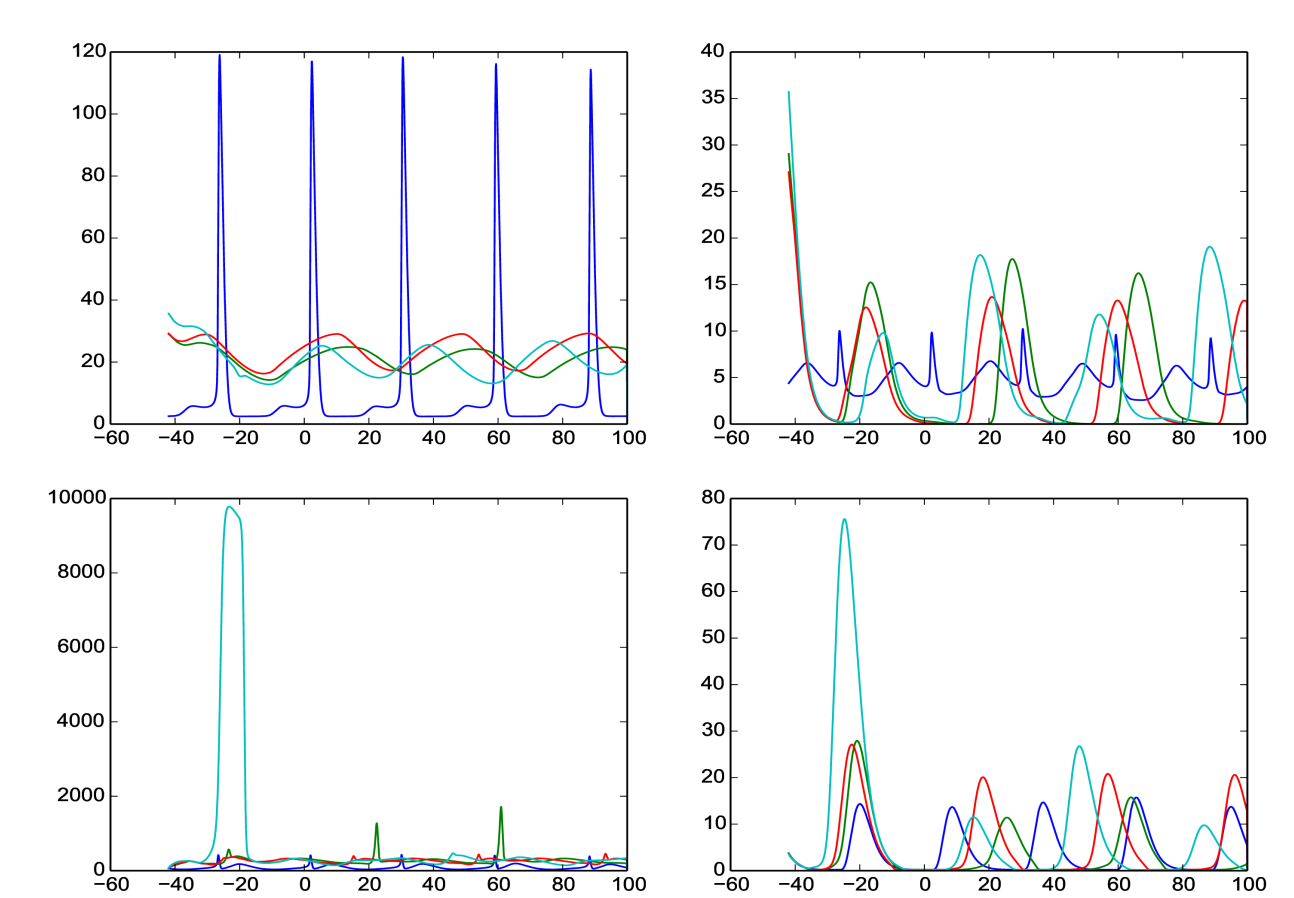
- Calculate joint distribution for parameters
- Computation of high dimensional integrals w.r.t. posterior measure

$$\frac{d\mu^z}{d\mu_0}(\theta) = \frac{1}{C}\rho(z - y(\theta))$$

- High dimensional problem, large computational effort → MCMC methods
- Metropolis-Hastings algorithm:  
construct Markov chain with stationary distribution  $\pi^z(\theta)$   
via a proposal and an acceptance distribution  
→ no need to sample normalization constant

## Analysis of the Parameter Distribution

- **Goal:** Automatically detect pathological situations
- Not all trajectories lie in the same limit cycle
- Discretisation of the parameter space, **calculation of transition probabilities** of the Markov chain  
 → transition matrix



### Simulation results for nominal parameters together with PCOS parameter sets

- Analysis of the resulting **stochastic matrix** in order to learn more about the parameter space
- Several bimodal parameter distributions are detected, which give a hint to a **clustering** of important parameter values
- In particular, we found a set of parameter values that leads to the simulation of the **polycystic ovary syndrome (PCOS)**

## Publications

S. Röblitz, C. Stötzel, P. Deuflhard, H.M. Jones, D.-O. Azulay, P. van der Graaf, S.W. Martin: A mathematical model of the human menstrual cycle for the administration of GnRH analogues , *Journal of Theoretical Biology* 321, pp. 8-27, 2013.