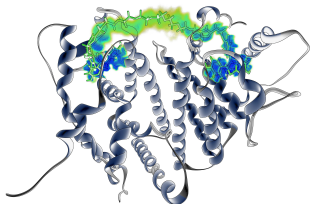


**From Molecular
Simulations to Physiology**
—
**The Role of Mathematics
in Estrogen Modelling**

Susanna Röblitz

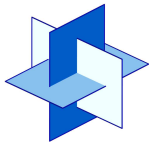


September 26, 2012



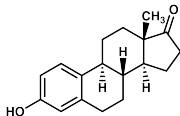
Zuse Institute Berlin

AG Systems Biology
AG Molecular Design

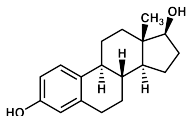


DFG Research Center
MATHEON

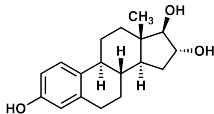
What are estrogens?



estrone (E1)

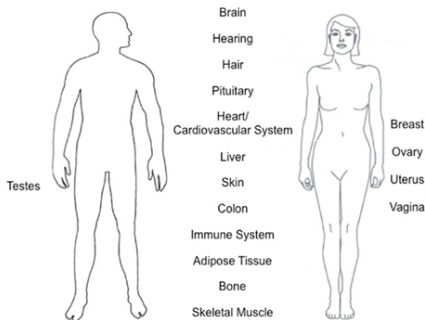


estradiol (E2)



estriol (E3)

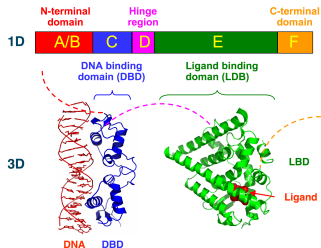
- ▶ group of compounds named for their importance in the **estrous cycle** of humans and other animals



- ▶ bone remodelling, coagulation, fluid balance, lung function,...

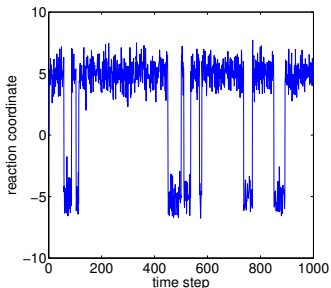
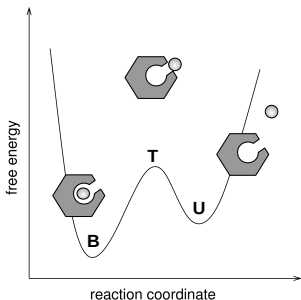
The molecular viewpoint

Structural Organization of Nuclear Receptors



1. ligand binds to ER
2. dimerization
3. binding to specific DNA sequence
4. stimulation or inhibition of gene transcription
(depending on cell type, ligand, and receptor type)

- ▶ understand drug delivery and binding processes
- ▶ development of new drugs with same potency but lower adverse effects
- ▶ infer estrogenic potency of chemical compounds



binding affinity:

$$\Delta A = -\frac{1}{\beta} \ln \left(\frac{w_B}{w_U} \right)$$

w_B : probability to be in the **bound** state (B)

w_U : probability to be in the **unbound** state (U)

molecular dynamics

point concept:
trajectory simulation

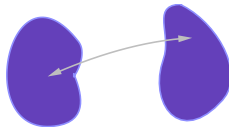


Molecular dynamics

$$(p(\tau), q(\tau)) = \Phi^\tau(p(0), q(0))$$

conformation dynamics

set concept:
metastable conformations



HMC with proposal step

$$q_{i+1} = \Pi_q \Phi^\tau(q_i, p_i), p_i \sim \eta(p)$$

Transfer operator approach

$$\mathcal{T}^\tau f(q) = \int_{\mathbb{R}^d} f(\Pi_q \Phi^{-\tau}(q, p)) \eta(p) dp$$

[Schütte, Fischer, Huisinga, Deuffhard (1999)]

metastable conformations

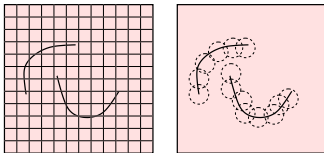
$$\mathcal{T}^T C_J(q) \approx C_J(q), \quad J = 1, \dots, n_c$$

meshfree discretization:

$$C_J(q) = \sum_{i=1}^N \chi_J(i) \varphi_i(q)$$

[Weber (2006)]

partition of unity concept:



$$0 \leq \varphi_i(q) \leq 1 \quad \forall i, q$$

$$\sum_i \varphi_i(q) = 1 \quad \forall q$$

+

$$0 \leq \chi_J(i) \leq 1 \quad \forall i, J$$

$$\sum_J \chi_J(i) = 1 \quad \forall i$$

→

$$0 \leq C_J(q) \leq 1 \quad \forall J, q$$

$$\sum_J C_J(q) = 1 \quad \forall q$$

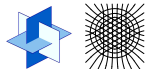
Galerkin method:

$$P^T \chi_J \approx \chi_J$$

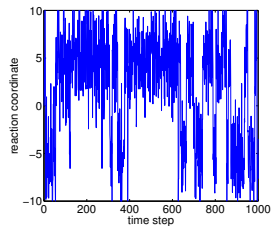
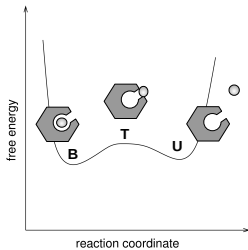
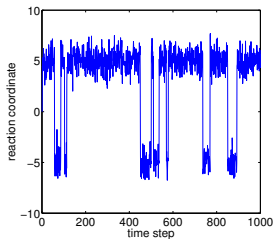
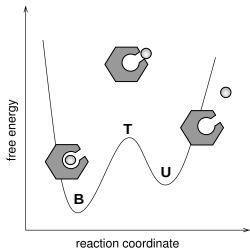
→ PCCA+

(calculation of matrix entries by high-dim. Monte Carlo quadrature [SR (2008)])

Why soft conformations?

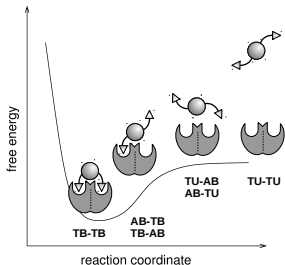


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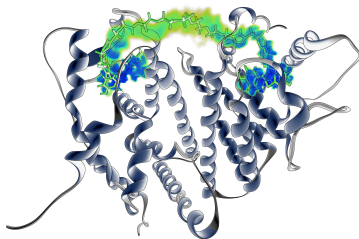


[Fackeldey, Bujotzek, Weber (2012)]

- ▶ **slow** diffusion towards the binding site, **fast** binding
- ▶ **spacer** between weak ligands promotes **separation of timescales** and drives thermodynamic equilibrium towards (doubly) bound state (**multivalence** principle)



desirable potential energy surface

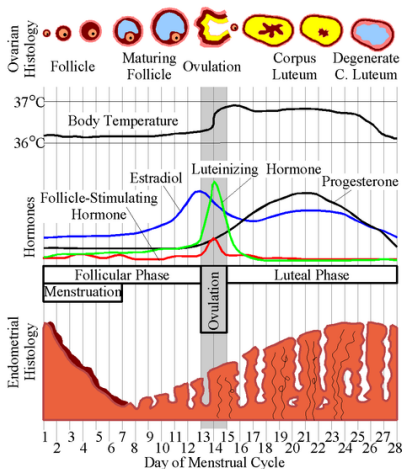


2 raloxifen ligands connected by a flexible spacer (ER antagonist)

[Shan,Bujotzek,Abendroth,Seitz,Weber,Haag (2011)], [Weber,Bujotzek,Haag (2012)]

The physiological viewpoint

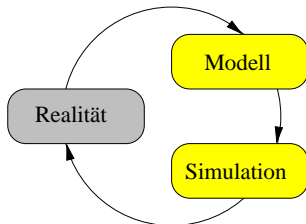
The human menstrual cycle



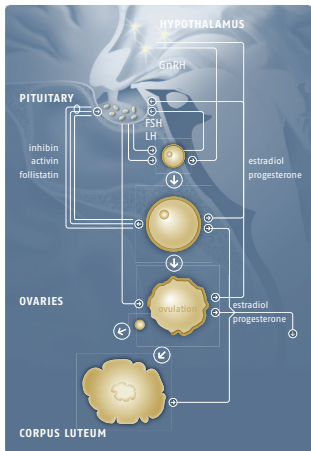
(Average values. Durations and values may differ between different females or different cycles.)

- ▶ consider 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

Mathematical task:

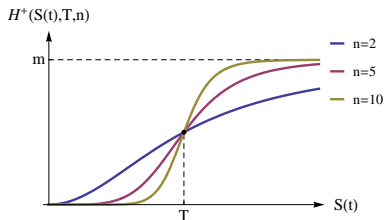


- ▶ **Model development** and **parametrization** such that simulation results match given **measurement data**



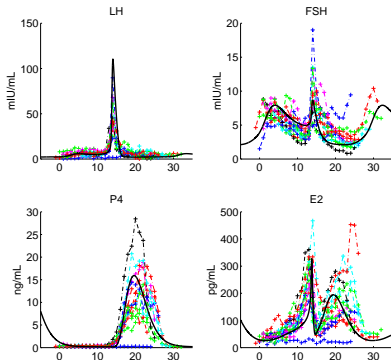
- ▶ define model components and interactions (e.g. from literature)
- ▶ formulate (semi-quantitative) model equations

$$y'(t) = f(y(t), p), y(0) = y_0$$



Inverse Problem:
formulation as nonlinear
least-squares problem

$$\sum_{i=1}^M \|D_i^{-1}(y(t_i, p) - z_i)\|_2^2 \rightarrow \min$$



Biology: dependencies between parameters, rank-deficient Jacobian
 \rightsquigarrow only a few parameters can be identified from the data

- ▶ solution of nonlinear least squares problem by error-oriented global Gauss-Newton method

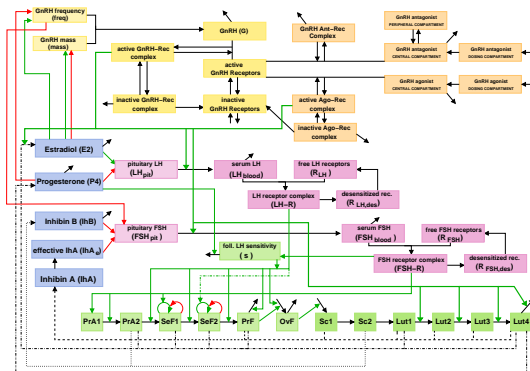
$$\|F'(p^{(k)})\Delta p^{(k)} + F(p^{(k)})\|^2 \rightarrow \min$$
$$p^{(k+1)} = p^{(k)} + \lambda_k \Delta p^{(k)}, k = 0, 1, 2, \dots$$



[Deuffhard: Newton Methods for Nonlinear Problems, 2004]

- ▶ Identifiability
 - ▶ natural monotonicity test
 - ▶ asymptotic convergence rate (incompatibility factor $\kappa < 1$)
 - ▶ adaptive rank strategy
 - ▶ adaptive trust region strategy

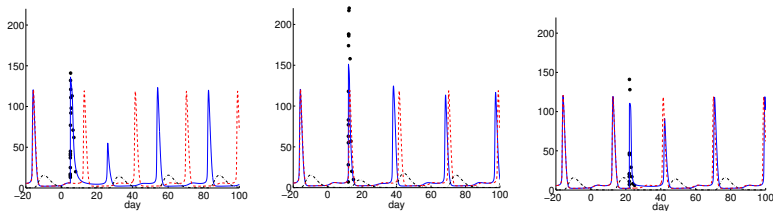
GynCycle: a mathematical model of the human menstrual cycle



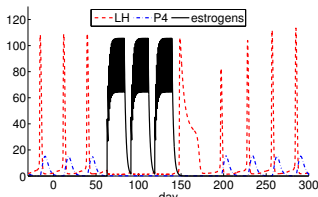
2007: 49 DDEs, 208 parameters, 9 identifiable [Reinecke, Deuffhard (2007)]

2011: 33 ODEs, 114 parameters, 63 identifiable [Röblitz et al. (2012)]

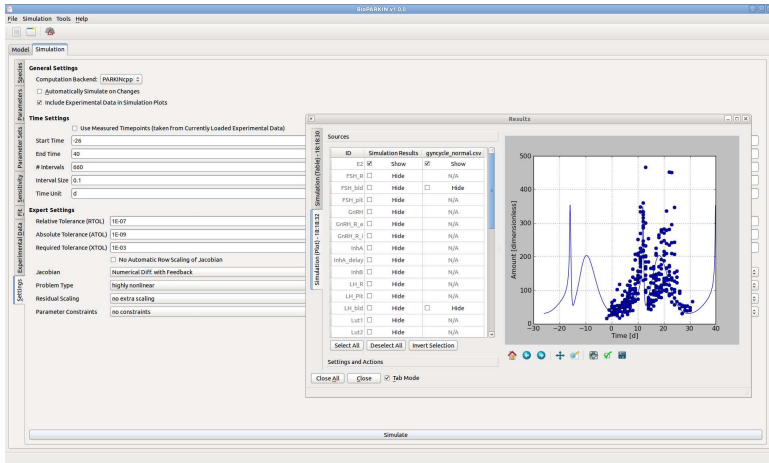
- ▶ analyzing the role of dose and timing of certain drugs



- ▶ simulating the effect of birth control pills



integrated software environment including visualization, parameter identification and simulation bioparkin.zib.de



The screenshot displays the BioPARKIN v1.0.0 software interface. The main window is titled "Simulation" and contains several configuration panels:

- General Settings:**
 - Computation Backend: PARKINcpp
 - Automatically Simulate on Changes
 - Include Experimental Data in Simulation Plots
- Time Settings:**
 - Use Measured Timepoints (taken from Currently Loaded Experimental Data)
 - Start Time: -26
 - End Time: 40
 - # Intervals: 660
 - Interval Size: 0.1
 - Time Unit: d
- Expert Settings:**
 - Relative Tolerance (RTOL): 1E-07
 - Absolute Tolerance (ATOL): 1E-09
 - Required Tolerance (XTOL): 1E-03
 - No Automatic Row Scaling of Jacobian
 - Jacobian: Numerical Diff. with Feedback
 - Problem Type: highly nonlinear
 - Residual Scaling: no extra scaling
 - Parameter Constraints: no constraints

On the right side, a "Sources" window is open, displaying a table of simulation results:

| ID | Simulation Results | gycycle_normal.csv |
|-----------|---|--|
| FSH_R | <input type="checkbox"/> Show <input type="checkbox"/> Hide | <input checked="" type="checkbox"/> Show |
| FSH_Sd | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| FSH_pH | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| GnRH | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| GnRH_R_a | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| GnRH_R_j | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| hPVA | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| hVA_delay | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| hVb | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| LH_R | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| LH_Pn | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| LH_Sd | <input type="checkbox"/> Hide <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| Lut1 | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |
| Lut2 | <input type="checkbox"/> Hide | <input type="checkbox"/> Hide |

Below the table are buttons for "Select All", "Deselect All", and "Invert Selection". At the bottom of the Sources window, there are "Settings and Actions" and "Close All", "Close", and "Tab Mode" buttons.

The "Results" window shows a plot of "Amount [dimensionless]" versus "Time [d]". The plot features a blue line representing a simulation and blue dots representing experimental data points. The x-axis ranges from -30 to 40, and the y-axis ranges from 0 to 500. The simulation shows a peak around -10 days and a larger, more complex peak starting around 0 days, which closely follows the distribution of the experimental data points.

Soon, before undergoing real surgery or treatment, doctors will be able to test medications or surgery on **virtual patients**.



Scientists from different areas are working on projects that will help create **personalized** replicas of living bodies. Thus they will have the ability to optimize their work **without any risk to the patient**.



"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."