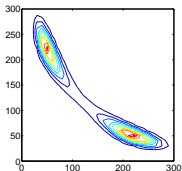
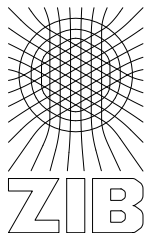


# Rare events in chemical reaction systems

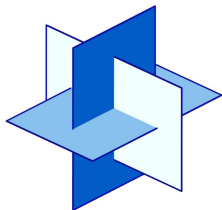
Susanna Röblitz



ECMTB 2011, Kraków

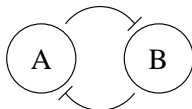


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mutually repressing gene pair (e.g. bacteriophage- $\lambda$ ) with two competing proteins

[Gardner et al., Nature 403 (2000)]

mechanisms:

reaction	mechanism	propensity	stoichiometric vector
$r_1$	$\star \rightarrow A$	$\alpha_1 = c_1 / (c_2 + B^\beta)$	$\nu_1 = (1, 0)$
$r_2$	$A \rightarrow \star$	$\alpha_2 = c_3 A$	$\nu_2 = (-1, 0)$
$r_3$	$\star \rightarrow B$	$\alpha_3 = c_4 / (c_5 + A^\gamma)$	$\nu_3 = (0, 1)$
$r_4$	$B \rightarrow \star$	$\alpha_4 = c_6 B$	$\nu_4 = (0, -1)$

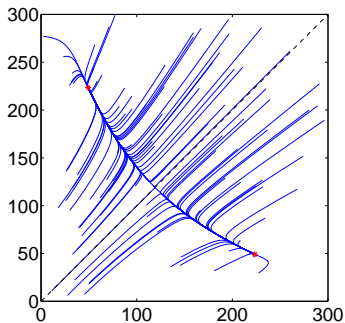
parameters:

$c_1$	$c_2$	$c_3$	$c_4$	$c_5$	$c_6$	$\beta$	$\gamma$
$3 \cdot 10^3 s^{-1}$	$1.1 \cdot 10^4$	$0.001 s^{-1}$	$3 \cdot 10^3 s^{-1}$	$1.1 \cdot 10^4$	$0.001 s^{-1}$	2	2

## ordinary differential equations

$$A' = c_1/(c_2 + B^\beta) - c_3A$$

$$B' = c_4/(c_5 + A^\gamma) - c_6B$$



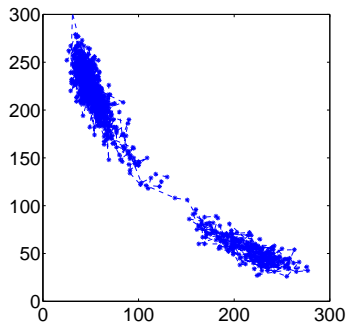
## continuous-time discrete-space

## Markov chain (SSA [Gillespie, 1977])

time to next reaction:

$$\tau \sim W \exp(-W\tau), \quad W = \sum_r \alpha_r$$

probability of reaction  $r$ :  $\alpha_r$



**discrete** partial differential equation

$$\begin{aligned}\partial_t p(x, t) &= \sum_{\substack{r=1 \\ x-\nu_r \geq 0}}^R \alpha_r(x - \nu_r) p(x - \nu_r, t) - \sum_{\substack{r=1 \\ x+\nu_r \geq 0}}^R \alpha_r(x) p(x, t) \\ &= \mathcal{M}p(x, t)\end{aligned}$$

$p(x, t)$  probability density of state  $x$  at time  $t$   
 $x \in \mathbb{N}^d$  state: copy numbers of  $d$  species,  $d$  large  
 $\nu_r \in \mathbb{N}^d$  stoichiometric vector  
 $\alpha_r : \mathbb{N}^d \mapsto \mathbb{R}_+$  reaction propensity

$$\mathcal{M}^* q = \sum_{r=1}^R \alpha_r(x) [q(x + \nu_r) - q(x)]$$

**metastability analysis:** reduced description of the dynamical system in terms of its **nearly invariant (metastable) sets/functions**

conservation law:  $\sum_{x \in \mathbb{N}^d} \mathcal{M}p(x, t) = 0$

set partitioning:  $\mathbb{N}^d = \bigcup_k \Omega_k, \Omega_i \cap \Omega_j = \emptyset$

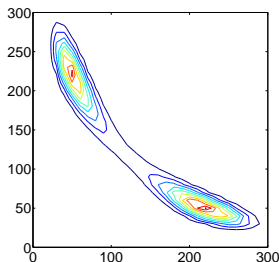
$$\sum_{x \in \Omega_k} \mathcal{M}p(x, t) \approx 0$$

partition of unity:

$$C_k: \mathbb{N}^d \rightarrow [0, 1], \sum_k C_k(x) = \mathbb{1}_{\mathbb{N}^d} \forall x \in \mathbb{N}^d$$

$$\sum_{x \in \mathbb{N}^d} C_k(x) \mathcal{M}p(x, t) \approx 0$$

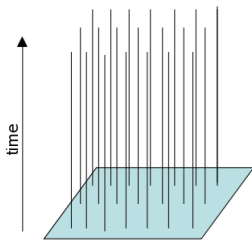
$$\boxed{\mathcal{M}^* C_k(x) \approx 0}$$



**Conformation Dynamics:** [Deuffhard et al. 1999, Schütte et al. 1999, Weber 2006]

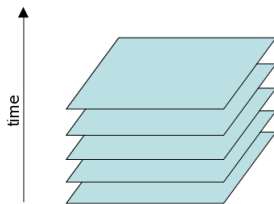
$$p_t = \mathcal{M}p, \quad p(x, 0) = p_0(x)$$

## Method of lines

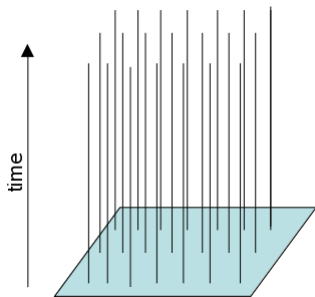


- ▶ space discretization first
- ▶ sequence of time-like initial value problems

## Method of time layers (Rothe method)

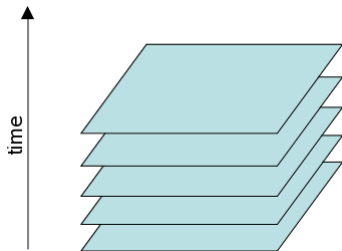


- ▶ time discretization first
- ▶ sequence of spatial boundary value problems



- ▶ (adaptive) sparse grids  
[Hegland et al., 2006, 2008]
- ▶ Galerkin spectral methods  
[Engblom, 2008]
- ▶ dynamical low-rank approach  
[Jahnke/Huisinga 2008]

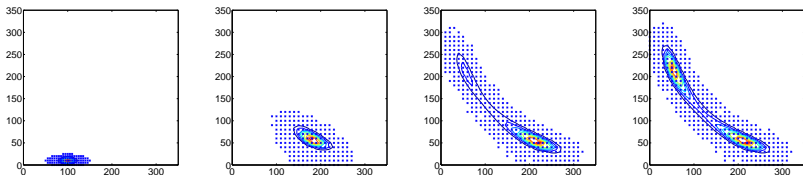
complicated adaptation of space discretization during time integration



- ▶ hp-finite elements  
[Wulkow 1996, Deuffhard et al. 2008]
- ▶ adaptive wavelet method  
[Jahnke 2010]

tensor product structure: “curse of dimensionality”

⇒ meshfree methods



1. time discretization: implicit Euler method combined with a second order correction step
2. spatial discretization:  $p_k(x) \approx \sum_{i=1}^N (a_k)_i \varphi_i(x)$

$$(\Delta \mathbf{a}_k^{(1)})^T (S - \tau Q) = \tau \mathbf{a}_k^T Q,$$

with

$$Q_{ij} = \langle \mathcal{M} \varphi_i, \psi_j \rangle_\eta, \quad S_{ij} = \langle \varphi_i, \psi_j \rangle_\eta = \sum_{x \in \mathbb{N}^D} \varphi_i(x) \psi_j(x) \eta(x)$$

$\{\psi_i\}$  partition of unity  $\Rightarrow Q$  has eigenvalue 0

1. stationary distribution (ill-conditioned problem!):

$$\mathcal{M}\pi(x) = 0, \pi(x) = \sum_{i=1}^N w_i \varphi_i(x) \Rightarrow w^T Q = 0$$

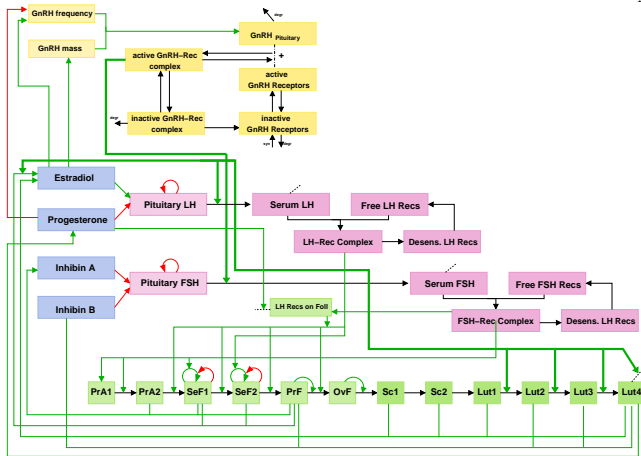
2. metastable functions:

$$\mathcal{M}^* C_k(x) \approx 0, C_k(x) = \sum_{i=1}^N \chi_{i,k} \psi_i(x) \Rightarrow Q \chi_k \approx 0$$

- ▶ transformation of **eigenvectors** of  $Q$  to **membership vectors**  $\chi_k$  by **Robust Perron Cluster Analysis** (PCCA+) [Deuffhard/Weber 2005, Röblitz 2008]
- ▶ projection onto metastable functions results in coarse grained transition rate matrix  
toggle switch example:  $Q_c = 10^{-5} \begin{pmatrix} -0.3288 & 0.3288 \\ 0.3094 & -0.3094 \end{pmatrix}$

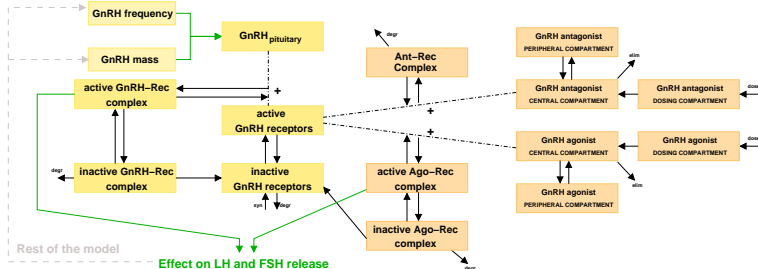
1. an error-oriented adaptive solution method for the CME with special regard to rare events
2. identification of processes in biological or chemical reaction networks that can be described by the CME

# A model of the female menstrual cycle



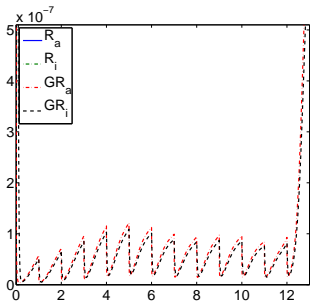
GynCycle: 33 ODEs, 114 parameters

[Röblitz et al. 2011]

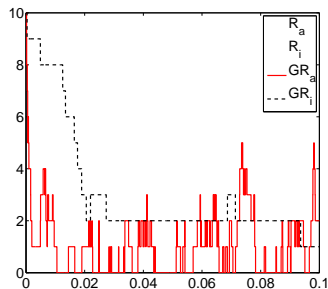


- ▶ **Antagonists:** competitive and reversible binding to GnRH receptors, resulting in an immediate drop in gonadotropin secretion
- ▶ **Agonists:** activation of GnRH receptor resulting in initially increased secretion of gonadotropins, followed by a drop caused by **receptor downregulation/desensitization**

## A small number or nothing?



deterministic (ODE)

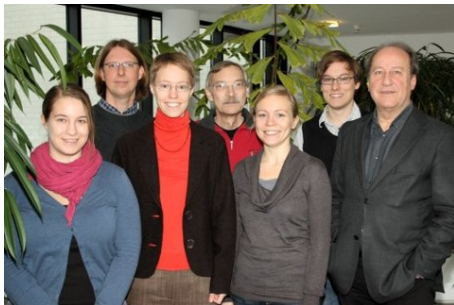


stochastic (CME)

Future work:

- ▶ description via CME, parameter identification
- ▶ coupling between CME and reaction rate equations

**Thank you for your attention!**



special thanks to: Peter Deuffhard, Claudia Stötzel

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Zuse Institute Berlin

Computational Systems Biology Group

<http://www.zib.de/en/numerik/csb.html>