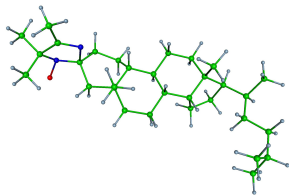
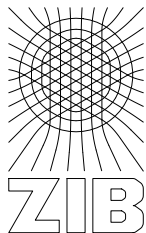


# Stable computation of probability densities for metastable dynamical systems

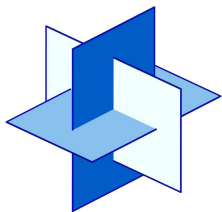
Susanna Kube



ICIAM, Zurich, July 2007

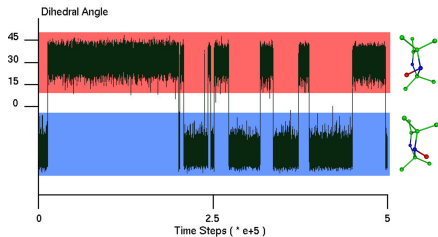


Zuse Institute Berlin



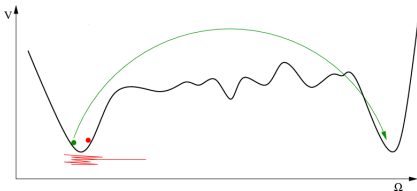
DFG Research Center

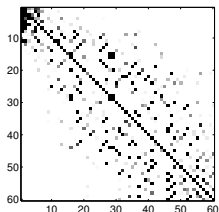
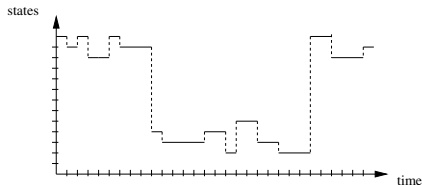
MATHEON



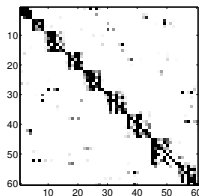
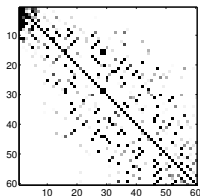
stationary  
density?

The trajectory gets trapped in valleys of the potential energy surface.





- ▶ modeling as a Markov chain on a finite dimensional state space
- ▶ state space is high dimensional
- ▶ count transition frequencies
- ▶ stochastic transition probability matrix  $P$



## Robust Perron Cluster Analysis (PCCA+)

[Weber 2006]

Perron-Cluster of eigenvalues:  $\{\lambda_i\}_{i=1}^{nc} \approx 1$

Deviation from the completely decoupled chain:  $\varepsilon = 1 - \lambda_2$

Stationary density:

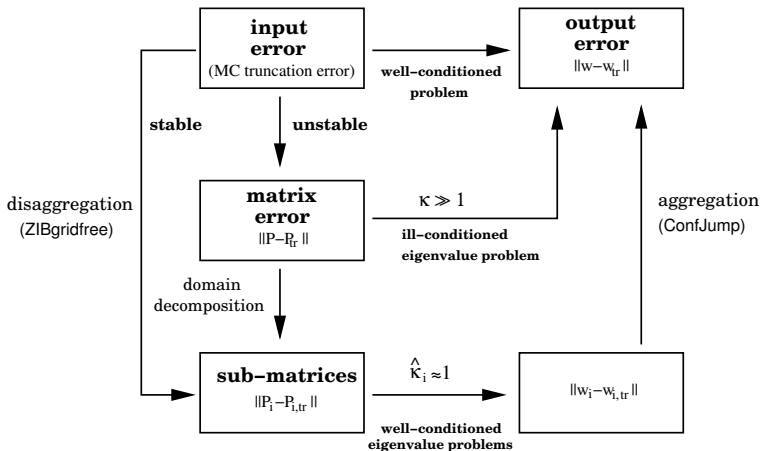
$$\mathbf{w}^\top P = \mathbf{w}^\top$$

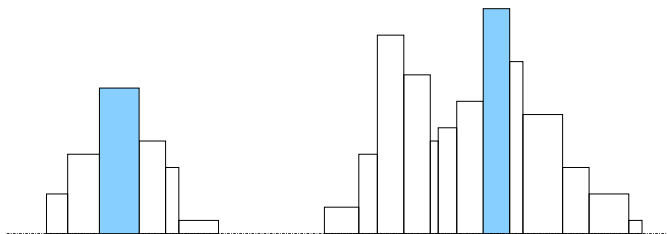
Condition number:

$$\|\mathbf{w} - \mathbf{w}_{tr}\|_\infty \leq \kappa \|P - P_{tr}\|_\infty$$

$$\kappa \sim \mathcal{O}(1/\varepsilon) \gg 1$$

[Meyer 1994]

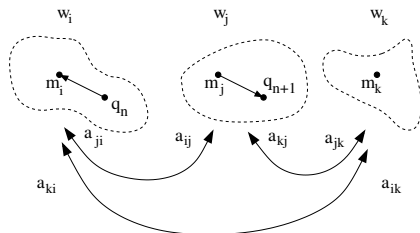




Assumption: **partial densities**  $w_i$  are correct, but the **scaling factors**  $\sigma_i$  are wrong

$$\mathbf{w} = (\sigma_1 w_1, \sigma_2 w_2, \dots, \sigma_{n_c} w_{n_c})$$

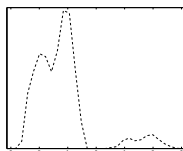
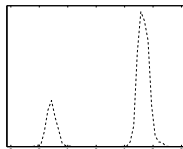
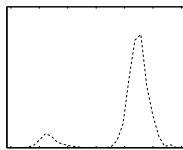
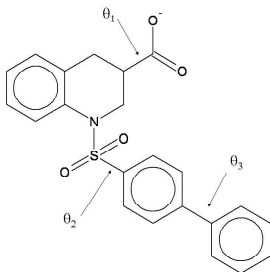
Idea: reweighting of **selected subdomains**



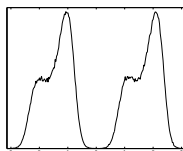
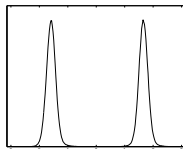
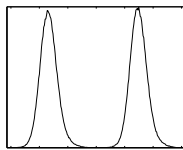
- ▶ hybrid Monte Carlo (HMC) within the single subdomains
- ▶ **jumps** between the subdomains

- ▶ When to jump?: jump rate  $r \in [0, 1]$
- ▶ Where to jump?: reversibility and high acceptance ratio
  - ▶ jump proposition matrix  $A$ 
    - ▶ symmetric and stochastic,  $A_{ij} = A_{ji}(\Delta V_{ij})$
  - ▶ unique mapping of points (depends on shape and energy level of the jump regions)

possible MMP-8 inhibitor with three dihedral angles which induce symmetric conformational changes



without reweighting



after reweighting

**Thank you for your attention!**

Further information

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

M.Weber, S.Kube, L.Walter, P.Deuflhard: *Stable computation of probability densities for metastable dynamical systems*. Accepted for publication in SIAM J. Multiscale Model. Simul.

Preprint available as ZR-06-39 under

<http://www.zib.de/bib/pub/pw/index.en.html>