Computation of equilibrium densities in metastable dynamical systems by domain decomposition

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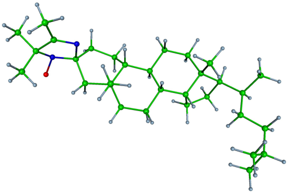

ICNAAM 2008

DFG Research Center

MATHEON

ZIB Scientific Computing:

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Cooperations:

FU Berlin:

- Biocomputing: Christof Schütte
- Applied Mathematics: Caroline Lasser
- Computational Molecular Biology: Frank Noé

DFG Research Center **"Matheon"**

Molecular Dynamics

Modelling of molecules in classical MD:

$$H(q,p) = \frac{1}{2} p^\top M^{-1} p + V(q)$$

$$V = V_{\text{bond}} + V_{\text{angle}} + V_{\text{torsion}} + V_{\text{Coulomb}} + V_{\text{VdW}}$$

$q \in \mathbb{R}^{3s}$: positions of all atoms, $p \in \mathbb{R}^{3s}$: momenta

Corresponding equations of motion:

$$\dot{q} = M^{-1} p, \qquad \dot{p} = -\nabla V$$

Ensemble averages

Invariant density in the canonical ensemble (Boltzmann):

$$\mu(q,p) = \underbrace{\frac{1}{Z_p}\exp\left(-\frac{\beta}{2}p^\top M^{-1}p\right)}_{=\eta(p)} \underbrace{\frac{1}{Z_q}\exp(-\beta V(q))}_{=\pi(q)}, \quad \beta = 1/k_B\mathcal{T}$$

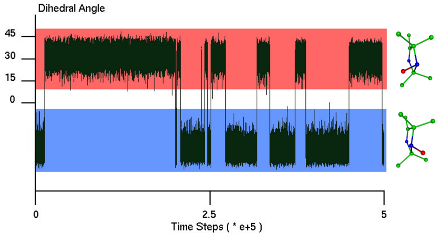
Ensemble averages:

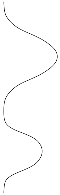
$$\langle A \rangle \equiv \int_\Omega A(q)\pi(q)\,dq \approx \frac{1}{M}\sum_{k=1}^{M} A(q_k), \quad q_k \sim \pi(q)$$

HMC (Hamiltonian dynamics with randomized momenta):

$$q_{n+1} = \Pi_q \Phi^\tau(q_n, p_n), \quad p_n \sim \eta(p)$$

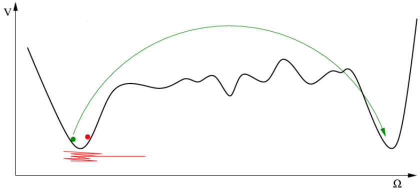
Metastable dynamical systems



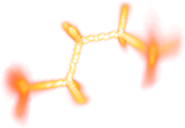


stationary density?

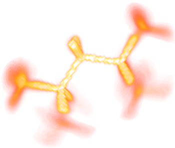
The trajectory gets trapped in valleys of the potential energy surface.



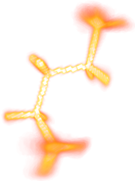
Example: Pentane



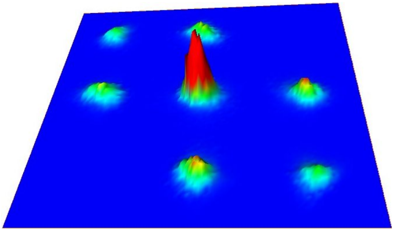
(g+/t)

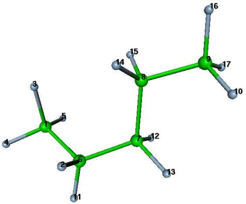


(transition state)

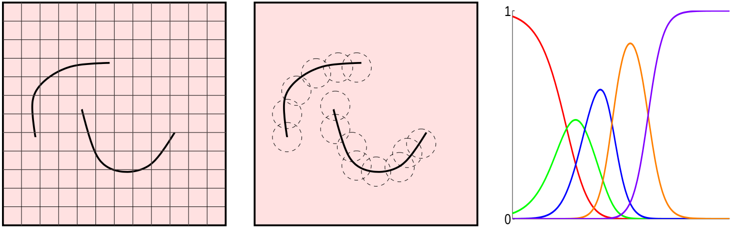


(t/g+)





Discretization



partition of unity:

$$\sum_{i=1}^{N} \phi_i(q) = 1, \quad \phi_i(q) \geq 0 \qquad \forall q \in \Omega$$

Mass matrix

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$$S(i,j) \equiv \frac{\int_\Omega \phi_i(q)\,\phi_j(q)\,\pi(q)\,dq}{\int_\Omega \phi_i(q)\,\pi(q)\,dq}$$

partial densities:

$$\pi_i(q) \equiv \frac{\phi_i(q)\pi(q)}{\int_\Omega \phi_i(q)\pi(q)}$$

$$\pi_i(q) \propto \exp(-\beta\, V_i(q)), \quad V_i(q) = V(q) - \beta^{-1}\log(\phi_i(q))$$

Monte Carlo integration:

$$S(i,j) = \int_\Omega \phi_j(q)\pi_i(q)\,dq \approx \frac{1}{n_i}\sum_{k=1}^{n_i}\phi_j(q_k^{(i)}), \quad q_k^{(i)} \sim \pi_i(q).$$

Discrete stationary density

$$\pi(q) = \sum_{i=1}^{N} w_i \pi_i(q)$$

w_i is the statistical weight of basis function $\phi_i(q)$:

$$w_i \equiv \int_\Omega \phi_i(q)\pi(q)\,dq$$

The vector $\mathbf{w} = [w_1, \ldots, w_N]^\top$ is the left eigenvector of S corresponding to the eigenvalue $\lambda = 1$ (Perron-Frobenius)!

$$\boxed{\mathbf{w}^\top S = \mathbf{w}^\top}$$

Error Estimation

$$\widetilde{S} = \overline{S} + E, \qquad \widetilde{\mathbf{w}}^\top \widetilde{S} = \widetilde{\mathbf{w}}^\top$$

- Row-wise correlated random matrices:

$$\mathbb{E}[E(i,j)] = 0 \quad \text{and} \quad \mathbb{E}[E(i,j)E(k,l)] = \delta_{ik} C_i(j,l)$$

- 1st order Taylor series expansion:

$$\widetilde{\mathbf{w}} \doteq \overline{\mathbf{w}} + \sum_{i=1}^{N} G_i^{\mathbf{w}} E(i,:)^\top, \quad G_i^{\mathbf{w}}(k,l) = \frac{\partial w_k}{\partial s_{il}}\Big|_{\overline{A}}, \quad \overline{A} = \overline{S}^\top - I$$

- probability distribution: $E(i,:) \sim \mathrm{Dir}(\alpha_i)$
- parameter estimation from sampling data (ML estimator)

Adaptive sampling

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Central limit theorem:

$$\widetilde{\mathbf{w}} \sim \mathrm{MVN}(\overline{\mathbf{w}}, \sum_{i=1}^{N} G_i^{\mathbf{w}} C_i (G_i^{\mathbf{w}})^\top)$$

Equilibration of sampling effort and uncertainties

$$i = \arg\max_k \| G_k^{\mathbf{w}} C_k (G_k^{\mathbf{w}})^\top \|_2$$

Increase number of sampling points in the selected basis function, update the row, and repeat the analysis.

If a maximal allowed number of points is reached $\rightarrow$ refinement

Hierarchical refinement

- current basis

$$\{\phi_1, \dots, \phi_N\} : \Omega \to [0,1]$$

- function selected for refinement: $\phi_k(q)$
- temporal set of basis functions (partition of unity, positivity)

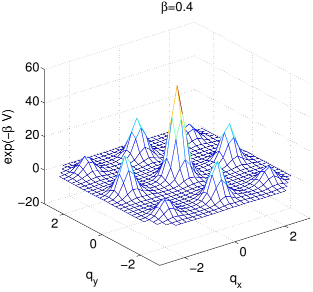
$$\{\widetilde{\phi}_{k1}, \dots, \widetilde{\phi}_{ks}\} : \Omega \to [0,1]$$

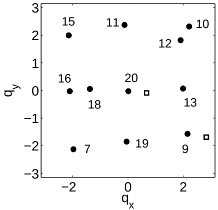
- new basis functions

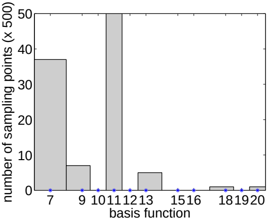
$$\phi_{ki}(q) := \phi_k(q)\widetilde{\phi}_{ki}(q), \quad i = 1, \dots, s.$$

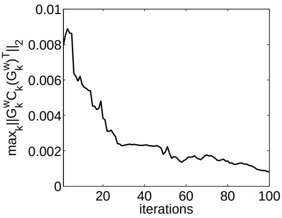
$$\{\phi_1, \dots, \phi_{k-1}, \phi_{k+1}, \dots, \phi_N, \phi_{k1}, \dots, \phi_{ks}\}$$

Example









$$U = \int_\Omega V(q)\pi(q)dq$$
$$= -5.03$$

$$U_0 = -2.63$$

$$U_{100} = -4.45$$

Finally

Thank you for your attention!

Further information

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

Open positions:

- Matheon A4 ("Towards a mathematics of biomolecular flexibility"), PhD or Postdoc