Hierarchical Refinement in Conformation Dynamics

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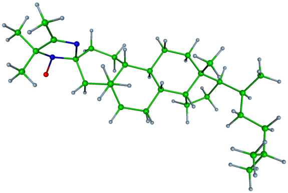


CSE09

DFG Research Center

Matheon

Molecular Dynamics

Matheon

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:

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

$$(q(t+\tau), p(t+\tau)) = \Psi^\tau(q(t), p(t))$$

Canonical ensemble (n,V,T)

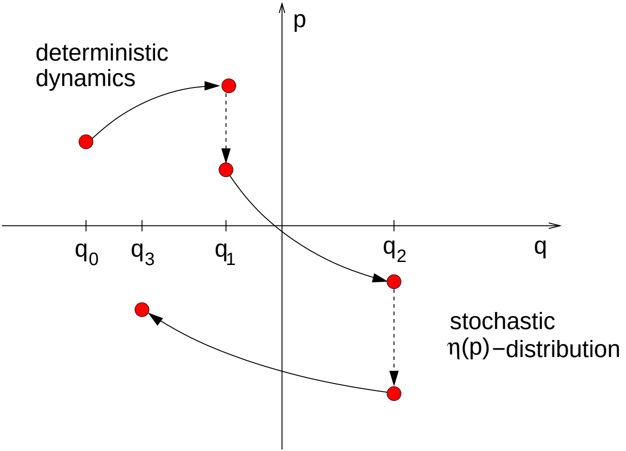
Invariant density in the canonical ensemble (Boltzmann):

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

Ensemble averages:

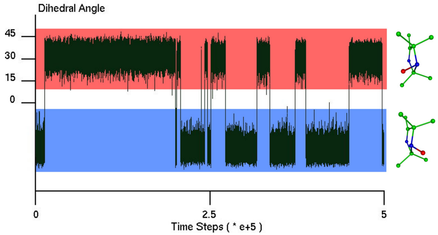
$$\langle A\rangle \equiv \int_\Omega A(q)\pi(q)\,dq \approx \frac{1}{M}\sum_{k=1}^{M} A(q_k), \quad q_k \sim \pi(q)$$

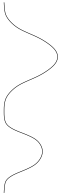
Hybrid Monte Carlo (HMC)



[Duane, Kennedy, Pendleton,Roweth (1987)]

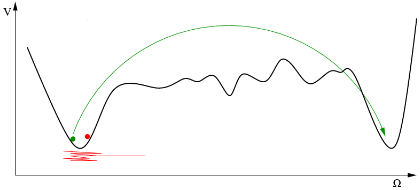
Metastable dynamical systems





stationary density?

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

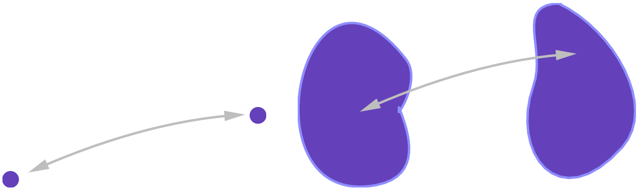


Conceptual change

molecular dynamics | **conformation dynamics**

point concept:
trajectory simulation

set concept:
metastable conformations



deterministic

stochastic

[Deuflhard, Schütte (1997)]

Conformations as almost invariant sets

Transfer operator:

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

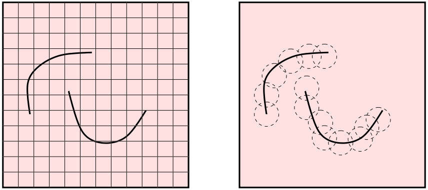
[Schütte, Fischer, Huisinga, Deuflhard 1998]

- Probability to be within A
  $w(A) = \int_A \pi(q)dq = \langle \chi_A, \chi_A \rangle_\pi$
- Probability to move from A $\rightarrow$ B during time τ
  $w(A,B,\tau) = \langle T^\tau \chi_A, \chi_B \rangle_\pi / w(A)$
- Probability to stay within A during time τ
  $w(A,A,\tau) = \langle T^\tau \chi_A, \chi_A \rangle_\pi / w(A)$

Conformations: almost invariant subsets of the position space Ω

$$w(A,A,\tau) \approx 1 \quad \leftrightarrow \quad T^\tau \chi_A \approx \chi_A$$

Discretization



Voronoi tesselation: set of nodes $\{q_1, \ldots, q_N\} \in \Omega$

$$\phi_i(q) = \begin{cases} 1, & \text{if } d(q, q_i) = \min_j d(q, q_j) \\ 0, & \text{else} \end{cases}$$

partition of unity

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

Eigenvalue Problem

$$T^\tau u = \lambda u, \qquad \lambda \approx 1$$

Galerkin approach:

$$u(q) = \sum_{i=1}^{N} \alpha_i \phi_i(q)$$

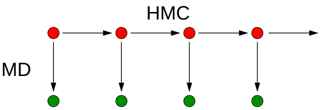
$$\sum_{i=1}^{N} \alpha_i \frac{\langle T^\tau \phi_i, \phi_j \rangle_\pi}{\langle \phi_j \rangle_\pi} = \lambda \sum_{i=1}^{N} \alpha_i \frac{\langle \phi_i, \phi_j \rangle_\pi}{\langle \phi_j \rangle_\pi}, \quad \forall j$$

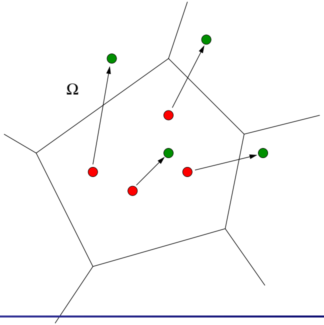
$$\boxed{P\alpha = \alpha\lambda \qquad \text{(stochastic)}}$$

Simulation

$$P(i,j) \;\equiv\; \frac{\int_\Omega \mathcal{T}^\tau \phi_j(q)\, \phi_i(q)\, \pi(q)\, dq}{\int_\Omega \phi_i(q)\, \pi(q)\, dq} = \int_\Omega \mathcal{T}^\tau \phi_j(q)\, \pi_i(q)\, dq$$

$$\approx \; \frac{1}{n_i}\frac{1}{m_{ik}} \sum_{k=1}^{n_i} \sum_{l=1}^{m_{ik}} \phi_j(\Pi_q \Psi^\tau(q_k^{(i)}, p_l^{(i\,k)}))$$





Convergence

running multiple sampling chains (≈ 5)
(starting points from high-temperature pre-sampling)

Gelman-Rubin convergence indicator

- comparison of within-chain-variance and between-chain-variance
- convergence factor $r \downarrow 1$

algorithm:

- increase number of sampling points
- maximum number of sampling points is reached $\rightarrow$ refinement

Hierarchical refinement

- current basis

$$\{\phi_1, \ldots, \phi_N\} : \Omega \rightarrow [0, 1]$$

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

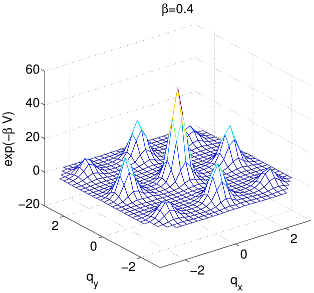
$$\{\widetilde{\phi}_{k1}, \ldots, \widetilde{\phi}_{ks}\} : \Omega \rightarrow [0, 1]$$

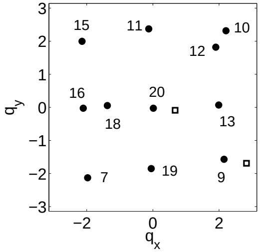
- new basis functions

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

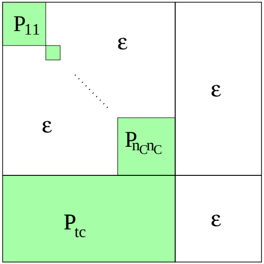
$$\{\phi_1, \ldots, \phi_{k-1}, \phi_{k+1}, \ldots, \phi_N, \phi_{k1}, \ldots, \phi_{ks}\}$$

Example


β=0.4
exp(−β V)
60
40
20
0
−20
2
0
−2
q_y
−2
0
2
q_x


15
11
10
12
16
20
18
13
7
19
9
3
2
1
0
−1
−2
−3
q_y
−2
0
2
q_x

Robust Perron Cluster Analysis (PCCA+)



$$PX = X\Lambda, \quad \Lambda = \mathrm{diag}(\lambda_1, \ldots, \lambda_{n_C})$$

$$\lambda_1 = 1, \lambda_{n_C} > 1 - \varepsilon$$

Transformation of eigenvectors X to membership vectors χ

$$\chi = X\mathcal{A} \qquad \text{(invariance)}$$

$$\text{maximize} \quad I(\mathcal{A}) = \sum_{i=1}^{n_C} \frac{\langle \chi_i, \chi_i \rangle_\pi}{\langle \chi_i, e \rangle_\pi} \leq n_C$$

under the conditions

1. $\chi_j(i) \geq 0 \quad \forall i \in \{1, \ldots, N\}, j \in \{1, \ldots, n_C\}$ (positivity),
2. $\sum_{j=1}^{n_C} \chi_j(i) = 1 \quad \forall i \in \{1, \ldots, N\}$ (partition of unity),

[Deuflhard, Weber (2005), Röblitz (2008)]

Perturbation theory for invariant subspaces

$$\widetilde{P} = P + E, \qquad \widetilde{P}\widetilde{X} = \widetilde{X}\widetilde{\Lambda}$$

Schur decomposition

$$[X_1, X_2]^H (P, E) [X_1, X_2] = \left(\begin{pmatrix} L_1 & H \\ 0 & L_2 \end{pmatrix}, \begin{pmatrix} E_{11} & E_{12} \\ E_{21} & E_{22} \end{pmatrix} \right)$$

perturbed subspace

$$\widetilde{X}_1 = X_1 + X_2 Q$$

error bound

$$\|Q\| \leq \kappa \|E_{21}\|$$

[Stewart, Sun (1990)]

Error Estimation

- Row-wise correlated random matrices:

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

- stochastic norm [G. W. Stewart, 1990]:

$$\|E\|_s^2 \equiv \mathbb{E}(\|E\|_F^2)$$

$$\|E_{21}\|_s^2 = \sum_{k=1}^{N} \|X_2(k,:)\|_2^2 \operatorname{trace}(X_1^H C_k X_1)$$

$\longrightarrow$ computation of error bounds

Probability distributions

random vector $z = (z_1, \ldots, z_N)$, $\sum_{i=1}^{N} z_i = n$, $z_i > 0$

single chain	multiple chains
multinomial distribution with Dirichlet prior $z \mid p \sim \text{Mult}(n, p)$, $p \sim \text{Dir}(\alpha)$ $p \mid z \sim \text{Dir}(\alpha + z)$	compound Dirichlet-multinomial (Polya distribution)
$E(i,:) \sim \text{Dir}(\alpha_i)$	$E(i,:) \sim \frac{1}{n}\text{Polya}(\alpha_i)$
$f_D(p, \alpha) = \frac{1}{Z(\alpha)} \sum_{i=1}^{N} p_i^{\alpha_i - 1}$	$f_P(z; n, \alpha) = \int_p f_M(z; n, p) f_D(p; \alpha)\, dp$

Adaptive sampling

[Singhal Hinrichs, Pande (2005, 2007)]

$$\|E_{21}\|_s^2 = \sum_{k=1}^{N} \|X_2(k,:)\|_2^2 \mathrm{trace}(X_1^H C_k X_1)$$

Equilibration of sampling effort and uncertainties

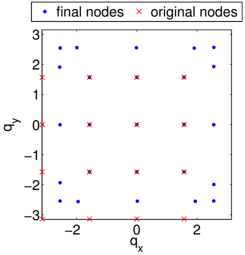
$$i = \arg\max_k \mathrm{trace}(X_1^H C_k X_1)\|X_2(k,:)\|_2^2$$

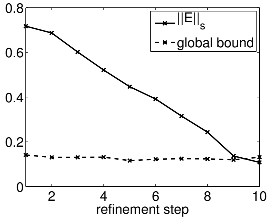
Increase number of sampling points in the selected basis function, update the row, and repeat the analysis.

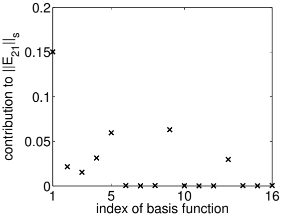
If maximum number of sampling points is reached $\rightarrow$ refinement

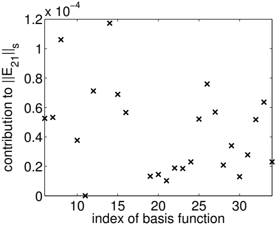
Example

Equilibration of errors and sampling effort









Discrete stationary density

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

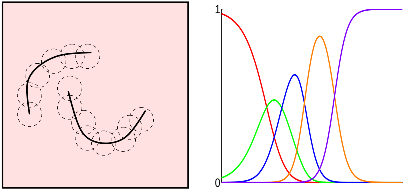
w_i is the statistical weight of basis function $\phi_i(q)$:

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

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

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

Discretization



radial basis functions

$$\phi_i(q) = \frac{\exp(-\alpha\, d(q,q_i)^2)}{\sum_{j=1}^N \exp(-\alpha\, d(q,q_j)^2)}, \quad i = 1, \dots N$$

partition of unity

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

Mass matrix

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

partial densities:

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

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

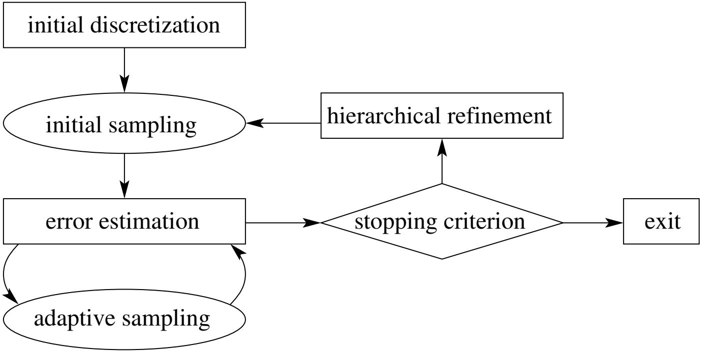
Monte Carlo integration:

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

[Weber (2006)]

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

Algorithm



[Röblitz (2008)]

Final remarks

- adaptive and hierarchical method for
  - the identification of metastable conformations
  - sampling from the stationary distribution
- trivially parallelizable; enormous gain in computing time

Outlook

- application to the analysis of given data

Project Group

ZIB Computational Drug Design:

Peter Deuflhard	conformation dynamics, PCCA+
Marcus Weber	PCCA+, mesh-free methods
Susanna Röblitz	error analysis, hierarchical refinement, PCCA+
Alexander Bujotzek	DPP-4 inhibition, entropy estimation
Martina Zech	reweighting strategies
Olga Scharkoi	μ-opioid receptor agonists
Vedat Durmaz	toxicology of flame retardants
Karsten Andrae	entropy estimation of PEG derivatives

Cooperations:

DFG Research Center Matheon (Christof Schütte)
SFB-765 “Multivalence” (Rainer Haag)
BAM (Roland Becker)
Charité (Christoph Stein, Hua Fan)

Finally

Thank you for your attention!

Further information

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