Mean field approximation of transfer operators and time-scale bridging in conformation dynamics

Gero Friesecke (TU Munich)

ENUMATH, Leicester, 9 September, 2011
M3: Numerical Methods for Molecular Dynamics
(Organisers: T.Lelièvre and R.Davidchack)

Reference: Multiscale Model. Simul. 8 (2009), 254-268

Joint work with Oliver Junge and Peter Koltai (TU Munich)

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Typical phenomenon in simulations

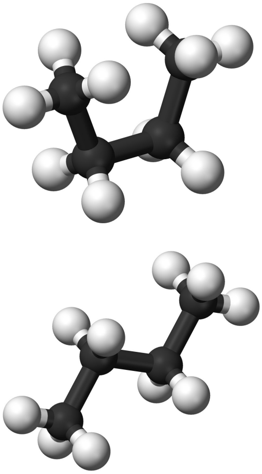
- Irregular small oscillations around metastable states ("conformations") at short timescales

  10^{-14} sec

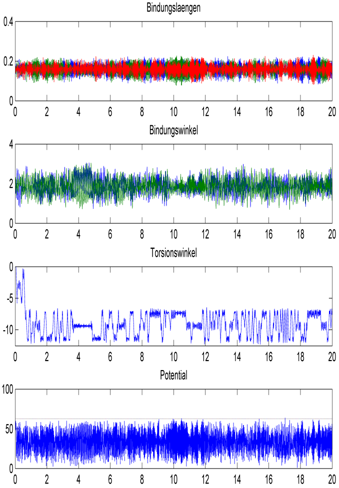
- Transitions to different metastable states at much larger timescales

  10^{-12} sec for small peptides; 10^{-6} to 10^{2} sec for proteins

Example: Molecular dynamics simulation of butane



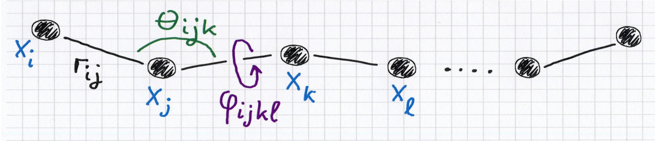
Butane (cis and trans conformation)



Dynamics of C-C bondlengths, C-C-C bond angles, and C-C-C-C torsion angle (Friesecke/Junge/Koltai)

Hamiltonian of n-Butane

$CH_3 — CH_2 — CH_2 — CH_2 \cdots CH_2 — CH_3$



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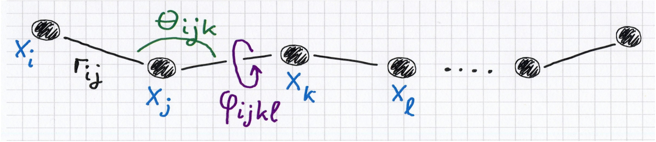

$x_i \in \mathbb{R}^3$ position of i^{th} CH_2 group, $p_i \in \mathbb{R}^3$ momenta

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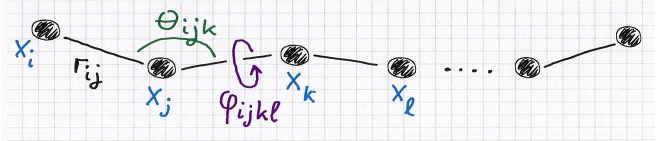

$x_i \in \mathbb{R}^3$ position of i^{th} CH_2 group, $p_i \in \mathbb{R}^3$ momenta

$$H = \sum_i \frac{|p_i|^2}{2m} + V(x_1, .., x_n)$$

$$V = \sum_{i,j} V_{bond}(r_{ij}) + \sum_{i,j,k} V_{ang}(\theta_{ijk}) + \sum_{i,j,k,\ell} V_{tor}(\phi_{ijk\ell})$$

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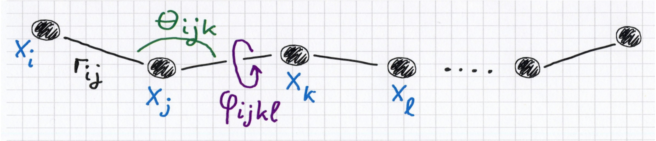

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1st-neighbour bond potential depending on $r_{ij} = |x_i - x_j|$
2nd-neighbour angular potential dep. on $\theta_{ijk} = \arccos \frac{x_i - x_j}{r_{ij}} \cdot \frac{x_k - x_j}{r_{kj}}$
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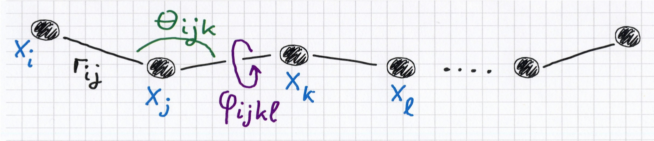

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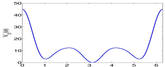
$V_{bond} = \frac{1}{2} k_{bond}(r_{ij} - r_0)^2, \quad V_{ang} = k_{ang}(\cos\theta_{ijk} - \cos\theta_0)^2, \quad V_{tor} =$



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  $\Longrightarrow$ get Fermi-Pasta-Ulam as an invariant submanifold
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- $n = 4$ (standard Butane), $V_{ang} = V_{tor} = 0$, $k_{bond} \to \infty$
  $\Longrightarrow$ get Thurston triple linkage

  Thurston/Weeks, Sci.Amer., 1984; Hunt/MacKay, Nonlinearity, 2003

Key questions from an applications point of view

$\longrightarrow$ biophysics, molecular biology, drug design, protein folding pb., ...

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  Occur at long timescales, way beyond reliable trajectory simulation.

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Biological examples (more complex than butane): retinal cis-trans transition; DNA α-β transition; hemoglobin T-R transition

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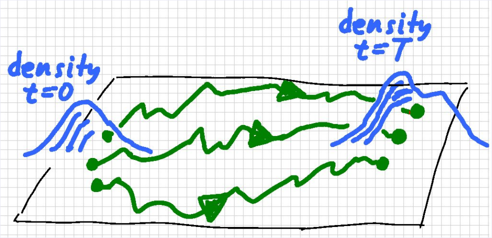

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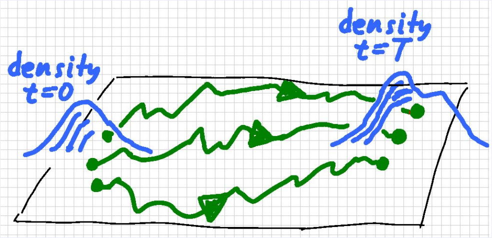

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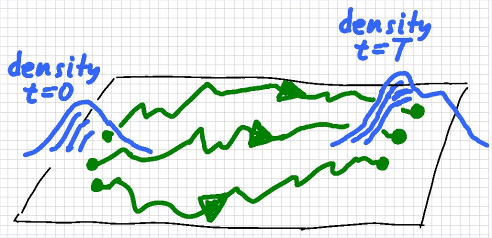

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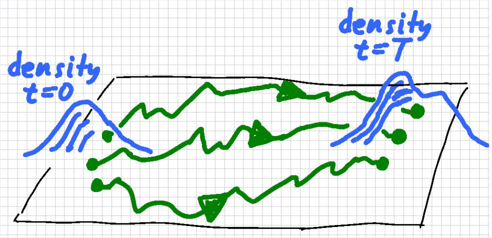

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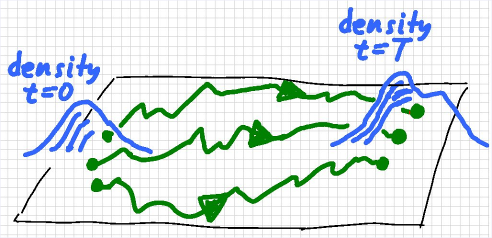

- transfer operator = map from density$|_{t=0}$ to density$|_{t=T}$
- invariant measure = eigenfunction with e-value 1
- conformations = joint nodal domains of first k eigenfctns
- lifetimes can be estimated via distance of eigenvalues from 1

Huisinga/Schmidt, 2005

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no. of computational DOF's $\sim$ linear in no. of subsystems

Partially inspired by Hartree-Fock approximation to many-electron Schroedinger eq.

Exact transfer operator for Hamiltonian MD

P = push-forward of measure under Hamiltonian flow

$$P\mu(\Omega) = \mu(\Phi^{-1}(\Omega))$$

where Φ = time-T map of Hamiltonian flow, i.e.
$\Phi(q_0, p_0) = (q(t), p(t))$ with

$$\dot{q} = M^{-1}p, \quad \dot{p} = -\nabla V(q)$$

$(p, q) = (p_1, q_1, \ldots, p_N, q_N) \in \mathbb{R}^{6N}$

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$p(x, \Omega)$ = stochasic transition fctn = prob. that a trajectory initially at x ends up in set A after time T

$$\dot{q} = M^{-1}p, \quad \dot{p} = -\nabla V(q) - \gamma M^{-1}p + \sqrt{2\gamma\beta^{-1}}\,\dot{W}$$

Unique invariant measure, alias eigenstate with e-val. 1 i.e. $P\mu = \mu$: *const* $e^{-\beta H}$ Gibbs-Boltzmann

Mean field approach

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- Step 4 Solve nonlinear problem by Roothaan type algorithm + sparse Ulam method, yielding approximate eigenstates

1. PDE formulation of transfer operator

MD: Evolution of trajectories

$$\dot{z} = f(z), \quad z = \begin{pmatrix} q \\ p \end{pmatrix}, \quad f = \begin{pmatrix} \frac{\partial H}{\partial p} \\ -\frac{\partial H}{\partial q} \end{pmatrix}$$

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

Mass matrix M depends on q when inner coordinates (bondlengths, bond angles, torsion angles) are used

Liouville eq.: Evolution of densities on phase space

$$\frac{\partial u}{\partial t} + div_z(f\, u) = 0, \quad u = u(z,t)$$

Special case: 'sharp' trajectories $u(z,t) = \delta(z - z(t))$

Preserves positivity of u and total mass $\int u(z,t)\, dz \longrightarrow$ evol. on prob.densities

Preserves (expected value of) energy, $E(t) = \int H(z)\, u(z,t)\, dz$

Langevin case: Fokker-Planck equation

Transfer operator via Liouville eq.

$$Pu(\cdot, 0) = u(\cdot, T)$$

Mean field approx. of Liouville eq.

Partition phase space coord's $z = (q, p)$ into subsystem coord's

$$z = (z_1, .., z_N) \in \mathbb{R}^{2d}, \quad z_i = (q_i, p_i) \in \mathbb{R}^{2d_i}, \quad \textstyle\sum_{i=1}^N d_i = d$$

Subsystem densities

$$u_i(z_i, t) := \int_{\mathbb{R}^{2(d-d_i)}} u(z, t)\, d\widehat{z}_i$$

Exact evolution of subsystem densities

$$\partial_t u_i + div_{z_i}(u_i\, f_i^{exact}) = 0, \quad f_i^{exact} = \frac{\int u(z, t)\, f_i(z)\, d\widehat{z}_i}{\int u(z, t)\, d\widehat{z}_i} \quad (*)$$

Not a closed system, f_i^{exact} depends on full density u and not just the u_j

Mean field approximation: Replace $u(z, t)$ in (*) by $\prod_j u_j(z_j, t)$

$$f_i^{mf}(z_i, t) = \int_{\mathbb{R}^{2(d-d_i)}} \textstyle\prod_{j\neq i} u_j(z_j, t)\, f_i(z)\, d\widehat{z}_i$$

Closed system, $f_i^{mf} = f_i^{mf}[u_1, .., u_N](z_i, t)$

Coupled system of N nonlinear partial integrodifferential eqns on subsystem phase spaces $\mathbb{R}^{2d_i}$

Physically: Each subsystem experiences force of ensemble of other subsystems at 'typical' states at time t

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Key point: high-D, linear equation → low-D, nonlinear system

Summary: Mean field approx. of Liouville eq.

Recall $u(z_1,..,z_N) = u_1(z_1)\cdot \ldots \cdot u_N(z_N)$, $z_i = (q_i,p_i) \in \mathbb{R}^{2d_i}$

Mean field eq.

$$\frac{\partial u_i}{\partial t} + div(f_i^{eff}\, u_i) = 0,$$

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Mean field transfer operator

$$P^{mf}(u_1|_{t=0}\otimes\cdots\otimes u_N|_{t=0}) = u_1|_{t=T}\otimes\cdots\otimes u_N|_{t=T}$$

Mean field approximation of transfer operator eigenstates

Recall: transfer operator = time T map of Liouville eq.,
$Pu(\cdot, 0) = u(\cdot, T)$

Variational principle for eigenstates of P^{exact}:

$$\max_v \langle v, P^{exact} v\rangle \text{ subject to } \langle v, v\rangle = 1, \ \langle f, g\rangle = \int f\, g\, d\mu$$

'Hartree-Fock' like variational principle for eigenstates of P^{mf}:

$$\max_{v_1,..,v_N} \langle v_1 \otimes \cdots \otimes v_N, P^{mf} v_1 \otimes \cdots \otimes v_N\rangle$$

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- Total energy $E = \int H(z) \prod_i u_i(z_i, t)\, dz$ conserved
- Model is exact for a non-interacting system, i.e. if $H = \sum_i H_i(z_i)$ then $u_1(z_1) \cdot \ldots \cdot u_N(z_N)$ solves the original Liouville eq.

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- Model is exact for a non-interacting system, i.e. if $H = \sum_i H_i(z_i)$ then $u_1(z_1) \cdot \ldots \cdot u_N(z_N)$ solves the original Liouville eq.
- For fixed u_j, $j \neq i$, the eq. for u_i is the Liouville eq. for an underlying time-dependent Hamiltonian ODE,

$$\dot{q}_i = \frac{\partial H_i^{eff}}{\partial p_i}, \quad \dot{p}_i = -\frac{\partial H_i^{eff}}{\partial q_i},$$

where

$$H_i^{eff}(z_i,t) = \int_{\mathbb{R}^{2(d-d_i)}} H(z_1,..,z_N) \prod_{j \neq i} u_j(z_j,t)\,d\widehat{z}_i$$

Validation of mean field model, I: Theoretical properties

Theorem (F./Junge/Koltai)

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Importantly, H_i^{eff} does not depend on u_i, only on the other u_j. This facilitates iterative updating methods via sample trajectories.

A surprising property of the mean field model

Theorem (F., Junge, Koltai)

Consider a Hamiltonian with weakly interacting subsystems,

$$H(z) = H_0(z) + \epsilon\, H_{int}(z), \quad H_0(z) = \sum_i H_i(z_i).$$

Then

$$||u^{exact} - u^{mf}||_{L^1} = O(\varepsilon^2),$$

uniformly for $0 \le t \le T$.

Naively, would expect the error to be of the order of the coupling constant, $\mathrm{O}(\varepsilon)$. Result says that the mean field model resolves coupling between subsystems correctly to leading order!

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In standard coordinates, the Hamiltonian H is strongly coupled in the particle positions, $V = V(q_1, .., q_N)$.

But in inner coordinates (bondlengths, bond angles, torsion angles), the potential energy decouples completely (in chain molecules with first, second and third neighbour interactions, i.e. bond, angular and torsion potentials)! The only remaining complying is in the kinetic energy.

Validation of mean field model, II: Numerical comparisons to exact model

Example: Two-oscillator toy system

$$H = \frac{p_1^2}{2m_1} + \frac{p_2^2}{2m_2} + V(q_1, q_2)$$

$$V = (\tfrac{3}{2}q_1^4 + \tfrac{1}{4}q_1^3 - 3q_1^2 - \tfrac{3}{4}q_1 + 3)(2q_2^4 - 4q_2^2 + 3) = V_1(q_1)V_2(q_2)$$

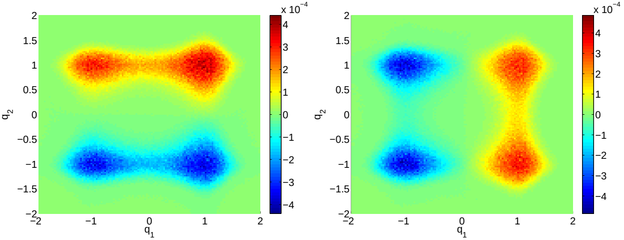
Mean field approximation to Liouville eq. reads explicitly:

$$\partial_t u_i(z_i, t) = \begin{pmatrix} -m_i^{-1} p_i \\ \nabla_{q_i} V_i(q_i) \int V_j(q_j)\, u_j(z_j, t)\, dz_j \end{pmatrix} \cdot \nabla_{z_i} u_i(z_i, t), \quad i = 1, 2,$$

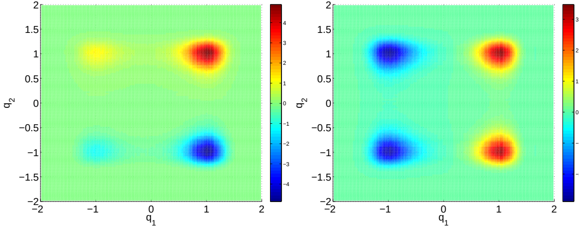
Mean field transfer operator = time T map of above nonl.system

Want to find leading eigenstates of this operator (≈ conformations)

Example: Two-oscillator toy system

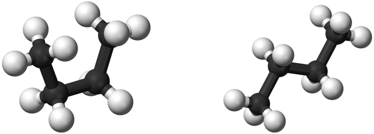


Dominant eigenfunctions of (spatial) transfer op., exact (16384 elements)

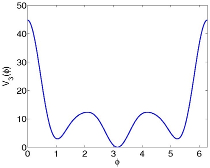


Mean field approximation (128 elements)

Example: Butane



$$
\begin{aligned}
V_3(\phi) \quad = \quad & K_\phi \left(1.116 - 1.462\cos\phi - 1.578\cos^2\phi + 0.368\cos^3\phi \right. \\
& \left. +3.156\cos^4\phi + 3.788\cos^5\phi\right), \quad K_\phi = 8.314\,\frac{\text{kJ}}{\text{mol}}
\end{aligned}
$$



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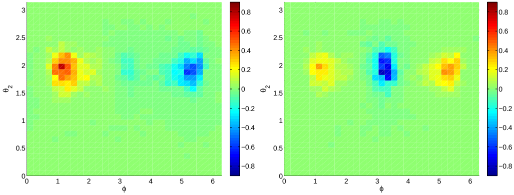
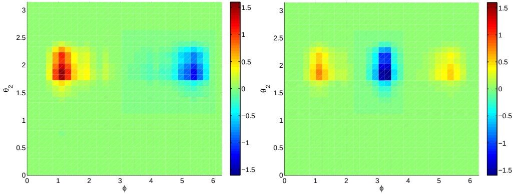


Dominant eigenvectors of full transfer operator

$\lambda_2 = 0.985$ (left), $\lambda_3 = 0.982$ (right), slice at $q_1 = \theta_1 = \pi_2$, $32 \times 32 \times 32$ grid, $T = 0.5 \cdot 10^{-13}$s



Mean field approximation to these eigenvectors

10 Roothaan iterations

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Need to solve:

$$\max_{u_1,..,u_N} \left\langle u_1 \otimes \cdots \otimes u_N,\, P^{mf}(u_1 \otimes \cdots \otimes u_N) \right\rangle$$

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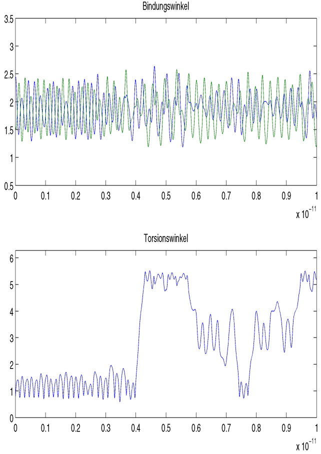
In original QChem context, algorithm proven to converge, cf. Roothaan 1952, Cances/Le Bris 2000

Hamilton versus Langevin

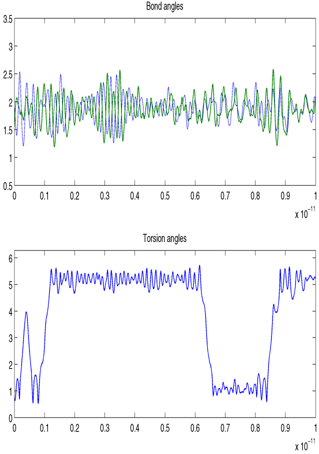
Test system: butane

United atom model
Inner coordinates: r_1, r_2, r_3, θ_1, θ_2, ϕ

Hamilton versus Langevin, I: orbits look similar



Bond angle and torsion angle evolution, MD



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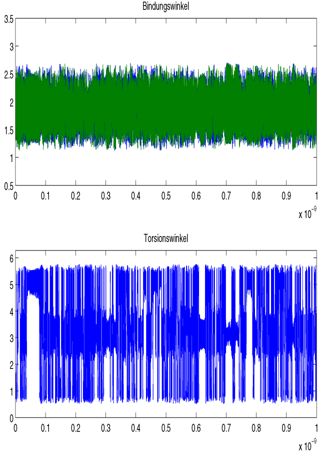

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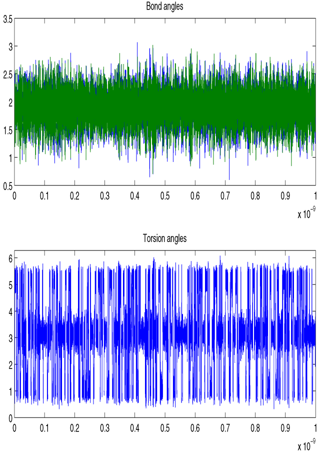
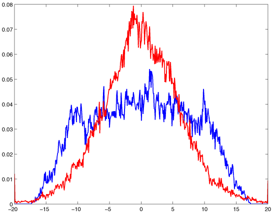
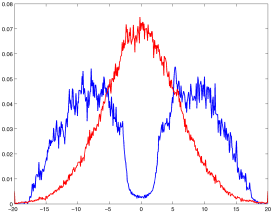


Bond angle and torsion angle evolution, Langevin

Hamilton versus Langevin, III: position-momentum correlations are completely different



Distribution of torsion angle momentum $\dot\phi$, conditioned on $|\phi - \phi_1| < 0.03$. Blue=MD, Red=Langevin



Distribution of torsion angle momentum $\dot\phi$, conditioned on $|\phi - \phi_0| < 0.03$. Blue=MD, Red=Langevin

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THANKS FOR ATTENTION
http://www-m7.ma.tum.de