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

Gero Friesecke (TU Munich)

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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)
Molecular dynamics

Molecular dynamics = Hamiltonian dynamics applied to systems of atoms

Valid as a good approximation to quantum dynamics as long as there is no bond breaking/bond formation, due to small mass ratio $m_e / m_{\text{nuc}} \sim 10^{-4}$


Often, also add small amount of damping+noise (emulate environment e.g. solvent), of which more later

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
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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

\[ H = \sum_{i} |p_i|^2 + \frac{1}{2} k_{\text{bond}} (r_{ij} - r_0)^2 
+ \frac{1}{2} k_{\text{ang}} \left( \cos \theta_{ijk} - \cos \theta_0 \right)^2 
+ \frac{1}{2} k_{\text{tor}} \phi_{ijk\ell}^2 \]
Hamiltonian of n-Butane

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \cdots \quad \text{CH}_2 \quad \text{CH}_3 \\
\end{align*}
\]

\[
x_i \in \mathbb{R}^3 \text{ position of } i^{th} \text{ CH}_2 \text{ group, } p_i \in \mathbb{R}^3 \text{ momenta}
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Hamiltonian of n-Butane

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

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

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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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Connection of n-Butane Hamiltonian to other models

$\theta_0 = 180^\circ$ (preferred bond angle is straight)

$\Rightarrow$ get Fermi-Pasta-Ulam as an invariant submanifold

all $x_i$ and $p_i$ collinear, i.e. purely longitudinal motion

$n = 4$ (standard Butane), $V_{\text{ang}} = V_{\text{tor}} = 0$, $k_{\text{bond}} \to \infty$

$\Rightarrow$ get Thurston triple linkage

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Key questions from an applications point of view

→ biophysics, molecular biology, drug design, protein folding pb., ...

Mathematical definition of 'conformation'.
Heuristically, neighbourhood of a local energy min. But which nbhd should you take?

Computational methods which track conformation changes for large systems.
Occur at long timescales, way beyond reliable trajectory simulation.

Biological examples (more complex than butane): retinal cis-trans transition; DNA α-β transition; hemoglobin T-R transition
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\text{transfer operator} = \text{map from density } | \ t=0 \ \text{to density } | \ t=T
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\[
\text{invariant measure} = \text{eigenfunction with } \lambda = 1
\]

\[
\text{conformations} = \text{joint nodal domains of first } k \ \text{eigenfunctions}
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\text{lifetimes can be estimated via distance of eigenvalues from 1}
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Huisinga/Schmidt, 2005
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Key advantage for small systems

Suffices to compute transfer operator for short time

Catch for large systems

No. of computational DOF's exponential in no. of atoms

Eigenfunctions are functions on phase space

For $M$ atoms: functions on $\mathbb{R}^{6M}$ implies $\mathbb{R}^{10}$ gridpts implies $\mathbb{R}^{6M} \to 10^M$ gridpts

Our proposal: Keep transfer operators, but make mean field approximation (w.r.to small subsystems)

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

Partially inspired by Hartree-Fock approximation to many-electron Schroedinger eq.
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Exact transfer operator for Hamiltonian MD

\[ \mathcal{P} = \text{push-forward of measure under Hamiltonian flow} \]

\[ P_\mu(\Omega) = \mu(\Phi^{-1}(\Omega)) \]

where \( \Phi = \text{time-T map of Hamiltonian flow, i.e.} \)
\[ \Phi(q_0, p_0) = (q(t), p(t)) \]
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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\( p(x, \Omega) = \text{stochastic transition fctn = prob. that a trajectory initially at } x \text{ ends up in set } A \text{ after time } T \)

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

Unique invariant measure, alias eigenstate with e-val. 1 i.e. \( P_\mu = \mu: \text{const } e^{-\beta H} \text{ Gibbs-Boltzmann} \)
Mean field approach
F./Junge/Koltai, Multiscale Model. Simul., 2009

Step 1 PDE formulation of transfer operator (Liouville eq.)
Step 2 Mean field approximation of Liouville eq. (w.r. to a partitioning into subsystems)
Step 3 Approximate variational principle for eigenstates of exact transfer operator by 'Hartree-Fock' like nonlinear variational principle
Step 4 Solve nonlinear problem by Roothaan type algorithm + sparse Ulam method, yielding approximate eigenstates
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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**

\[
\frac{\partial u}{\partial t} + \text{div}_z(f u) = 0, \quad u = u(z, t)
\]

Special case: ‘sharp’ trajectories \( u(z, t) = \delta(z - z(t)) \)

Preserves positivity of \( u \) and total mass \( \int u(z, t) \, dz \rightarrow \) 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

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

Subsystem densities

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

Exact evolution of subsystem densities

$$\partial_t u_i + \text{div}_{z_i}(u_i f_i^{\text{exact}}) = 0, \quad f_i^{\text{exact}} = \frac{\int u(z, t) f_i(z) \, d\hat{z}_i}{\int u(z, t) \, d\hat{z}_i} \quad (\star)$$

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

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

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

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

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 $\rightarrow$ low-D, nonlinear system
Summary: Mean field approx. of Liouville eq.

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

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$N$ coupled nonlinear partial integro-differential equations on $\mathbb{R}^{2d_i}$

(Original Liouville equation is a linear PDE on $\mathbb{R}^{2d}$, $d = \sum_i d_i$)
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Mean field transfer operator

\[
P^{mf} \left( u_1 \big|_{t=0} \otimes \cdots \otimes u_N \big|_{t=0} \right) = u_1 \big|_{t=T} \otimes \cdots \otimes u_N \big|_{t=T}
\]
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 $P^{mf}$:

$$\max_{v_1, \ldots, v_N} \left\langle v_1 \otimes \cdots \otimes v_N, P^{mf} v_1 \otimes \cdots \otimes v_N \right\rangle$$
Validation of mean field model, I: Theoretical properties

Theorem (F./Junge/Koltai)

▶ Total densities

\[ \int_{\mathbb{R}^2} d\mathbf{u}_i(z_i, t) \] conserved

▶ 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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\[ H_{\text{eff}}^i(z_i, t) = \int_{\mathbb{R}^2} (d - d_i) H(z_1, \ldots, z_N) \prod_{j \neq i} u_j(z_j, t) \, d\hat{z}_i \]

Importantly, \( H_{\text{eff}}^i \) does not depend on \( u_i \), only on the other \( u_j \). This facilitates iterative updating methods via sample trajectories.
Validation of mean field model, I: Theoretical properties

Theorem (F./Junge/Koltai)

Total densities
\[ \int_{\mathbb{R}^2} du_i(z_i, t) \text{conserved} \]

Total energy
\[ E = \int H(z_i) \prod_i u_i(z_i, t) \text{dz}_i \text{conserved} \]

Model is exact for a non-interacting system, i.e. if
\[ H = \sum_i H_i(z_i) \]
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Validation of mean field model, I: Theoretical properties

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- Total densities \( \int_{\mathbb{R}^{2d}} u_i(z_i, t) \, dz_i \) conserved

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\]

Importantly, \( H_{\text{eff}}^i \) 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,

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

Then

\[ \| u^{\text{exact}} - u^{\text{mf}} \|_{L^1} = O(\epsilon^2), \]

uniformly for \( 0 \leq t \leq T \).

Naively, would expect the error to be of the order of the coupling constant, \( O(\epsilon) \). Result says that the mean field model resolves coupling between subsystems correctly to leading order!
How to partition into subsystems?

The previous theorem (leading order correctness for weakly coupled subsystems) helps to choose a good partitioning. In standard coordinates, the Hamiltonian \( H \) is strongly coupled in the particle positions, \( V = V(q_1, \ldots, q_N) \). 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.
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Validation of mean field model, II:
Numerical comparisons to exact model
Example: Two-oscillator toy system

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

\[ V = (\frac{3}{2}q_1^4 + \frac{1}{4}q_1^3 - 3q_1^2 - \frac{3}{4}q_1 + 3)(2q_2^4 - 4q_2^2 + 3) = V_1(q_1)V_2(q_2) \]

Mean field approximation to Liouville eq. reads explicitly:

\[ \partial_t u_i(z_i, t) = \left( -m_i^{-1}p_i \nabla_i V_i(q_i) \int V_j(q_j) u_j(z_j, t) dz_j \right) \cdot \nabla_i u_i(z_i, t), \quad i = 1, 2, \]

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

Want to find leading eigenstates of this operator ($\approx$ conformations)
Example: Two-oscillator toy system

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

Mean field approximation (128 elements)
Example: Butane

\[ V_3(\phi) = K_\phi \left( 1.116 - 1.462 \cos \phi - 1.578 \cos^2 \phi + 0.368 \cos^3 \phi + 3.156 \cos^4 \phi + 3.788 \cos^5 \phi \right), \quad K_\phi = 8.314 \frac{\text{kJ}}{\text{mol}} \]
Example: Butane

Dominant eigenvectors of full transfer operator

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

Mean field approximation to these eigenvectors

10 Roothaan iterations
Computational method for finding eigenstates

Need to solve:

\[
\max_{u_1, \ldots, u_N} \langle \hat{u}_N \otimes \cdots \otimes \hat{u}_N, \mathcal{P}_{mf} (\hat{u}_N \otimes \cdots \otimes \hat{u}_N) \rangle
\]

Algorithm

Set \( u(0) := u_N \otimes \cdots \otimes u_N \)

Solve \( \mathcal{P}_{mf}, i (\hat{u}_N^{(N+1)} i) \)

\( \lambda_i u_N^{(N+1)} i = \lambda_i u_N^{(N+1)} i \), cycling through \( i \)

Set \( u^{(N+1)} := u^{(N+1)}_1 \otimes \cdots \otimes u^{(N+1)}_N \)

Inspired by Roothaan algorithm for solving the Hartree-Fock equations in quantum chemistry. Inner step: sparse Ulam method

Nice math. structure (operator \( \mathcal{P} \) self-adjoint, cf. time-reversibility, and linear in \( u_i \) for fixed \( u_j, j \neq i \))

In original QChem context, algorithm proven to converge, cf. Roothaan 1952, Cances/Le Bris 2000
Computational method for finding eigenstates

Need to solve:

$$\max_{u_1, \ldots, u_N} \left\langle u_1 \otimes \cdots \otimes u_N, P_{mf} (u_1 \otimes \cdots \otimes u_N) \right\rangle$$
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Algorithm

Set \( u^{(0)} := u_1^{(0)} \otimes \cdots \otimes u_d^{(0)} \)

Solve \( P_{mf, i}^{mf}(\hat{u}_i^{(N)})u_i^{(N+1)} = \lambda_i u_i^{(N+1)} \), cycling through \( i \)

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Algorithm

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Hamilton versus Langevin

Test system: butane

United atom model
Inner coordinates: \( r_1, r_2, r_3, \theta_1, \theta_2, \phi \)
Hamilton versus Langevin, I: orbits look similar

Bond angle and torsion angle evolution, MD

Bond angle and torsion angle evolution, Langevin
Hamilton versus Langevin, II: orbits look similar

Bond angle and torsion angle evolution, MD

Bond angle and torsion angle evolution, Langevin

Gero Friesecke (TU Munich) Transfer operators and time scale bridging 75
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
Summary and future

▶ Have derived a mean field approximation to transfer operators which offers hope towards systematic application to large molecules.

Key point: linear PDE on $\mathbb{R}^6 \rightarrow \text{system of nonl. PDE'S in low dim's}$

▶ Theoretical properties of mean field system and performance tests on small systems very promising

▶ Currently under way: larger scale examples

▶ Future: mathematical framework which includes coupling with electronic structure and photons (Example: Retinal)

THANKS FOR ATTENTION

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