Stochastic path integral approaches to the dynamics of bio-molecules



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Outline

Part I: Dynamics of rare biomolecular transitions

biomolecules (in particular proteins)
decoupling of time scales
Theoretical description
MD numerical simulations
Idea

Problems in practical applications

Part II: Stochastic Path Integral Methods to Biomolecular dynamics

- Dominant Reaction Pathways (DRP)
- Effective Stochastic Theory (EST)

Part 1

Dynamics of Biomolecules





Amino-acids

 Proteins are bio-polymers made of 20 different types of amino-acids:

Н

 $NH_2 - C_{d} - CO_2H$

R

Ala, Ile, Leu, Met, Phe, Pro,Trp, Val, Asp, Cys, Gln, Gly, Ser, Thr, Tyr,Arg, His, Lys, Asp, Glu

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Poly-Peptide Chain

Frankfrankstrakter Energetics:

- * Bonded ~ 100 Kcal/mole
- * Non-Bonded ~ 1 Kcal/mole
- * KT (T=300° K) = 0.6 kcal/mole

Relevant low-energy dof:

Torsional Angles



Some open theoretical research fields

 Protein folding/misfolding
 order-disorder transitions in natively unfolded proteins
 Protein-protein interaction (involved in cell signaling)

Protein Native State

At room temperature, proteins assume a "unique" and well-defined 3D conformation (native state).



The Protein Folding Problem:

"Part I": What is the sequence-structure relationship? i.e. can we predict the native state given the chemical composition of the poly-peptide chain? <u>Implications</u>: drug design, ...

"Part II": Understanding the networks of transition pathways which take from the denatured conformations to the native state: how does a protein fold? <u>Implications:</u> amiloydogenic pathologies,...

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Multiple kinetic time scales:





Theoretical Modeling of Biomolecular Physics

Mathematical representation of biomolecules (choice of the relevant degrees of freedom)

- Theory for the dynamics
 - Quantum mechanics
 - Newtonian dynamics
 - Langevin dynamics

Theory for the interactions



Theoretical modeling of biomolecules

First principles: solving the time-dependent Schroedinger equation for a system consisting of ~10,000 atoms, in which electrons and nuclei interact through the Coulomb force and are subject to the Pauli principle.

Classical MD simulations:

* Replacing the chemistry of electrons with empiric interactions between atomic nuclei

* Describing the dynamics of atomic nuclei at the classical level

Is it justified? Does it work?

Molecular Dynamics

Explicit Solvent:

All atom: protein atoms + solvent atoms Newton's Eq.s $M_i \ddot{x}_i = -\nabla_i U(X, Y)$ $i = 1, \dots, N_p$ $m_k \ddot{y}_k = -\nabla_k U(X, Y)$ $k = 1, \dots, N_s$

Implicit Solvent:

Only protein atoms Modify Newton's Eq. Introduce effective interactions

 $M_i \ddot{x}_i = -\nabla_i U(X) - \gamma \dot{x}_k + R_k(t)$

Molecular Dynamics

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$$I_i \ddot{x}_i = -\nabla_i U(X) - \gamma \dot{x}_k + R_k(t)$$

Over-damped Langevin Dynamics

$$m\ddot{X} = -\gamma\dot{X} - \nabla U(X) + R(t)$$

For molecules this term is damped after 0.1 ps, while the shortest dynamics takes place at ns time scale

$$\dot{X} = -\frac{1}{\gamma} \nabla U(X) + \xi(t)$$
$$\langle \xi_i(t)\xi_j(0)\rangle = 3 \frac{k_B T}{\gamma} \delta(t) \delta_{ij}$$

MD simulations

In overdamped Langevin dynamics: $\dot{x}(t) = -\frac{1}{\gamma} \nabla U(x(i)) + R(t)$ $x(i+1) = x(i) - \frac{\Delta t}{\gamma} \nabla U(x(i)) + \sqrt{2D\Delta t} \eta(i)$

In all-atom Hamiltonian MD Velocity-Verlet + Nose'-Hoover,

MD simulations

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$$x(i+1) = x(i) - \frac{\Delta t}{\gamma} \nabla U(x(i)) + \sqrt{2D\Delta t}\eta(i)$$

interested in trying for yourself ? see me later...

In all-atom Hamiltonian MD Velocity-Verlet + Nose'-Hoover,

Computational Limitations of the Molecular Dynamics Simulations



Conformational transitions are so-called RARE EVENTS

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Rare Events by MD simulations

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For protein folding: Typical # of <u>time</u> steps ~ 10¹²

. . . .







Conclusions of part I

- Classical simulations of bio-molecules may provide at least reasonable standpoint
- The Langevin dynamics offers a scheme for implicit solvent simulations
- Unfortunately the direct integration of the Eq. of motion is very inefficient

....we need new ideas, rather than better computers....

....and that's where more advanced stochastic approaches can be useful...(hopefully!)

Part II

Stochastic Path Integral Methods for the Dynamics of Biomolecules



* How to avoid investing time simulating the wondering in the meta-stable state?

* How to avoid the problems related to the decoupling of time scales?



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Path integral representation of Langevin dynamics

 $\begin{aligned} \mathbf{X}_{l+1} - \mathbf{X}_{l} &= -\frac{D_{0} \ \Delta t}{k_{B}T} \nabla U(\mathbf{X}_{l}) + \sqrt{2D_{0}\Delta t} \ \mathbf{R}_{l}, \\ \langle R_{i \ l}^{a} \ R_{j \ l'}^{b} \rangle &= \ \delta_{ij} \ \delta_{ll'} \ \delta^{ab}. \end{aligned}$

Goal: compute the prob. of a given path: $(\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_{N_t})$.

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Goal: compute the prob. of a given path: $(\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_{N_t})$. Step 1: compute the prob. of a sequence of random forces: $(\mathbf{R}_1, \mathbf{R}_2, \dots, \mathbf{R}_{N_t})$

$$\mathcal{P}(\mathbf{R}_1, \dots, \mathbf{R}_{N_t}) = \left(\frac{1}{2\pi}\right)^{\frac{3N_p N_t}{2}} \prod_{j=1}^{N_t} \exp\left[-\frac{\mathbf{R}_j^2}{2}\right] \cdot \prod_{i=1}^{N_t} d\mathbf{R}$$

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Step 2: use Eq. (1) to change variable from R's to X's:

$$P(\mathbf{X}_1|\mathbf{X}_{N_p}; N_t \Delta t) = \int \left(\prod_{i=1}^{N_t} d\mathbf{X}_i\right) e^{-\frac{\sum_{l=1}^{N_t-1} \left(\mathbf{x}_{l+1} - \mathbf{x}_l + D_0 \frac{\Delta t}{k_B T} \nabla U(\mathbf{x}_l)\right)^2}{4D_0 \Delta t}}$$

Resolution of the ambiguity

Step 3: Expand the exponent. It contains an Ito integral

 $(I) \int_{x_1}^{x_N} \nabla U(x) \cdot dx \equiv \lim_{\substack{N \to \infty \\ \Delta t \to 0}} \sum_{l=1}^{N-1} (x_{l+1} - x_l) \cdot \nabla U(x_l)$

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But the Fundamental Theorem of the Ito Calculus is

$$(I)\int_{x_1}^{x_N} \nabla U(x) \cdot dx = U(x_N) - U(x_1) \left[-\frac{1}{\beta\gamma} \int_0^t d\tau \ \nabla^2 U(x(\tau)), \right]$$

Path Integral representation

Hence, we arrive to:

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \int_{x(0)=x_i}^{x(t)=x_f} \mathcal{D}x \ e^{-S_{eff}[x(\tau)]}$$
$$S_{eff}[\mathbf{X}(t)] = \int_0^t d\tau \left(\frac{\dot{\mathbf{x}}^2}{4D_0} + V_{eff}(\mathbf{X})\right)$$
$$V_{eff}(\mathbf{X}) = \frac{D_0}{4(k_B T)^2} \left((\nabla U(\mathbf{X}))^2 - 2k_B T \nabla^2 U(\mathbf{X})\right)$$

Fokker-Planck Equation

The probability $P(X_{f},t|X_{i})$ is the Green's function of the Fokker-Planck operator (by inspection: try differentiating with respect to t)

$$\left\{ \frac{\partial}{\partial t} - D\nabla [(\nabla + \beta \nabla U(x))] \right\} P(x_f, t | x_i) = \delta(x_f - x_i)\delta(t)$$

This is equivalent to saying that it is the solution of the Fokker-Planck Eq.

$$\frac{\partial}{\partial t}P(x,t) = D\nabla \left[\left(\nabla + \beta \nabla U(x) \right) P(x,t) \right]$$

With the initial condition: $\lim_{t
ightarrow 0} P(x,t) = \delta(x_f-x_i)$

Thermal Equilibrium

An important property: in the long-time limit:

Hence, the LE (FP) describe the approach to thermal equilibrium.

Thermal Equilibrium

An important property: in the long-time limit:

$$P(x,t) \rightarrow \frac{1}{Z} \exp\left(-\frac{U(x)}{k_B T}\right)$$

Hence, the LE (FP) describe the approach to thermal equilibrium.

Quantum analogy

If we perform the simple substitution:

$$P(x,t) \equiv e^{-\frac{\beta U(x)}{2}} \psi(x,t) \qquad \left(\beta \equiv \frac{1}{k_B T}\right)$$

Into the Fokker-Planck Eq., we obtain a new Eq.:

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 $\hat{H}_{eff}\psi(x,t) = -\frac{\partial}{\partial t}\psi(x,t)$

 $= -\frac{1}{\beta\gamma} \nabla^2 + \beta V_{eff}(x)$ \hat{H}_{eff} $\hat{H}_{eff} \dot{\psi}(x,t) = -\frac{\partial}{\partial t} \psi(x,t)$

 $V_{eff}(x) = \frac{1}{4\gamma} \left((\nabla U(x))^2 - \frac{2}{\beta} \nabla^2 U(x) \right).$ $\hat{H}_{eff} = -\frac{1}{\beta\gamma} \nabla^2 + \beta V_{eff}(x)$ $\hat{H}_{eff}\psi(x,t) = -\frac{\partial}{\partial t}\psi(x,t)$

Quantum analogy

The Langevin diffusion of a system subject to a potential U can be mapped on the propagation in imaginary time of a system subject to the quantum Hamiltonian containing the effective potential V_{eff}

Conditional probabilities as stochastic path integrals

Consider the time-dependent conditional probability:

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \int_{x(0) = x_i}^{x(t) = x_f} \mathcal{D}x \ e^{-S_{eff}[x(\tau)]}$$

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The microscopic connection

$$V_{eff}(x) = \frac{\beta}{4\gamma} \left((\nabla U(x))^2 - \frac{2}{\beta} \nabla^2 U(x) \right)$$

Empirical force fields Quantum Chemistry

Gromos, Amber, Charmm, ...

Quantum Chemistry calculations

DFT, PM3, PM6, ...

The microscopic connection

$$V_{eff}(x) = \frac{\beta}{4\gamma} \left((\nabla U(x))^2 - \frac{2}{\beta} \left[\nabla^2 U(x) \right] \right)$$

Expensive part!
one needs to be
clever

Empirical force fields Quantum Chemistry

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The Dominant Reaction Pathways (DRP) approach

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \int_{x(0) = x_i}^{x(t) = x_f} \mathcal{D}x \ e^{-S_{eff}[x(\tau)]}$$

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The most probable (DOMINANT) REACTION PATHWAYS are those which minimize the effective action S_{eff} .

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The most probable (DOMINANT) REACTION PATHWAYS are those which minimize the effective action S_{eff}.

In the low temperature limit $\beta \rightarrow \infty$, thermal fluctuations around the DRP provide small corrections
Hamilton-Jacobi Action

The effective action S_{eff} is simplectic: E_{eff} is conserved!

We can by-pass the direct solution of Newton equations and obtain directly the most probable folding trajectories using Hamilton-Jacobi (HJ) least-action principle

$$S_{HJ} = \sqrt{\beta\gamma} \int_{x_i}^{x_f} dl \sqrt{E_{eff} + V_{eff}[x(l)]}$$

NB: first derived in R. Elber & D.Shalloway, JCP 112 (2000) 5539.

Configuration space:

P.F., M.Sega, F.Pederiva and H.Orland, "Dominant Protein Folding Pathways", Phys. Rev. Lett. 97 (2006), 108101

Configuration space:

Reactant state



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Transition path times

The information about the time evolution is not lost: it can be recovered starting from the well-known HJ relationship

$$t(x) = \int_{x_i}^x dl \frac{1}{\sqrt{\frac{4}{\beta\gamma}(E_{eff} + V_{eff}[x(l)])}}$$

This represents the time along the path, after the transition has been initiated.



E. Autieri, P.F, M.Sega, F.Pederiva, and H.Orland, "Dominant Reaction Pathways in High Dimensional Systems", JCP 2008



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Problem: account for small fluctuations around the DRPs:

Step 1: convert to the time reprⁿ: $\Delta \tau_{n,n+1} = \frac{\Delta l_{n,n+1}}{\sqrt{4D(V_{eff}[X(n)] + E_{eff})}} \xrightarrow{X_{D}} \xrightarrow$

 $P(X_f, \tau(N)|X_i) = e^{-\frac{\beta}{2}(U(X_f) - U(X_i))} \int \prod_{n=1}^N dX(n) e^{-\beta \sum_{n=1}^{N-1} \Delta \tau_{n,n+1} \left[\frac{\gamma}{4} \left(\frac{X(n+1) - X(n)}{\Delta \tau_{n,n+1}}\right)^2 + V_{eff}[X(n)]\right]}$

Step 3: Sample by Monte Carlo

TIME STEPS ARE CHOSEN LARGE OR SMALL ACCORDING TO THE DRP

E. Autieri, P.F, M.Sega, F.Pederiva, and H.Orland, "Dominant Reaction Pathways in High Dimensional Systems", JCP 2008

The DRP algorithm

Step 1: "throw the first rope" (as in TPS)

- e.g.: high temperature unfolding, biased dynamics, ...
- Step 2: Minimize numerically the HJ effective action
 - e.g.: simul. annealing, FIRE, ...
 - Step 3: Sample thermal fluctuations around DRP if necessary

Exploration of the path space

- Simple simulated annealing algorithms tend to get stuck in local minima
- However we have found that MD-based algorithms (e.g. FIRE) are much more efficient



Computational Gain:

In HJ formalism time variable has disappeared -> no more problems with decoupling of time scales!



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For protein folding: Typical # of <u>time</u> steps ~ 10¹²

. . .

The Dominant Reaction Pathways are determined in the Hamilton-Jacobi formalism, i.e. following the evolution from x_i to x_f by discretized distance steps:

Distance

 \cap

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 $\left(\right)$

dl

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Distance

0

dl

2dl

3dl

4dl

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Finding the transition state

The transition state is usually defined from commitment analysis:

$P(X_f|X_{TS}) = P(X_i|X_{TS})$

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To leading-order in k_BT one obtains the condition:

$$U(X_f) + \frac{2}{\sqrt{k_B T}} \sqrt{\frac{1}{\gamma}} \int_{X_{TS}}^{X_f} dl \sqrt{V_{eff}(X_{TS})} + E_{eff}$$
$$= U(X_i) + \frac{2}{\sqrt{k_B T}} \sqrt{\frac{1}{\gamma}} \int_{X_{TS}}^{X_i} dl \sqrt{V_{eff}(X_{TS})} + E_{eff}$$

Which can be easily solved, once the DRP is known.

Reaction Rates (quick and dirty)

Reactant Product Dividing surface TS

$$k \equiv \int_{TS} d\vec{\sigma} \cdot \vec{J}$$

$$\vec{J}(x,t|x_i) = -\frac{1}{\gamma} \left(k_B T \vec{\nabla} + \vec{\nabla} U(x) \right) P(x,t|x_i)$$

Calculating the rates involves evaluating the Fokker-Planck probability INCLUDING THE NORMALIZATION

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Step 1

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Calculating the rates involves evaluating the Fokker-Planck probability INCLUDING THE NORMALIZATION

Non-Equilibrium fluctuations

Saddle point expansion beyond the leading order:

$$\begin{split} S_{eff}[x] &\simeq S_{eff}[\bar{x}] + \frac{\delta S[\bar{x}]}{\delta x} \ y(\tau) + \frac{1}{2} \frac{\delta^2 S[\bar{x}]}{\delta x \delta x} \ y^2(\tau) + \dots \\ & y(\tau) = x(\tau) - \bar{x}(\tau) \\ P(x_f, t | x_i) &\simeq e^{-S_{eff}[\bar{x}]} \ \int \mathcal{D}y \ e^{-\frac{1}{2} \frac{\delta^2 S[\bar{x}]}{\delta x \delta x} \ y^2(\tau)} \\ &= \mathcal{N} \sqrt{\frac{1}{\det F[\bar{x}]}} \ e^{-S_{eff}[\bar{x}]} \\ F[\bar{x}] &= \frac{1}{2} \frac{\delta^2 S[\bar{x}]}{\delta x \delta x} = \left(-\frac{1}{2D} \frac{d^2}{dt^2} + V_{eff}''[\bar{x}]\right) \\ \end{split}$$
Fluctuation Operator

Non-Equilibrium fluctuations

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 Fluctuation Operator

Determining
$$P(x,t|x_i)$$

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \mathcal{N} \times \int_{x_i}^{x_f} \mathcal{D}x \ e^{-\int_0^t d\tau \frac{\beta\gamma}{4} \dot{x}^2 + V_{eff}[x(\tau)]}$$

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Expand around the DRP:

$$\begin{aligned} x(\tau) &= \bar{x}(\tau) + y(\tau) \\ & \bigstar \\ \mathsf{DRP} \end{aligned}$$

Determining
$$P(x,t|x_i)$$

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \mathcal{N} \times \int_{x_i}^{x_f} \mathcal{D}x$$

Expand around the DRP:

$$\mathcal{N} \quad e^{-S_{eff}[\bar{x}]} \int_0^0 \mathcal{D}y \ e^{-\int_0^t d\tau \frac{\beta\gamma}{4} \dot{y}^2 + y(\tau)\hat{F}[\bar{x}]y(\tau)}$$

 $e^{-\int_0^t d\tau \frac{\beta\gamma}{4} \dot{x}^2 + V_{eff}[x(\tau)]}$

$$x(\tau) = \bar{x}(\tau) + y(\tau)$$

$$\uparrow$$
DRP

Determining
$$P(x,t|x_i)$$

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \mathcal{N} \times \int_{x_i}^{x_f} \mathcal{D}x$$

Expand around the DRP:

Fluctuation operator: $\hat{F} = -rac{eta\gamma}{2}rac{d^2}{d au^2} + \partial_i\partial_j V_{eff}[ar{x}(au)]$

 $e^{-\int_0^t d\tau \frac{\beta\gamma}{4} \dot{x}^2 + V_{eff}[x(\tau)]}$
Determining
$$P(x,t|x_i)$$

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} \mathcal{N} \times \int_{x_i}^{x_f} \mathcal{D}x$$

Expand around the DRP:

 $x(\tau)$

Fluctuation operator: $\hat{F} = -\frac{\beta\gamma}{2}\frac{d^2}{d\tau^2} + \partial_i\partial_j V_{eff}[\bar{x}(\tau)]$ $P(x_f, t|x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} e^{-S_{eff}[\bar{x}]} \mathcal{N} \sqrt{\frac{1}{\det F[\bar{x}]}}$

 $e^{-\int_0^t d au rac{eta\gamma}{4}\dot{x}^2 + V_{eff}[x(au)]}$

coordinate labels

$$\hat{F}[\bar{x}]_{k,m}^{i,j} = \frac{-\beta}{\Delta t_{m+1,n} + \Delta t_{m,m-1}} \delta_{i,j} \times \left[\frac{\delta_{k,m+1}}{\Delta t_{m+1,n}} - \delta_{k,m} \left(\frac{1}{\Delta t_{m+1,n}} + \frac{1}{\Delta t_{m+1,n}} \right) + \frac{\delta_{k,m-1}}{\Delta t_{m+1,n}} \right] \\
\downarrow + \frac{\partial^2 V_{eff}(\bar{x}(k))}{\partial x_i \partial x_j} \delta_{k,m}$$

time slice labels

Fluctuation operator:
$$\hat{F} = -\frac{\beta\gamma}{2}\frac{d^2}{d\tau^2} + \partial_i\partial_j V_{eff}[\bar{x}(\tau)]$$

 $P(x_f, t|x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} e^{-S_{eff}[\bar{x}]} \mathcal{N} \sqrt{\frac{1}{\det F[\bar{x}]}}$

Fluctuation determinants

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} e^{-S_{eff}[\bar{x}]} \mathcal{N} \sqrt{\frac{1}{\det F[\bar{x}]}}$$

Fluctuation determinants

$$P(x_f, t | x_i) = e^{-\frac{\beta}{2}(U(x_f) - U(x_i))} e^{-S_{eff}[\bar{x}]} \sqrt{\frac{1}{\det F[\bar{x}]}}$$

division of two large numbers

Fluctuation determinants

$$P(x_{f}, t|x_{i}) = e^{-\frac{\beta}{2}(U(x_{f}) - U(x_{i}))} e^{-S_{eff}[\bar{x}]} \sqrt{\frac{1}{\det F[\bar{x}]}}$$

division of two large numbers

Trick: multiply and devide by the probability for an harmonic oscillator



2. to lowest order in k_BT it may be neglected!

The reaction current:

$$\vec{J}(x_{f},t|x_{i}) = P_{HO}(x_{i},t|x_{i}) \ e^{-\frac{\beta}{2}(U(x_{f})-U(x_{i}))} \ \frac{e^{-S_{eff}[\bar{x}]}}{e^{-S_{eff}[\bar{x}_{HO}]}}$$
$$\times \sqrt{\det\left(\hat{F}^{-1}[\bar{x}_{HO}]\ \hat{F}[\bar{x}]\right)} \ \frac{1}{2} \ \left(\vec{\bar{x}}_{f} - \frac{1}{\gamma} \ \vec{\nabla}U(x_{f}) \ \right)$$

"Eyring" approximation:

 $k \equiv \int_{TS} d\vec{\sigma} \cdot \vec{J} \simeq |\vec{J}(x_{TS})| \times \prod_{i=1}^{d} \left[\sqrt{2\pi \langle (y^i - \bar{x}_{TS}^i)^2 \rangle} \right]$ Evaluated from

Found using the DRP formula Evaluated from the DRP formula

Eq. fluct. in the plane $\perp \vec{v}_{DRP}(x_{TS})$

This is the only part of the calculation which does not follow from a systematic expansion in k_BT . It should be improved

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Example 1: Protein folding



This simple model can be studied also with "traditional" MD simulations

Validation of DRP: Compare the results obtained by MD and by DRP

Predicting the structure of the folding trajectories



PF, A. Lonardi and H.Orland, "Dominant Reaction Pathways in Protein Folding: a Direct Validation Against MD Simulations", JCP 2010 in press

Predicting the structure of the folding trajectories



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Example 2: Alanine-dipeptide



Free energy landscape (from MD simulations) with superimposed two DRP trajectories.

GROMOS96 was used.

M.Sega, PF, F.Pederiva, G Garberoglio and H.Orland, "Quantitative Protein Dynamics from Dominant Folding Pathways", Phys. Rev. Lett. 99 (2007), 118102

Example 2: Alanine-dipeptide



M.Sega, PF, F.Pederiva, G Garberoglio and H.Orland, "Quantitative Protein Dynamics from Dominant Folding Pathways", Phys. Rev. Lett. 99 (2007), 118102

Example 3: cyclobuthenebutadiene transition



Computational cost: with Car-Parinello: impossible to simulate it! with DRP: 64 CPU hours

S.a Beccara, G. Garberoglio, PF, F.Pederiva "Ab-initio dynamics of rate thermally activated transitions", JCP (comm.) 132 (2010), 11102.

Example 3: cyclobuthenebutadiene transition



S.a Beccara, G. Garberoglio, PF, F.Pederiva "Ab-initio dynamics of rate thermally activated transitions", JCP (comm.) 132 (2010), 11102.

Temperature dependence of reaction mechanism





Important: for conformational transitions (e.g. protein folding) the T=0 limit is not appropriate

Folding pathways of an alpha-helix from quantum chemistry calculations

Most probable trajectory of atomic nuclei and electron densities during the folding of an alpha helix:

The molecular energy is not obtained from empiric force fields, but by directly solving the all-electron Schroedinger eq.

Results





Does Classical MD make sense in non-equilibrium conditions?



Reaction Rates



Test 2: Entropic barrier



Test 2: Entropic barrier



Test 3: a toy cis-trans transition



Test 3: a toy cis-trans transition





Potential limitations to be faced:

Difficulties in performing an efficient exploration of the path space

The dominant paths may not be representative of the real transition paths

The DRP approach is useless if:

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Iarge entropy of the reactant ("all routes to Rome" scenario)



The DRP approach is useless if:

- Iarge entropy of the reactant ("all routes to Rome" scenario)
- The large number of DRP's with same boundary conditions



The DRP approach is useless if:

- Iarge entropy of the reactant ("all routes to Rome" scenario)
- The large number of DRP's with same boundary conditions
- The large thermal fluctuations around a given DRP



Test on the folding mechanism of



MD and DRP trajectories have the same spread:

the uncertainty on the folding mechanism is dominated by the large entropy of the reactant => SAME INFORMATION AS IN MD

PF, A. Lonardi and H.Orland, "Dominant Reaction Pathways in Protein Folding: a Direct Validation Against MD Simulations", JCP 133, 045104 (2010) 72

Effective Stochastic Theories

i.e. "how to turn gaps into a virtue"



Computational Limitations of the Molecular Dynamics Simulations



Computational Limitations of the Molecular Dynamics Simulations



Computational Limitations of the Molecular Dynamics Simulations


Computational Limitations of the Molecular Dynamics Simulations



We need alternative techniques to long-time dynamics: Path integral-based techniques can be extremely useful



Introduction

Stating the Goal:

Effective stochastic theory which generates the correct long-time stochastic dynamics, at a lower time-resolution power:



Averaging out the fast dynamics



Kim Atta: Long Exposure Photography Project

Conditional probabilities as path integrals

Consider the time-dependent conditional probability:



Conditional probabilities as path integrals

Consider the time-dependent conditional probability:



Periodic path integral formulation

For simplicity and without loss of generality consider:

$$Z(t) \equiv \int d\mathbf{X} \ P(\mathbf{X}|\mathbf{X};t) = \oint \mathcal{D}\mathbf{X} \ e^{-S_{eff}[\mathbf{X}]}.$$

Arbitrary correlation functions can be rigorously obtained from Z(t):

$$\langle O_1[\mathbf{X}(\tau_1)] \ O_2[\mathbf{X}(\tau_2)] \rangle = \frac{\oint \mathcal{D}\mathbf{X} \ O_1[\mathbf{X}(\tau_1)] \ O_2[\mathbf{X}(\tau_2)] \ e^{-S_{eff}[\mathbf{X}]}}{\oint \mathcal{D}\mathbf{X} \ e^{-S_{eff}[\mathbf{X}]}} \qquad \tau_1, \tau_2 \ll t$$

The separation of time scales in stochastic molecular dynamics

Perform Fourier analysis:

$$\tilde{\mathbf{X}}(\tau) = \mathbf{X}(\tau+t) = \sum_{n} \tilde{\mathbf{X}}(\omega_n) e^{i\omega_n t}.$$

If the system displays separation of time scales:

Fourier Spectrum





$$Z(t) = \oint \mathcal{D}\mathbf{X}_{<} \oint \mathcal{D}\mathbf{X}_{>} e^{-S_{eff}[\mathbf{X}_{<} + \mathbf{X}_{>}]}$$
$$\equiv \oint \mathcal{D}\mathbf{X}_{<} e^{-S_{eff}[\mathbf{X}_{<}]} e^{-S_{>}[\mathbf{X}_{<}]} = Z^{EST}(t)$$

$$Z(t) = \oint \mathcal{D}\mathbf{X}_{<} \oint \mathcal{D}\mathbf{X}_{>} e^{-S_{eff}[\mathbf{X}_{<} + \mathbf{X}_{>}]}$$
$$\equiv \oint \mathcal{D}\mathbf{X}_{<} e^{-S_{eff}[\mathbf{X}_{<}]} e^{-S_{>}[\mathbf{X}_{<}]} = Z^{EST}(t)$$

The result is a low-energy effective theory, with new effective action which mocks the effect of the hard modes

The EST yields by construction the same long time dynamics











 $e^{-\beta S_{>}[x_{<}]} = \int \mathcal{D}x_{>} \sum_{k=1}^{k} \frac{1}{k!} \ (-\beta S_{int})^{k} \ e^{-\beta \int_{0}^{t} d\tau \ \frac{\gamma}{4}} \ \dot{x}_{>}^{2}$

 $e^{-\beta S_{>}[x_{<}]} = \int \mathcal{D}x_{>} \sum_{i} \frac{1}{k!} (-\beta S_{int})^{k} e^{-\beta \int_{0}^{t} d\tau \frac{\gamma}{4}} \dot{x}_{>}^{2}$

 $-\beta S_{int}[x_{>}+x_{<}] = -\beta \int_{0}^{t} d\tau \ \frac{\partial V_{eff}(x_{<}(\tau))}{\partial x^{i}} \ x_{>}(\tau) -\beta \ \frac{1}{2} \ \int_{0}^{t} d\tau \ \frac{\partial^{2} V_{eff}(x_{<}(\tau))}{\partial x^{i} x^{j}} x^{i}_{>}(\tau) x^{j}_{>}(\tau) + \dots$

 $e^{-\beta S_{>}[x_{<}]} = \int \mathcal{D}x_{>} \sum_{k} \frac{1}{k!} (-\beta S_{int})^{k} e^{-\beta \int_{0}^{t} d\tau \frac{\gamma}{4}} \dot{x}_{>}^{2}$

 $-\beta S_{int}[x_{>}+x_{<}] = -\beta \int_{0}^{t} d\tau \ \frac{\partial V_{eff}(x_{<}(\tau))}{\partial x^{i}} \langle x_{>}(\tau) + \beta \ \frac{1}{2} \ \int_{0}^{t} d\tau \ \frac{\partial^{2} V_{eff}(x_{<}(\tau))}{\partial x^{i} x^{j}} \langle x_{>}^{i}(\tau) x_{>}^{j}(\tau) + \dots$

$$e^{-\beta S_{>}[x_{<}]} = \int \mathcal{D}x_{>} \sum_{k} \frac{1}{k!} \ (-\beta S_{int})^{k} \ e^{-\beta \int_{0}^{t} d\tau \ \frac{\gamma}{4}} \ \dot{x}_{>}^{2}$$

$$-\beta S_{int}[x_{>}+x_{<}] = -\beta \int_{0}^{t} d\tau \ \frac{\partial V_{eff}(x_{<}(\tau))}{\partial x^{i}} \langle x_{>}(\tau) \rangle \beta \ \frac{1}{2} \int_{0}^{t} d\tau \ \frac{\partial^{2} V_{eff}(x_{<}(\tau))}{\partial x^{i} x^{j}} \langle x_{>}^{i}(\tau) x_{>}^{j}(\tau) + \dots$$

The Effective action is exactly represented as the sum of an infinite number of analytically calculable correlation functions in the free Brownian theory!

Feynmann diagram approach

To compute these integrals we use field theory and define

Fast mode
propagator:

$$\begin{aligned}
\overline{\tau_{1} \quad \tau_{2}} = \langle X_{>}^{i}(\tau_{1})X_{>}^{j}(\tau_{2})\rangle &= \sum_{b\Omega \leq |\omega_{n}| \leq \Omega} \delta_{ij} \frac{2}{\beta \gamma \omega_{n}^{2}} e^{i\omega_{n} (\tau_{1} - \tau_{2})} \\
\text{N-leg vertexes:} \quad \mathbf{v}_{N} \quad \mathbf{v}_{n} \quad \mathbf{v}_{N} = V_{N}(\tau) = \frac{\partial^{N} V_{eff}[\mathbf{X}_{<}(\tau)]}{\partial X^{1} \dots \partial X^{N}} \\
\text{Then:} \quad \left\{ Z(t) = \oint \mathcal{D}\mathbf{X}_{<} e^{-S_{eff}[\mathbf{X}_{<}] - \text{sum of connected diagrams}} \right\}$$

Examples of diagrams



2. Infinitely many diagrams to compute

Facing problem 1: local effective vertexes

In the limit of large separation of time scales, all non-local vertexes become local! Non-locality is replaced by time derivatives



Effective locality is a common feature to all effective field theories: E.g. multipole expansion

Facing problem 2: Slow-mode perturbative expansion

KEY OBSERVATION:

Different contributions contain come with inverse powers of the UV cut-off scale:

$$\propto \left(\frac{1-b}{b\Omega}\right)^L, \qquad (L=0,1,2,3)$$

To any desided accuracy one only needs to compute a finite number of diagrams (those with lowest L)!!!

How can we know what diagrams to compute?



Slow-mode Effective Actions:

 $V_{eff}^R(x_{<})$ L=0: $S_{>}[x_{<}] = 0$ (doing nothing) $S_{>}[x_{<}] = \frac{1}{\pi\gamma\beta} \frac{1-b}{b\Omega} \int_{0}^{t} d\tau \ \Delta V_{eff}(x_{<}(\tau)).$ L=1: • L=2: $S_{>}[x_{<}] = \frac{1}{\pi\beta\gamma} \frac{1-b}{b\Omega} \int_{0}^{t} d\tau \Delta V_{eff}(x_{<}(\tau))$ $+ \frac{1}{2} \left(\frac{1}{\pi \beta \gamma} \frac{1-b}{b\Omega} \right)^2 \int_0^t d\tau \ \Delta^2 V_{eff}(x_{<}(\tau))$

O.Corradini, PF, and H.Orland, "Simulating stochastic dynamics using large time steps", Phys. Rev. E 80, 061112 (2009) 90

Effective Langevin Equation



Can we find an effective memory-less langevin Eq. which generates directly the EST path integral?

Clearly such a theory could be simulated using large time steps

Ansatz

$\dot{\mathbf{X}} = -\frac{D(\mathbf{X}_i)}{k_B T} \nabla U(\mathbf{X}_i) + (1 - \alpha) \nabla D(\mathbf{X}_i) + \sqrt{2D(\mathbf{X})} \eta(t),$







Matching ELE with EST
$$\dot{\mathbf{x}} = -\frac{D(\mathbf{X}_i)}{k_BT} \nabla U(\mathbf{X}_i) + \nabla D(\mathbf{X}_i) + \sqrt{2D(\mathbf{X})} \eta(t),$$
 $\frac{d(\mathbf{X})}{D_0} \ll 1$ $\frac{\nabla^2 d(\mathbf{X})}{b\Omega} \ll 1$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}}$ $\hat{\boldsymbol{\zeta}$ $\hat{\boldsymbol{\zeta}$

the averages are over ordinary LE paths

$$\begin{split} & \underbrace{\mathbf{X} = -\frac{D(\mathbf{X}_{i})}{k_{B}T} \nabla U(\mathbf{X}_{i}) + \nabla D(\mathbf{X}_{i}) + \sqrt{2D(\mathbf{X})} \eta(t), \qquad \underbrace{\frac{d(\mathbf{X})}{D_{0}} \ll 1}_{D_{0}} \underbrace{\frac{\nabla^{2}d(\mathbf{X})}{b\Omega} \ll 1} \\ & \underbrace{\swarrow}_{D_{0}} & \underbrace{\swarrow}_{D_{0}} \\ & \underbrace{\swarrow}_{D_{0}} \\ & \underbrace{\swarrow}_{D_{0}} \\ & \underbrace{\checkmark}_{D_{0}} \\ & \underbrace{\overbrace{}_{D_{0}} \\ & \underbrace{\underbrace{}_{D_{0}} \\ & \underbrace{\underbrace{}_{D_{0}} \\ & \underbrace{\underbrace{}_{D_{0}} \\ & \underbrace{$$

The Effective Lagevin Eq.

$\langle V_{eff}(\mathbf{X}(\tau)) \ d(\mathbf{X}(\tau)) \rangle \simeq \langle V_{eff}(\mathbf{X}(\tau)) \rangle \ \langle \ d(\mathbf{X}(\tau)) \rangle$

 $\langle d(\tau) \rangle \geq D_0 \frac{\langle V_{eff}^R(\mathbf{X}(\tau)) \rangle}{\langle V_{eff}(\mathbf{X}(\tau)) \rangle}.$

PF, "Molecular Dynamics at low time resolution" JCP 133, 164106 (2010)


time-dependent rescaling of the time intevals

PF, "Molecular Dynamics at low time resolution" JCP 133, 164106 (2010)

The ELE algorithm

- generate paths using a large integration time step
- Use such paths to compute <d(t)>
 rescale time interval according to

$$D_0(t_{i+1} - t_i) \rightarrow (D_0 + \langle d(i) \rangle) (t_{i+1} - t_i),$$



Application

1-D toy model



Long time dynamics



Short-time dynamics (breakdown)



Thermal unfolding of an amino-acid chain



PF, "Molecular Dynamics at low time resolution" JCP 133, 164106 (2010)

Conclusions

Stochastic dynamics can be used to investigate the equilibrium and non-equilibrium dynamics of biomolecules

The gap in time scales makes the direct integration of the Langevin Eq. inefficient

Path integral approaches become useful to

study rare transitions (DRP)

integrate out fast modes (EST)

Thank you for your attention!

