Molecular equilibrium sampling and free energy computations: some open topics

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Presentation 1

- Joint work with: T. Lelièvre and G. Stoltz (MicMac INRIA project team, ENPC, Marne-la-Vallée, France). Talk mainly based on ideas out of:
  - 11’ T. Lelièvre, MR and G. Stoltz: Langevin dynamics with constraints and computation of free energy differences.
  - 10’ T. Lelièvre, MR and G. Stoltz: Free energy computation: a mathematical perspective.
- In this talk, I will focus on:
  Errors in equilibrium sampling and free energy computation of molecular systems coupled to a thermostat (NVT = fixed number of particles, volume and temperature).

Presentation 1

- Errors is a puzzling aspect of the field: everyone computes but no one knows how far we are from ”reality”.
- In this talk I will NOT focus on:
  - Extraction of dynamical quantities (exit times, Transition State Theory, etc..)
  - Computation of non-equilibrium steady states.
  - Errors in computation of (effective) potentials quantum chemistry.

Presentation 1

- There are still open questions from the mathematical/theoretical side.
- In particular some source of errors remained uncontrolled , e.g.:
  - Time-step errors.
  - Quantum corrections.
  - Model reduction.
- Important in practice:
  - To track the origin of errors/aberrations in simulations.
  - To increase efficiency by focusing on the bottlenecks errors.

OVERVIEW ON MOLECULAR SAMPLING AND FREE ENERGY

Molecular dynamical simulation: A hierarchy of models

REALITY HAS AN EQUATION !!. N = number of atoms. Globally neutral.

- Building block: Full Schrödinger operator (q position of nuclei, x position of electrons, Z_i= number of protons in nucleus i, N_i = number of neutrons in nucleus i) in atomic units:

$$\begin{cases} \varepsilon^2 = \dfrac{m_e}{m_p} \sim 10^{-3}, \\ H_n = -\displaystyle\sum_{i\in\mathrm{nuc}} \frac{\varepsilon^2}{2(Z_i+N_i)}\Delta_{q_i} + \sum_{i\in\mathrm{nuc},j\in\mathrm{nuc}} \frac{Z_iZ_j}{|q_j-q_i|}, \\ H_e = -\dfrac{1}{2}\Delta_x + \displaystyle\sum_{i\in e,j\in e} \frac{1}{|x_j-x_i|}, \\ V_c(x,q) = -\displaystyle\sum_{i\in\mathrm{nuc},j\in e} \frac{Z_i}{|x_j-q_i|}, \\ H_{tot} = H_p + H_e + V_c\times, \end{cases}$$

Molecular dynamical simulation: A hierarchy of models

- You need to add spin variable to electrons and skew-symmetry constraint.
- Schrödinger equation: $i\varepsilon\partial_t\psi = H_{tot}\psi$.
- Usual temperature, in atomic unit, is small: $\beta \sim 10^3$.

Towards classical Molecular dynamics

- Standard route: the Born-Oppenheimer approximation:
  - Electrons are fast (in fact stationary) and nuclei are slow .
  - So that you neglect coupling between eigenstates of the electrons (adiabatic assumption).
  - You get the decoupled equations for $k = 0 \dots \infty$:

$$\begin{cases} i\varepsilon\partial_t\Psi_n = H_n\Psi_n + E_e^k(q) \times \Psi_n, \\ (H_e + V_c(.,q)\Psi_{e,q} = E_e^k(q)\Psi_{e,q} \quad \text{(k-th eigenvalue problem).} \end{cases}$$

Towards classical Molecular dynamics

- Taking $\varepsilon \to 0$ (semi-classical limit), and $k = 0$ (groundstate), we get ab-inito classical dynamics:

$$\begin{cases} Z_i \ddot{q}_i = -\nabla_{q_i} E_e^0(q), \quad i = 1 \dots N. \\ (H_e + V_c(.,q))\Psi_{e,q} = E_e^0(q)\Psi_{e,q} \quad \text{(eigenvalue/minimization problem).} \end{cases}$$

- It is the standard ab-initio model for MD.

Effective potential and coarse-graining

- In many cases effective potentials are used with 2,3,4- body effective potentials.
- Even if untrue in practice, we assume that we have a standard matching procedure (MP) to compute effective potentials n-body potentials from any N-body potential:

$$\text{molecular system} \xrightarrow{MP} (V_n(q_{i_1}, \dots, q_{i_n}), i_1 \dots i_n \in C_N^n, n = 2 \dots N)$$

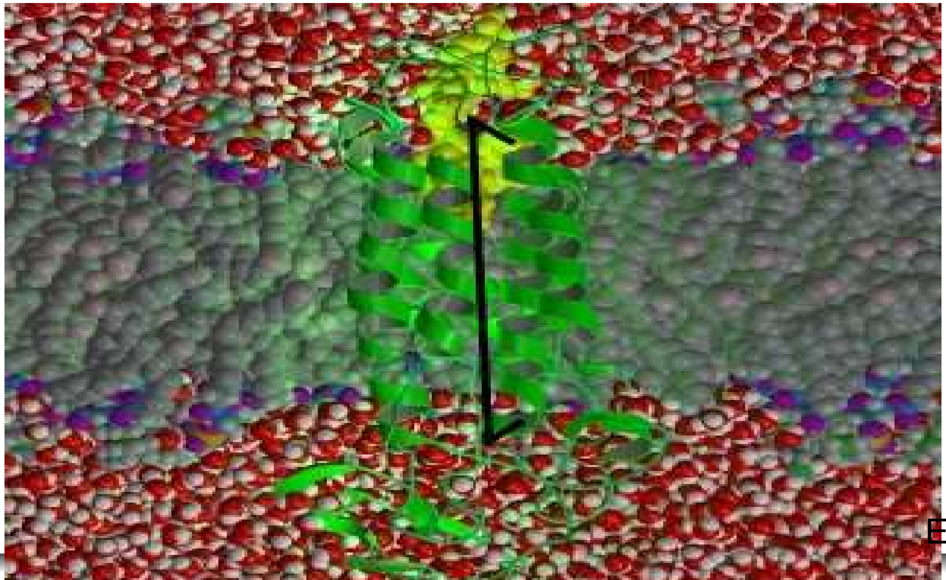
- In principle: independant of ε, β, Δt. Computed from idealized quantum calculation, not by fitting parameters to reality !!
- This step requires a lot of quantum chemistery, and sometimes kitchen/crystal ball science (CHARMM force field).
- Other topic: Coarse-graining = model reduction in ${}^{6\tilde{N}}$ models ($\tilde{N} < N$ meta-atoms).

Molecular simulation: Multi-timescale problem

- Short range interaction (covalent): Rapidly oscillating quantity ($\sim 10^{-15}$ s).
- Large range interaction (electrostatic): ($\sim 10^{-12}$ s).
- Reaction coordinates (slow macroscopic variables $\sim 10^{-9}$ s, limit of computational range):

$$\xi_{\text{slow}} : \mathbb{R}^{3N} \longrightarrow \mathbb{R}$$

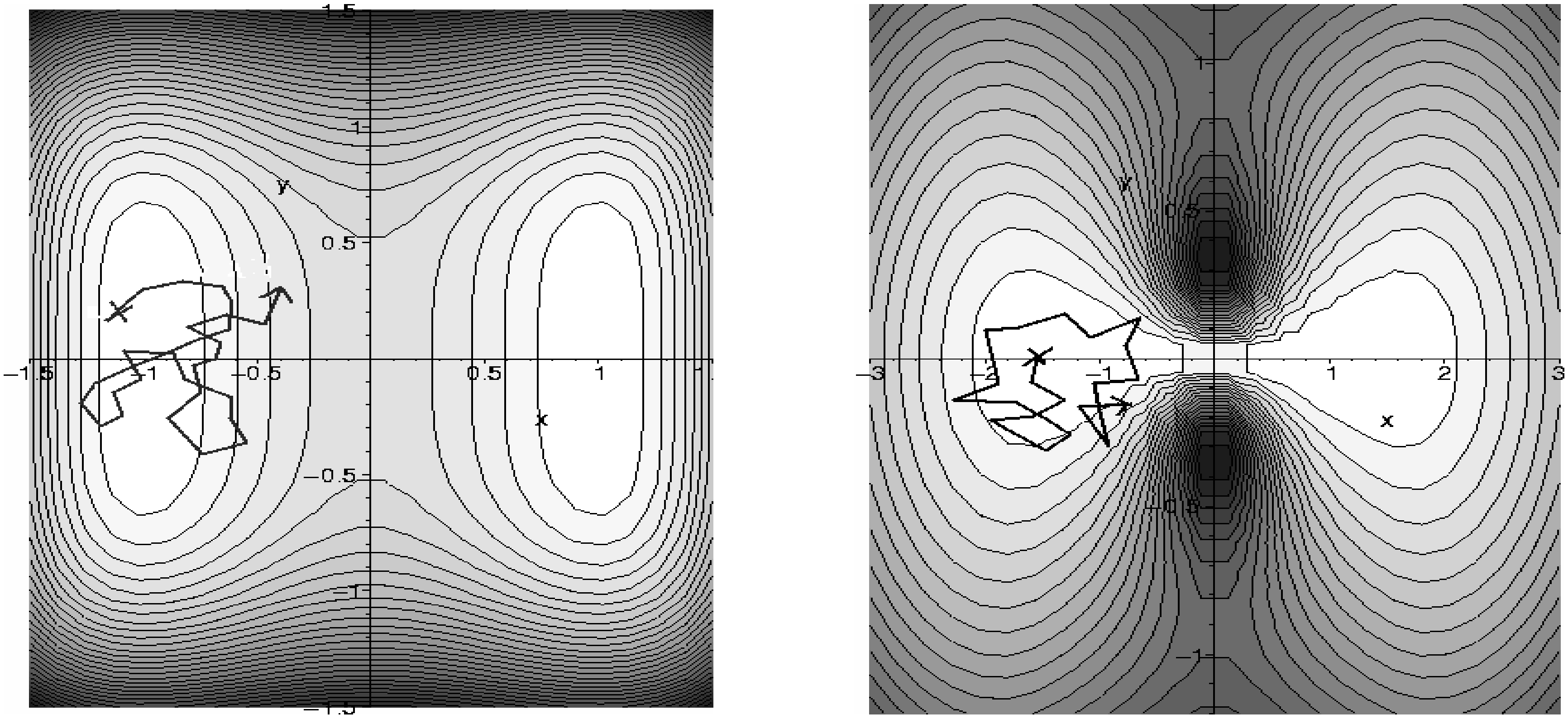
Example:



Slow degrees of freedom: Meta-stability

Dynamical barriers = metastability = exponential slowdown of equilibrium convergence:

- Energetic (low temperature) or entropic (high temperature) barriers:



Thermostatted models

- Introduction of a coupling with a thermostat of temperature, $\beta^{-1} = k_b T$.
- Ergodic assumption:

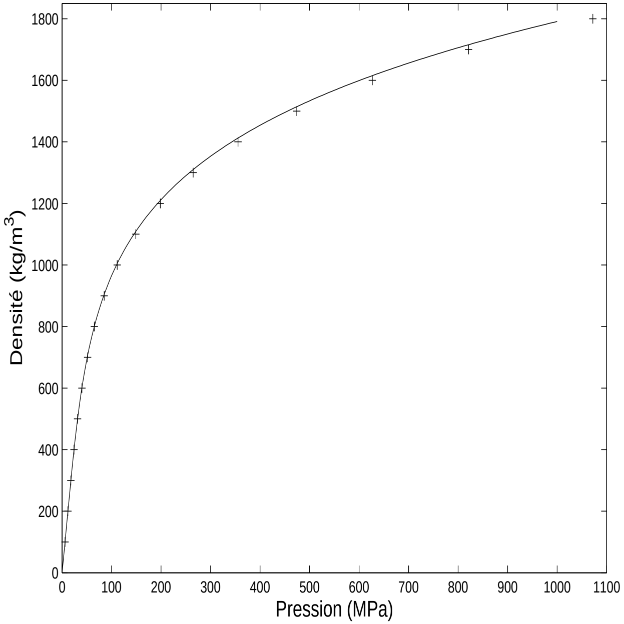
$$\begin{array}{ccc} \text{Time average} & = & \text{Spatial average} \\ \frac{1}{T}\int_0^T \varphi(q(t))\,dt & \xrightarrow{T\to\infty} & \langle\varphi\rangle \end{array}$$

- Typical configurations given by Boltzmann Law (NVT case):

$$\langle\varphi\rangle = \frac{\int \varphi(q) e^{-\beta V(q)} dq}{\int e^{-\beta V(q)} dq}$$

NVT computations

- Statistical nature of quantities to be computed:
- Boltzmann gives all equilibrium physical quantities. Ex: pressure $\propto E_c - 2\langle q \cdot \nabla V(q) \rangle$.
- Non-ideal equation of state of Argon at 300 K:



What is free energy F ?

- Free energy is defined by the equilibrium (marginal) distribution of $\xi_{\mathrm{slow}} \in \mathbb{R}^d$, a ”slow” variable, or reaction coordinates. For any observable φ of ξ_{slow}

$$\langle \varphi(\xi_{\mathrm{slow}}(q)) \rangle = \frac{\displaystyle\int_{\mathbb{R}^d} \varphi(z) e^{-\beta F(z)} dz}{Z}$$

- Define $\mathcal{M}_z = \{q \in \mathbb{R}^d | \xi_{\mathrm{slow}}(q) = z\}$ the sub-manifold associated with the value z of the raction coordinate ξ_{slow}.
- Define $\delta_{\xi_{\mathrm{slow}}(q)=z}(dq)$ the conditional surface measure on $\mathcal{M}_z$ verifying the slice integration $dq = \delta_{\xi_{\mathrm{slow}}(q)=z}(dq) dz$

What is free energy F ?

- We get, up to an additive constant:

$$\boxed{F(z) = -\beta^{-1} \ln \int_{\mathcal{M}_z} \mathrm{e}^{-\beta V(q)} \delta_{\xi_{\mathrm{slow}}(q)=z}(dq)}$$

- Goal: numerical computation of $z \mapsto F(z)$

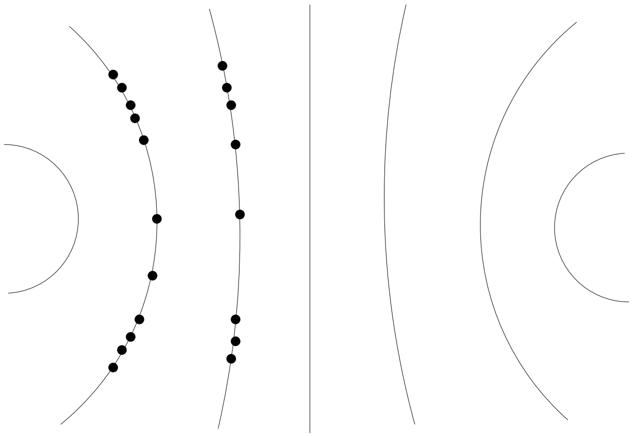
Computing free energy F

- In fact in the context of the present talk (error analysis), free energy computation is arguably reducible to the sampling problem.
- We need to add non-equilibrium simulation of Jarzynski type. But, I arguably the discussion on errors is strictly similar to the case of sampling.
- Two main class of methods:
    - Adaptive biasing methods.
    - Non-equilibrium simulation of Jarzynski type (Thermodynamic Integration as a limit).

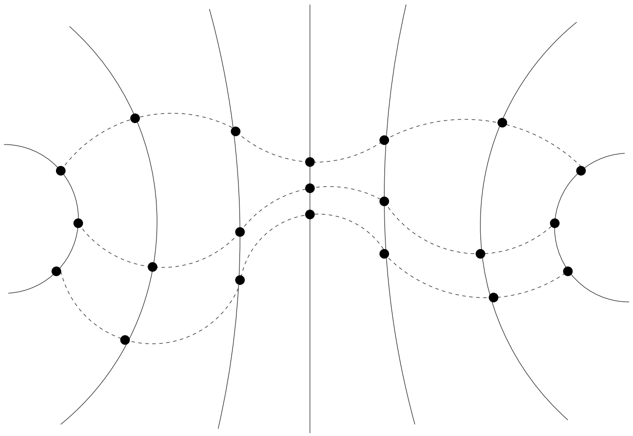
Computation strategies

The ennemy is metastability.

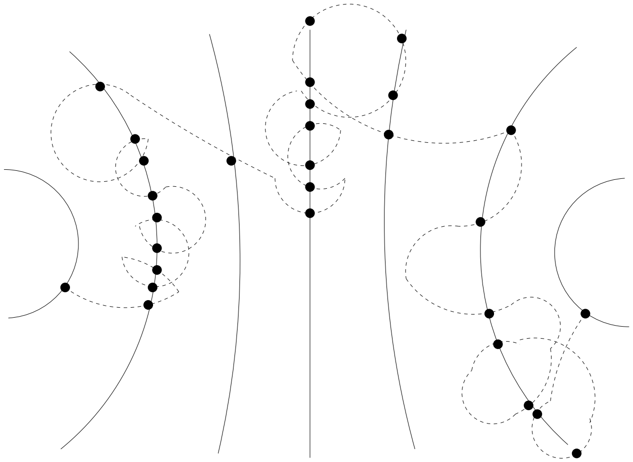
Fixed constraint



Switching constraint



Biasing (with or without adaptivity)



Adaptive biasing

- Compute adaptively a biasing potential of the form:

$$F_{\mathrm{approx}}(\xi_{\mathrm{slow}}(q))$$

- Perform sampling with the biasing potential F_{approx}.
- The bias is removable since F_{approx} and the equlibrium distribution is known.

Jarzynski non-equilibrium dynamics.

- Add a constraining force (switching) to a molecular system of the form $-\nabla_q \xi_{\mathrm{slow}} \lambda(t)$, where $\lambda(t)$ is a Lagrange multiplier with constraints $\xi_{\mathrm{slow}}(q_t) = z(t)$.
- Take care with the thermostat.
- Starts at equilibrium .
- Compute the energy variation of the system which is only due to the switching (denoted $\mathcal{W}_T$ = the work).
- Use the identity: $F(z(T)) - F(z(0)) = -\beta \ln \mathbb{E}(\mathrm{e}^{-\beta(\mathcal{W}_{0,T} + Corr_T - Corr_0)})$.
- Requires several replicas to average $\mathbb{E}$.

ERRORS

Errors in molcular simulations

- Quantum errors:
  - Error in adiabatic decoupling. (”conical crossings”+ε, β,See later)
  - Non-classical behavior of nuclei. (ε, β, See later)
- Model reduction errors:
  - $1, 2, 3$-body effective potentials. (Really a mess).
  - ”Constraints” errors (due to ”freezing” fast degrees of freedom). (See later).
  - Coarse-graining. (Really model dependent).
- Errors in time-stepping
  - Time-step errors. (Δt, See later)
  - Bonus: efficiency of the sampling method. (See later)

ERRORS FROM TIME-STEP
AND SAMPLING EFFICIENCY

Classical + thermostat

- Here: Newton equation with stochastic thermostat. V is assumed to be a known classical potential. N-body system.
- Equilibrium distribution: NVT $\propto \mathrm{e}^{-\beta V(q)} dq$ for positions.

Context

- Model: a stiff Hamiltonian system $H : \mathbb{R}^{6N} \rightarrow \mathbb{R}$:

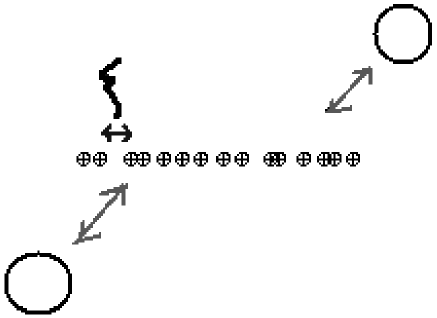
$$\boxed{H(p,q) = \frac{1}{2} p^T M^{-1} p + V(q)}$$

- $M = \mathrm{diag}(m_1, ..., m_N)$.
- Assume: fastest degrees of freedom (fDOFs) are known

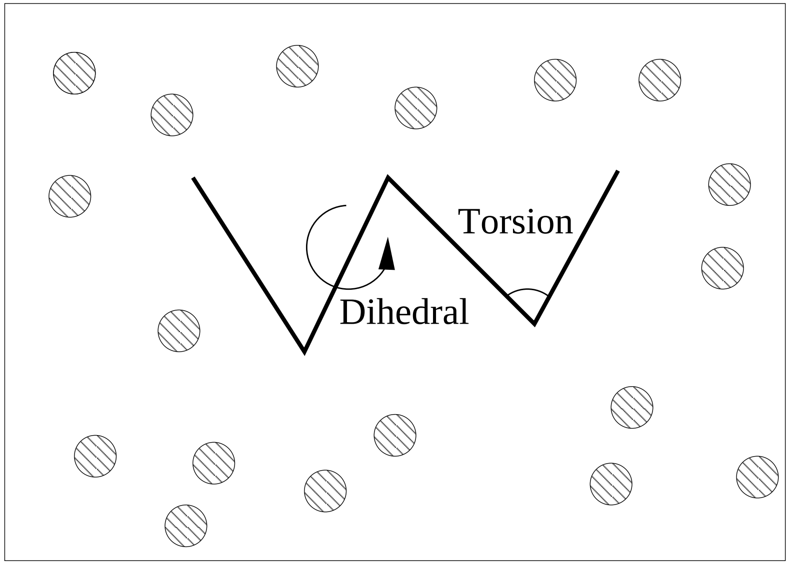
$$\begin{cases} \xi_{\text{fast}} : \mathbb{R}^{3N} \rightarrow \mathbb{R}^{n}, \\ \{q \in \mathbb{R}^{3N} | \xi_{\text{fast}}(q) = 0\} ='' \text{ slow manifold}''. \end{cases}$$

Model

- Ex.: Large molecule + slow environment:



- ξ_{fast} can be: bond lengths, bond angles, dihedral angles .



Sampling with Langevin Dynamics

- Coupling with a thermostat: Newton/Hamiltonian motion + Ornstein-Uhlenbeck process.

$$\boxed{\begin{cases} dQ_t = M^{-1} P_t dt \\ dP_t = \underbrace{-\nabla V(Q_t)}_{Hamilton} - \underbrace{\gamma M^{-1} P_t dt}_{Dissipation} + \underbrace{\sigma dW_t}_{Fluctuation} \end{cases} \qquad \sigma\sigma^T = \frac{2\gamma}{\beta} = 2\gamma k_b T}$$

- Equilibrium distribution: $\frac{1}{Z} \mathrm{e}^{-\beta H(p,q)}$.

Symplecticity/Reversibility of Hamilton's equations

- Newton/Hamilton $H(q,p) = \frac{1}{2} p^T M^{-1} p + V(q)$ = kin. + pot. energy :

$$\boxed{\begin{cases} \frac{d}{dt}\begin{pmatrix} q_t \\ p_t \end{pmatrix} = J \nabla_{q,p} H(q_t, p_t) \qquad (1) \\ J := \begin{pmatrix} 0 & Id \\ -Id & 0 \end{pmatrix} \end{cases}}$$

- J = symplectic matrix:
  - Conservation of phase-space measure $dqdp$ (Liouville theorem = int. by parts).
  - Conservation of energy H.
- Reversibility $t \mapsto (q_{T-t}, -p_{T-t})$ is still solution of (1).

Equilibrium properties Of Ornstein-Uhlenbeck equations

- Ornstein-Uhlenbeck process on momenta (stochastic thermostat):

$$\boxed{dP_t = -\gamma M^{-1} P_t + \sigma \, dW_t, \quad \sigma\sigma^T = \frac{2\gamma}{\beta}, \quad (1)}$$

- Symmetry: $t \mapsto -P_t$ solution of (1).
- Reversibility wrt to equilibrium distribution: If

$$\mathrm{Law}(P_0) = \frac{1}{Z} \mathrm{e}^{-\beta \frac{1}{2} p^T M^{-1} p} \, dp$$

then the probability distribution of paths is invariant under time reversal:

$$\mathrm{Law}\left(t \mapsto P_t, \, t \in [0,T]\right) = \mathrm{Law}\left(t \mapsto \pm P_{T-t}, \, t \in [0,T]\right)$$

Mixing properties Of Ornstein-Uhlenbeck equations

- Ergodicity, whatever P_0:

$$\lim_{T\to+\infty}\frac{1}{T}\int_0^T \varphi(P_t)\,dt = \int_{\mathbb{R}^{3N}} \varphi(p)\frac{1}{Z_k}\mathrm{e}^{-\beta\frac{1}{2}p^T M^{-1} p}\,dp \qquad a.s.$$

- Mixing, whatever P_0:

$$\lim_{t\to+\infty} Law(P_t) \overset{\exp}{\to} \frac{1}{Z_k}\mathrm{e}^{-\beta\frac{1}{2}p^T M^{-1} p}\,dp.$$

Equilibrium properties Of Langevin equations

- Reversibility up to momenta reversal wrt to invariant distribution: If

$$\mathrm{Law}(Q_0, P_0) = \frac{1}{Z} \mathrm{e}^{-\beta H} \, dq \, dp$$

then the probability distribution of paths is invariant under time reversal:

$$\mathrm{Law}\,(t \mapsto (Q_t, P_t, \; t \in [0,T])) = \mathrm{Law}\,(t \mapsto (Q_{T-t}, -P_{T-t}), \; t \in [0,T])$$

THIS IS DETAILED BALANCE

- Ergodicity + mixing from the hypoellipticity of associated operator:

$$\lim_{T \to +\infty} \frac{1}{T} \int_0^T \varphi(Q_t, P_t) \, dt = \int_{\mathbb{R}^{6N}} \varphi(q,p) \frac{1}{Z} \mathrm{e}^{-\beta H(q,p)} \, dq \, dp \qquad a.s.$$

Numerical scheme 1

- Hamiltonian dynamics: Verlet explicit integration.

$$\left\{\begin{aligned} p^{n+1/2} &= p^n - \frac{\Delta t}{2}\nabla V(q^n), \\ q^{n+1} &= q^n + \Delta t\, M^{-1} p^{n+1/2}, \\ p^{n+1} &= p^{n+1/2} - \frac{\Delta t}{2}\nabla V(q^{n+1}) \end{aligned}\right.$$

- Conserve qualitative properties of continuous Hamiltonian dynamics:
  - Time-reversible under $p \to -p$.
  - Conserve symplectic form ($2d$- area in all planes) and thus volume $dpdq$.
  - Quasi-conservation of energy $H_{\Delta t,n} = H + O(\Delta t^2 \times \log(\Delta t\, n))$
  - Does not work if H is not separable $H = T(p) + V(q)$.

Numerical scheme 2

- One can thus get detailed balance up to an energy drift, that is to say:

$$\mathrm{e}^{-\beta H(q_n,p_n)} \underbrace{\delta_{\Phi(q_n,p_n)}}_{\text{numerical flow}}(dq_{n+1}\,dp_{n+1})\,dq_n\,dp_n =$$

$$\underbrace{\mathrm{e}^{-\beta(H(q_n,p_n)-H(q_{n+1},p_{n+1}))}}_{\text{energy variation}} \times$$

$$\mathrm{e}^{-\beta(H(q_{n+1},p_{n+1}))}\delta_{\Phi(q_{n+1},p_{n+1})}(dq_n\,dp_n)\,dq_{n+1}\,dp_{n+1},$$

- Versions when adding a Orstein-Uhlenbeck thermostat process.

A time-step correction method: Generalized Hybrid Monte-Carlo

- GHMC = Metropolis for time-step errors of Langevin equations .
  1. Evolve momenta according to the Ornstein-Uhlenbeck process during Δt compute the energy $H(q^n, p^{n+1/4})$.
  2. Integrate the Hamiltonian equations of motion according to the Verlet scheme. Get $(\tilde{q}^{n+1}, \tilde{p}^{n+1})$ and compute the energy $H(\tilde{q}^{n+1}, \tilde{p}^{n+1})$.
  3. Accept the proposal with probability

$$\min\left(1, \exp(-\beta(H(\tilde{q}^{n+1}, \tilde{p}^{n+1}) - H(q^n, p^{n+1/4})))\right)$$

     otherwise, reject and reverse momenta by setting $(q^{n+1}, p^{n+1}) = (q^n, -p^{n+1/4})$;

- Ergodic Markov chain reversible wrt exact stationary distribution $\mathrm{e}^{-\beta H(q,p)} dq dp$ up to $p \to -p$ (detailed balance).

Overdamped dynamics:

- Replace step (1) by immediate equilibrium (high friction limit).
- Verlet yields Euler discretized overdamped stochastic differential equation:

$$Q^{n+1} = Q^n - \Delta t^2/2M^{-1} \underbrace{\nabla V(Q^n)}_{drift} + \Delta t \sqrt{\beta^{-1} M^{-1}} \underbrace{\mathcal{N}(0,1)}_{diffusion}$$

- Yields Metropolis algorithm when add the rejection rule.
- Yields a Markov chain reversible wrt $\mathrm{e}^{-\beta V(q)} dq$.

Sampling efficiency

- The average rejection rate in Metropolis/ Hybrid Monte Carlo (both Langevin and overdamped) ONLY depend the time-step and NOT on the friction. This enables to define a critical time step with rejection prescribed at $1/50$ valid independantly on the friction parameter.
- However, if we denote the mixing time of Langevin dynamics T_{mix}, the computational cost of discretized Langevin without Metropolis step is:

$$N_{mix} = T_{mix}/\Delta t_{crit}.$$

Sampling efficiency

- Now denote the mixing "time" $T^2_{mix,ov}$ of the overdamped dynamics:

$$dQ_s = -M^{-1}\nabla_q V\,ds + \sqrt{2\beta^{-1}M^{-1}}dW_s.$$

$T^2_{mix,ov}$ is homogenous to $[T^2]$ but independent of Δt_{crit} . Then according to the effective time step of overdamped above:

$$N_{mix,ov} = 2T^2_{mix,ov}/\Delta t^2_{crit}.$$

- Thus if $\Delta t_{crit} << T_{mix,ov}$ then:

$$\frac{N_{mix}}{N_{mix,ov}} = \frac{\Delta t_{crit}}{T_{mix,ov}}\frac{T_{mix}}{T_{mix,ov}} << 1$$

Correcting with Metropolis

- Langevin is much better than overdamped (OPEN: to precise)..
- BUT Momenta flip in GHMC make sampling efficiency similar to overdamped (OPEN: to precise).
- Another porblem:Rejections in Metropolis depends badly on dimensionality of fast-degrees of freedom.
- Open practical/theoretical question: how can we obtain a compromise between time-step bias and sampling efficiency ??
  If your favorite chemists gives you a code, can you construct a black box algorithm which computes the ”good” time-step, computes weights and rejections, in order to achieve this compromise ?

Removing time-step in Jarzynski simulation

- d evolving constraints associated with the reaction coordinate;

  Hamiltonian:

$$\begin{cases} H(p,q) = \frac{1}{2} p^T M^{-1} p + V(q) \\ \xi_{\mathrm{slow}}(q) = z(t) & \qquad (C) \end{cases}$$

Verlet integrator with constraints

- Verlet explicit integration + constraints solver with Newton/Gauss solver .

$$\begin{cases} p^{n+1/2} = p^n - \dfrac{\Delta t}{2} \nabla V(q^n) - \nabla \xi_{\mathrm{slow}}(q^n) \lambda^{n+1/2}, \\ q^{n+1} = q^n + \Delta t \; M^{-1} p^{n+1/2}, \\ \xi_{\mathrm{slow}}(q^{n+1}) = z(t_{n+1}) \quad (C_q), \\ p^{n+1} = p^{n+1/2} - \dfrac{\Delta t}{2} \nabla V(q^{n+1}) - \nabla \xi_{\mathrm{slow}}(q^{n+1}) \lambda^{n+1} \\ \nabla \xi_{\mathrm{slow}}(q^{n+1})^T M^{-1} p^{n+1} = \frac{z(t_{n+1}) - z(t_n)}{\Delta t} \quad (C_p), \end{cases}$$

- Time-reversible under $p \to -p$ and $z(t_{n+1}) \leftrightarrow z(t_n)$. Conservation of the symplectic structure.

Conservation of the symplectic structure

- It may seem surprising to obtain symplecticity for a mapping between two different phase-space.
- In fact, the numerical flow is symplectic in the full phase-space $\mathbb{R}^{6N}$, and symplecticity is inherited on constraints manifolds.
- One can thus get detailed balance up to an energy drift, that is to say:

$$\mathrm{e}^{-\beta H(q_n,p_n)} \underbrace{\delta_{\Phi_{z_n,z_{n+1}}(q_n,p_n)}}_{\text{numerical flow at } z_n}(dq_{n+1}\,dp_{n+1}) \; \underbrace{\sigma_{z_n}}_{\text{phase-space measure}}(dq_n\,dp_n) =$$

$$\underbrace{\mathrm{e}^{-\beta(H(q_n,p_n)-H(q_{n+1},p_{n+1}))}}_{\text{work = energy variation}} \times$$

$$\mathrm{e}^{-\beta(H(q_{n+1},p_{n+1}))}\delta_{\Phi_{z_{n+1},z_n}(q_{n+1},p_{n+1})}(dq_n\,dp_n)\,\sigma_{z_{n+1}}(dq_{n+1}\,dp_{n+1}),$$

Exact discrete Jarzynski identity

- Add carefully a thermostat.
- Define the work as

$$\mathcal{W}_{0,T} = \sum_n \underbrace{\Delta H_n}_{\text{energy variation of hamiltonian int}}$$

- This yields a discrete Jarzynski identity:

$$F(z(T)) - F(z(0)) = -\beta \ln \mathbb{E}(\mathrm{e}^{-\beta(\mathcal{W}_{0,T} + Corr_T - Corr_0)})$$

Exact discrete Jarzynski identity

- Thus time-reversibility + symplecticity yields:
  - (i) Detailed balance up to a factor.
  - (ii) Metropolis correction in dynamics with rejection.
  - (iii) Time-step correcting weights in non-equilibrium Jarzynski.
- OPEN: Show theoretically following idea: there is an incompressible source of error : bias from time-step in Langevin $\sim$ variance from mixing slow-down in Metropolis $\sim$ variance in Jarzynski work exponential weights. I DO NOT KNOW HOW TO DO BUT I SUSPECT IT IS TRUE IN SOME REGIME .

open problem

- OPEN 2: IS THERE A WAY TO ACHIEVE A BIAS/VARIANCE COMPROMISE REGIME ?
- OPEN 3: CAN YOU PROVE THAT NOTHING MORE CLEVER CAN BE DONE (no trick theorem) ?

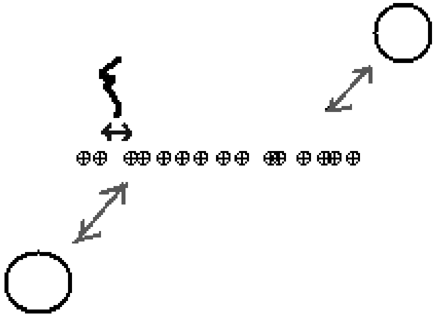
ERRORS FROM CONSTRAINTS

Molecular constraints

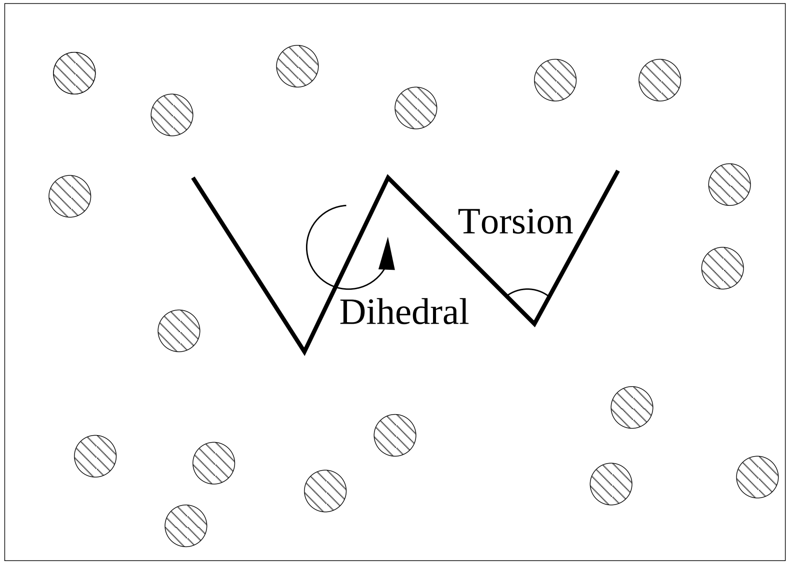
- Many MD codes enforce holonomic constraints on ξ_{fast} to enlarge time-step.
- This is called molecular constraints and introduce errors (assuming you know that the free dynamics is true !!!).
- Assuming that the free dynamics is true, I will show how to recover exact sampling for free (IMMP, MR, P. Plechac 2010).

Model

- Ex.: Large molecule + slow environment:



- ξ_{fast} can be: bond lengths, bond angles, dihedral angles .



Verlet integrator with constraints

- Verlet explicit integration + constraints solver with Newton/Gauss solver .

$$\begin{cases} p^{n+1/2} = p^n - \frac{\Delta t}{2}\nabla V(q^n) - \nabla\xi_{\text{fast}}(q^n)\lambda^{n+1/2}, \\ q^{n+1} = q^n + \Delta t\, M^{-1}p^{n+1/2}, \\ \xi_{\text{fast}}(q^{n+1}) = 0 \quad (C_q), \\ p^{n+1} = p^{n+1/2} - \frac{\Delta t}{2}\nabla V(q^{n+1}) - \nabla\xi_{\text{fast}}(q^{n+1})\lambda^{n+1} \\ \nabla\xi_{\text{fast}}(q^{n+1})^T M^{-1}p^{n+1} = 0 \quad (C_p), \end{cases}$$

- Same properties as non-constrained case: Time-reversible under $p \to -p$, conserve $\sigma_{T^*\Sigma}(dpdq)$. Quasi-conserve energy $H_{\Delta t,n} = H + O(\Delta t^2 \times \log(\Delta t n))$. Can be Metropolized to GHMC.

Mass-matrix penalisation

- Idea from *Bennett* 70's. Penalize fDOFs with mass-matrix penalty:

$$\boxed{M = Diag(m_1, ..m_d) \to M_\nu(q) = M + \nu^2 \nabla_q \xi_{\text{fast}} (\nabla_q \xi_{\text{fast}})^T}$$

- ν is the penalty parameter ($\nu = 0$ gives back original dynamics).
- The dependance $q \mapsto M_\nu(q)$ needs to be corrected to conserve equilibrium distribution:

$$\begin{aligned} V(q) \to V_{\text{eff},\nu}(q) &= V(q) + \frac{1}{2\beta} \ln \det(M_\nu(q)) \\ &= V(q) + \frac{1}{2\beta} \ln \det(\nu^{-2} Id + (\nabla_q \xi_{\text{fast}})^T M^{-1} \nabla_q \xi_{\text{fast}}) \end{aligned}$$

- Pb: Hamiltonian non longer separable and $q \mapsto M_\nu(q)$ can be stiff.

The Implicit Mass-Matrix Method

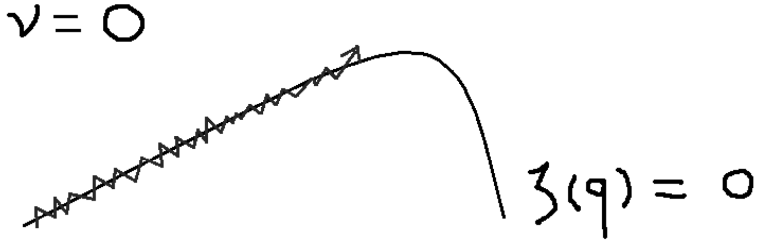
- Extend state-space with n new DOFs with mass 1 (z, p_z) associated with each fDOFs; and n constraints. Extended Hamitonian:

$$\boxed{\begin{cases} H_{\mathrm{IMMP}}(p, p_z, q, z) = \frac{1}{2} p^T M^{-1} p + \underbrace{\dfrac{1}{2} p_z^T p_z}_{\text{penalty}} + V_{\mathrm{eff},\nu}(q) \\ \xi_{\mathrm{fast}}(q) = \frac{z}{\nu} \qquad\qquad (C) \end{cases}}$$

- Formulation equivalent to explicit mass-matrix penalisation M_ν.
- When $\nu \to 0$, exact Hamiltonian is recovered.
- When $\nu \to +\infty$, Hamiltonian system with constraints $\xi_{\mathrm{fast}}(q) = 0$.

Picture

- Velocities are penalized away from the tangent slow bundle.
- Boltzmann distribution in position is conserved.



Equilibrium properties.

- Since the model is Hamiltonian, you can recover all the weighting/Metropolis tools and perform (exact sampling) in position:

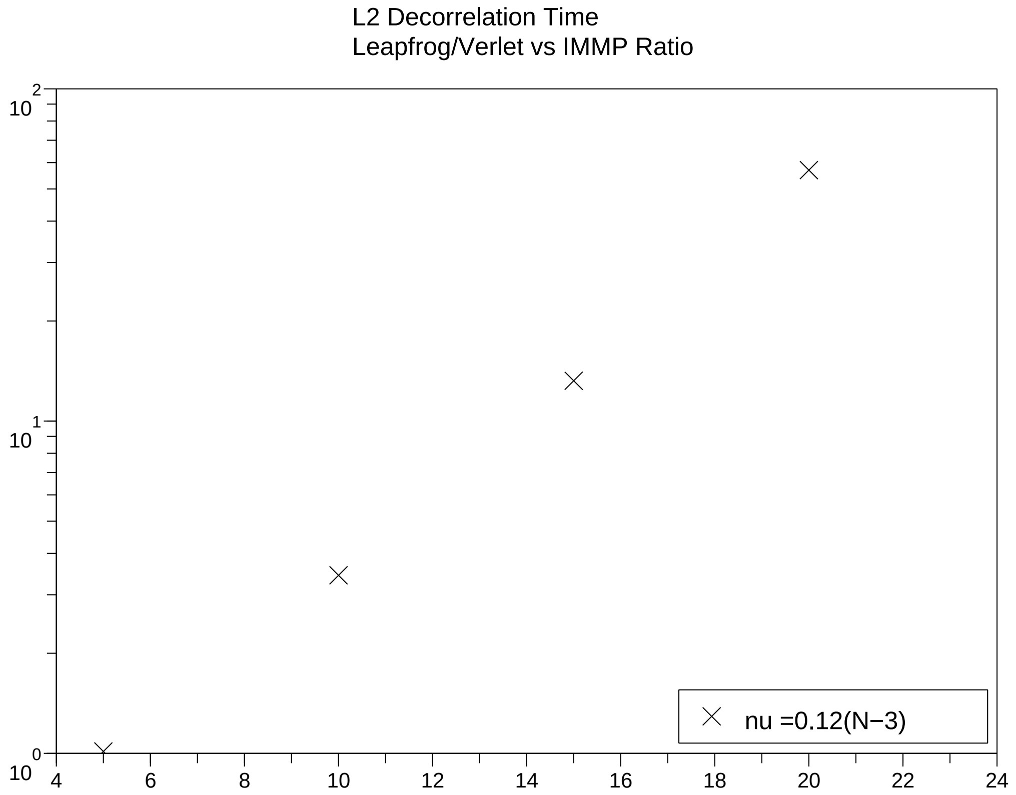
$$\propto \mathrm{e}^{-\beta V(q)} dq.$$

- The fastest degrees of freedom are slowed down as desired !!

Numerical results: Alkane+sampling

$\xi_{\text{fast}} =$ torsion angles, the rest is constrained. SIMU !!

l^2 decorrelation time of the end-to-end alkane length in terms of Monte-Carlo iteration steps. The ratio between the Verlet integration and the IMMP integration is given. Note that the y-axis is in logarithmic scale, and an exponential gain occurs.



ERRORS FROM QUANTUM

Errors from quantum

- The subject IS NOT cleaned up at all.
- (i) Errors from failure of semi-classical limit for nuclei.
- (ii) Errors from failure of adiabatic decoupling .

Errors from semi-classical

- A simple computation shows that

$$\hbar\omega >> \beta^{-1}$$

where ω is the frenquency of most bond oscillations !! (low temperature case). This is in apparent contradiction with the classicality of the nuclei dynamics.

- (i) OPEN: study the commutation of the limit $\varepsilon \to 0$ and $\beta \to +\infty$ for a given potential. It is not clear to me what is happening. A possible route: starts directly from the Gibbs quantum state:

$$\frac{\mathrm{Tr}(e^{-\beta H_\varepsilon} \, .,)}{\mathrm{Tr}(e^{-\beta H_\varepsilon})}.$$

Errors from semi-classical

- (ii) OPEN: study the commutation between the (i) process and the Matching Procedure to compute effective potential.
- (iii) OPEN: Find a non-controversial effective potential for bonded interactions.

Errors from lost of adiabaticity

- The cause is conical crossing (or ”diabolic points”), and is defined as the submanifold where $E_e^0(q) = E_e^1(q)$.
- Many real life examples exhibit case where the chemistery DO USE canonical crossing (coupling with light).
- Here again, the dynamics is quite well-known (surface hopping, Landau-Zener formula ...), but :
- (i) OPEN: expand the semi-classical limit of the quantum Gibbs distribution.
- (ii) OPEN: find all Langevin versions of surface hopping that samples the expanded Gibbs distribution.
- (ii) OPEN: find the most efficient one...

Benchmarking

- Even for simple cases there is a lack of benchmarking.
- It would be useful to make a systematic study of ALL sources of errors on simple molecular examples, and a review on the most reasonable methods.