Langevin dynamics with constraints and free energy computations

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Presentation

- 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:
  Jarzynski-like non-equilibrium simulation and thermodynamic integration with Langevin dynamics and constraints.

Program

- Free energy and phase-space.
- Markov fluctuation theory.
- Discussion on numerical schemes.

Part I: Free energy and phase-space.

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

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

- $M = \mathrm{diag}(m_1, ..., m_N)$.
- Introduction of a coupling with a thermostat of temperature, $\beta^{-1} = k_b T$.

- The resulting dynamics shall be an ergodic Markov process satifying the statistical assumption:

$$\underbrace{\frac{1}{T}\int_0^T \varphi(q(t),p(t))\,dt}_{\text{Time average}} \quad \underbrace{\xrightarrow{T\to\infty}}_{=} \quad \underbrace{\langle\varphi\rangle}_{\text{Spatial average}}$$

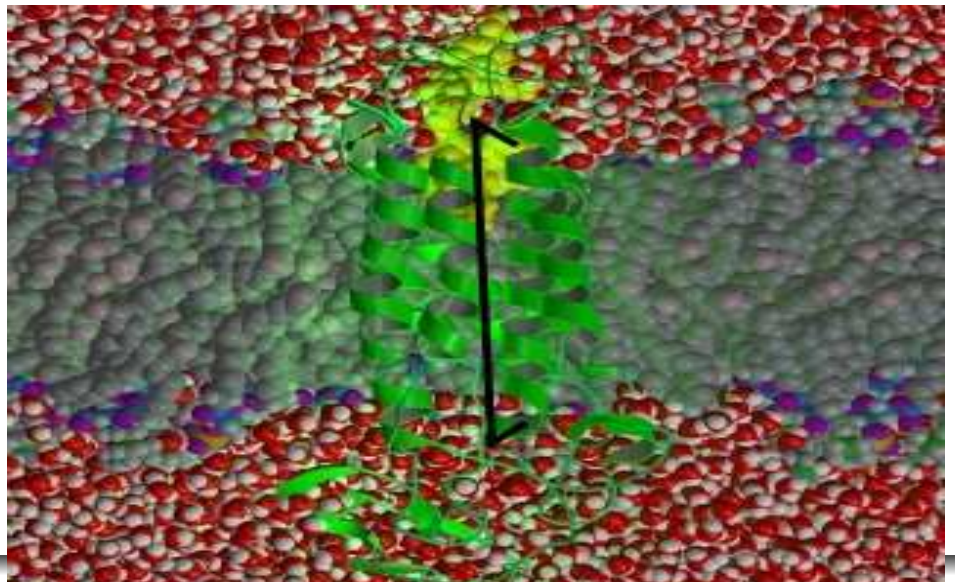
- Typical configurations given by Boltzmann Law (NVT case):

$$\langle\varphi\rangle = \frac{\int \varphi(q,p) e^{-\beta H(q,p)} dqdp}{\int e^{-\beta H(q,p)} dqdp}$$

- 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):

$$\xi : \mathbb{R}^{3N} \to \mathbb{R}^d$$

Example:



What is free energy F ?

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

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

- Define $\Sigma_z = \{q \in \mathbb{R}^d | \xi_{\text{slow}}(q) = z\}$ the sub-manifold associated with the value z of the raction coordinate ξ.
- Define $\delta_{\xi(q)=z}(dq)$ the conditional surface measure on Σ_z verifying the slice integration $dq = \delta_{\xi(q)=z}(dq)dz$

What is free energy F ?

- We get, up to an additive constant:

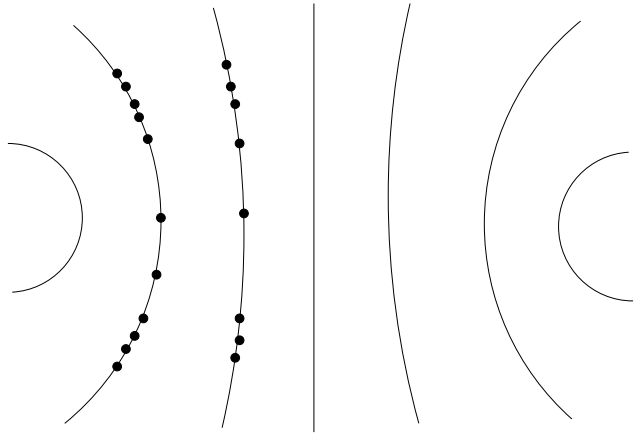
$$\boxed{F(z) = -\beta^{-1} \ln \int_{\Sigma_z} \mathrm{e}^{-\beta V(q)} \delta_{\xi(q)=z}(dq)}$$

- Goal: numerical computation of $z \mapsto F(z)$
- Gives information on the dynamics of $t \mapsto \xi(q_t)$ (Transition State Theory). when the time scale of the latter is separated from the other degrees of freedom's ones (averaging principle).

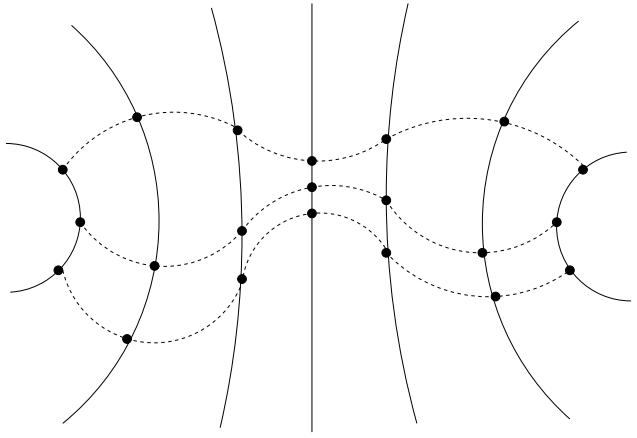
Computing free energy F

- Two main class of methods:
  - Adaptive biasing methods.
  - Non-equilibrium simulation of Jarzynski type (and Thermodynamic Integration as a limit).

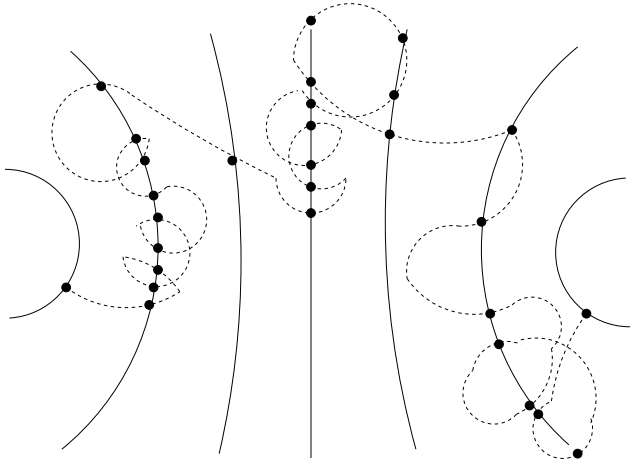
Fixed constraint



Switching constraint



Biasing (with or without adaptivity)



- Add a constraining force (switching) to a molecular system of the form $+\nabla_q \xi \,.\, d\lambda(t)$, where $d\lambda(t)$ is a Lagrange multiplier with constraints $\xi(q_t) = z(t)$.
- Starts at equilibrium .
- Compute the total energy variation of the system which is only due to the switching (denoted $\mathcal{W}_{0,T}$ = the work).
- Use the identity: $F(z(T)) - F(z(0)) = -\beta \ln \mathbb{E}(\mathrm{e}^{-\beta(\mathcal{W}_{0,T} + \mathrm{Corr}_T - \mathrm{Corr}_0)})$.
- Corr is a corrector induced by the constraints on momenta.
- Requires several replicas to average with respect to $\mathbb{E}$.

- Assume the switching is infinitely slow and small.
- The Jarzynski identity formally becomes of the Thermodynamic Integration form:

$$F(z+dz) - F(z) = \langle \delta \mathcal{W} \rangle_z + \langle \mathrm{Corr} \rangle_{z+dz} - \langle \mathrm{Corr} \rangle_z,$$

where $\delta \mathcal{W}$ is the virtual work= virtual energy variation only due to a virtual switching dz.

- $\langle \quad \rangle_z$ is the equlibrium distribution with constraint $\xi(q) = z$.

- When we perform evolving constraints $t \mapsto z(t)$ on a mechanical system with state (q, p), the state of the system must satisfy the holonomic constraints:

$$\begin{cases} \xi(q) = z \\ \nabla\xi(q) M^{-1} p = \dot{z}. \end{cases}$$

- This defines a new (symplectic) phase-space denoted $\Sigma_{z,\dot{z}}$ with a phase-space symplectic measure $\sigma_{\Sigma_{z,\dot{z}}}(dqdp)$.
- This also defines a free energy:

$$F_{\mathrm{rgd}}(z, \dot{z}) = -\frac{1}{\beta} \ln \int_{\Sigma_{z,\dot{z}}} \mathrm{e}^{-\beta H(q,p)} \sigma_{\Sigma_{z,\dot{z}}}(dqdp).$$

- This free energy is related the first free energy to be computed through:

$$F(z) - F_{\mathrm{rgd}}(z,\dot{z}) = -\frac{1}{\beta}\ln\langle \mathrm{e}^{-\beta \mathrm{Corr}_{z,\dot{z}}}\rangle_{z,\dot{z}},$$

- Where (i) $\mathrm{Corr}_{z,\dot{z}}(q) = \frac{1}{2\beta}\ln \det G_M(q)) - \frac{1}{2}\dot{z}^T G_M^{-1}(q)\dot{z}$.
- Where (i) $\langle \quad \rangle_{z,\dot{z}}$ is the Gibbs probability distribution proportional to $\mathrm{e}^{-\beta H(q,p)}\sigma_{\Sigma_{z,\dot{z}}}(dqdp)$.
- Where (iii) $G_M(q) = \nabla\xi M^{-1}\nabla\xi(q)$ (Gram matrix of constraints).
- Thus if you can compute averages with respect to $\langle \quad \rangle_{z,\dot{z}}$, you can compute F out of F_{rgd} (and vice versa).

Part II: Markov fluctuation theory.

- Markov fluctuation theory is a Markov formalism which enables to derive statistical mechanical concepts and fluctuation theorems for open classical systems.
- We present things in discrete time, and we abuse notations and NEVER mention momenta reversal when it is necessary.
- $n = 0 \dots N$ is the time parameter.
- $\zeta : \mathbb{N} \to \mathbb{R}^{2d}$ are the "thermodynamical" parameters that evolves in time (THINK $\zeta = (z, \dot{z})$.
- $(E_\zeta, \mathrm{ref}_\zeta(dx))$ is the measurable state space indexed by ζ (THINK phase-space: E_ζ is the phase-space $\sigma_{\Sigma_{z,\dot{z}}}(dqdp)$, and the (non-finite) reference measure $\mathrm{ref}_\zeta(dx)$ is the associated phase-space measure).

- $P_{\zeta,\zeta'}(x, dx') = P_{\zeta,\zeta'}(x, x')\mathrm{ref}_{\zeta'}(dx')$ is the probability transition of a Markov chain from state space E_ζ to $E_{\zeta'}$. (THINK: combination of a mechanical dterministic dynamics with evolving constraints and fluctuation/dissipation of momenta due to coupling with a thermostat).
- $\pi_\zeta(dx) = pi_\zeta(x)\mathrm{ref}_\zeta(dx)$ is a stationary probability density in E_ζ related in some sense to the dynamics. (THINK: it is the stationary distribution of the latter dynamics when the constrinats do not evolve).
- Denote the path distribution under the latter dynamics:

$$\mathrm{Law}_{\zeta(0\ldots n)}(dx_0 \ldots dx_n) =$$
$$\pi_{\zeta(0)}(dx_0)P_{\zeta(0),\zeta(1)}(x_0, dx_1)\ldots P_{\zeta(n-1),\zeta(n)}(x_{n-1}, dx_n).$$

- In this context, we can define some concepts of entropy:
  - The entropy production is given by the log-likelyhood between the path distribution and its time reversal:

$$S_{\mathrm{prod}}(x_0,\ldots,x_n;\zeta(0\ldots n)) := \ln \frac{d\mathrm{Law}_{\zeta(0\ldots n)}}{d\mathrm{Law}_{\zeta(n\ldots 0)}}(x_0,\ldots,x_n).$$

  - Its average yields the relative entropy between the paths distribution and its time reversal:

$$\int S_{\mathrm{prod}}(\,.\,;\zeta(0\ldots n))\, d\mathrm{Law}_{\zeta(0\ldots n)} = \mathrm{Ent}(\mathrm{Law}_{\zeta(0\ldots n)} \| \mathrm{Law}_{\zeta(n\ldots 0)}) \geq 0$$

  - The positivity of the latter is a form of the second law of thermodynamics.

- The state (microscopic) entropy is given by the log-likelyhood between π and the reference distribution:

$$S_\zeta(x) := -\ln \frac{d\pi_\zeta}{d\mathrm{ref}_\zeta}(x) = -\ln \pi_\zeta(x).$$

Its average is the Shannon entropy of π_ζ.

- The exchanged entropy is the difference between the two:

$$\begin{aligned} S_{\mathrm{exch}}(x_0,\ldots,x_n;\zeta(0\ldots n)) &= S_{\zeta(n)}(x_n) - S_{\zeta(0)}(x_0) - S_{\mathrm{prod}}(x_0,\ldots,x_n;\zeta(0\ldots n)) \\ &= \sum_{m=0}^{n-1} \ln \frac{P_{\zeta_m,\zeta_{m+1}}(x_m,x_{m+1})}{P_{\zeta_{m+1},\zeta_m}(x_{m+1},x_m)}. \end{aligned}$$

- The exchanged entropy does not depend on π and is thus explicitly computable in general.

- The latter notions of entropy have two fundamental properties:
  - They are additive in the following sense:

$$S(x_0,\ldots,x_n;\zeta(0\ldots n)) + S(x_n,x_{n+1};\zeta(n\ldots n+1)) = S(x_0,\ldots,x_{n+1};\zeta(0\ldots n+)).$$

  - They are skew-symmetric under time-reversal:

$$S(x_n,\ldots,x_0;\zeta(n\ldots 0)) = -S(x_0,\ldots,x_n;\zeta(0\ldots n)).$$

- Fluctuation theorems are based on the following consequence of skew symmetry: for any $\theta \in [0,1]$ and for any path functionals ψ:

$$\mathbb{E}_{\zeta(0\ldots n)}\left(\psi(X_0,\ldots,X_n)\mathrm{e}^{-\theta S_{\mathrm{prod}}(X_0,\ldots,X_n;\zeta(0\ldots n))}\right) = \mathbb{E}_{\zeta(n\ldots 0)}\left(\psi(X_n^b,\ldots,X_0^b)\mathrm{e}^{-(1-\theta)S_{\mathrm{prod}}(X_0^b,\ldots,X_n^b;\zeta(n\ldots 0))}\right)$$

- In the above, $(X_0,\ldots,X_n)$ (resp. $(X_0^b,\ldots,X_n^b)$) is distributed according to $\mathrm{Law}_{\zeta(0\ldots n)}$ (resp. $\mathrm{Law}_{\zeta(n\ldots 0)}$).

- The Galavotti-Cohen theory is a large deviation theory of the latter identity when:
  - The system is stationary: ζ is fixed through time and thus irrelevant, and π is the stationary distribution of the dynamics P:

$$\pi(y) = \int_E P(x,y)\pi(x)\mathrm{ref}(dx).$$

  - There is a lack of detailed balance (non-equilibrium): $S_{\mathrm{prod}} \neq 0$.

- The asymptotics $n \to +\infty$ is considered so that by the law of large number and using additivity of entopy:

$$\lim_{n\to+\infty} \frac{1}{n} S_{\mathrm{prod}}(X_0, \ldots, X_n) = \lim_{n\to+\infty} \frac{1}{n} S_{\mathrm{exch}}(X_0, \ldots, X_n) = ep.$$

- ep is called the steady state entropy production.
- The fact that S_{exch} is explicitly computable yields pertubative theory (Kubo, Onsager, linear response).

- The Jarzynski-Crooks theory is the oppsite case
  - The system is not stationary: $\zeta(0 \dots n)$ really depends on time.
  - There is a detailed balance (equilibrium) if ζ is kept fixed and π is a Gibbs state.
- From the fact that π is Gibbsian, one can derive notions of energy, free energy, work, heat, etc..
- So we introduce the notation:

$$\pi_\zeta(dx) = \frac{\mathrm{e}^{-\beta H_\zeta} \mathrm{ref}_\zeta(dx)}{Z_\zeta},$$

- Where in the above $H_\zeta(x)$ is the energy of state x and β the inverse temperature. Z_ζ is the associated normalisation constant.

- Assume now that the Markov transition is given in the combination form:

$$P_{\zeta,\zeta'}(x, dx''') = \int_{x' \in E_\zeta, x'' \in E_{\zeta'}} T_\zeta(x, dx') D_{\zeta,\zeta'}(x', dx'') T_\zeta(x'', dx''')$$

- T_ζ is a Markov probability transition that verfies the detailed balance:

$$\pi_\zeta(dx)\, T_\zeta(x, dx') = \pi_\zeta(dx')\, T_\zeta(x', dx).$$

THINK: any reasonable dynamics of a coupling with a thermostat .

- $D_{\zeta,\zeta'}$ is a deterministic transition that verifies time symmetry and conserve the reference measure so that the following modified detailed balance :

$$\mathrm{ref}_\zeta(dx)\, D_{\zeta,\zeta'}(x, dx') = \mathrm{ref}_{\zeta'}(dx')\, D_{\zeta',\zeta}(x', dx).$$

THINK: a time dependent Hamiltonian flow.

- Note that if $\zeta = \zeta'$ (stationarity) and D conserves energy, then the Gibbs distribution is the equilibrium distribution of the full Markov dynamics (detailed balance):

$$\pi_\zeta(dx)\, P_{\zeta,\zeta}(x, dx') = \pi_\zeta(dx')\, P_{\zeta,\zeta}(x', dx).$$

- We can now refine the path by considering the following addition of states:

$$(x_n, x_{n+1}) \to (x_n, x_{n+1/4}, x_{n+3/4}, x_{n+1}),$$

where $x_{n+1/4}$ is obtained after the first transition $T_{\zeta(n)}$, $x_{n+3/4}$ after $D_{\zeta(n),\zeta(n+1)}$ and x_{n+1} after the second transition $T_{\zeta(n+1)}$.

- This enables to define the heat exchanged between time n and $n+1$ by the energy variation due to T:

$$\mathcal{Q}(n,n+1) = H_{\zeta(n+1)}(x_{n+1}) - H_{\zeta(n+1)}(x_{n+3/4}) + H_{\zeta(n)}(x_{n+1/4}) - H_{\zeta(n)}(x_n)$$

- As well as the work received between time n and $n+1$ by energy variation due to D: :

$$\mathcal{W}(n,n+1) = H_{\zeta(n+1)}(x_{n+3/4}) - H_{\zeta(n)}(x_{n+1/4}).$$

- The energy conservation (first law of thermodynamics) amounts to the decomposition:

$$H_{\zeta(n+1)}(x_{n+1}) - H_{\zeta(n)}(x_n) = \mathcal{Q}(n, n+1) + \mathcal{W}(n, n+1).$$

- We need to extend mutatis mutandis the notions of S_{prod} and S_{exch} by incorporating the new states $x_{n+1/4}, x_{n+3/4}$.
- A direct computation using the detailed balance conditions of the transitions T_ζ and $D_{\zeta,\zeta'}$ yields the following formula for the entropy exchange:

$$S_{\mathrm{exch}}(x_n, x_{n+1/4}, x_{n+3/4}, x_{n+1}; \zeta(n \dots n+1)) = \beta \mathcal{Q}(n, n+1)$$

- The definition of entropy state for Gibbs distribution yields:

$$S_{\zeta(n+1)}(x_{n+1}) - S_{\zeta(n)}(x_n) = \beta(H_{\zeta(n+1)}(x_{n+1}) - H_{\zeta(n)}(x_n)) + \ln \frac{Z_{\zeta(n+1)}}{Z_{\zeta(n)}}$$
$$= \beta(H_{\zeta(n+1)}(x_{n+1}) - H_{\zeta(n)}(x_n) - (F_{\mathrm{rgd},\zeta(n+1)} - F_{\mathrm{rgd},\zeta(n)})),$$

- In the above we define the free energy by $F_{\mathrm{rgd},\zeta} = -\frac{1}{\beta} \ln Z_\zeta$.

- As a consequence the identity $S_{\zeta(n+1)} - S_{\zeta(n)} = S_{\rm exch} + S_{\rm prod}$ can be rewritten as:

$$S_{\rm prod}(x_n, x_{n+1}; \zeta(n, n+1)) = \beta \mathcal{W}(n, n+1) + \ln \frac{Z_{\zeta(n+1)}}{Z_{\zeta(n)}}.$$

- The fluctuation theorem then yields the Crooks-Jarzynski identity: for any $\theta \in [0, 1]$ and for any path functionals ψ:

$$\mathbb{E}_{\zeta(0\ldots n)} \left(\psi(X_0, \ldots, X_n) \mathrm{e}^{-\theta \mathcal{W}(X_0, X_{1/4}, \ldots, X_n; \zeta(0\ldots n))} \right) =$$
$$\frac{Z_{\zeta(n)}}{Z_{\zeta(0)}} \mathbb{E}_{\zeta(n\ldots 0)} \left(\psi(X_n^b, \ldots, X_0^b) \mathrm{e}^{-(1-\theta) \mathcal{W}(X_0, X_{1/4}, \ldots, X_n; \zeta(n\ldots 0))} \right)$$

- With the work given by $\mathcal{W}(x_m, x_{m+1/4}, x_{m+3/4}, x_{m+1}; \zeta(n, n+1)) = H_{\zeta(m+1)}(x_{m+3/4}) - H_{\zeta(m)}(x_{m+1/4})$.

- In the limit of infinitely slow and small switching, we formally get:

$$S_{\mathrm{prod}} = 0;$$

that is to say the transformation is quasi-static .

- As a consequence, at least formally:

$$-\frac{1}{\beta} \ln \frac{Z_{\zeta+d\zeta}}{Z_\zeta} = \int_{E_\zeta} f_\zeta(x) \pi_\zeta(dx).d\zeta$$

where $f_\zeta(x).d\zeta$ (force times displacement) is the energy variation of a virtual deterministic transition $D_{\zeta,\zeta+d\zeta}$ and starting at x.

Part III: Numerical schemes.

- The Langevin equations with constraints we consider can be derived without ambiguity from two ingredients:
  - An Hamiltonian dynamics arising from the Lagrangian:

$$\mathcal{L}(q,\dot{q}) = \frac{1}{2}\dot{q}M\dot{q} - V(q),$$

    subject to the time evolving constraint: $\xi(q(t)) = z(t)$.
  - A stochastic dynamics given by an Orstein-Uhlenbeck process on the tangential part of momenta (the part verifying $\nabla\xi(q)M^{-1}p = 0$).
  - We directly give the equations of motion and study the qualitative properties on the numerical schemes.

- The equations of motion are then given by:

$$\begin{cases} dq_t = M^{-1} p_t \, dt, \\ dp_t = -\nabla V(q_t)\, dt - \underbrace{\gamma_P(q_t) M^{-1} p_t \, dt}_{Dissipation} + \underbrace{\sigma_P(q_t)\, dW_t}_{Fluctuation} + \underbrace{\nabla \xi(q_t)\, d\lambda_t}_{Constraining force}, \\ \xi(q_t) = z(t), \end{cases} \qquad (C_q)$$

- In the above, the fluctuation dissipation identity shall hold:

$$\sigma_P \sigma_P^T = \frac{2\gamma_P}{\beta} = 2\gamma_P k_b T,$$

and γ_P only apply to the tangential part of velocity: $\gamma_P(q)v = 0$ if v is orthogonal (for M) to the submanifold $\xi(q) = z$.

- λ_t is the Lagrange multiplier associated with the constraints (C_q) and is unambiguous

- We fix a time schedule:

$$0, \Delta t, \ldots, N\Delta t = T,$$

and abuse notation $z(n) \equiv z(n\Delta t)$.

- The state space at time n is chosen to be the phase-space $\Sigma_{z(n), \frac{z(n+1)-z(n)}{\Delta t}}$ that is to say (q, p) must satisfy:

$$\xi(q) = z(n); \qquad \nabla\xi(q) M^{-1} p = \frac{z(n+1) - z(n)}{\Delta t}.$$

This choice will be motivated later on.

- In the part II notation:

$$\zeta(n) := (z(n), \frac{z(n+1) - z(n)}{\Delta t}); \qquad E_{\zeta(n)} := \Sigma_{z(n), \frac{z(n+1)-z(n)}{\Delta t}}.$$

- As in part II, we want to construct the scheme from a splitting of the form :

$$P_{\zeta(n),\zeta(n+1)} = T_{\zeta(n)} D_{\zeta(n),\zeta(n+1)} T_{\zeta(n+1)};$$

- T_ζ is a Markov transition of an Orstein-Uhlenbeck process on tangent space (time step $\frac{\delta t}{2}$).
- $D_{\zeta(n),\zeta(n+1)}$ is a deterministic transition given by a velocity-Verlet scheme with constraints (time dependent RATTLE).

- The velocity-Verlet scheme is a variational integrator obtained from the discrete Lagrangian:

$$\mathcal{L}_d(q_{n+1/4}, q_{n+3/4}) = \frac{1}{2}\frac{(q_{n+3/4} - q_{n+1/4})^T}{\Delta t} M \frac{(q_{n+3/4} - q_{n+1/4})}{\Delta t} - \frac{1}{2}(V(q_{n+1/4}) + V(q_{n+3/4})),$$

with constraints $\xi(q_{n+1/4}) = z(n)$ and $\xi(q_{n+3/4}) = z(n+1)$.

- The variational structure yields time-symmetry and symplecticity (and in particular conservation of phase-space measure).

- The equations of motion are then:

$$\begin{cases} p^{n+1/2} = p^{n+1/4} - \dfrac{\Delta t}{2}\nabla V(q^{n+1/4}) - \nabla\xi(q^{n+1/4})\lambda^{n+1/4}, \\ q^{n+1} = q^n + \Delta t\ M^{-1}p^{n+1/2}, \\ \xi(q^{n+1}) = z(t_{n+1}) \quad (C_q), \\ p^{n+3/4} = p^{n+1/2} - \dfrac{\Delta t}{2}\nabla V(q^{n+3/4}) - \nabla\xi(q^{n+3/4})\lambda^{n+3/4} \\ \nabla\xi(q^{n+1})^T M^{-1}p^{n+1} = \star \quad (C_p), \end{cases}$$

- $\star$ can be chosen arbitrarily. We have chosen $\star = \frac{z(n+1)-z(n)}{\Delta t}$ so that at the next iteration, (C_q) is already enforced up to order $O(\Delta t^2)$.

- The Markov transition probability T associated with the thermostat coupling is integrated using a mid-point rule:

$$p^{n+1/4} = p^n - \frac{\delta t}{4}\gamma_P(q^n)\left(p^n + p^{n+1/4}\right) + \sqrt{\frac{\Delta t}{2}}\sigma_P(q^n)G^n.$$

  G^n is a normalized Gaussian random vector.

- The latter implicit scheme can be computed exactly using projections and by solving a linear system.

- It can be shown to:
  - (i) Leaves invariant the orthogonal part of momentum.
  - (ii) Satisfy detailed balance with respect to the Gibbs distribution (associated to the usual kinetic energy) on tangent space.

Exact discrete Jarzynski identity

- By gathering carefully all the discussion of the present talk, we obtain an exact Crooks-Jarzynski identity for the preceeding numerical scheme.
- Define the work as

$$\mathcal{W}_{z(0\dots N)} = \sum_{n=0}^{N-1} \underbrace{H(q^{n+3/4}, p^{n+3/4}) - H(q^{n+1/4}, p^{n+1/4})}_{\text{energy variation of hamiltonian integrator}}$$

- We are then able to prove the exact Jarzynski identity:

$$F(z(N)) - F(z(0)) = -\beta \ln \mathbb{E}(\mathrm{e}^{-\beta(\mathcal{W}_{z(0\dots N)} + \mathrm{Corr}_{z(N),\frac{z(N+1)-z(0)}{\Delta t}} - \mathrm{Corr}_{z(0),\frac{z(1)-z(0)}{\Delta t}})}$$

- The use of the work:

$$\mathcal{W}(n, n+1) = H(q^{n+3/4}, p^{n+3/4}) - H(q^{n+1/4}, p^{n+1/4})$$

is unstable in the thermodynamical limit . The reason: it keeps track of the time step errors and does not become small.

- The infinitesimal work as a nice expression as " dispalcement times force" in the time continuous limit:

$$\delta\mathcal{W}(q_t, p_t) = dH(q_t, p_t) = \underbrace{\dot{q}_t}_{\text{displacement}} \underbrace{\nabla\xi(q_t)d\lambda_t}_{\text{force}} = \dot{z}(t)d\lambda_t,$$

where in the above we have used the principle: the work is the energy variation of the dynamics only due to the Hamiltonian part of the time continuous dynamics.

- As a consequence, a consistant (for $\Delta t \to 0$) choice for the work is:

$$\mathcal{W}(n, n+1) = \left(\frac{z(n+1) - z(n)}{\Delta t} \right)^T \left(\lambda^{n+1/4} + \lambda^{n+3/4} \right),$$

where $(\lambda^{n+1/4}, \lambda^{n+3/4})$ are the Lagrange multipliers in the Verlet scheme.

- One can check that the latter choice is indeed asymptotically preserving in the thermodynamical integration limit, in the sense that we may show that that:

$$F_{rgd}(z+dz,0) - F_{rgd}(z,0) = \langle \frac{\lambda^{n+1/4} + \lambda^{n+3/4}}{\Delta t} \rangle_{z(t),0,\Delta t}.dz + O(\Delta t^2),$$

where in the above $\langle \quad \rangle_{z(t),0,\Delta t}$ denotes the stationary distribution of the scheme with fixed (non-evovling) constraints.

- Note that $\langle \quad \rangle_{z(t),0,\Delta t} = \pi_{z(t),0} + O(\Delta t^2)$ an $\frac{\lambda^{n+1/4}+\lambda^{n+3/4}}{\delta t}$ is indeed of order 0 in Δt.
- All the preceeding formulas (Crooks and TI) still hold in the time continuous limit.

Conclusion

- We hace present a formal Markov fluctuation theory to derive exact Crooks identities for numerical schemes in molecular simulation.
- There is a compromise to between time-step errors and unstability of the weights.
- OPEN problem: Is there a systematic way to optimize such a compromise ?