Effective dynamics for the (overdamped) Langevin equation

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joint work with T. Lelièvre (ENPC and INRIA)

Enumath conference, MS *Numerical methods for molecular dynamics*

Molecular simulation

Some quantities of interest in molecular dynamics:

- thermodynamical averages wrt Gibbs measure:

$$\langle \Phi \rangle = \int_{\mathbb{R}^n} \Phi(X)\, d\mu, \quad d\mu = Z^{-1} \exp(-\beta V(X))\, dX, \quad X \in \mathbb{R}^n$$

- or dynamical quantities:
  - diffusion coefficients
  - rate constants
  - residence times in metastable basins

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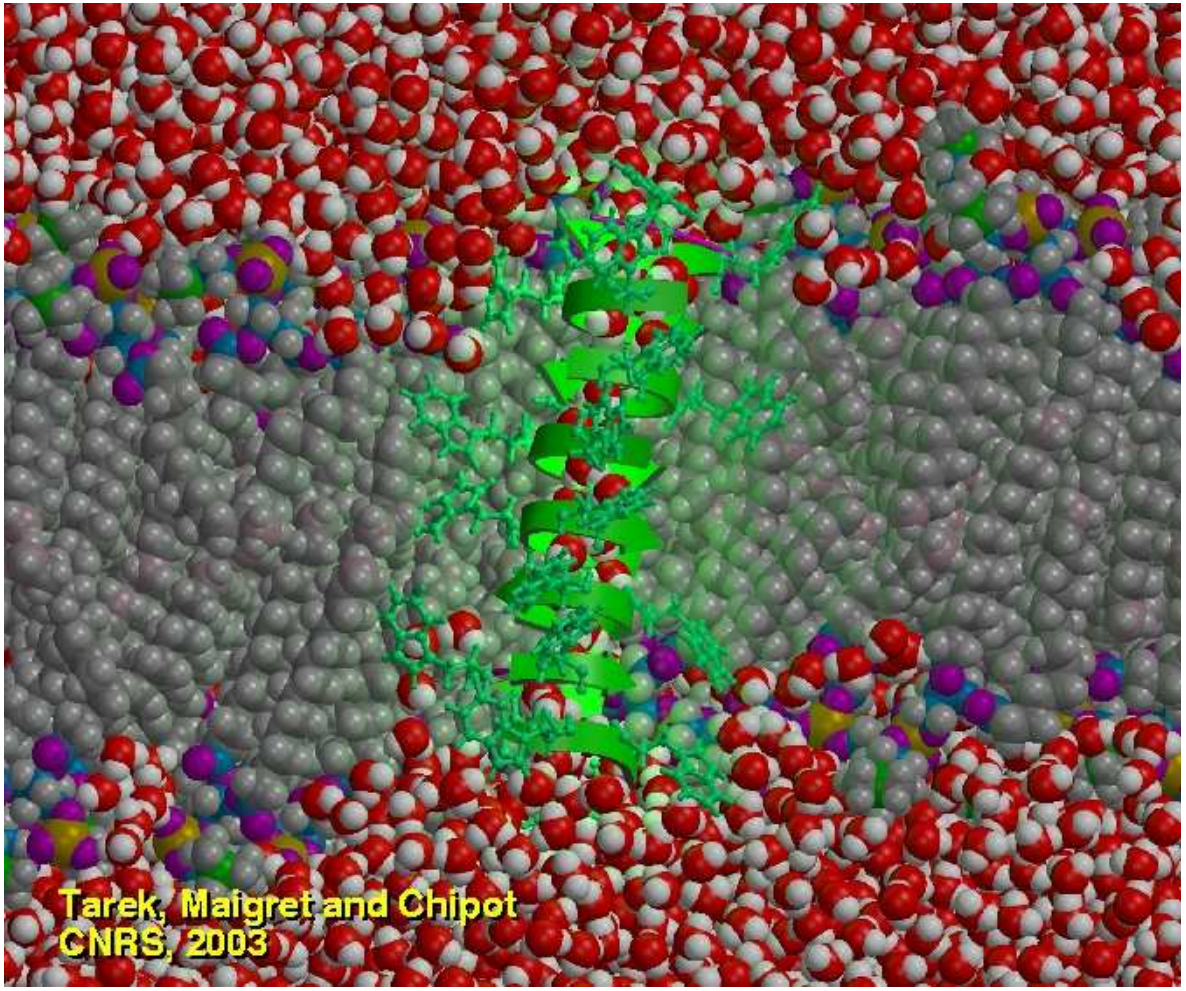
In practice, quantities of interest often depend on a few variables.

Reduced description of the system, that still includes some dynamical information?

Example of a biological system



Courtesy of Chris Chipot, CNRS Nancy

Reference dynamics

We are interested in dynamical properties. Two possible choices for the reference dynamics of the system:

- overdamped Langevin equation:

$$dX_t = -\nabla V(X_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t, \quad X_t \in \mathbb{R}^n$$

- Langevin equation (with masses set to 1):

$$\begin{aligned} dX_t &= P_t\,dt, & X_t \in \mathbb{R}^n, \\ dP_t &= -\nabla V(X_t)\,dt - \gamma P_t\,dt + \sqrt{2\gamma\beta^{-1}}\,dW_t, & P_t \in \mathbb{R}^n. \end{aligned}$$

For both dynamics,

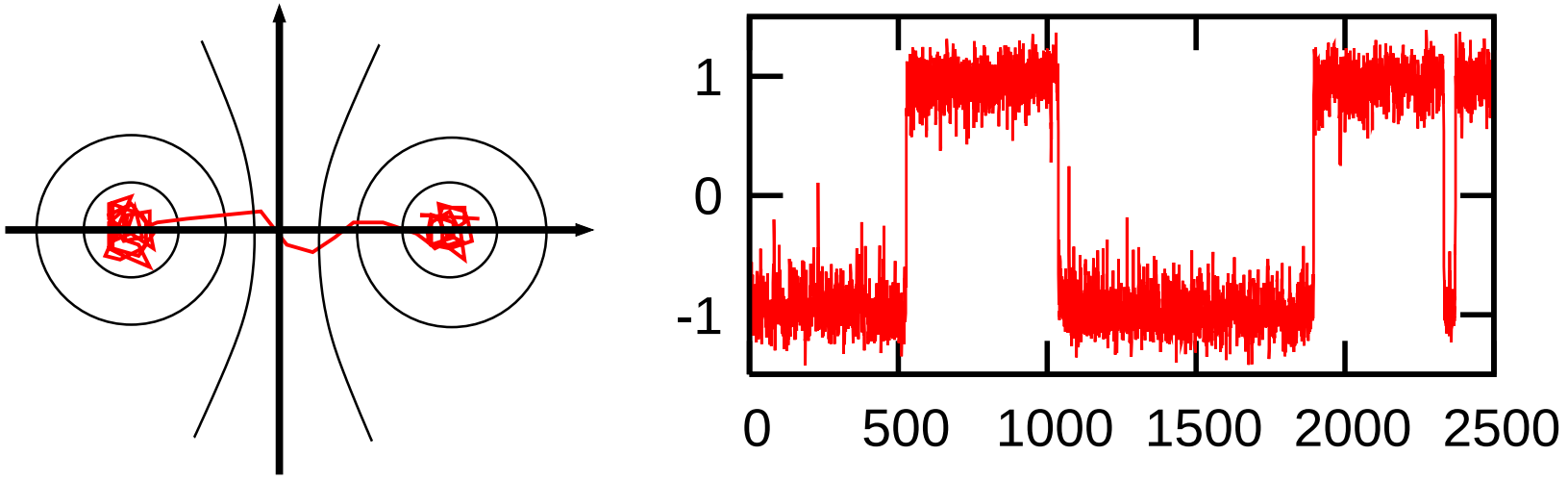
$$\frac{1}{T}\int_0^T \Phi(X_t)\,dt \longrightarrow \int_{\mathbb{R}^n} \Phi(X)\,d\mu, \quad d\mu = Z^{-1}\exp(-\beta V(X))\,dX.$$

We will mostly argue with overdamped Langevin, and next turn to Langevin.

Metastability and reaction coordinate

$$dX_t = -\nabla V(X_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t, \quad X_t \equiv \text{position of all atoms}$$

- in practice, the dynamics is metastable: the system stays a long time in a well of V before jumping to another well:



- we assume that wells are fully described through a well-chosen reaction coordinate

$$\xi : \mathbb{R}^n \mapsto \mathbb{R}$$

$\xi(x)$ may e.g. be a particular angle in the molecule.

Quantity of interest: path $t \mapsto \xi(X_t)$.

Our aim

$$dX_t = -\nabla V(X_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t \quad \text{in} \quad \mathbb{R}^n$$

Given a reaction coordinate $\xi : \mathbb{R}^n \mapsto \mathbb{R}$,
propose a dynamics z_t that approximates $\xi(X_t)$.

- preservation of equilibrium properties:
  when $X \sim d\mu$, then $\xi(X)$ is distributed according to $\exp(-\beta A(z))\,dz$,
  where A is the free energy.

  The dynamics z_t should be ergodic wrt $\exp(-\beta A(z))\,dz$.

- recover in z_t some dynamical information included in $\xi(X_t)$.

Related approaches: Mori-Zwanzig formalism, asymptotic expansion of the generator (Papanicolaou, ...), averaging principle for SDE (Pavliotis and Stuart, Hartmann, ...), effective dynamics using Markov state models (Schuette and Sarich, Lu), ...

A super-simple case: $\xi(x,y) = x$

Consider the dynamics in two dimensions: $X = (x,y) \in \mathbb{R}^2$,

$$\begin{aligned} dx_t &= -\partial_x V(x_t, y_t)\, dt + \sqrt{2\beta^{-1}}\, dW_t^x, \\ dy_t &= -\partial_y V(x_t, y_t)\, dt + \sqrt{2\beta^{-1}}\, dW_t^y, \end{aligned}$$

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and assume that $\xi(x,y) = x$. Let $\psi(t,X)$ be the density of X at time t:

$$\text{for any } \mathcal{B} \subset \mathbb{R}^2, \qquad \mathbb{P}(X_t \in \mathcal{B}) = \int_{\mathcal{B}} \psi(t,X) dX$$

Introduce the mean of the drift over all configurations satisfying $\xi(X) = z$:

$$\widetilde{b}(t,z) := -\frac{\displaystyle\int_{\mathbb{R}} \partial_x V(z,y)\ \psi(t,z,y)\, dy}{\displaystyle\int_{\mathbb{R}} \psi(t,z,y)\, dy} = -\,\mathbb{E}\left[\partial_x V(X) \mid \xi(X_t) = z\right]$$

and consider $dz_t = \widetilde{b}(t,z_t)\, dt + \sqrt{2\beta^{-1}}\, dB_t$

Then, for any t, the law of z_t is equal to the law of x_t (Gyongy 1986)

Making the approach practical

$$\widetilde{b}(t,z) = -\fint_{\mathbb{R}} \partial_x V(z,y)\, \psi(t,z,y)\, dy = -\,\mathbb{E}\left[\partial_x V(X) \mid \xi(X_t) = z\right]$$

$\widetilde{b}(t,z)$ is extremely difficult to compute . . . Need for approximation:

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$$b(z) := -\fint_{\mathbb{R}} \partial_x V(z,y)\, \psi_\infty(z,y)\, dy = -\,\mathbb{E}_\mu\left[\partial_x V(X) \mid \xi(X) = z\right]$$

with $\psi_\infty(x,y) = Z^{-1}\exp(-\beta V(x,y))$.

Effective dynamics:

$$\boxed{dz_t = b(z_t)\, dt + \sqrt{2\beta^{-1}}\, dB_t}$$

Idea: $\widetilde{b}(t,x) \approx b(x)$ if the equilibrium in each manifold

$$\Sigma_x = \{(x,y), \quad y \in \mathbb{R}\}$$

is quickly reached: x_t is much slower than y_t.

The general case: $X \in \mathbb{R}^n$ and arbitrary ξ

$$dX_t = -\nabla V(X_t)\, dt + \sqrt{2\beta^{-1}}\, dW_t, \quad \xi : \mathbb{R}^n \to \mathbb{R}$$

From the dynamics on X_t, we obtain (chain rule)

$$d\left[\xi(X_t)\right] = \left(-\nabla V \cdot \nabla \xi + \beta^{-1}\Delta\xi\right)(X_t)\, dt + \sqrt{2\beta^{-1}}\ \ |\nabla\xi|(X_t)\ \ dB_t$$

where B_t is a 1D brownian motion.

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where B_t is a 1D brownian motion.

Introduce the average of the drift and diffusion terms:

$$b(z) := \fint \left(-\nabla V \cdot \nabla\xi + \beta^{-1}\Delta\xi\right)(X)\ \psi_\infty(X)\, \delta_{\xi(X)-z}\, dX$$

$$\sigma^2(z) := \fint |\nabla\xi(X)|^2\ \psi_\infty(X)\, \delta_{\xi(X)-z}\, dX$$

Eff. dyn.: $\boxed{dz_t = b(z_t)\, dt + \sqrt{2\beta^{-1}}\, \sigma(z_t)\, dB_t}$

The approximation makes sense if, in the manifold

$$\Sigma_z = \{X \in \mathbb{R}^n, \quad \xi(X) = z\},$$

X_t quickly reaches equilibrium. $\xi(X_t)$ much slower than evolution of X_t in Σ_z.

Some remarks

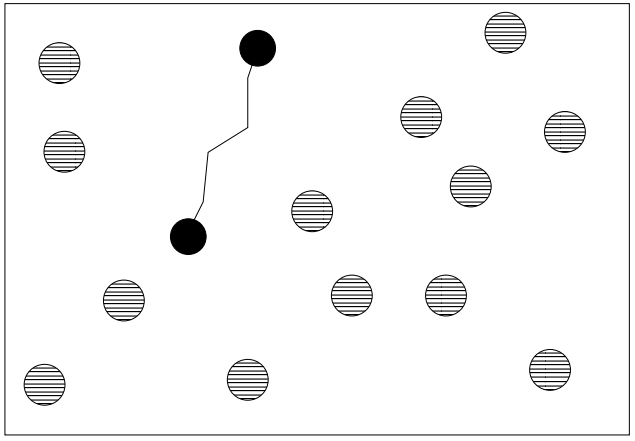
Effective dynamics:

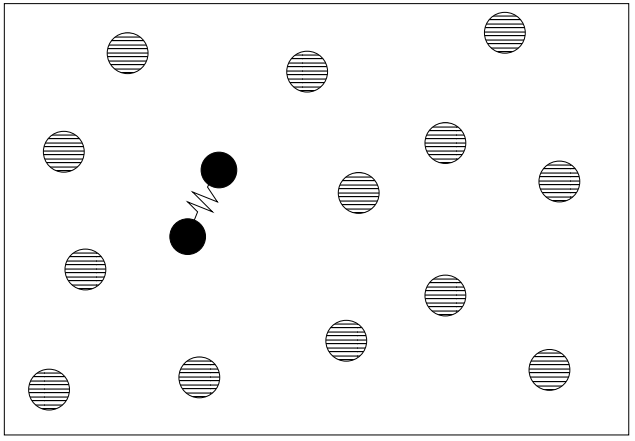
$$\boxed{dz_t = b(z_t)\,dt + \sqrt{2\beta^{-1}}\,\sigma(z_t)\,dB_t}$$

- OK from the statistical viewpoint: the dynamics is ergodic wrt $\exp(-\beta A(z))dz$.
- Using different arguments, this dynamics has been obtained by **[E and Vanden-Eijnden 2004]**, and **[Maragliano, Fischer, Vanden-Eijnden and Ciccotti, 2006]**.
- In the following, we will
  - numerically assess its accuracy
  - derive error bounds

In practice, we pre-compute $b(z)$ and $\sigma(z)$ for values on a grid (remember z is scalar), and next linearly interpolate between these values.

Dimer in solution: comparison of residence times





- solvent-solvent, solvent-monomer: truncated LJ on $r = \|x_i - x_j\|$:

$$V_{WCA}(r) = 4\varepsilon \left(\frac{\sigma^{12}}{r^{12}} - 2\,\frac{\sigma^{6}}{r^{6}} \right)$$ if $r \leq \sigma$, 0 otherwise (repulsive potential)

- monomer-monomer: double well on $r = \|x_1 - x_2\|$

Reaction coordinate: the distance between the two monomers

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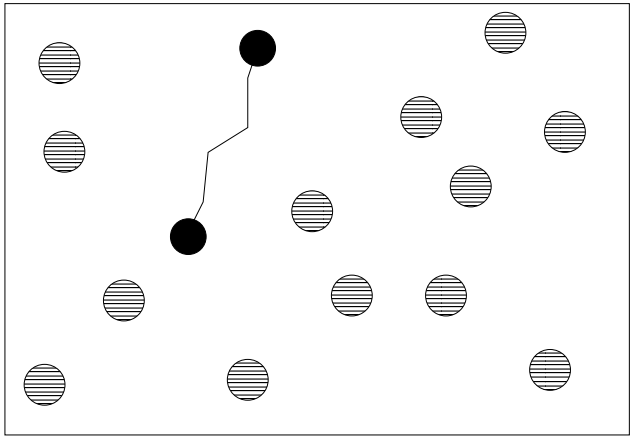

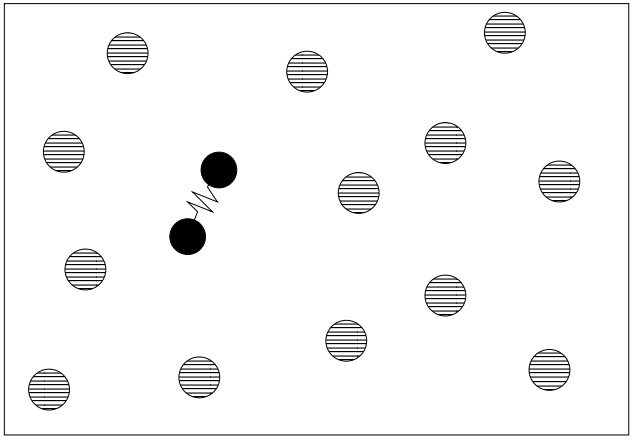

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Reaction coordinate: the distance between the two monomers

β	Reference dyn.	Effective dyn.
0.5	262 ± 6	245 ± 5
0.25	1.81 ± 0.04	1.68 ± 0.04

Accuracy assessment: some background materials

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$$dX_t = -\nabla V(X_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t$$

Let $\psi(t,X)$ be the probability distribution function of X_t:

$$\mathbb{P}\left(X_t \in \mathcal{B}\right) = \int_{\mathcal{B}} \psi(t,X)\,dX$$

Under mild assumptions, $\psi(t,X)$ converges to $\psi_\infty(X) = Z^{-1}\exp(-\beta V(X))$ exponentially fast:

$$H\left(\psi(t,\cdot)|\psi_\infty\right) := \int \psi(t,\cdot)\,\ln\frac{\psi(t,\cdot)}{\psi_\infty} \leq C\exp(-2\rho t)$$

Relative entropy is interesting because $\|\psi(t,\cdot)-\psi_\infty\|_{L^1}^2 \leq 2H\left(\psi(t,\cdot)|\psi_\infty\right)$.

The larger ρ is, the faster the convergence to equilibrium.

Remark: ρ is the Logarithmic Sobolev inequality constant of ψ_∞.

A convergence result

$$dX_t = -\nabla V(X_t)\,dt + \sqrt{2\beta^{-1}}dW_t, \quad \text{consider } \xi(X_t)$$

Let $\psi_{\text{exact}}(t,z)$ be the probability distribution function of $\xi(X_t)$:

$$\mathbb{P}\left(\xi(X_t) \in I\right) = \int_I \psi_{\text{exact}}(t,z)\,dz$$

On the other hand, we have introduced the effective dynamics

$$dz_t = b(z_t)\,dt + \sqrt{2\beta^{-1}}\,\sigma(z_t)\,dB_t$$

Let $\phi_{\text{eff}}(t,z)$ be the probability distribution function of z_t.

Introduce the error

$$E(t) := \int_{\mathbb{R}} \psi_{\text{exact}}(t,\cdot)\,\ln\frac{\psi_{\text{exact}}(t,\cdot)}{\phi_{\text{eff}}(t,\cdot)}$$

We would like $\psi_{\text{exact}} \approx \phi_{\text{eff}}$, e.g. E small ...

Decoupling assumptions

$$\Sigma_z = \{X \in \mathbb{R}^n,\ \xi(X) = z\}\,, \quad d\mu_z \propto \exp(-\beta V(X))\,\delta_{\xi(X)-z}$$

- assume that the Gibbs measure restricted to Σ_z satisfy a Logarithmic Sobolev inequality with a large constant ρ, uniform in z (no metastability in Σ_z).

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- assume that the coupling between the dynamics of $\xi(X_t)$ and the dynamics in Σ_z is weak:
  If $\xi(x,y) = x$, we request $\partial_{xy} V$ to be small.
  In the general case, recall that the free energy derivative reads

$$A'(z) = \int_{\Sigma_z} F(X) d\mu_z$$

  We assume that $\max |\nabla_{\Sigma_z} F| \leq \kappa$.

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- assume that $|\nabla \xi|$ is close to a constant on each Σ_z, e.g.

$$\lambda = \max_X \left| \frac{|\nabla \xi|^2(X) - \sigma^2(\xi(X))}{\sigma^2(\xi(X))} \right| \text{ is small}$$

Error estimate

$$E(t) = \text{error} = \int_{\mathbb{R}} \psi_{\text{exact}}(t,\cdot)\, \ln \frac{\psi_{\text{exact}}(t,\cdot)}{\phi_{\text{eff}}(t,\cdot)}$$

Under the above assumptions, for all $t \geq 0$,

$$E(t) \leq C(\xi, \text{Initial Cond.}) \left(\lambda + \frac{\beta^2 \kappa^2}{\rho^2} \right)$$

Hence, if the coarse variable ξ is such that

- ρ is large (fast ergodicity in Σ_z),
- κ is small (small coupling between dynamics in Σ_z and on z_t),
- λ is small ($|\nabla \xi|$ is close to a constant on each Σ_z),

then the effective dynamics is accurate:

$$\text{at any time, law of } \xi(X_t) \approx \text{law of } z_t.$$

Remark: this is not an asymptotic result, and this holds for any ξ.

This bound may be helpful, in some cases, to discriminate between various reaction coordinates.

Rough estimation in a particular case

Standard expression in MD: $V_\varepsilon(X) = V_0(X) + \frac{1}{\varepsilon} q^2(X)$: $\nabla q \equiv$ fast direction

$$E(t) = \text{error} = \int_{\mathbb{R}} \psi_{\text{exact}}(t,\cdot) \, \ln \frac{\psi_{\text{exact}}(t,\cdot)}{\phi_{\text{eff}}(t,\cdot)}$$

- If $\nabla\xi \cdot \nabla q = 0$, then the direction $\nabla\xi$ is decoupled from the fast direction ∇q, hence ξ is indeed a slow variable, and it turns out that

$$E(t) = O(\varepsilon).$$

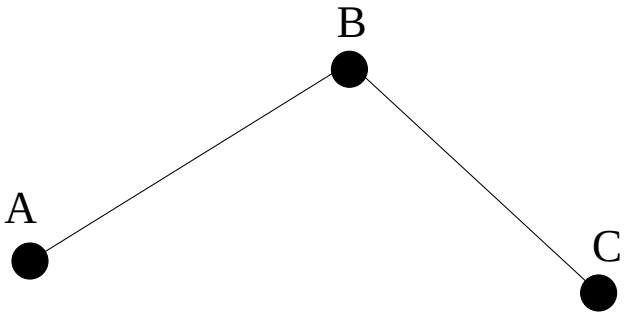
- If $\nabla\xi \cdot \nabla q \neq 0$, then the variable ξ does not contain all the slow motion, and bad scale separation:

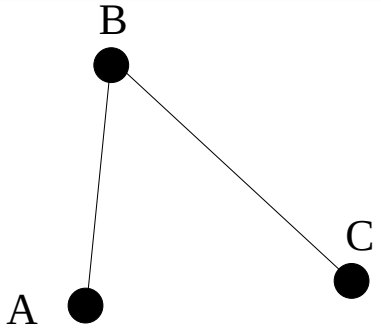
$$E(t) = O(1),$$

hence the laws of $\xi(X_t)$ and of z_t are not close one to each other.

The condition $\nabla\xi \cdot \nabla q = 0$ seems important to obtain good accuracy.

Tri-atomic molecule





$$V(X) = \frac{1}{2}\, k_2\, (r_{AB} - \ell_{eq})^2 + \frac{1}{2}\, k_2\, (r_{BC} - \ell_{eq})^2 + k_3\, W_{\rm DW}(\theta_{ABC}), \quad k_2 \gg k_3,$$

where $W_{\rm DW}$ is a double well potential.

Reaction coordinate	Orthogonality condition	Reference residence time	Residence time using Eff. Dyn.
$\xi_1(X) = \theta_{ABC}$	yes	0.700 ± 0.011	0.704 ± 0.011
$\xi_2(X) = r_{AC}^2$	no	0.709 ± 0.015	0.219 ± 0.004

Extension to the Langevin equation

- We have considered until now the overdamped Langevin equation:

$$dX_t = -\nabla V(X_t)\, dt + \sqrt{2\beta^{-1}}\, dW_t$$

- Consider now the Langevin equation:

$$\begin{aligned} dX_t &= P_t\, dt \\ dP_t &= -\nabla V(X_t)\, dt - \gamma P_t\, dt + \sqrt{2\gamma\beta^{-1}}\, dW_t \end{aligned}$$

- Can we extend the numerical strategy?

Joint work with F. Galante and T. Lelièvre.

Building the effective dynamics - 1

$$dX_t = P_t\,dt, \quad dP_t = -\nabla V(X_t)\,dt - \gamma P_t\,dt + \sqrt{2\gamma\beta^{-1}}\,dW_t$$

We compute

$$d\left[\xi(X_t)\right] = \nabla\xi(X_t)\cdot P_t\,dt$$

We introduce the coarse-grained velocity

$$v(X,P) = \nabla\xi(X)\cdot P \in \mathbb{R}$$

and have (chain rule)

$$d\left[v(X_t,P_t)\right] = \left[P_t^T\nabla^2\xi(X_t)P_t - \nabla\xi(X_t)^T\nabla V(X_t)\right]dt - \gamma v(X_t,P_t)\,dt + \sqrt{2\gamma\beta^{-1}}\ \left|\nabla\xi(X_t)\right|\ dB_t$$

where B_t is a 1D Brownian motion.

We wish to write a closed equation on $\xi_t = \xi(X_t)$ and $v_t = v(X_t,P_t)$.

Introduce $D(X,P) = P^T\nabla^2\xi(X)P - \nabla\xi(X)^T\nabla V(X)$.

Building the effective dynamics - 2

Without any approximation, we have obtained

$$\begin{aligned} d\xi_t &= v_t\, dt, \\ dv_t &= D(X_t, P_t)\, dt - \gamma v_t\, dt + \sqrt{2\gamma\beta^{-1}}\, |\nabla\xi(X_t)|\, dB_t \end{aligned}$$

To close the system, we introduce the conditional expectations with respect to the equilibrium measure $\mu(X,P) = Z^{-1}\exp[-\beta\left(V(X) + P^TP/2\right)]$:

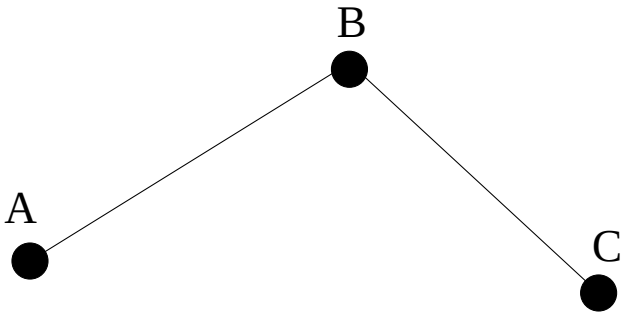
$$\begin{aligned} D_{\text{eff}}(\xi_0, v_0) &= \mathbb{E}_\mu\left(D(X,P) \mid \xi(X) = \xi_0, v(X,P) = v_0\right) \\ \sigma^2(\xi_0, v_0) &= \mathbb{E}_\mu\left(|\nabla\xi|^2(X) \mid \xi(X) = \xi_0, v(X,P) = v_0\right) \end{aligned}$$

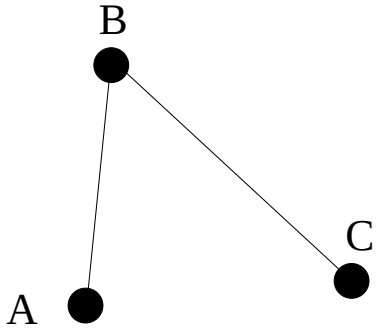
Effective dynamics:

$$d\xi_t = v_t\, dt, \qquad dv_t = D_{\text{eff}}(\xi_t, v_t)\, dt - \gamma v_t\, dt + \sqrt{2\gamma\beta^{-1}}\, \sigma(\xi_t, v_t)\, dB_t$$

Again, this dynamics is consistent with the equilibrium properties: it preserves the equilibrium measure $\exp\left[-\beta A(\xi_0, v_0)\right]\, d\xi_0\, dv_0$.

Numerical results: the tri-atomic molecule





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where W_{DW} is a double well potential.

Reaction coordinate: $\xi(X) = \theta_{ABC}$.

Inverse temp.	Reference	Eff. dyn.
β = 1	9.808 $\pm$ 0.166	9.905 $\pm$ 0.164
β = 2	77.37 $\pm$ 1.23	79.1 $\pm$ 1.25

Excellent agreement on the residence times in the well.

Pathwise accuracy (ongoing work with T. Lelièvre and S. Olla)

Going back to the overdamped case, with $\xi(x,y) = x$, can we get pathwise accuracy, e.g.

$$\mathbb{E}\left[\sup_{0\leq t\leq T} |x_t - z_t|^2\right] \leq \frac{C(T)}{\rho} \quad ?$$

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- z_t is the effective dynamics trajectory:

$$dz_t = -b(z_t)\,dt + \sqrt{2\beta^{-1}}dB_t$$

- (x_t, y_t) is the exact trajectory:

$$\begin{aligned} dx_t &= -\partial_x V(x_t,y_t)\,dt + \sqrt{2\beta^{-1}}dB_t \\ &= -b(x_t)\,dt + e(x_t,y_t)\,dt + \sqrt{2\beta^{-1}}dB_t \end{aligned}$$

By construction, $b(x) = \mathbb{E}_\mu\left[\partial_x V(X)|\xi(X) = x\right]$, hence

$$\forall x, \quad \mathbb{E}_\mu\left[e(X)|\xi(X) = x\right] = 0.$$

Poisson equation

Let L^x be the Fokker-Planck operator corresponding to a simple diffusion in y, at fixed x:

$$L^x \phi = \text{div}_y(\phi \nabla_y V) + \beta^{-1} \Delta_y \phi$$

For any x,

$$\mathbb{E}_\mu \left[e(X) | \xi(X) = x \right] = 0 \Longrightarrow \exists u(x, \cdot) \text{ s.t. } (L^x)^\star u(x, \cdot) = e(x, \cdot)$$

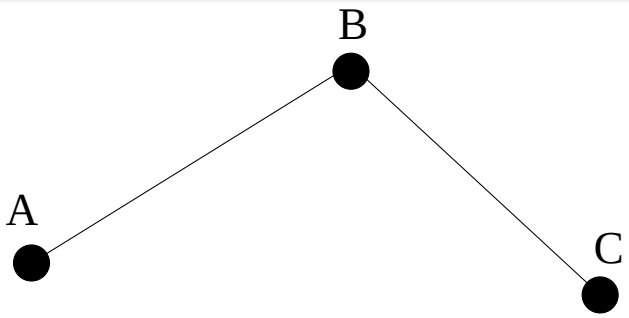
Assume that L^x satisfies a (large) spectral gap $\rho \gg 1$. Then, $\|u\| \leq C/\rho \ll 1$.

We have not been able to show a bound on $\mathbb{E}\left[\sup_{0 \leq t \leq T} |x_t - z_t|^2\right]$, but we have shown that

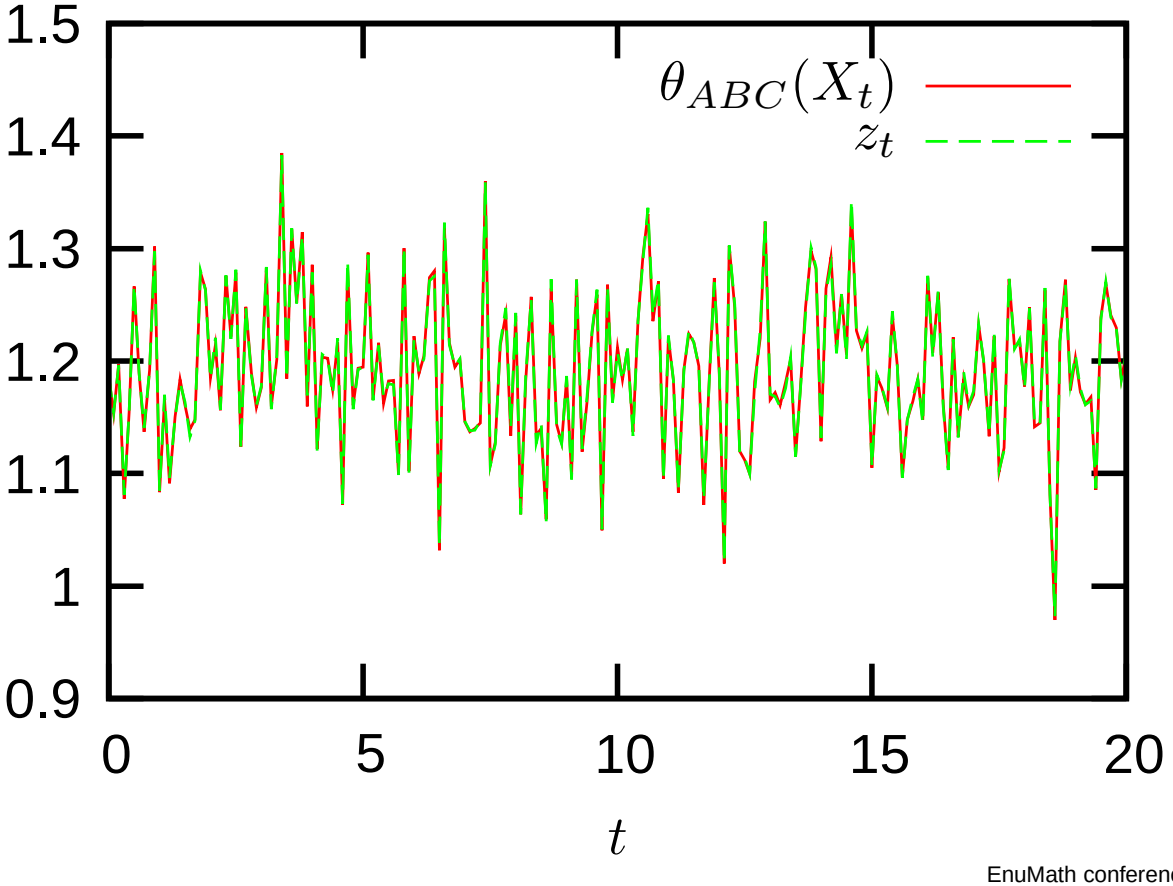
$$\mathbb{P}\left(\sup_{0 \leq t \leq T} |x_t - z_t| \geq c \rho^{-\alpha} \right) \leq \frac{C}{\ln(\rho)}$$

for any $0 \leq \alpha < 1/2$. This somewhat explains the good results we observe on the residence times.

Numerical illustration: the tri-atomic molecule



$$V(X) = \frac{1}{2}\, k_2\, (r_{AB} - \ell_{eq})^2 + \frac{1}{2}\, k_2\, (r_{BC} - \ell_{eq})^2 + k_3\, W(\theta_{ABC}), \quad k_2 \gg k_3$$



Conclusions

- We have proposed a “natural” way to obtain a closed equation on $\xi(X_t)$.
- Encouraging numerical results and rigorous error bounds (marginals at time t and in probability on the paths).

Once a reaction coordinate ξ has been chosen, computing the drift and diffusion functions $b(z)$ and $\sigma(z)$ is as easy/difficult as computing the free energy derivative $A'(z)$.

The approach can be extended to the Langevin equation.

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