The Adaptive Biasing Force algorithm with non-conservative forces

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Setting

- N particles, $q = (q_1, \dots, q_N) \in \mathcal{D}$ their positions.
- Potential energy $V \in \mathcal{C}^2(\mathcal{D})$, interaction force $\mathcal{F} = -\nabla V$
- **Boltzmann-Gibbs measure:**

$$\mu(\mathrm{d}q) = Z_\mu^{-1} e^{-\beta V(q)}\,\mathrm{d}q, \quad Z_\mu = \int_{\mathcal{D}} e^{-\beta V(q)}\,\mathrm{d}q$$

- **Canonical Mean/ thermodynamic quantity:**

$$\psi \in \mathcal{C}_0^\infty(\mathcal{D}) \text{ observable, and } \mathbb{E}_\mu[\psi] = \int_{\mathcal{D}} \psi\,\mathrm{d}\mu$$

Goal: being able to sample μ!

Overdamped Langevin dynamics

- **Dynamics:**

$$\mathrm{d}Q_t = -\nabla V(Q_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t$$

- **Infinitesimal generator:**

$$\mathcal{L}\varphi(X) = \lim_{t\to+\infty} \frac{\mathbb{E}_\mu[\varphi(X_t)] - \varphi(X)}{t} = -\nabla V \cdot \nabla\varphi(X) + \beta\Delta\varphi(X)$$

- **Fokker-Planck equation:**

$$\partial_t \pi_t = \mathcal{L}^* \pi_t$$

- **Ergodicity:** $(Q_t)_{t\geq 0}$ is ergodic with respect to μ. In other words:

$$\forall \psi \in \mathcal{C}_0^\infty(\mathcal{D}), \quad \lim_{\tau\to+\infty} \frac{1}{\tau}\int_0^\tau \psi(Q_t)\,\mathrm{d}t = \mathbb{E}_\mu[\psi]$$

- **Problem:** Metastability!

What is metastability?

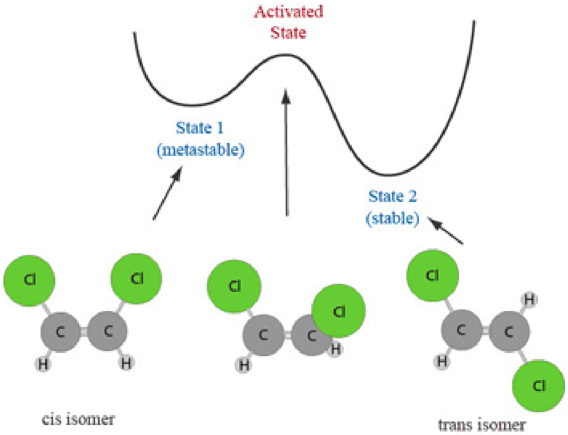

Figure: cis–trans isomerization of 1,2-Dichloroethene
(http://chemcollective.org/chem/entropy/reactcoord.php)

Reaction coordinate

- $\xi : \mathcal{D} \to \mathcal{M}$, with $\mathcal{M}$ manifold of dimension $d' \leq dN$.
- $\Sigma_z = \{q \in \mathcal{D} \,|\, \xi(q) = z\}$
- **Free energy:**

$$A(z) = -\beta^{-1} \ln(Z_{\Sigma_z}), \quad Z_{\Sigma_z} = \int_{\Sigma_z} e^{-\beta V(q)} \, \delta_{\xi(q)-z}(\mathrm{d}q)$$

- **Local mean force:** F $(\rightsquigarrow (\nabla\xi)^\top \nabla\xi, V, \beta)$
- **Free energy derivative:** $\nabla A(z) = \mathbb{E}[F(Q) \,|\, \xi(Q) = z]$
- **Property:** If $Q \sim \mu$ then $\xi(Q) \sim \mu_A$:

$$\mu_A = \xi \star \mu(\mathrm{d}z) = \frac{e^{-\beta A(z)} \, \mathrm{d}z}{\int_{\mathcal{M}} e^{-\beta A(z)} \, \mathrm{d}z}. \tag{1}$$

From now on

- Position $q = (x, y) \in \mathbb{T}^n$
- Stochastic process $Q_t = (X_t, Y_t) \quad \forall t \geq 0$
- with $x \in \mathbb{T}^m$, $y \in \mathbb{T}^{n-m}$ and $\xi(x, y) = x$
- $\nabla A(z) = \mathbb{E}[\nabla_x V(x, y) \,|\, \xi(x, y) = x = z]$

$\rightsquigarrow$ Convergence results are expressed using the relative entropy of two measures:

$$\mathcal{H}(\mu|\nu) = \begin{cases} \int \ln(\frac{\mathrm{d}\mu}{\mathrm{d}\nu})\mathrm{d}\mu & \text{if } \mu \ll \nu \\ +\infty & \text{else.} \end{cases}$$

The idea

- ξ is a **generalized coordinate**
- (q, ξ) extended coordinates
- Methods using ξ: **generalized ensemble methods**

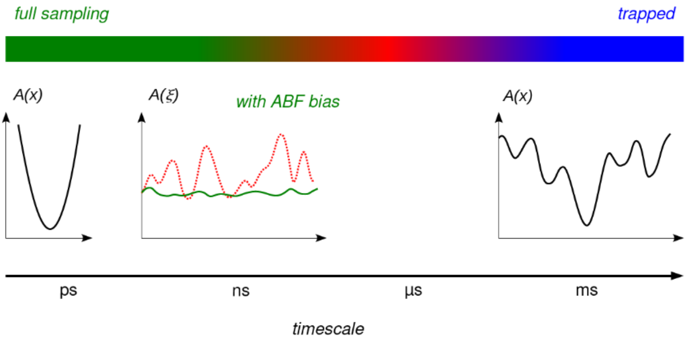

Figure: Concept of ABF (Jérôme Hénin, CECAM workshop, Paris, 2021)

First attempt

- **Biased Overdamped Langevin:**

$$\begin{cases} \mathrm{d}X_t = \left(-\nabla_x V + \nabla A \circ \xi\right)(X_t, Y_t)\,\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^1 \\ \mathrm{d}Y_t = -\nabla_y V(X_t, Y_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^2 \end{cases}$$

- **Fokker-Planck equation:**

$$\partial_t \pi_t = \beta^{-1}\Delta\pi_t - \nabla\cdot((-\nabla V + \nabla A \circ \xi)\pi_t)$$

- Stationary measure: $\pi_\infty \propto e^{-\beta(V - A\circ\xi)}$
- $\xi \star \pi_\infty$ is the uniform law!

ABF

- **ABF:**

$$\begin{cases} \mathrm{d}X_t = (-\nabla_x V + G_t \circ \xi)(X_t, Y_t)\,\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^1 \\ \mathrm{d}Y_t = -\nabla_y V(X_t, Y_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^2 \\ G_t(z) = \mathbb{E}[\nabla_x V(X_t, Y_t) \,|\, \xi(X_t, Y_t) = z] \end{cases}$$

- **Fokker-Planck equation:**

$$\partial_t \pi_t = \beta^{-1}\Delta\pi_t - \nabla \cdot ((-\nabla V + G_t \circ \xi)\pi_t)$$

- **Known results**: T.Lelièvre, F.Otto, M.Rousset, G.Stoltz – 2007
  - (i) $\lim_{t\to+\infty} G_t = \nabla A$
  - (ii) $\lim_{t\to+\infty} \pi_t = \pi_\infty$
  - (iii) **Flat histogram property:** the law $\pi_t^\xi = \xi \star \pi_t$ of $(\xi(Q_t))_{t\geq 0}$ is s.t $\lim_{t\to+\infty} \pi_t^\xi = \lambda$: no more energy barriers.

Projected Adaptive Biasing Force method

- In simulations, the converged bias $G = \lim_{t \to +\infty} G_t$ is *a priori* not a gradient, and yet we are looking for ∇A!
- **PABF:**

$$\begin{cases} \mathrm{d}X_t = \left(-\nabla_x V + \nabla H_t \circ \xi\right)(X_t, Y_t)\,\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^1 \\ \mathrm{d}Y_t = -\nabla_y V(X_t, Y_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^2 \\ \nabla H_t(z) = \mathrm{P}_{L^2(\lambda)}(G_t) = \mathrm{P}_{L^2(\lambda)}(\mathbb{E}[\nabla_x V(X_t, Y_t) \,|\, \xi(X_t, Y_t) = z]) \end{cases}$$

- **Fokker-Planck equation:**

$$\partial_t \pi_t = \beta^{-1} \Delta \pi_t - \nabla \cdot \left(\left(-\nabla V + \nabla H_t \circ \xi\right)\pi_t\right)$$

▶ (H. Alrachid, T. Lelièvre, 2015): technical trick regarding the projection.

Problem

- **Question:** How about nonconservative forces (i.e for a generic interacting force $\mathcal{F}$)?

- **Motivation:**
  - Implementing $-\nabla V$ (*ab initio* MD approximations). *A priori* the force $\mathcal{F} = -\nabla V + \varepsilon g$ is not conservative!
  - Is there a stationary measure to the Fokker-Planck equation?
  - Provided it exists, do we still have long-time convergence?
  - Can one obtain an estimation of the error made on the system's free energy?

Final model

Dynamics:

$$\begin{cases} \mathrm{d}X_t = & \mathcal{F}_1(X_t, Y_t)\mathrm{d}t + B_t(X_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^1 \\ \mathrm{d}Y_t = & \mathcal{F}_2(X_t, Y_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}W_t^2 \end{cases} \tag{2}$$

where the bias B_t is either:

- $G_t(.) = \mathbb{E}\left[-\mathcal{F}_1(X_t, Y_t) \,|\, \xi(X_t, Y_t) = \,.\right]$ (ABF)
- $\nabla H_t = \mathrm{P}_{L^2(\lambda)}(G_t)$ (Projected ABF)

where $\mathrm{P}_{L^2(\nu)}(G)$ is the Helmholtz projection in $L^2(\nu)$ of the vector field G.

Fokker-Planck equation:

$$\partial_t \pi_t = \beta^{-1}\Delta\pi_t - \nabla\cdot((\mathcal{F} + B_t \circ \xi)\pi_t) \tag{3}$$

Flat histogram property

Proposition

For both the ABF and PABF algorithm, under several assumptions, π_t^ξ *converges towards the Lebesgue measure as* $t \to \infty$. *More precisely, for all* $t \geq 0$

$$\mathcal{H}(\pi_t^\xi | \lambda) \leqslant e^{-8\beta^{-1}\pi^2 t} \mathcal{H}(\pi_0^\xi | \lambda) .$$

Furthermore, there exists $C > 0$ *such that for all initial distribution* $\pi_0^\xi \in L^2(\mathbb{T}^m)$, *for all* $t \geq 1$:

$$\|\pi_t^\xi - 1\|_\infty \leqslant Ce^{-4\beta^{-1}\pi^2 t} \|\pi_0^\xi - 1\|_2 .$$

$\rightsquigarrow$ Flat histogram property verified in all cases.

- Entropic: PDE satisfied by π_t^ξ + deriving the entropy + Gronwall.
- L-∞: Nash inequality + PDE satisfied by π_t^ξ.

Existence result

Theorem

For both the ABF and PABF algorithms, under several assumptions, there exists a couple of stationary measure and bias $(\pi_\infty^{\mathcal{F}}, B_\infty^{\mathcal{F}})$ *to* (3)*, such that* $\pi_\infty^{\mathcal{F}} \in \mathcal{C}^0(\mathbb{T}^n)$ *is stricly positive. As a consequence,*

- (i) $\pi_\infty^{\mathcal{F}}$ *satisfies a log-Sobolev inequality for some constant* $R > 0$,
- (ii) *the conditional density* $y \mapsto \pi_{\infty,x}^{\mathcal{F}}(y) := \pi_\infty^{\mathcal{F}}(x,y)/\pi_\infty^{\mathcal{F},\xi}(x)$ *satisfies a log-Sobolev inequality for some constant* ρ*, for all* $x \in \mathbb{T}^m$.

$\leadsto$ **Note:** $\pi_\infty^{\mathcal{F}}$ different for ABF and PABF.

- Invariant probability measures of homogeneous diffusions.
- Fixed point problem.

Long-time convergence: conservative case

Theorem

Let us consider the ABF and PABF algorithms under several assumptions. Let us suppose moreover that $\mathcal{F} = -\nabla V$, with $V \in \mathcal{C}^2(\mathbb{T}^n)$. Then, there exists $K > 0$ such that, for all $\varepsilon > 0$ and for all $t \geq 0$:

$$\mathcal{H}\left(\pi_t | \pi_\infty^{\mathcal{F}}\right) \leq K \left(1 + \frac{1}{\varepsilon^2}\right) e^{-(\Lambda - \varepsilon)t},$$

with $\pi_\infty^{\mathcal{F}} = \mu_A$ being given by (1), $\Lambda = \left(8\pi^2 \wedge 2\rho\right) \beta^{-1}$ (ABF) and $\Lambda = \left(4\pi^2 \wedge 2\rho\right) \beta^{-1}$ (PABF). Furthermore, $\left(\pi_\infty^{-\nabla V}, B_\infty^{-\nabla V}\right) = (\mu_A, \nabla A)$ is the unique fixed point of (3).

⇝ PABF case: theoretical gap filled.

- Classical proof skeleton + property of the Helmholtz decomposition.

Long-time convergence: non-conservative case

Theorem

Let us consider the ABF and PABF algorithms under several assumptions (among which $\mathcal{F}_1$ is M-Lipschitz). Let $\pi_\infty^{\mathcal{F}}$,ρ be a stationary measure for (3) *and a constant such as in Theorem 1. Suppose moreover that $M\beta < 2\rho$. Then there exists $K \geq 0$ such that, for all $t \geq 0$:*

$$\mathcal{H}\left(\pi_t | \pi_\infty^{\mathcal{F}}\right) \leq K e^{-\Lambda t}$$

with $\Lambda = 2R(1 - \frac{M\beta}{2\rho})\beta^{-1}$.
As a consequence, the dynamics (3) *admits a unique stationary measure.*

$\rightsquigarrow$ It is ok to use ABF and PABF with non-conservative forces.

- Classical proof skeleton + Helmholtz decomposition.

Error bounds

Proposition

For the PABF algorithm, for all $V \in \mathcal{C}^2(\mathbb{T}^n)$ *and* $p \geq 1$*, there exists* $K_V > 0$ *and* $K_p > 0$ *such that the following holds. For all* $\mathcal{F} \in \mathcal{C}^1(\mathbb{T}^n)$ *satisfying* $\|\mathcal{F} + \nabla V\|_\infty \leq 1$*, for all stationary measure* $\pi_\infty^{\mathcal{F}}$ *of* (3)*, considering the corresponding bias* $\nabla H_\infty^{\mathcal{F}}$*, one has*

$$\|\nabla A - \nabla H_\infty^{\mathcal{F}}\|_{L^p(\mathbb{T}^m)} \;\leq\; K_V K_p \|\mathcal{F} + \nabla V\|_\infty \,,$$

and, for all $\psi \in L^\infty(\mathbb{T}^n)$*, considering*

$$\hat{I}_\psi \;:=\; \frac{\int_{\mathbb{T}^n} \psi(x,y) e^{-\beta H_\infty^{\mathcal{F}}(x)} \pi_\infty^{\mathcal{F}}(x,y)\mathrm{d}x\mathrm{d}y}{\int_{\mathbb{T}^n} e^{-\beta H_\infty^{\mathcal{F}}(x)} \pi_\infty^{\mathcal{F}}(x,y)\mathrm{d}x\mathrm{d}y}\,,$$

one has

$$\left| \int_{\mathbb{T}^n} \psi \mathrm{d}\mu - \hat{I}_\psi \right| \;\leq\; K_V \,\|\psi\|_\infty \,\|\mathcal{F} + \nabla V\|_\infty \,.$$

Quick recap

- ABF and PABF are robust:
  - Stationary measure $\pi_{\infty}^{\mathcal{F}}$.
  - Flat histogram property.
  - Convergence of π_t towards $\pi_{\infty}^{\mathcal{F}}$.
  - Convergence of the bias.
  - Bound on the error made on the system's free energy.
- Convergence proof for ABF applied to the kinetic Langevin dynamics, where both momenta and positions are considered?

Now, some alchemy!

- **Alchemical reactions:** $\xi \equiv \lambda$ guides the system from an initial state $\lambda = 0$ to a final state $\lambda = 1$.
- **Extended Hamiltonian:**

$$\begin{aligned} H(q,p;\lambda) &= E_k(p,\lambda) + V(q,\lambda) \\ &= E_k(p,\lambda) + V_{elec}(q,\lambda) + V_{vdW}(q,\lambda) \end{aligned}$$

- $H(q,p;0) = H^{ini}(q,p)$, $H(q,p;1) = H^{end}(q,p)$.
- In-between states $\lambda \in (0,1)$ are allowed to not make sense physically!

Applications

Use: estimating free energy differences.

- Hydration FE
- Ligand-binding affinity

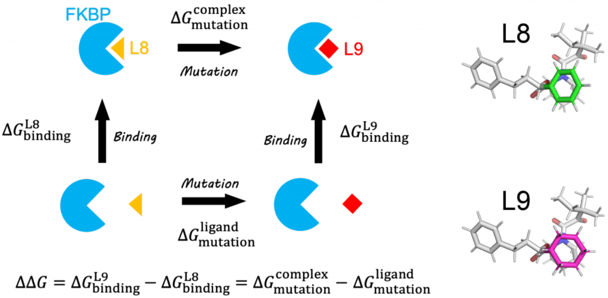

Figure: Thermodynamic cycle of protein-ligand binding and ligand mutation. (https://www.r-ccs.riken.jp/labs/cbrt/tutorials2019/genesis-tutorial-15-1/)

OSRW

"Random walk in orthogonal space to achieve efficient free-energy simulation of complex systems"

Lianqing Zheng, Mengen Chen, and Wei Yang, 2008

$\rightsquigarrow$ Choice of a particular reaction coordinate: (λ, F_λ).

Questions:

- How about using ABF with (λ, F_λ)?
- Is (λ, F_λ) the only good choice? Try with (λ, ξ) ?

Implementation

Treating alchemical reactions in `TinkerHP`

- Softcores: playing with forces ignition!
- Establish bridge between `TinkerHP` and `Colvars` software
- Implement and run λ–dynamics

Toy models: solvation of water in water, solvation of sodium in water

What remains to be done

- Comparing ABF to OSRW in `TinkerHP`: many ways to do it!

Thank you for your attention!

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