Parallel Replica algorithm for Langevin dynamics and Adaptative Metadynamics

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- **Molecular Dynamics** methods are used in **Biology, Material Science, Nuclear Physics** (protein folding, nuclear fuels propagation inside the nuclear reactor).

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Let N particles described by **position** $q_t^i \in \mathbb{R}^3$, and **momentum** $p_t^i \in \mathbb{R}^3$. The process $(X_t = (q_t, p_t))_{t\geq 0} := (q_t^1, \ldots, q_t^N, p_t^1, \ldots, p_t^N)_{t\geq 0}$ is solution of

$$\begin{cases} \mathrm{d}q_t = M^{-1} p_t \mathrm{d}t, \\ \mathrm{d}p_t = -\nabla V(q_t)\mathrm{d}t - \gamma M^{-1} p_t \mathrm{d}t + \sqrt{2\gamma\beta^{-1}}\mathrm{d}B_t, \end{cases}$$

with $V : \mathbb{R}^{3N} \mapsto \mathbb{R}$ the interaction potential, $\gamma > 0$ the friction parameter, M the mass matrix and $\beta^{-1} = k_B T$.

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Numerical discretization: $(q_{n\Delta t}, p_{n\Delta t}) \sim (\widehat{q}_n, \widehat{p}_n)$ such that (Velocity-Verlet integrator)

$$(\widehat{q}_{n+1}, \widehat{p}_{n+1}) = \Phi_{\Delta_t}(\widehat{q}_n, \widehat{p}_n).$$

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Problem: The sampling of some physical events takes too many iterations! (Typically 10^{-6} s with $\Delta t = 10^{-15}$ s).

An example in dimension 2

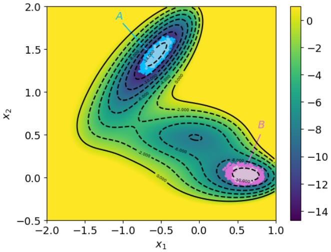

Figure: Sampling in a double well potential. 100 000 iterations

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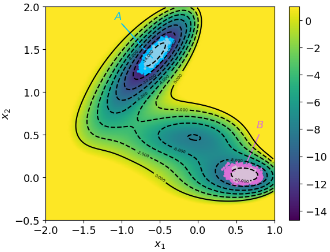

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- Transition events take a very long time: metastability because the system needs to overcome an energetic gap.
- Problem in large dimension where metastability correspond to entropic effects (narrow escapes).

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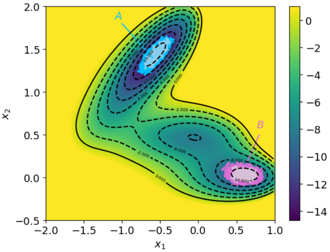

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How to sample **precisely** these transition events?

Parallel Replica algorithm

Conceived by Arthur Voter (Los Alamos National Laboratory) in 1998.

Objective: Parallelize the sampling of the first exit event (first exit time, exit point) from a domain D for the process $(X_t)_{t\geq 0}$.

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Parallel Replica: Assume that $(X_t)_{t\geq 0}$ stayed in D during τ_c "long enough". Let $\tau_\partial := \inf\{t > \tau_c : X_t \notin D\}$.

1. Initialize N independent replicas $(X_t^1)_{t\geq 0}, \dots, (X_t^N)_{t\geq 0}$ starting from X_{τ_c} and following the same dynamics as $(X_t)_{t\geq 0}$.
2. Make the N replicas evolve in D during τ_c (*rejection sampling*).
3. Let $\tau_\partial^i = \inf\{t > 0 : X_{t+\tau_c}^i \notin D\}$ and $i^* = \arg\min_{1\leq i\leq N} \tau_\partial^i$. Define

$$\left(\tau_\partial, X_{\tau_\partial}\right) := \left(N\tau_\partial^{i^*}, X_{\tau_\partial^{i^*}}^{i^*}\right).$$

If justified, the last step would ensure a **speed-up** of N in wall-clock time.

Quasi-stationary distribution

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Definition: Let $\tau_\partial := \inf\{t > 0 : X_t \notin D\}$. A probability measure ν on D is said to be a **QSD** on D of the process $(X_t)_{t\geq 0}$, if for all $A \subset D$,

$$\frac{\mathbb{P}_\nu(X_t \in A, \tau_\partial > t)}{\mathbb{P}_\nu(\tau_\partial > t)} = \nu(A).$$

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First exit event starting from the QSD and justification of ParRep

Assume that $X_0 \overset{\mathcal{L}}{=} QSD$, then, see Collet, Martinez, San Martin (2013),

- τ_∂ follows the exponential law,
- τ_∂ is independent of X_{τ_∂}.

Let $(X_0^N, \ldots, X_0^N)$ be i.i.d. according to the QSD and $i^* := \arg\min_{1\leq i\leq N} \tau_\partial^i$, then

$$(N\tau_\partial^{i^*}, X^{i^*}_{\tau_\partial^{i^*}}) \overset{\mathcal{L}}{=} (\tau_\partial, X_{\tau_\partial}).$$

Parallel Replica: Existence of a QSD and long time convergence to the QSD ?

Overdamped case

QSDs have been investigated for the overdamped Langevin dynamics $(\overline{q}_t)_{t\geq 0}$

$$\mathrm{d}\overline{q}_t = -\nabla V(\overline{q}_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}B_t,$$

on a $\mathcal{C}^2$ **bounded connected** set $\mathcal{O}$ of $\mathbb{R}^d$, where $\beta^{-1} = k_B T > 0$, $V \in \mathcal{C}^\infty(\mathbb{R}^d, \mathbb{R}^d)$ (see Gong, Qian and Zhao (1988), Le Bris, Lelièvre, Luskin, Perez (2012)).

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There exists a **unique** QSD $\overline{\mu}$ on $\mathcal{O}$. Besides, $\overline{\mu}$ satisfies

1. (Lebesgue density) $\overline{\mu}(\mathrm{d}q) = \overline{\psi}(q)\mathrm{d}q$,
2. (Spectral interpretation) $\overline{\psi}$ is the unique non-negative, normalized, classical solution in $\mathcal{C}^2(\mathcal{O}) \cap \mathcal{C}^b(\overline{\mathcal{O}})$ of the following eigenvalue problem

$$\begin{cases} \overline{\mathcal{L}}^*\overline{\psi} = -\overline{\lambda}\,\overline{\psi}, & \text{on } \mathcal{O}, \\ \overline{\psi} = 0, & \text{on } \partial\mathcal{O}, \end{cases}$$

where $\overline{\mathcal{L}}^* = \mathrm{div}(\nabla V \cdot) + \beta^{-1}\Delta$,

3. (Convergence) $\exists C > 0$, $\exists \alpha > 0$ s.t. $\forall t \geq 0$, $\forall \theta$ probability on $\mathcal{O}$,

$$\left\| \mathbb{P}_\theta(\overline{q}_t \in \cdot | \overline{\tau}_\partial > t) - \overline{\mu}(\cdot) \right\|_{TV} \leq C\mathrm{e}^{-\alpha t},$$

where $\overline{\tau}_\partial = \inf\{t > 0 : \overline{q}_t \notin \mathcal{O}\}$.

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Question: Extension to the Langevin process on $D := \mathcal{O} \times \mathbb{R}^d$?

Langevin process

Let $F \in \mathcal{C}^\infty(\mathbb{R}^d, \mathbb{R}^d)$, $\gamma \in \mathbb{R}$, $\sigma > 0$. Consider the **Langevin** process $(X_t = (q_t, p_t))_{t\geq 0}$ on $\mathbb{R}^{2d}$

$$\begin{cases} \mathrm{d}q_t = p_t \mathrm{d}t, \\ \mathrm{d}p_t = F(q_t)\mathrm{d}t - \gamma p_t \mathrm{d}t + \sigma \, \mathrm{d}B_t. \end{cases}$$

The **infinitesimal generator** $\mathcal{L}$ of $(q_t, p_t)_{t\geq 0}$ on $\mathbb{R}^{2d}$ (kinetic Fokker-Planck operator) is given by

$$\mathcal{L} = p \cdot \nabla_q + F(q) \cdot \nabla_p - \gamma p \cdot \nabla_p + \frac{\sigma^2}{2} \Delta_p.$$

Differences between the study of $(\overline{q}_t)_{t\geq 0}$ in $\mathcal{O}$ and $(q_t, p_t)_{t\geq 0}$ in $D = \mathcal{O} \times \mathbb{R}^d$:

- $\mathcal{L}$ is only **hypoelliptic** on $\mathbb{R}^{2d}$ but not elliptic,
- $\mathcal{O}$ is **bounded** but $D = \mathcal{O} \times \mathbb{R}^d$ is not.

Boundary of D

Partition of ∂D:

- $\Gamma^+ := \{(q,p) \in \partial\mathcal{O} \times \mathbb{R}^d : \langle p, n(q) \rangle > 0\}$ (*exiting velocities*),
- $\Gamma^- := \{(q,p) \in \partial\mathcal{O} \times \mathbb{R}^d : \langle p, n(q) \rangle < 0\}$ (*entering velocities*),
- $\Gamma^0 := \{(q,p) \in \partial\mathcal{O} \times \mathbb{R}^d : \langle p, n(q) \rangle = 0\}$ (*tangential velocities*),

where $n(q)$ is the unitary outward normal vector to $\mathcal{O}$ at $q \in \partial\mathcal{O}$.

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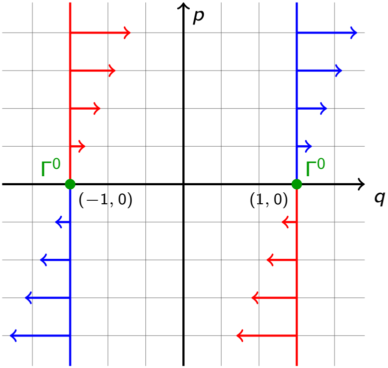

Figure: Boundary of $D = (-1,1) \times \mathbb{R}$

1. Transition density

Theorem (Transition density)

There exists a smooth function

$$(t, x, y) \mapsto \mathrm{p}_t^D(x, y) \in \mathcal{C}^\infty(\mathbb{R}_+^* \times D \times D) \times \mathcal{C}(\mathbb{R}_+^* \times \overline{D} \times \overline{D})$$

such that for all $t > 0$, $x \in \overline{D}$ and $f \in \mathrm{L}^\infty(D)$,

$$P_t^D f(x) := \mathbb{E}_x \left[1_{\tau_\partial > t} f(X_t) \right] = \int_D \mathrm{p}_t^D(x, y) f(y) \mathrm{d}y,$$

where $\tau_\partial = \inf\{t > 0 : X_t \notin D\}$.

Besides,

- $\forall t > 0, x \in D$, $\partial_t \mathrm{p}_t^D(x, y) = \mathcal{L}_x \mathrm{p}_t^D(x, y) = \mathcal{L}_y^* \mathrm{p}_t^D(x, y)$,
- $\mathrm{p}_t^D(x, y) = 0$ if $x \in \Gamma^+ \cup \Gamma^0$ or $y \in \Gamma^- \cup \Gamma^0$,
- $\mathrm{p}_t^D(x, y) > 0$ if $x \notin \Gamma^+ \cup \Gamma^0$ and $y \notin \Gamma^- \cup \Gamma^0$.

1. Transition density

For any $\alpha \in (0,1]$, let $(\widehat{X}_t^{(\alpha)} = (\widehat{q}_t^{(\alpha)}, \widehat{p}_t^{(\alpha)}))_{t\geq 0}$ be the solution on $\mathbb{R}^{2d}$ of

$$\begin{cases} \mathrm{d}\widehat{q}_t^{(\alpha)} = \widehat{p}_t^{(\alpha)}\mathrm{d}t, \\ \mathrm{d}\widehat{p}_t^{(\alpha)} = -\gamma\widehat{p}_t^{(\alpha)}\mathrm{d}t + \frac{\sigma}{\sqrt{\alpha}}\mathrm{d}B_t. \end{cases}$$

Let $\widehat{\mathrm{p}}_t^{(\alpha)}(x,y)$ be its transition density.

Theorem (Gaussian upper-bound)

For any $\alpha \in (0,1)$, $T > 0$, there exists $C > 0$ such that for all $t \in (0,T]$, for all $x, y \in D$,

$$\mathrm{p}_t^D(x,y) \leq C\widehat{\mathrm{p}}_t^{(\alpha)}(x,y).$$

This result is inspired from work on the parametrix method by Konakov, Menozzi, Molchanov (2010). One can show that $\widehat{\mathrm{p}}_t^{(\alpha)} \in \mathrm{L}^\infty(D\times D)\cap\mathrm{L}^1(D\times D)$ (thus in any $\mathrm{L}^p(D\times D)$ for $p\geq 1$).

2. Compactness

Compactness of the semigroup

For any $p \in [1, +\infty]$ and $t > 0$, the operator P_t^D is compact from $\mathcal{C}^b(\overline{D})$ to $\mathcal{C}^b(\overline{D})$.

Proof:

- $\widehat{\mathrm{p}}_t^{(\alpha)} \in \mathrm{L}^2(D \times D) \Rightarrow P_t^D$ is a Hilbert-Schmidt integral operator, hence compact in $\mathrm{L}^2(D)$.
- Propagate to $\mathcal{C}^b(\overline{D})$ using the Gaussian upper-bound.

Reference: Lelievre, R., Reygner - *Journal of Evolution Equations* (2022).

Krein-Rutman theorem

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Theorem (QSD existence/uniqueness and convergence properties)

There exists a unique QSD μ on $D = \mathcal{O} \times \mathbb{R}^d$ for the Langevin process $(X_t)_{t\geq 0}$. Besides, μ satisfies:

1. $\mu(\mathrm{d}x) = \psi(x)\mathrm{d}x$ on D,
2. ψ is the unique, normalized, non-negative classical solution in $\mathcal{C}^2(D) \cap \mathcal{C}^b(D \cup \Gamma^-)$ of the following eigenvalue problem
$$\begin{cases} \mathcal{L}^*\psi(x) = -\lambda\psi(x), & x \in D \\ \psi(x) = 0, & x \in \Gamma^- \end{cases}$$
3. There exists $\alpha > 0$ such that for all θ probability on D, there exists $C_\theta > 0$ and for all $t \geq 0$,
$$\left\|\mathbb{P}_\theta(X_t \in \cdot | \tau_\partial > t) - \mu(\cdot)\right\|_{TV} \leq C_\theta \mathrm{e}^{-\alpha t}.$$

Langevin exit point

Overdamped Langevin exit point

If $\overline{q}_0 \sim \overline{\mu}(\mathrm{d}q) = \overline{\psi}(q)\mathrm{d}q$ (QSD), then

$$\overline{q}_{\overline{\tau}_\partial} \sim \frac{\beta^{-1}}{\overline{\lambda}} |\partial_n \overline{\psi}(q)| \sigma_{\partial\mathcal{O}}(\mathrm{d}q),$$

where $\sigma_{\partial\mathcal{O}}$ is the surface measure on $\partial\mathcal{O}$.

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Proof: Integration by parts on

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If $(q_0, p_0) \sim \mu(\mathrm{d}q, \mathrm{d}p) = \psi(q,p)\mathrm{d}q\mathrm{d}p$ (QSD), then

$$(q_{\tau_\partial}, p_{\tau_\partial}) \sim \frac{1}{\lambda} |p \cdot n(q)| \, \psi(q,p) \sigma_{\partial\mathcal{O}}(\mathrm{d}q)\mathrm{d}p,$$

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Reference: Lelievre, R., Reygner - *Stochastic Process and its Applications* (2022)

Overdamped limit

Consider here $\gamma > 0$ and $\sigma = \sqrt{2\gamma\beta^{-1}}$. Let $\left(X_t^{(\gamma)} = (q_t^{(\gamma)}, p_t^{(\gamma)})\right)_{t\geq 0}$ be the Langevin process

$$\begin{cases} \mathrm{d}q_t^{(\gamma)} = p_t^{(\gamma)}\mathrm{d}t, \\ \mathrm{d}p_t^{(\gamma)} = F(q_t^{(\gamma)})\mathrm{d}t - \gamma p_t^{(\gamma)}\mathrm{d}t + \sqrt{2\gamma\beta^{-1}}\,\mathrm{d}B_t. \end{cases}$$

Let $(\overline{q}_t)_{t\geq 0}$ be the overdamped Langevin process

$$\mathrm{d}\overline{q}_t = F(\overline{q}_t)\mathrm{d}t + \sqrt{2\beta^{-1}}\mathrm{d}B_t.$$

Assume that F is globally Lipschitz, then for $T > 0$,

$$Law((q_{\gamma t}^{(\gamma)})_{t\in[0,T]}) \underset{\gamma\to\infty}{\longrightarrow} Law((\overline{q}_t)_{t\in[0,T]}).$$

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Question: Overdamped limit of the Langevin QSD ?

Overdamped limit

Overdamped limit of the Langevin QSD

Let $\mu^{(\gamma)}$ be the Langevin QSD on D and $\overline{\mu}$ be the overdamped Langevin QSD on $\mathcal{O}$, then

$$\mu^{(\gamma)}(\mathrm{d}\boldsymbol{q}\mathrm{d}\boldsymbol{p}) \underset{\gamma\to\infty}{\longrightarrow} \overline{\mu}(\mathrm{d}\boldsymbol{q})\frac{\mathrm{e}^{-\beta\frac{|\boldsymbol{p}|^2}{2}}}{(2\pi\beta^{-1})^{d/2}}\mathrm{d}\boldsymbol{p}.$$

Besides,

$$\lambda^{(\gamma)} \underset{\gamma\to\infty}{\sim} \frac{\overline{\lambda}}{\gamma}.$$

Reference: R. - *Electronic Journal of Probability* (2022).

Overdamped limit

Overdamped limit of the Langevin QSD

Let $\mu^{(\gamma)}$ be the Langevin QSD on D and $\overline{\mu}$ be the overdamped Langevin QSD on $\mathcal{O}$, then

$$\mu^{(\gamma)}(\mathrm{d}\boldsymbol{q}\mathrm{d}\boldsymbol{p}) \underset{\gamma\to\infty}{\longrightarrow} \overline{\mu}(\mathrm{d}\boldsymbol{q}) \frac{\mathrm{e}^{-\beta\frac{|p|^2}{2}}}{(2\pi\beta^{-1})^{d/2}}\mathrm{d}\boldsymbol{p}.$$

Besides,

$$\lambda^{(\gamma)} \underset{\gamma\to\infty}{\sim} \frac{\overline{\lambda}}{\gamma}.$$

Reference: R. - *Electronic Journal of Probability* (2022).

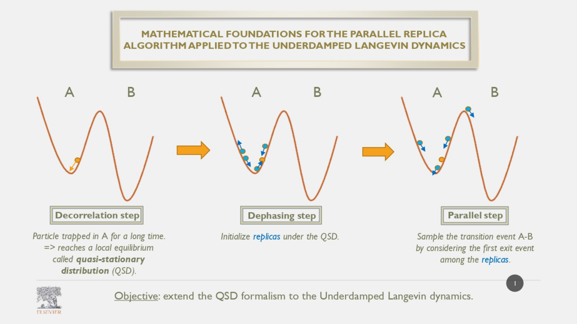
Stationary overdamped limit

Let $\mu_\infty^{(\gamma)}$ be the Langevin stationary distribution and $\overline{\mu_\infty}$ be the overdamped Langevin stationary distribution, then there exists $C > 0$ such that for all $\gamma \geq 2$,

$$\mathcal{W}\left(\mu_\infty^{(\gamma)}, \overline{\mu}_\infty \otimes \mathcal{L}(Z)\right) \leq C\frac{\sqrt{\log(\gamma)}}{\gamma}.$$

Reference: Monmarché, R. - *Electronic Communications in Probability* (2022)

Research letter



R. , Lelièvre and Reygner - Mathematical foundations for the Parallel Replica algorithm applied to the underdamped Langevin dynamics - *MRS Communications*, 2022.

Metadynamics for the Mueller potential

Consider the two-dimensional overdamped Langevin dynamics

$$\mathrm{d}X_t = -\nabla V(X_t)\mathrm{d}t + \sqrt{2k_B T}\mathrm{d}B_t,$$

where V is the Mueller potential defined by:

$$V(x_1, x_2) = \sum_{i=1}^{4} K_i \mathrm{e}^{a_i(x_1-\beta_i)^2 + b_i(x_1-\beta_i)(x_2-\gamma_i) + c_i(x_2-\gamma_i)^2}.$$

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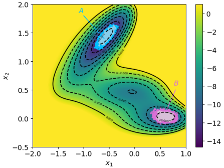


Figure: Sampling in the Mueller potential. 100 000 iterations

We want to sample a transition path between A and B using Metadynamics.

Metadynamics

Definition: A collective variable $s : \mathbb{R}^2 \mapsto \mathbb{R}$ captures the low-dimensional information of the system. A good collective variable takes different values in relevant *metastable states* and *transition states*.

Equilibrium distribution:

$$X_\infty \sim \mu(x) = \frac{\mathrm{e}^{-V(x)/k_B T}}{\alpha}.$$

Latent equilibrium distribution:

$$s(X_\infty) \sim p(s) = \int_{\mathbb{R}^2} \mu(x) \delta_{s(x)=s}(\mathrm{d}x).$$

Free energy:

$$F(s) = -k_B T \log(p(s)).$$

Metadynamics

Assuming one has an estimate $B \approx -F$.If we perturb the potential into $\tilde{V}(x) = V(x) + B(s(x))$.

$$
\begin{aligned}
s(\tilde{X}_\infty) \sim \tilde{p}(s) &\propto \int_{\mathbb{R}^2} \delta_{s(x)=s}(\mathrm{d}x)\mathrm{e}^{-(V(x)+B(s(x)))/k_B T} \\
&= \mathrm{e}^{-B(s)/k_B T} \int_{\mathbb{R}^2} \delta_{s(x)=s}(\mathrm{d}x)\mathrm{e}^{-V(x)/k_B T} \\
&= \mathrm{e}^{-B(s)/k_B T}\mathrm{e}^{-F(s)/k_B T} \approx 1.
\end{aligned}
$$

As a result,

$$
s(\tilde{X}_\infty) \sim \text{ Uniform}
$$

Problem: We need a free energy estimate first ...

Metadynamics

Build an approximation of F iteratively:

$$B_{t+1}(s) = B_t(s) + w\mathrm{e}^{-\frac{(s_t - s)^2}{2\sigma^2}}.$$

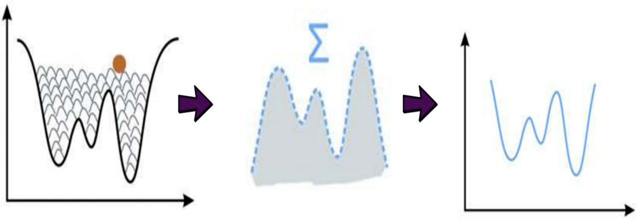
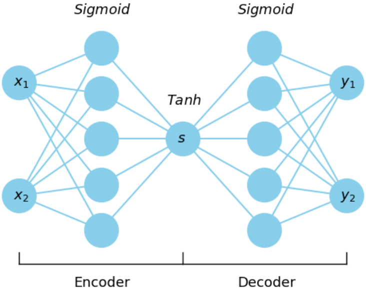


Figure: Metadynamics

Generates uniform samples on the path $A \leftrightarrow B$.

Autoencoder

Train the sampled data on an **autoencoder** to obtain the collective variable.



$$Loss = \|x - y\|^2.$$

Metadynamics trajectories

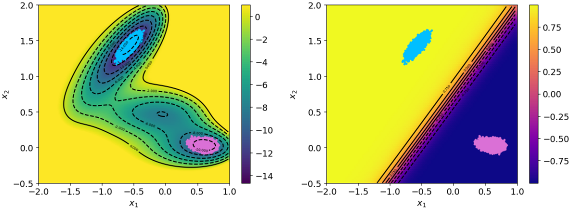
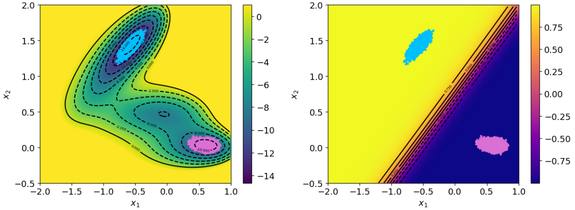


Figure: 50 000 Metadynamics iterations with autoencoder trained on the database of A and B

Metadynamics trajectories



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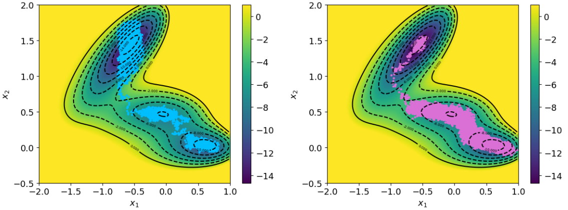

Figure: 25 000 Metadynamics iterations with CV as the orthogonal projection on $[AB]$

Adaptative Metadynamics

Train the autoencoder adaptatively on the previous trajectory after every 1000 Metadynamics iterations.

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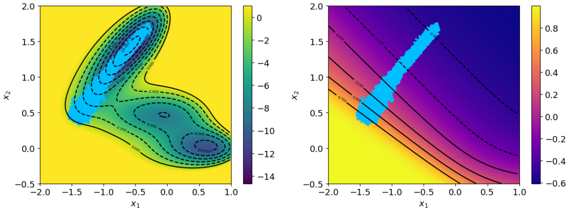

Figure: 40 000 Metadynamics iterations with autoencoder trained iteratively on the trajectory

Adaptative Metadynamics

Impose conditions on the path such that it visits A and B.

Adaptative Metadynamics

Impose conditions on the path such that it visits A and B.

$$Loss = \|x - AE(x)\|^2 + (\|AE(x_A) - x_A\|^2 + \|AE(x_B) - x_B\|^2)/2.$$

The path is defined by:

- (Latent projection) $s_A = s(x_A)$, $s_B = s(x_B)$
- (Discretization) $s_i = s_A + i(s_B - s_A)/N$, $(1 \leq i \leq N)$.
- Path is given by $(D(s_i))_{1 \leq i \leq N}$,

where D is the decoder of the autoencoder.

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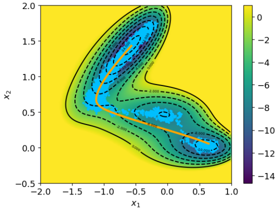

Figure: 38 000 Metadynamics iterations with autoencoder trained iteratively on the trajectory. Path is plotted in orange.

Adaptative Metadynamics

Consider a modified Mueller potential $\tilde{V}$ defined by:

$$\tilde{V}(x) = V(x) + (-100 + \|x - \eta\|^2)\mathrm{e}^{-2\|x-\eta\|^2},$$

with $\eta = [-1.7, 0.2]$.

Adaptative Metadynamics

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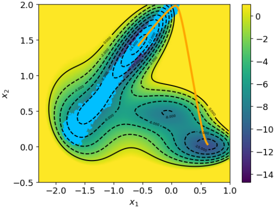

Figure: 100 000 Metadynamics iterations with autoencoder trained iteratively on the trajectory. Path in orange.

Adaptative Metadynamics

Penalize high energy configurations happening in the path.

$$Loss = \|x - y\|^2 + (\|AE(x_A) - x_A\|^2 + \|AE(x_B) - x_B\|^2)/2 + E_{path},$$

where

$$E_{path} = \sum_{i=1}^{N} \|D(s_{i+1}) - D(s_i)\|(V(D(s_i)) + C),$$

with $C > 0$ such that $V(D(s_i)) + C > 0$.

Adaptative Metadynamics

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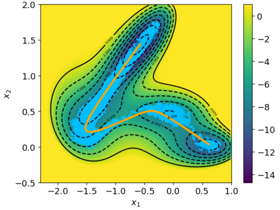

Figure: 100 000 Metadynamics iterations with autoencoder trained iteratively on the trajectory. Path in orange.

Reference: R., Boudier, Goryaeva, Marinica and Maillet - *Journal of Chemical Theory and Computation*, (2022).

Thank you for your attention!