Adaptive multilevel splitting to machine learn committor function

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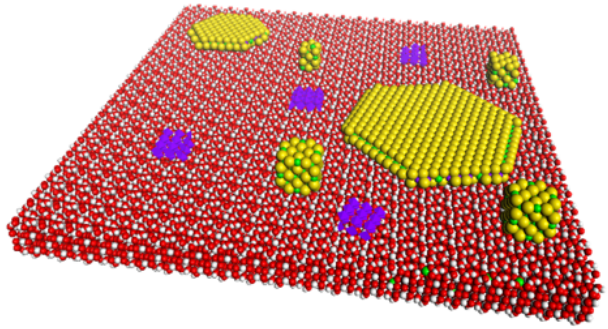
Motivations

To design efficient catalysts or understand the activity of proteins in biology, the knowledge of the various possible transformation and their rate is desired.



Numerical simulation can lead to these results which are not accessible from an experimental approach.

Modelled system

Classical system of N atoms is described by:

- Positions: $\mathbf{q} \in \Omega$ where $\Omega = \mathbb{R}^{3N}$ or $\left(\mathbb{T}^3\right)^N$
- Momenta: $\mathbf{p} \in \mathbb{R}^{3N}$
- Hamiltonian: $H(\mathbf{q}, \mathbf{p}) = \frac{1}{2}\mathbf{p}^T M^{-1}\mathbf{p} + V(\mathbf{q})$

V include the atom-atom interaction and the electron cloud - atom interaction. For chemical reaction, computationally expensive method must be used to evaluate V.
Positions and momenta are distributed according to Boltzmann–Gibbs measure:

$$\mu(d\mathbf{q}, d\mathbf{p}) = \frac{1}{Q}\mathrm{e}^{-\beta H(\mathbf{q},\mathbf{p})} d\mathbf{q} d\mathbf{p}, \tag{1}$$

Modelled system

Evolution in time of the system modelled by Langevin dynamics (friction $\gamma > 0$)

$$\begin{cases} d\mathbf{q}_t = M^{-1}\mathbf{p}_t dt \\ d\mathbf{p}_t = -\nabla V(\mathbf{q}_t)dt - \gamma \mathbf{p}_t dt + \sqrt{\frac{2\gamma}{\beta}} M^{\frac{1}{2}} d\mathbf{W}_t. \end{cases} \tag{2}$$

The description of the transformations in the system are reduced to answering:

- What are the main modes (metastable states $A_i \subset \Omega$) of Boltzmann–Gibbs measure (1) ?
- How much time does it take for (2) to go from one to another ?
- What is (are) the path(s) taken during these transitions ?

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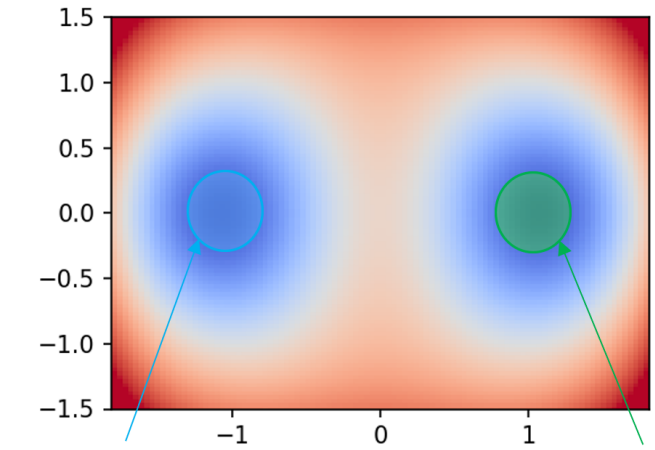
Hill relation

Assuming two metastable states A and B are identified:



The reaction rate is:

$$k_{A\to B} = \Phi_A \mathbb{P}^{\partial A}(\tau_A < \tau_B) \qquad (3)$$

with:

$$\tau_X = \inf\left\{ t \in (0; +\infty) \;\middle|\; \mathbf{q}_t \in X \right\}$$

- Φ_A is the frequency of exits of A (easy to compute)
- $\mathbb{P}^{\partial A}(\tau_A < \tau_B)$ is the probability of reaching B before A starting on ∂A (difficult to compute)

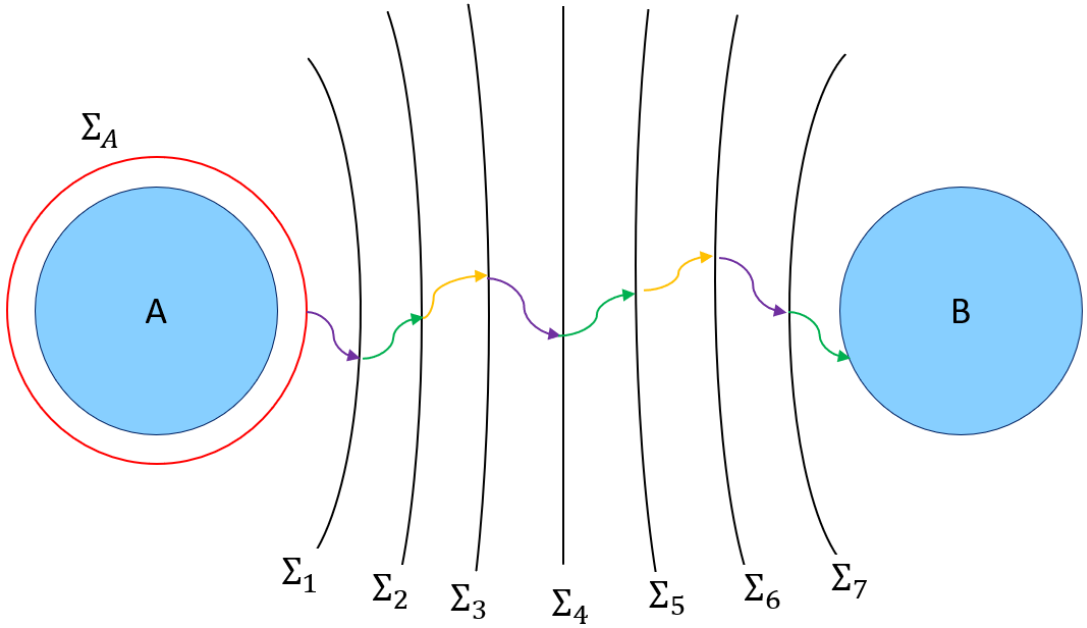
The Hill relation[1] is exact for the overdamped Langevin and Langevin dynamics[2,3]

[1] Hill, Free Energy Transduction in Biology, Elsevier Science and Technology Books, 2012
[2] Baudel, Guyader, Lelièvre, arXiv:2008.09790 2020
[3] Lelièvre, Ramil, Reygner, arXiv:2206.13264 2022

Splitting estimator

A surface Σ_A is placed to capture "actual exits" of A such that;

$$\mathbb{P}^{\partial A}(\tau_A < \tau_B) \approx \mathbb{P}^{\Sigma_A}(\tau_A < \tau_B).$$



$$\mathbb{P}^{\Sigma_A}(\tau_A < \tau_B) = \mathbb{P}^{\Sigma_A}(\tau_A < \tau_{\Sigma_1}) \left(\prod_{i=1}^{6} \mathbb{P}^{\Sigma_i}(\tau_A < \tau_{\Sigma_{i+1}}) \right) \mathbb{P}^{\Sigma_7}(\tau_A < \tau_{\partial B})$$

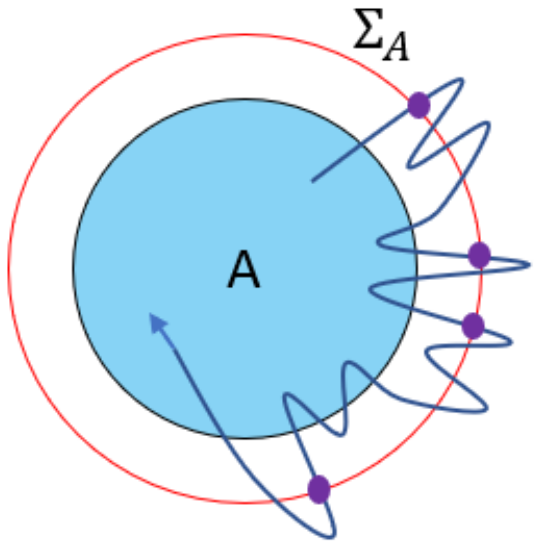
How to place Σ_i ?

How to compute $\mathbb{P}^{\Sigma_i}(\tau_A < \tau_{\Sigma_{i+1}})$?

Adaptive multilevel splitting (AMS)

AMS is a multiple replicas approach designed to place Σ_i automatically so that $\mathbb{P}^{\Sigma_i}(\tau_A < \tau_{\Sigma_{i+1}})$ is constant (minimize estimator variance).

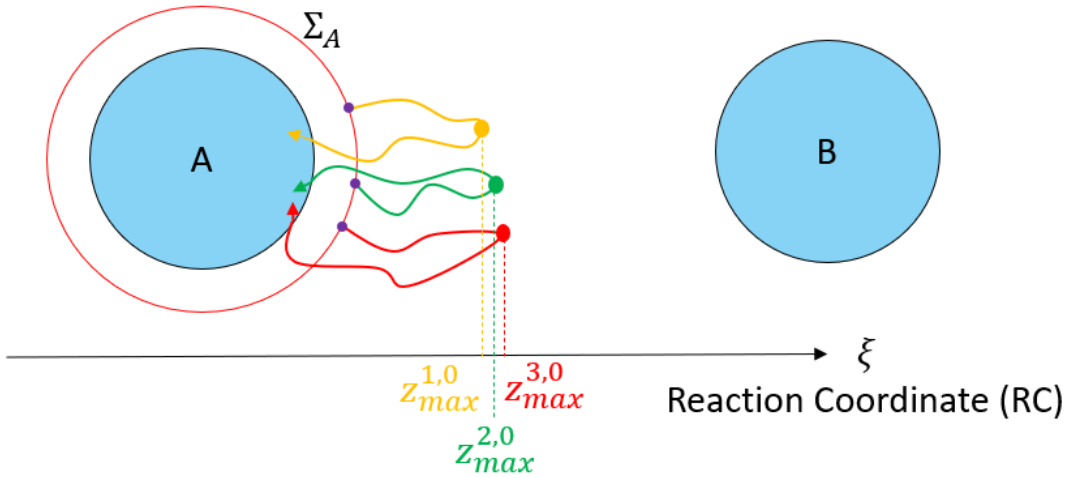
1. Initial conditions for replicas are sampled on Σ_A by running MD (discretized Langevin equation).[4]



[4] Cérou, Guyader, Stoch. Anal. Appl. 2007, 25, 417443

Adaptive multilevel splitting (AMS)

2. Run N_{rep} replicas until A or B is reached.

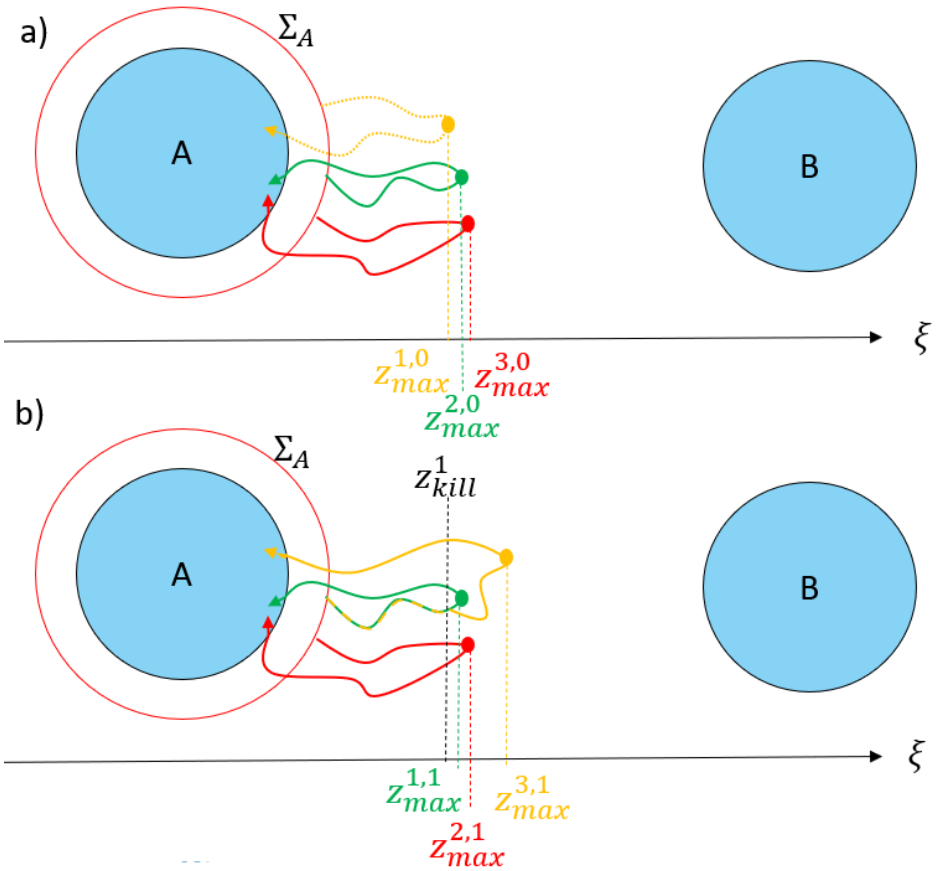


Classify the replicas using a 1D reaction coordinate (RC) $\xi : \Omega \to \mathbb{R}$.

Defining $\Sigma_1 = \left\{\mathbf{q} \in \Omega | \xi(\mathbf{q}) = z_{\max}^{1,0}\right\}$, we have:

$$\widehat{p}_{A\to\Sigma_1}(\Sigma_A) = \frac{N_{\mathrm{rep}}-1}{N_{\mathrm{rep}}}$$

Adaptive multilevel splitting (AMS)



3. Save the level $z_{\max}^{1,0} = z_{\text{kill}}^{1}$. Delete the 1^{st} replica, and replace it by branching randomly any of the remaining one.

Repeat step 3. until all replicas finish in B.

Adaptive multilevel splitting (AMS)

This algorithm is unbiased[5] but the variance depends on ξ.

The optimal ξ is the committor function $p_{A\to B}$ defined in any points $\mathbf{q} \in \Omega$ as the probability of reaching B before A when running the dynamics (2) starting from $\mathbf{q}$.

How this function can be learned ?

Is it possible to learn it "on the fly" ?

[5] Brehier, Gazeau, Goudenège, Lelièvre, Rousset, J. Appl. Probab. 2016, 26, 3559 3601.

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Committor function

We consider the overdamped Langevin dynamics ($\gamma \to +\infty$)

$$d\mathbf{q}_t = -\nabla V(\mathbf{q}_t)dt + \sqrt{\frac{2}{\beta}}d\mathbf{W}t$$

with infinitesimal generator:

$$\mathcal{L} = -\nabla V \cdot \nabla + \frac{1}{\beta}\Delta$$

$$p_{A\to B}(\mathbf{q}) = \mathbb{P}\left(\mathbf{q}_{\tau_{A\cup B}} \in B \middle| \mathbf{q}_0 = \mathbf{q}\right)$$

Committor function verifies the Backward Kolmogorov equation:

$$\begin{aligned} &\forall \mathbf{q} \in \Omega\backslash(\overline{A} \cup \overline{B}), \quad \mathcal{L}p_{A\to B}(\mathbf{q}) = 0, \\ &\forall \mathbf{q} \in \overline{A},\ p_{A\to B}(\mathbf{q}) = 0, \quad \forall \mathbf{q} \in \overline{B},\ p_{R\to P}(\mathbf{q}) = 1, \end{aligned} \tag{4}$$

$$\text{with } \overline{A} = A \cup \partial A \text{ and } \overline{B} = A \cup \partial B$$

Methods to learn the committor with neural networks

1^{st} method, point-wise approximation

- Multiple MD runs starting from various positions $\mathbf{q}$
- Define bins using a set of collective variables and use "infinitely" long unbiased MD trajectory[6] or multiple weighted trajectories[7]

$\rightarrow$ Drawback: CVs parameterizing the committor should be known

2^{nd} method, variational formulation[8,9,10]

$$\underset{f}{\operatorname{arginf}} \left\{ \int_{\Omega \setminus (\overline{A} \cup \overline{B})} |\nabla f(\mathbf{q})|^2 \, \mathrm{e}^{-\beta V(\mathbf{q})} d\mathbf{q}, \middle| f(\mathbf{q}) = 0, \, \mathbf{q} \in \overline{A}, \quad f(\mathbf{q}) = 1, \, \mathbf{q} \in \overline{B}. \right\}$$

$\rightarrow$ Drawback: a sampling of the Boltzmann–Gibbs measure is required.

[6] Frassek, Arjun, Bolhuis, J. Chem. Phys. 2021, 155, 064103.
[7] Lopes, Lelièvre, J. Comput. Chem. 2019, 40, 11981208
[8] Khoo, Lu, Ying, arXiv:1802.10275 2018
[9] Li, Lin, Ren, J. Chem. Phys. 2019, 151, 054112.
[10] Rotskoff, Vanden-Eijnden, arXiv:2008.06334, 2020

Methods to learn the committor with neural networks

3^{rd} method: fixed point with multiple evaluations[11]

$$\underset{f}{\operatorname{arginf}} \left\{ \int_{\Omega\backslash(\overline{A}\cup\overline{B})} \left(\left(I - \mathcal{P}^i\right) f(\mathbf{q}) - \left(\mathcal{P}^b \mathbb{1}_{\overline{B}}\right)(\mathbf{q}) \right)^2 \mu(d\mathbf{q}) \right\}.$$

where μ can be any measure defined on $\Omega\backslash(\overline{A}\cup\overline{B})$ and $\mathcal{P}$ is the propagator:

$$\begin{aligned}
\left(\mathcal{P} p_{A\to B}\right)(\mathbf{q}_0) =& \mathbb{E}^{\mathbf{q}_0}\left[p_{A\to B}\left(\mathbf{q}_{t\wedge\tau_{\overline{A}\cup\overline{B}}}\right)\right] \\
=& \mathbb{E}^{\mathbf{q}_0}\left[p_{A\to B}\left(\mathbf{q}_t \mathbb{1}_{t<\tau_{\overline{A}\cup\overline{B}}}\right)\right] + \mathbb{E}^{\mathbf{q}_0}\left[\mathbb{1}_{\overline{B}}\left(\mathbf{q}_{\tau_{\overline{A}\cup\overline{B}}} \mathbb{1}_{t\geqslant\tau_{\overline{A}\cup\overline{B}}}\right)\right] \\
=& \left(\mathcal{P}^i p_{A\to B}\right)(\mathbf{q}_0) + \left(\mathcal{P}^b \mathbb{1}_{\overline{B}}\right)(\mathbf{q}_0)
\end{aligned}$$

The committor verifies:

$$\forall \mathbf{q} \in \Omega\backslash(R\cup P), \quad \left(I - \mathcal{P}^i\right) p_{R\to P}(\mathbf{q}) - \left(\mathcal{P}^b \mathbb{1}_{\overline{B}}\right)(\mathbf{q}) = 0.$$

$\rightarrow$ Drawback: Multiple runs have to be started from the same point.

[11] Strahan, Finkel, Dinner, Weare, J. Comput. Phys. 2023, 488, 112152.

Methods to learn the committor with neural networks

4^{th} method: fixed point with an ergodic trajectory[12,13]

$$\underset{f}{\operatorname{arginf}} \left\{ \frac{1}{2} \int_{\Omega \setminus (\overline{A} \cup \overline{B})} f(\mathbf{q}) \left(I - \mathcal{P}^i \right) f(\mathbf{q}) \mathrm{e}^{-\beta V(\mathbf{q})} d\mathbf{q} \right.$$
$$\left. - \int_{\Omega \setminus (\overline{A} \cup \overline{B})} f(\mathbf{q}) \mathcal{P}^b \mathbb{1}_{\overline{B}}(\mathbf{q}) \mathrm{e}^{-\beta V(\mathbf{q})} d\mathbf{q} \right\}$$

$\rightarrow$ Drawback: an ergodic trajectory sampling the Boltzmann–Gibbs measure is required.

[12] Li, Khoo, Ren, Ying, In Proceedings of the 2nd Mathematical and Scientific Machine Learning Conference, Vol. 145, 2022.

[13] He, Chipot, Roux, J. Phys. Chem. Lett. 2022, 13, 92639271.

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Alternative loss

Itō formula leads to:

$$dp_{A\to B}(\mathbf{q}_t) = \mathcal{L}p_{A\to B}(\mathbf{q}_t)dt + \sqrt{\frac{2}{\beta}}\nabla p_{A\to B}(\mathbf{q}_t)\cdot d\mathbf{W}_t.$$

Then, $\forall \mathbf{q}_0 \in \Omega\backslash(\overline{A}\cup\overline{B})$:

$$p_{A\to B}(\mathbf{q}_t)\mathbb{1}_{t<\tau_{\overline{A}\cup\overline{B}}} + \mathbb{1}_{\overline{B}}(\mathbf{q}_{\tau_{\overline{A}\cup\overline{B}}})\mathbb{1}_{t\geqslant\tau_{\overline{A}\cup\overline{B}}} - p_{A\to B}(\mathbf{q}_0) = \int_0^{t\wedge\tau_{\overline{A}\cup\overline{B}}} \sqrt{\frac{2}{\beta}}\nabla p_{A\to B}(\mathbf{q}_s)\cdot d\mathbf{W}_s$$

Alternative approach:

$$\underset{f}{\operatorname{arginf}} \int_{\Omega\backslash(\overline{A}\cup\overline{B})} \left(f(\mathbf{q}_t)\mathbb{1}_{t<\tau_{\overline{A}\cup\overline{B}}} + \mathbb{1}_{\overline{B}}(\mathbf{q}_{\tau_{\overline{A}\cup\overline{B}}})\mathbb{1}_{t\geqslant\tau_{\overline{A}\cup\overline{B}}} - f(\mathbf{q}_0) \right.$$
$$\left. - \int_0^{t\wedge\tau_{\overline{A}\cup\overline{B}}} \sqrt{\frac{2}{\beta}}\nabla f(\mathbf{q}_s)\cdot d\mathbf{W}_s \right)^2 \mu(d\mathbf{q}_0).$$

Discretized loss

Using the Euler-Maruyama integration scheme:

$$\mathbf{q}_{n+1} = \mathbf{q}_n - \nabla V(\mathbf{q}_n)\Delta t + \sqrt{\frac{2\Delta t}{\beta}}\mathbf{G}_{n+1},$$

we run K trajectories of length N. Then the discretized loss writes:

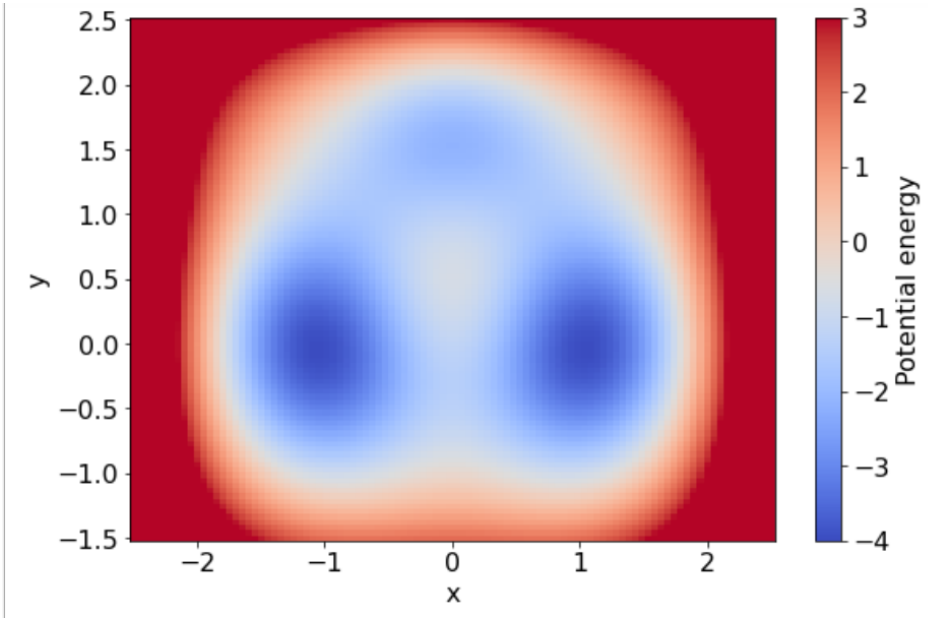
$$\mathcal{L}_\theta = \frac{1}{K}\sum_{k=1}^{K}\left(f_\theta(\mathbf{q}^k_{N\wedge\left\lfloor\frac{\tau_{\overline{A}\cup\overline{B}}}{\Delta t}\right\rfloor+1}) - f_\theta(\mathbf{q}^k_0) - \sum_{n=1}^{N\wedge\left\lfloor\frac{\tau_{\overline{A}\cup\overline{B}}}{\Delta t}\right\rfloor+1}\sqrt{\frac{2\Delta t}{\beta}}\nabla f_\theta(\mathbf{q}^k_n)\cdot\mathbf{G}^k_n\right)^2,$$

where f_θ is the neural network parameterizing the committor:

$$f_\theta(\mathbf{q}) = \left(1-\mathbb{1}_{\overline{A}}(\mathbf{q})\right)\left[\left(1-\mathbb{1}_{\overline{B}}(\mathbf{q})\right)p_\theta(\mathbf{q}) + \mathbb{1}_{\overline{B}}(\mathbf{q})\right].$$

Illustration of the method

On the entropic switch potential.[14]



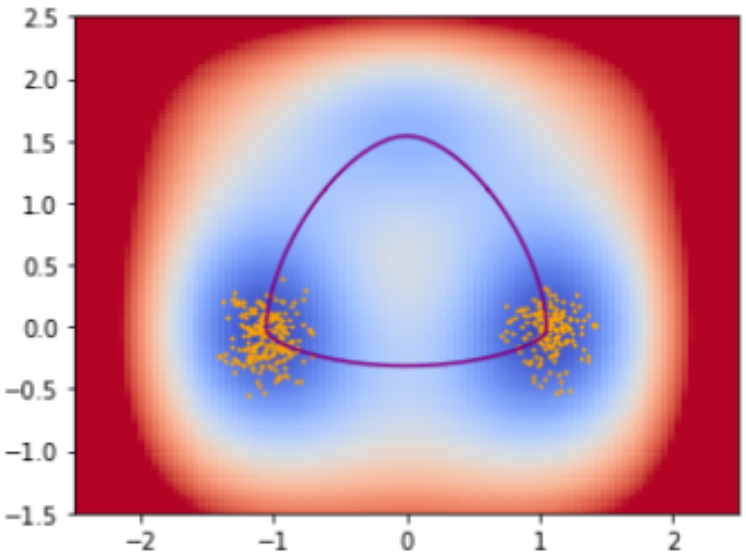
Using a feedforward model
3 hidden layers of 20 neurons with tanh activation function
Optimizer: Adam, learning rate .001

[14] Park, Sener, Lu, Schulten, J. Chem. Phys. 2003, 119, 1313-1319.

Illustration of the method

1. Define:
   A and B: Discs centered on minima.
Σ_A and Σ_B: Circles centered on minima

2. Run short MD starting from minima to gather initial conditions for AMS ($N\mathrm{rep} = 20$).



3. Minimize the loss $\mathcal{L}_\theta$ with trajectories of length $N = 1$

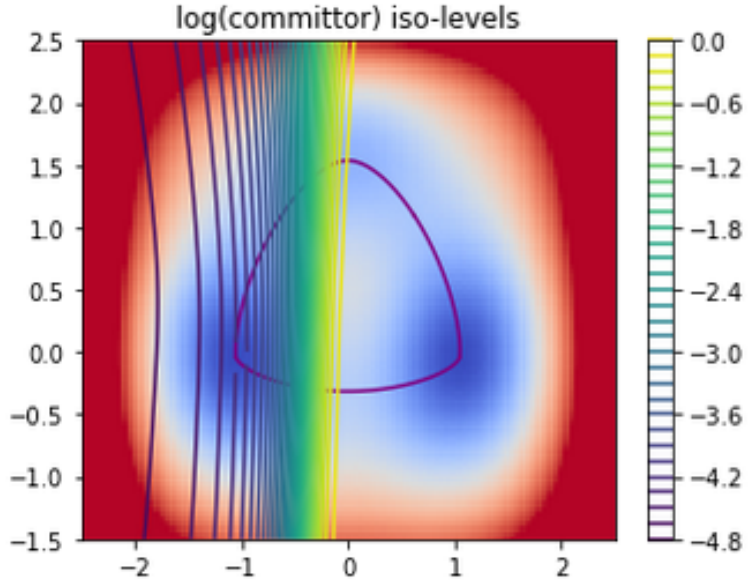
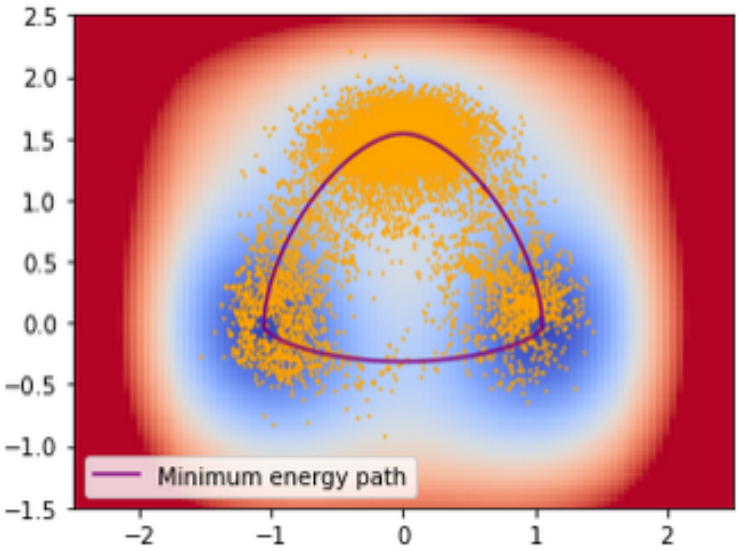


Illustration of the method

4. Run AMS forward ($A \to B$) and backward ($B \to A$) and gather all the sub-trajectories of length $N = 1$



5. Re-train the model.

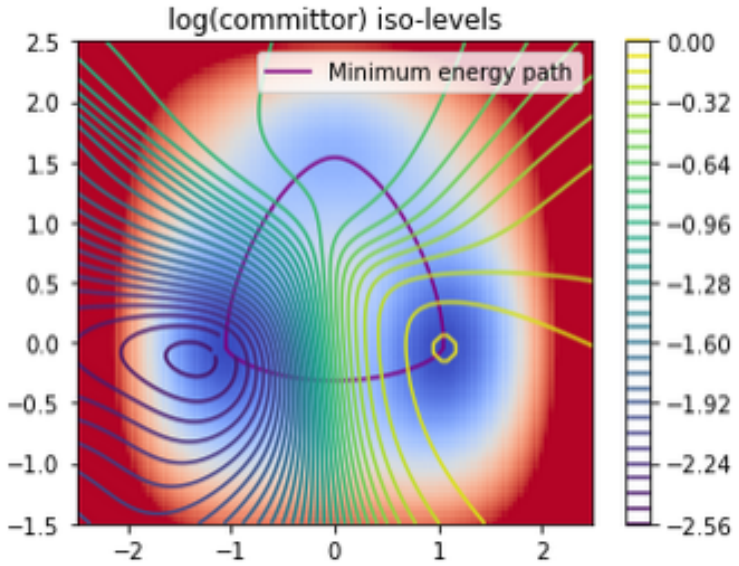
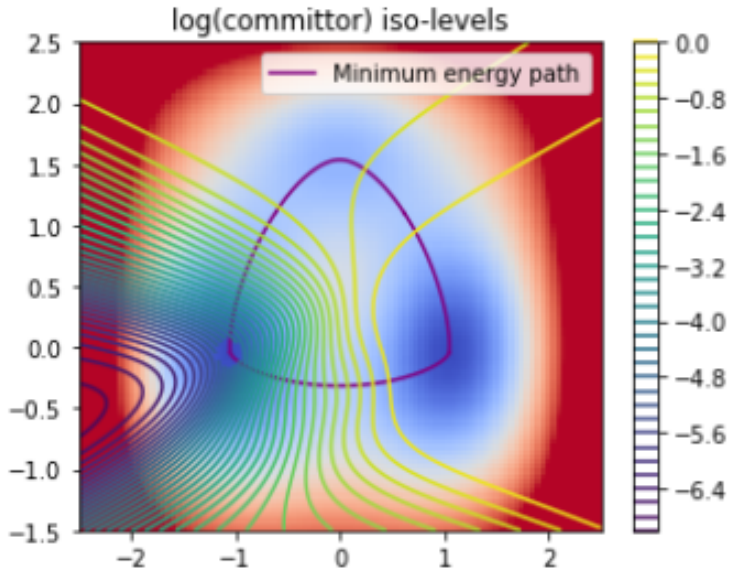


Illustration of the method

6. Gather new initial conditions.
7. Run AMS again ($N_{\mathrm{rep}} = 50$).
8. Add the new trajectories (possibly increase the length of trajectories)
9. Retrain the model.



Steps 6. to 9. are repeated (at a fixed N) until the training of the model is no longer influenced by the dataset.

Multiple training should be done (sensible to the initial weights and biases)

Convergence measured by linear regression between approximate committor values from one iteration to the other.

Comparison of reaction coordinates

10 AMS runs with 100 replicas at $\beta = 2$

Reaction coordinate	$\xi(x, y) = x$	NN committor	FE committor
Forward			
estimated standard deviation	$9.55\ 10^{-4}$	$7.43\ 10^{-4}$	$2.27\ 10^{-3}$
Mean estimated probability	$6.38\ 10^{-4}$	$3.96\ 10^{-3}$	$3.71\ 10^{-3}$
Backward			
estimated standard deviation	$1.18\ 10^{-3}$	$1.42\ 10^{-3}$	$7.39\ 10^{-4}$
Mean estimated probability	$1.46\ 10^{-3}$	$4.47\ 10^{-3}$	$3.80\ 10^{-3}$

Conclusion & perspectives

This method allows to define satisfying reaction coordinate for AMS (in the sense of AMS variance)

Compare this method to other methods to learn committor in the litterature.

Thank you!

Variational loss

$$\underset{f}{\operatorname{arginf}} \left\{ \int_{\Omega\setminus(\overline{A}\cup\overline{B})} |\nabla f(\mathbf{q})|^2 \, \mathrm{e}^{-\beta V(\mathbf{q})} d\mathbf{q}, \middle| f(\mathbf{q}) = 0, \, \mathbf{q} \in \overline{A}, \quad f(\mathbf{q}) = 1, \, \mathbf{q} \in \overline{B}. \right\}$$

$f_\lambda(\mathbf{q}) = p^*(\mathbf{q}) + \lambda\eta(\mathbf{q})$ where p^* is a critical point of the minimized functional.

$$\begin{aligned}
0 &= \frac{1}{2}\frac{\partial}{\partial\lambda} \int_{\Omega\setminus(\overline{A}\cup\overline{B})} |\nabla f_\lambda(\mathbf{q})|^2 \, \mathrm{e}^{-\beta V(\mathbf{q})} \, d\mathbf{q} \Big|_{\lambda=0} \\
&= \int_{\Omega\setminus(\overline{A}\cup\overline{B})} \nabla\eta(\mathbf{q}) \cdot \nabla p^*(\mathbf{q}) \mathrm{e}^{-\beta V(\mathbf{q})} \, d\mathbf{q} \\
&= \int_{\Omega\setminus(\overline{A}\cup\overline{B})} \nabla \cdot \left(\eta(\mathbf{q}) \nabla p^*(\mathbf{q}) \mathrm{e}^{-\beta V(\mathbf{q})} \right) \, d\mathbf{q} \\
&\quad - \int_{\Omega\setminus(R\cup P)} \eta(\mathbf{q}) \nabla \cdot \left(\nabla p^*(\mathbf{q}) \mathrm{e}^{-\beta V(\mathbf{q})} \right) \, d\mathbf{q}.
\end{aligned}$$

Variational loss

Since for all functions η such that $\forall \mathbf{q} \in (\partial R \cup \partial P), \eta(\mathbf{q}) = 0$

$$\int_{\Omega\setminus(\overline{A}\cup\overline{B})} \nabla \cdot \left(\eta(\mathbf{q})\nabla p^*(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}\right) d\mathbf{q} = \int_{\partial(\Omega\setminus(\overline{A}\cup\overline{B}))} \eta(\mathbf{q})\nabla p^*(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})} ds = 0,$$

We have

$$0 = -\int_{\Omega\setminus(\overline{A}\cup\overline{B})} \eta(\mathbf{q})\nabla \cdot \left(\nabla p^*(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}\right) d\mathbf{q}.$$

$$0 = -\int_{\Omega\setminus(\overline{A}\cup\overline{B})} \eta(\mathbf{q}) \left(\Delta p^*(\mathbf{q} - \beta\nabla p^*(\mathbf{q}) \cdot \nabla V(\mathbf{q})\right) \mathrm{e}^{-\beta V(\mathbf{q})} d\mathbf{q}$$

$$0 = -\int_{\Omega\setminus(\overline{A}\cup\overline{B})} \eta(\mathbf{q})\beta \left(\mathcal{L}_{\mathrm{ovd}} p^*\right)(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})} d\mathbf{q},$$

Fixed point justification

$\forall \mathbf{q}_0 \in \Omega \backslash (\overline{A} \cup \overline{B})$,

$$p_{A\to B}(\mathbf{q}_t)\mathbb{1}_{t<\tau_{\overline{A}\cup\overline{B}}}+\mathbb{1}_{\overline{B}}(\mathbf{q}_{\tau_{\overline{A}\cup\overline{B}}})\mathbb{1}_{t\geqslant\tau_{\overline{A}\cup\overline{B}}}-p_{A\to B}(\mathbf{q}_0) = \int_0^{t\wedge\tau_{\overline{A}\cup\overline{B}}} \sqrt{\frac{2}{\beta}}\nabla p_{A\to B}(\mathbf{q}_s)\cdot d\mathbf{W}_s$$

Taking the expectation with respect to the law of the process we get:

$$\forall \mathbf{q} \in \Omega \backslash (\overline{A} \cup \overline{B}), (\mathcal{P}^i - I)p_{A\to B}(\mathbf{q}) + \mathcal{P}^b \mathbb{1}_{\overline{B}}(\mathbf{q}) = 0.$$

Fixed point with ergodic trajectory

$$\operatorname*{arginf}_{f}\left\{\frac{1}{2}\int_{\Omega\setminus(\overline{A}\cup\overline{B})} f(\mathbf{q})\left(I-\mathcal{P}^{i}\right)f(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}-\int_{\Omega\setminus(\overline{A}\cup\overline{B})} f(\mathbf{q})\mathcal{P}^{b}\mathbb{1}_{\overline{B}}(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}\right\}$$

$$f_\lambda(\mathbf{q}) \;=\; p^*(\mathbf{q}) \;+\; \lambda\eta(\mathbf{q}),$$

$$\begin{aligned}
0 =& \frac{\partial}{\partial\lambda}\left(\frac{1}{2}\int_{\Omega\setminus(\overline{A}\cup\overline{B})} f_\lambda(\mathbf{q})\left(I-\mathcal{P}^{i}\right)f_\lambda(\mathbf{q},\lambda)\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}\right.\\
&\left.-\int_{\Omega\setminus(\overline{A}\cup\overline{B})} f_\lambda(\mathbf{q},\lambda)\mathcal{P}^{b}\mathbb{1}_{\overline{B}}(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}\right)\Bigg|_{\lambda=0}\\
=& \int_{\Omega\setminus(\overline{A}\cup\overline{B})} \eta(\mathbf{q})\left(I-\mathcal{P}^{i}\right)p^*(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}-\int_{\Omega\setminus(R\cup P)} \eta(\mathbf{q})\mathcal{P}^{b}\mathbb{1}_{\overline{B}}(\mathbf{q})\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}\\
=& \int_{\Omega\setminus(\overline{A}\cup\overline{B})} \eta(\mathbf{q})\left[\left(I-\mathcal{P}^{i}\right)p^*(\mathbf{q})-\mathcal{P}^{b}\mathbb{1}_{\overline{B}}(\mathbf{q})\right]\mathrm{e}^{-\beta V(\mathbf{q})}d\mathbf{q}.
\end{aligned}$$

The second equality holds as $\mathcal{P}^i$ is self adjoint on $L^2_\mu(\Omega\setminus(\overline{A}\cup\overline{B}))$[15]

[15] Li, Khoo, Ren, Ying, In Proceedings of the 2nd Mathematical and Scientific Machine Learning Conference, Vol. 145, 2022