FEAT:
Free energy Estimators with Adaptive Transport

Jiajun He & Yuanqi Du

Collaborators

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Carla P. Gomes

José Miguel Hernández-Lobato

Eric Vanden-Eijnden

Background

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👉 model evidence
👉 binding affinity
👉 potential of mean force
…

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$p_1(X)$

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$$= -\log \mathbf{E}_1 [\exp(-U_2 + U_1)]$$

R. W. Zwanzig. High-temperature equation of state by a perturbation method. i. nonpolar gases. *The Journal of Chemical Physics,* 22(8):1420–1426, 1954.

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- Bennett acceptance ratio (BAR):
  - 👉 An iterative, minimal-variance estimator

C. H. Bennett. Efficient estimation of free energy differences from monte carlo data. Journal of Computational Physics, 22(2):245–268, 1976. ISSN 0021-9991.

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$$\Delta f = -\log \frac{\mathbf{E}_1[g(-U_1 + U_2 - C)]}{\mathbf{E}_2[g(-U_2 + U_1 + C)]} + C$$

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$$\frac{g(x)}{g(-x)} = \exp(-x)$$

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1. Initialize C;
2. Calculate Δf; Set $C \leftarrow \Delta f$;
3. Repeat (2) until converge.

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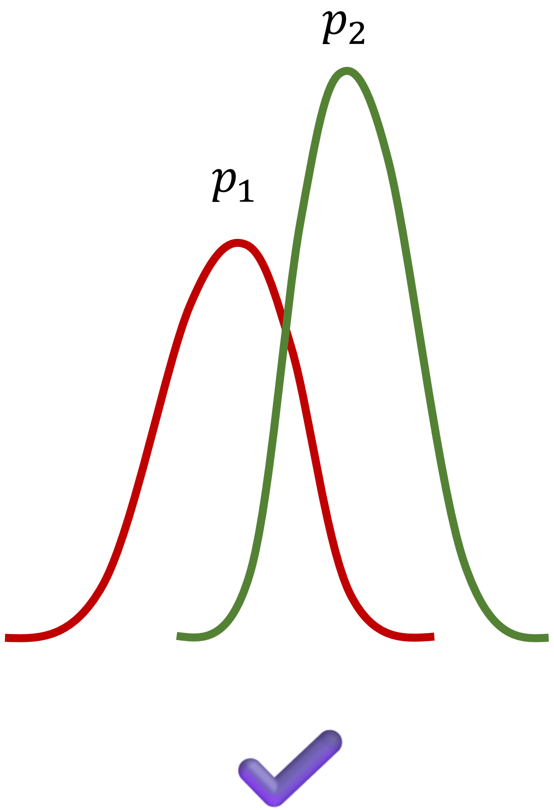

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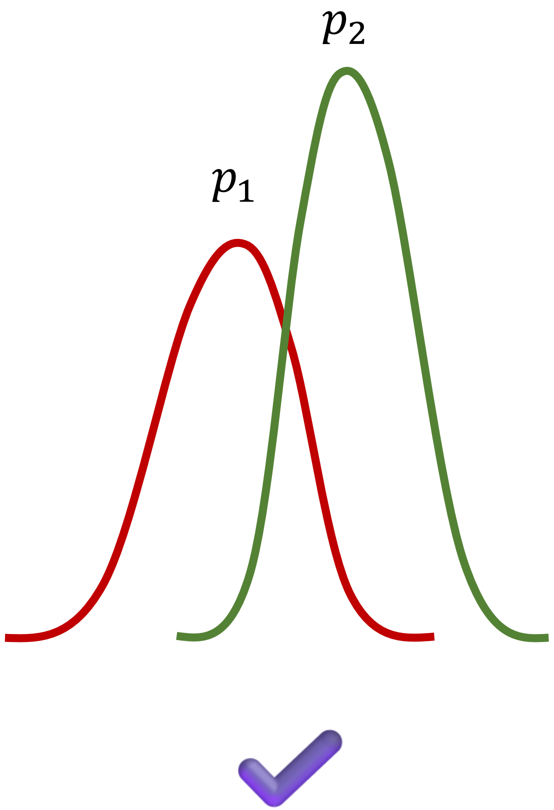

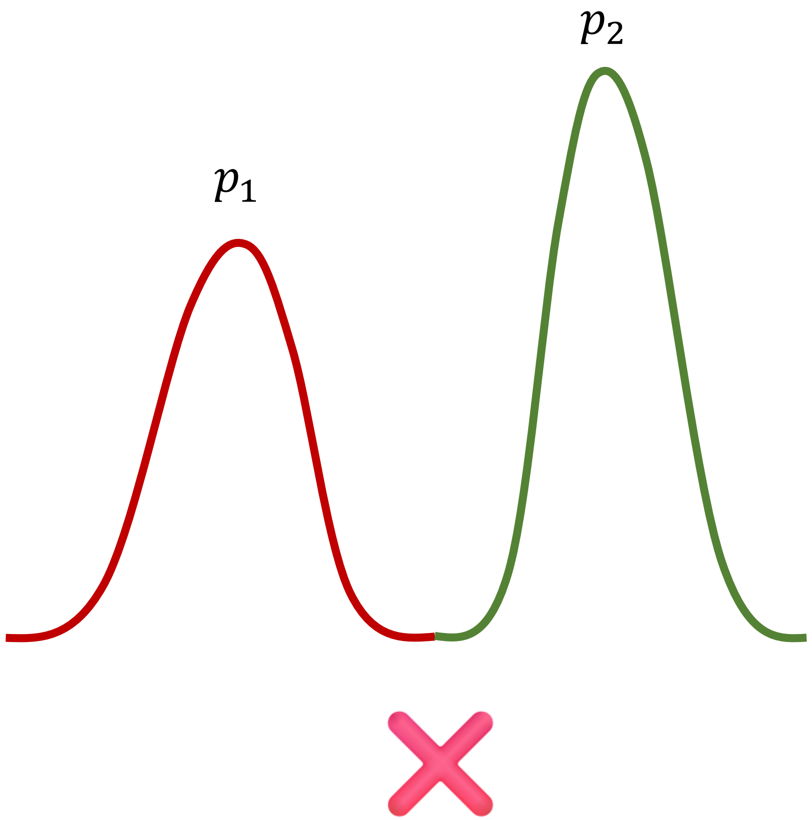

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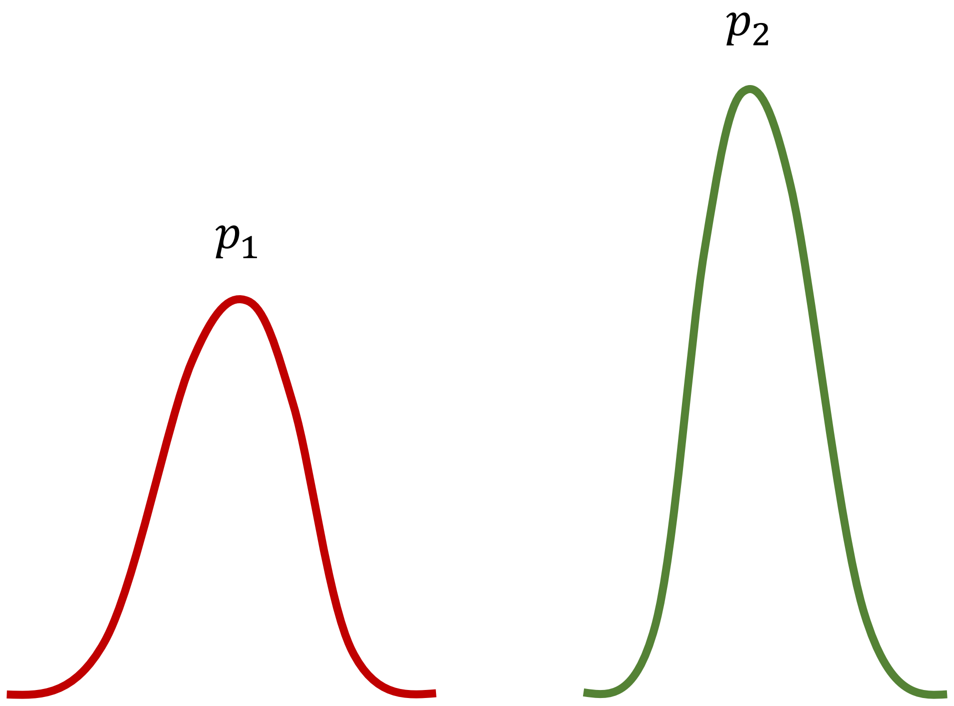

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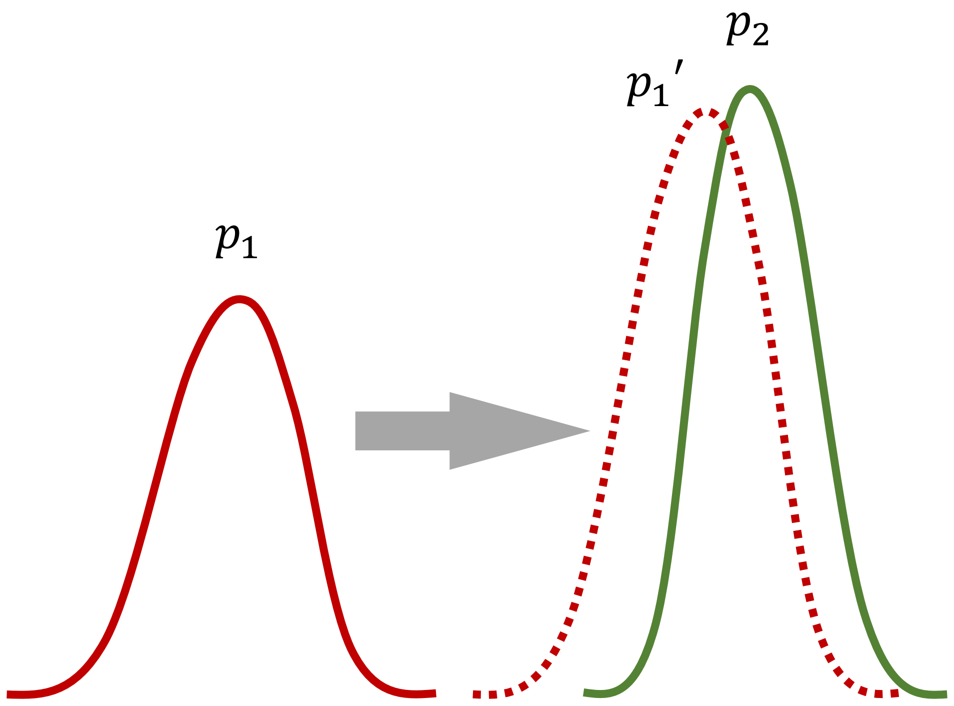

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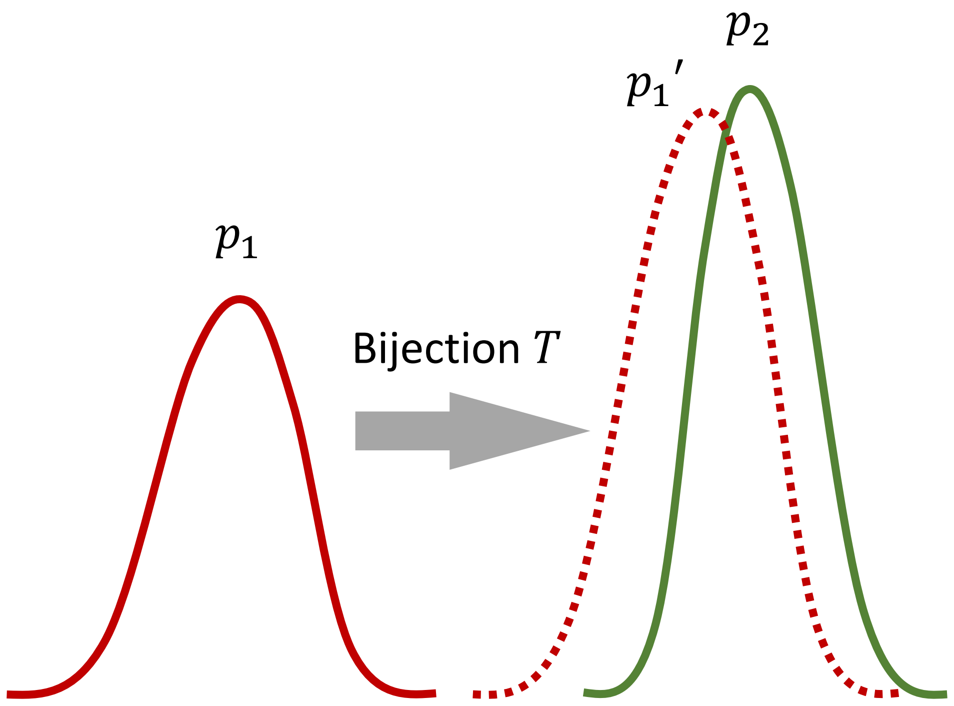

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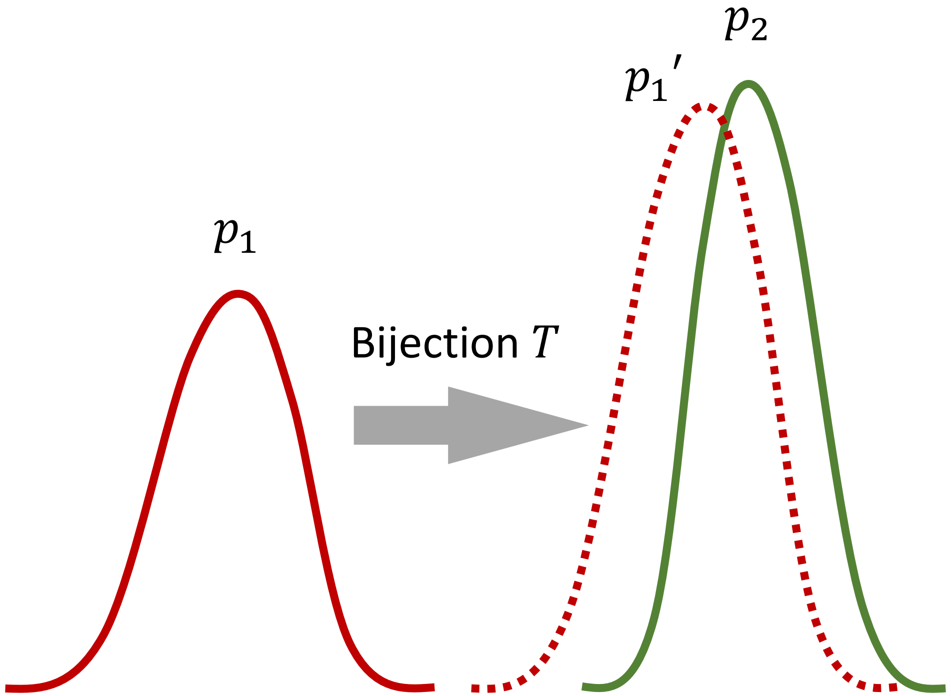

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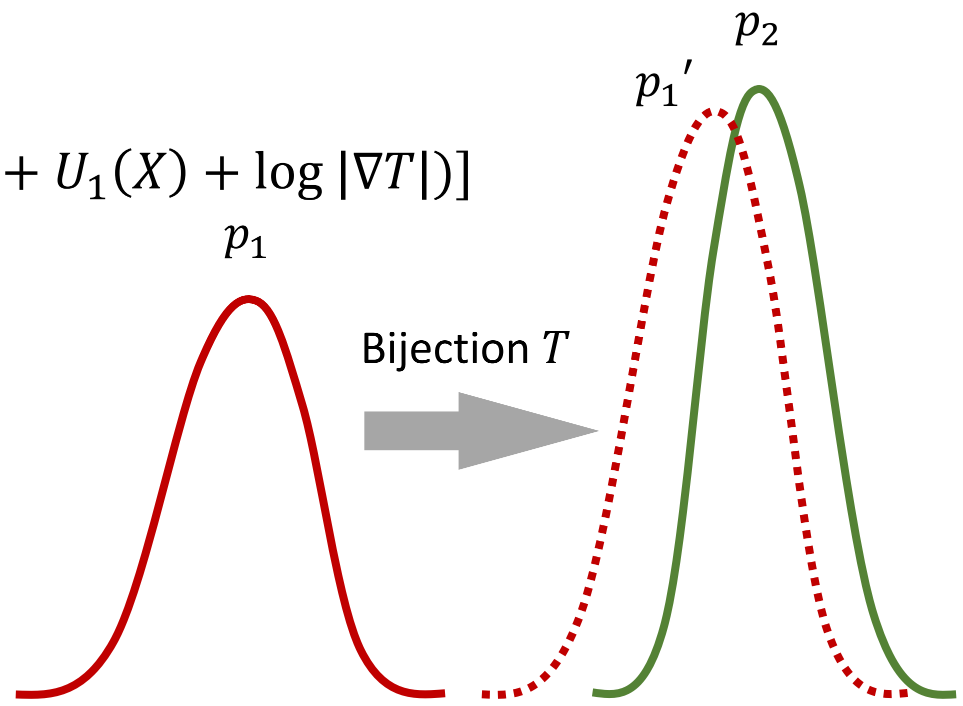

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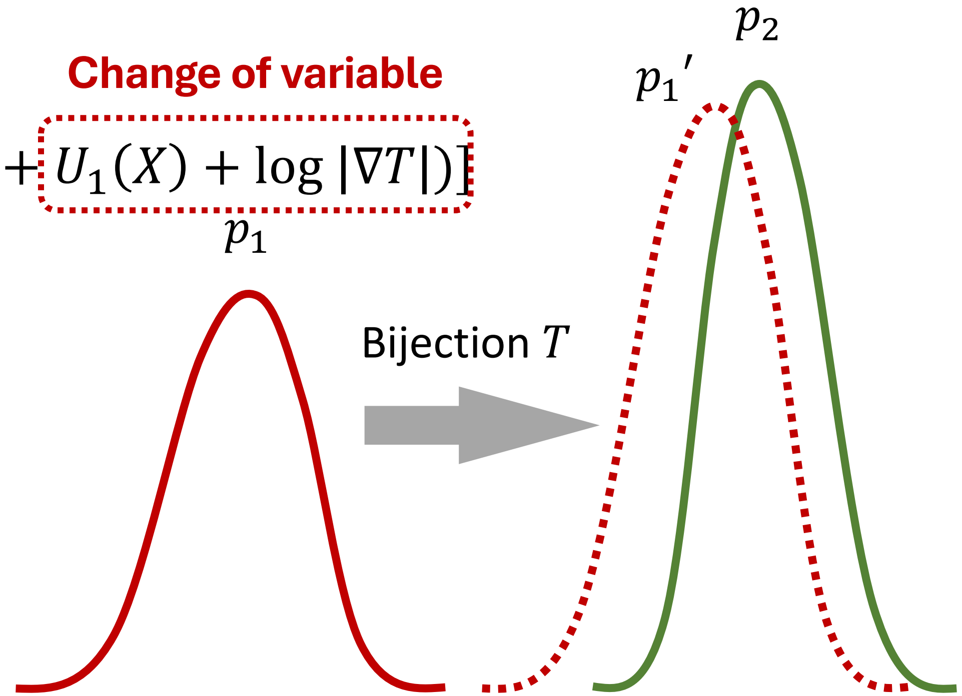

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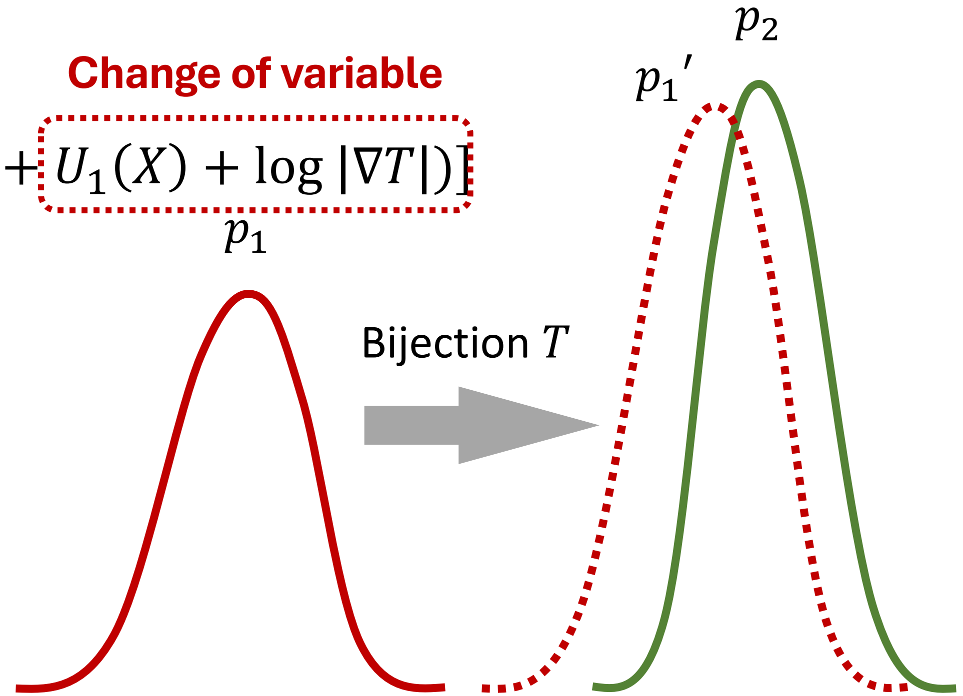
T can be
manually crafted [1];
learned by normalizing flow [2];
or flow matching [3].



[1] C. Jarzynski. Targeted free energy perturbation. *Physical Review E*, 65(4):046122, 2002. [2] P. Wirnsberger, et al. Targeted free energy estimation via learned mappings. *The Journal of Chemical Physics,* 153(14), 2020.
[3] L. Zhao and L. Wang. Bounding free energy difference with flow matching. *Chinese Physics Letters*, 40(12):120201, 2023.

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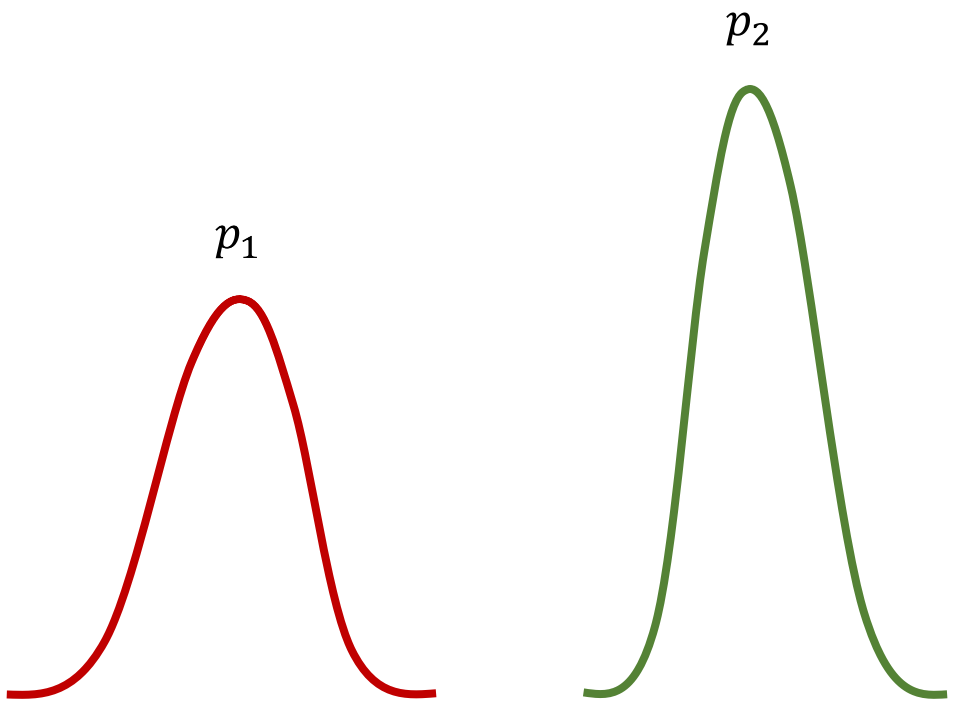
👉 Annealing to increase overlapping



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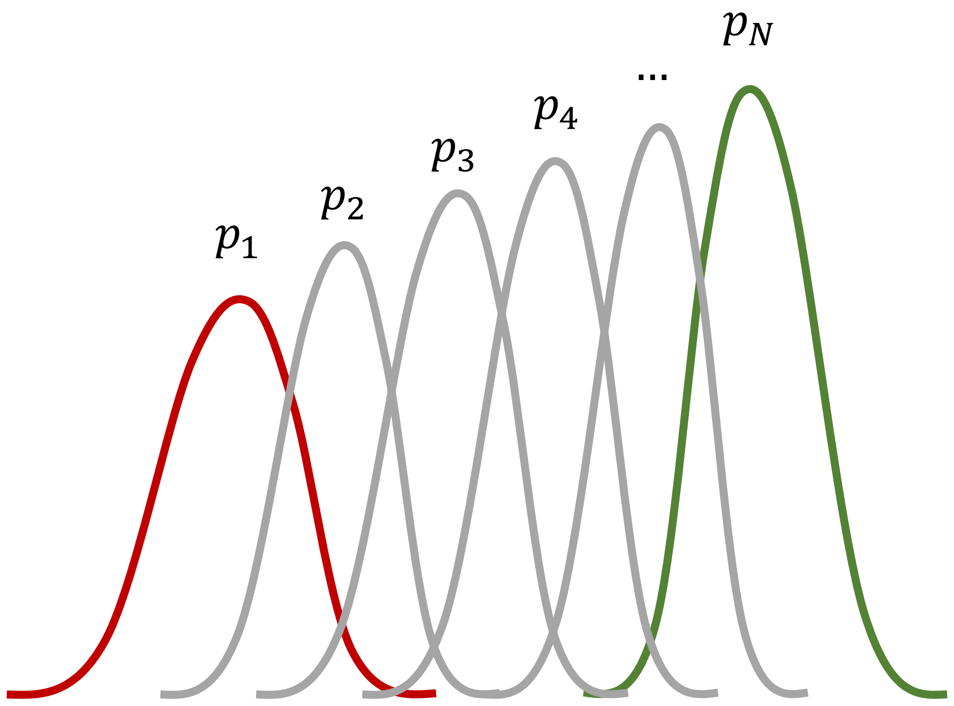

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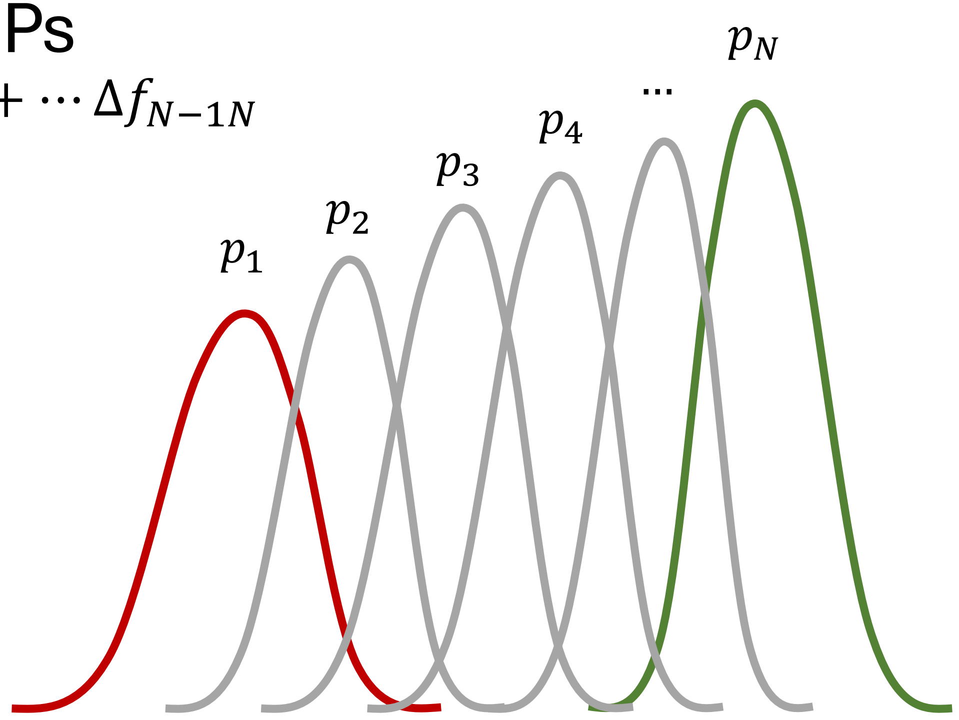
👉 Sequence of FEPs

$\Delta f_{1N} = \Delta f_{12} + \Delta f_{23} + \cdots \Delta f_{N-1N}$



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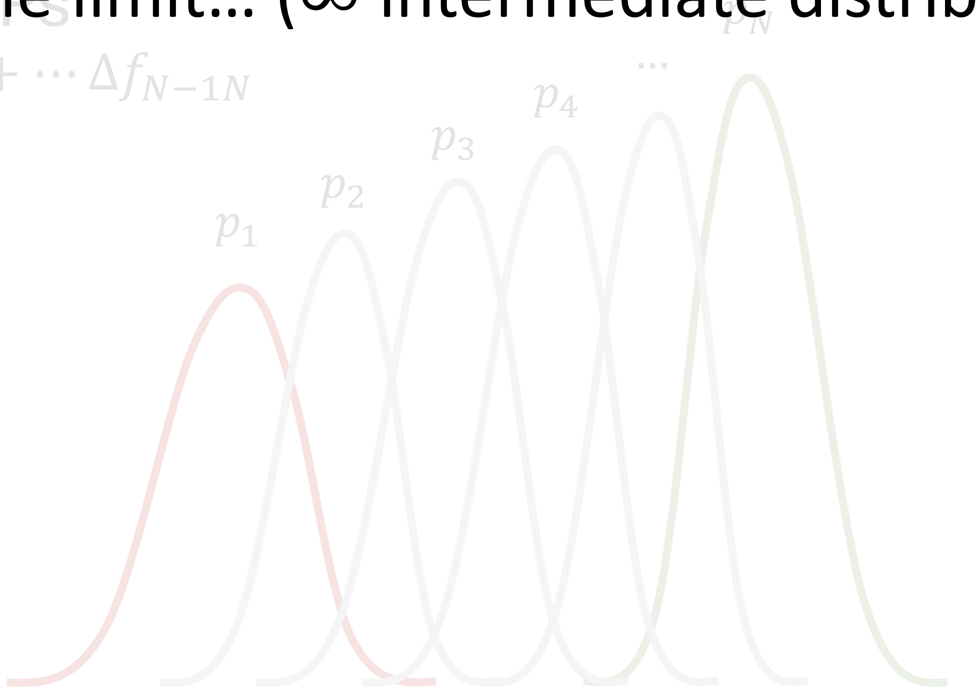
To the limit… (∞ intermediate distributions)



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"equilibrium"

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“equilibrium”

“non-equilibrium”?

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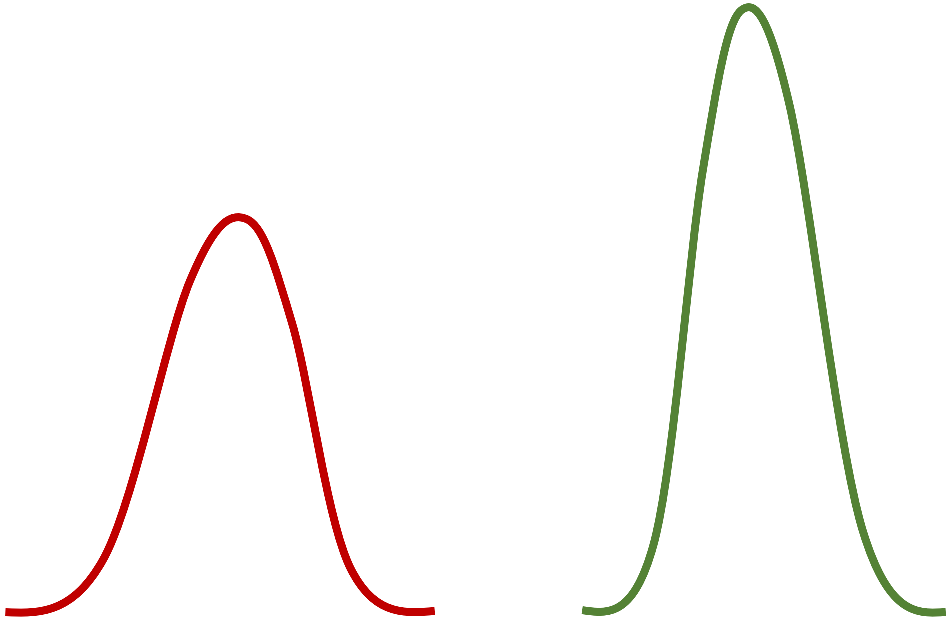

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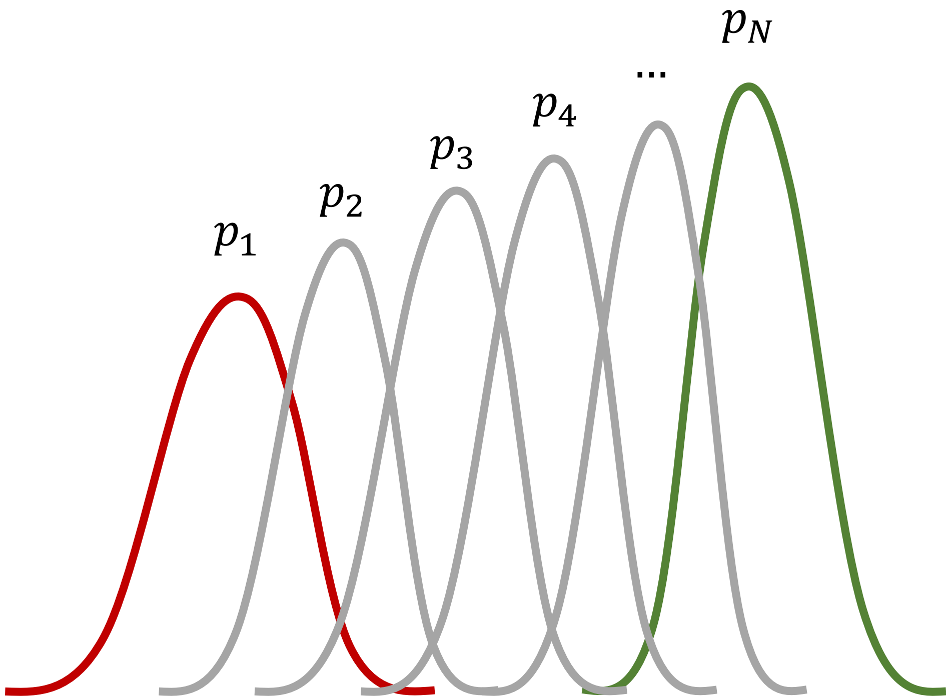

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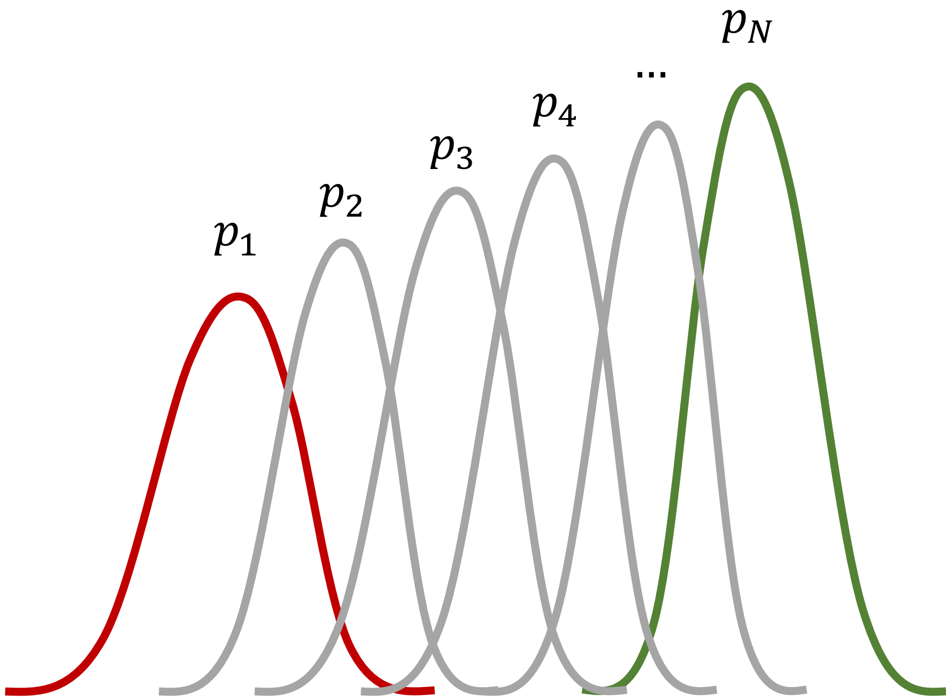

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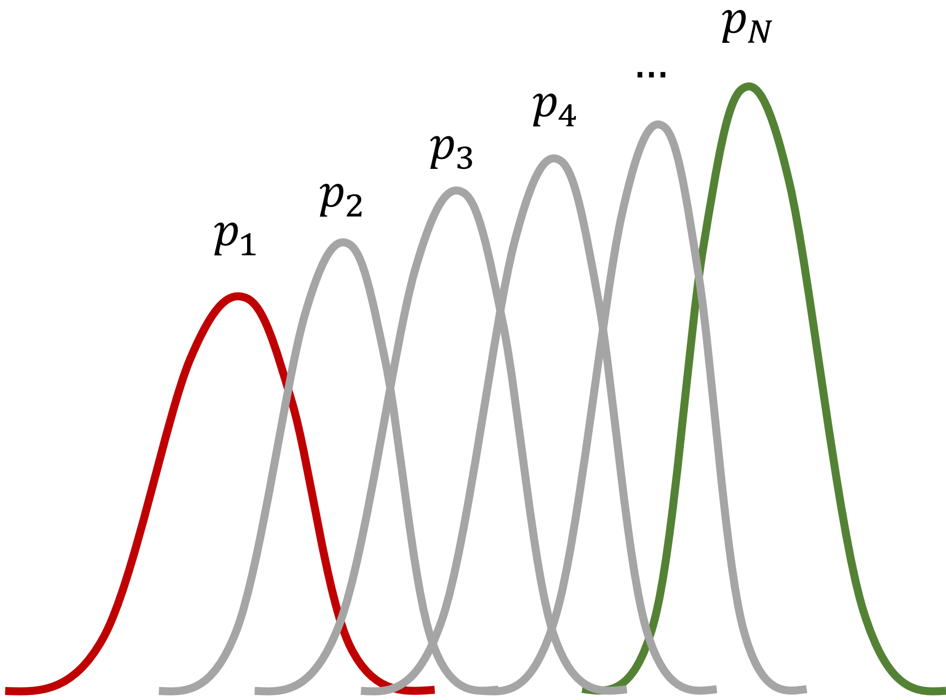

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MCMC with invariant density as p_t

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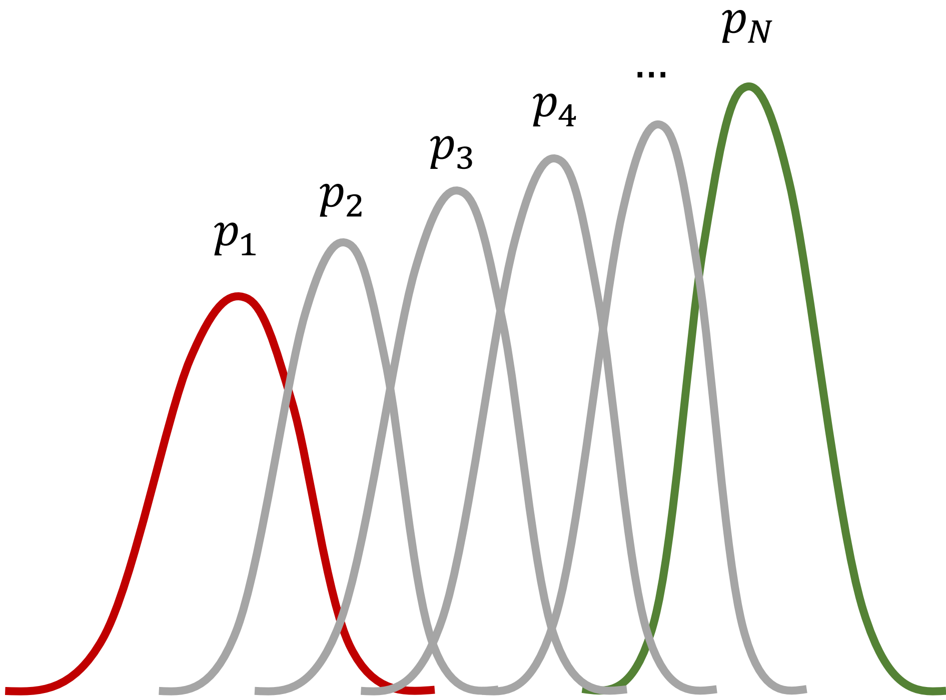

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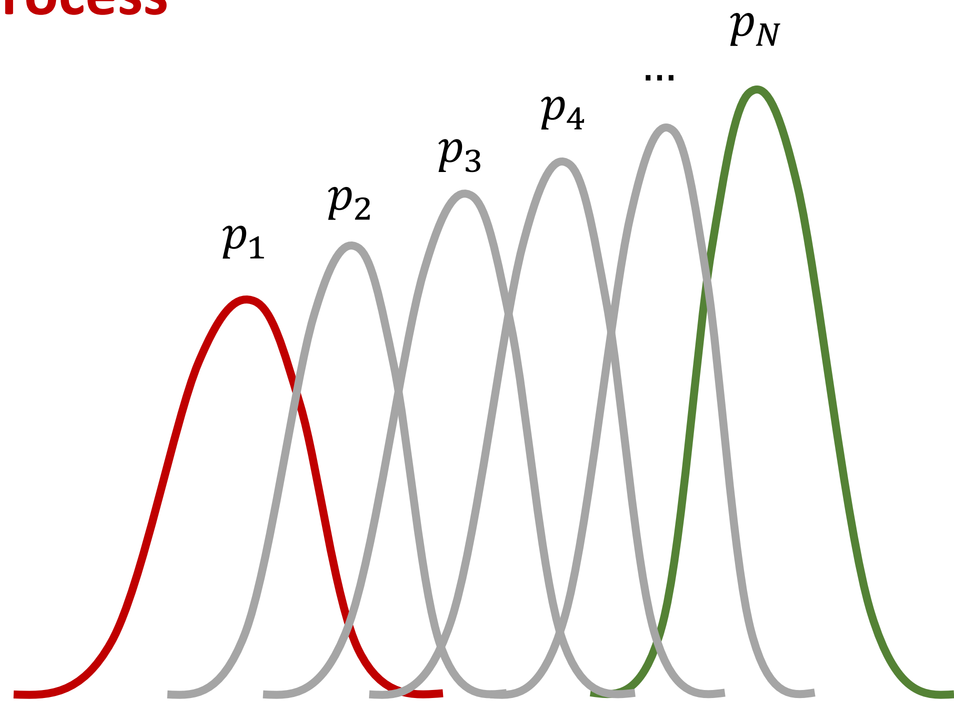

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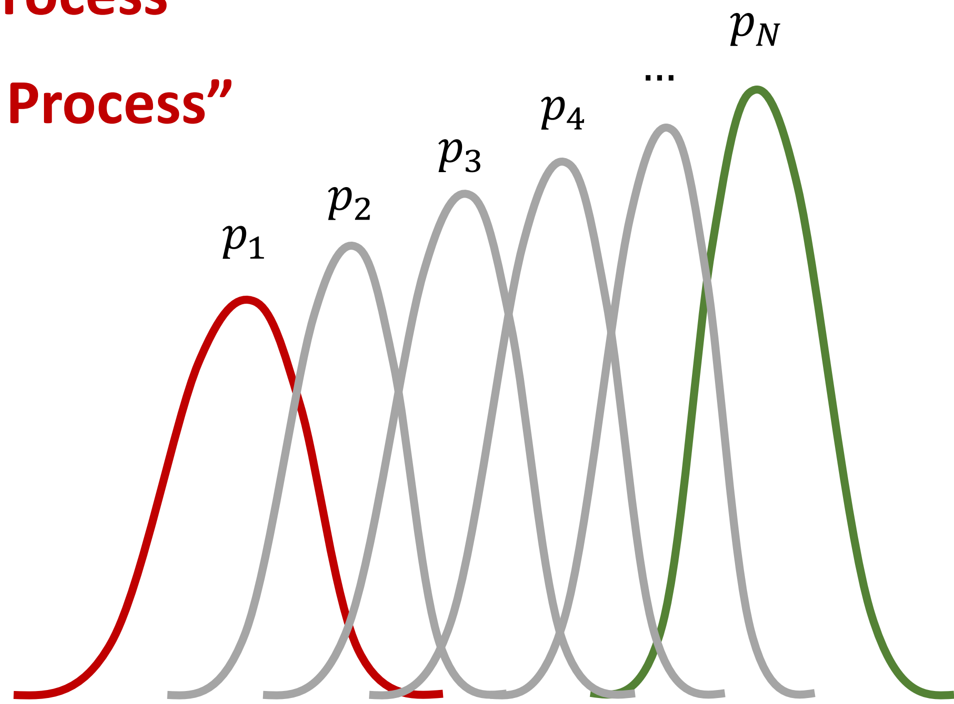

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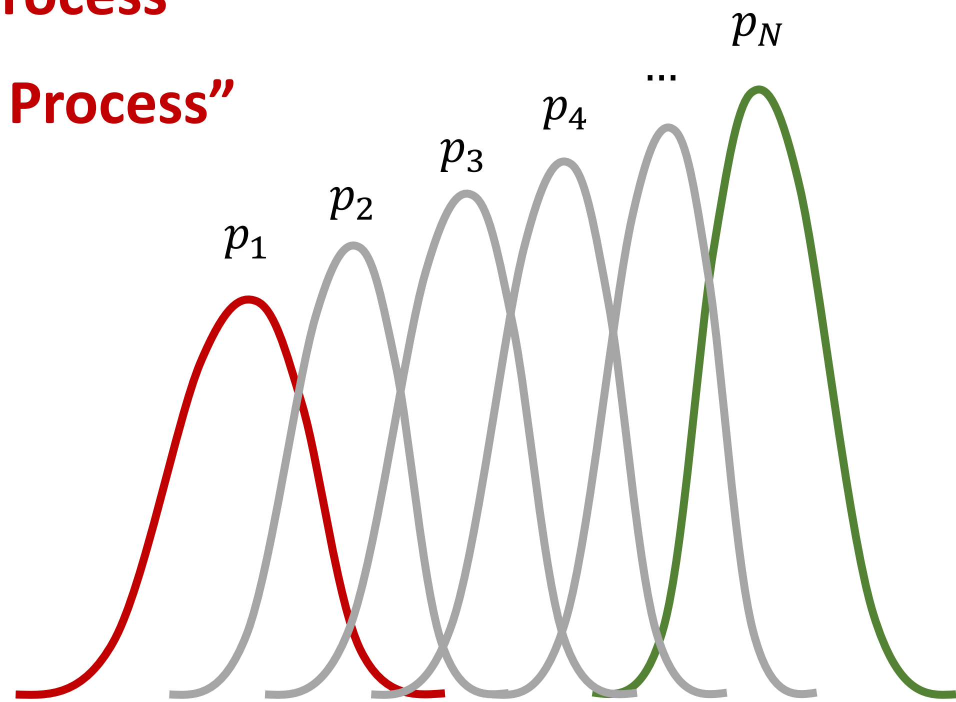

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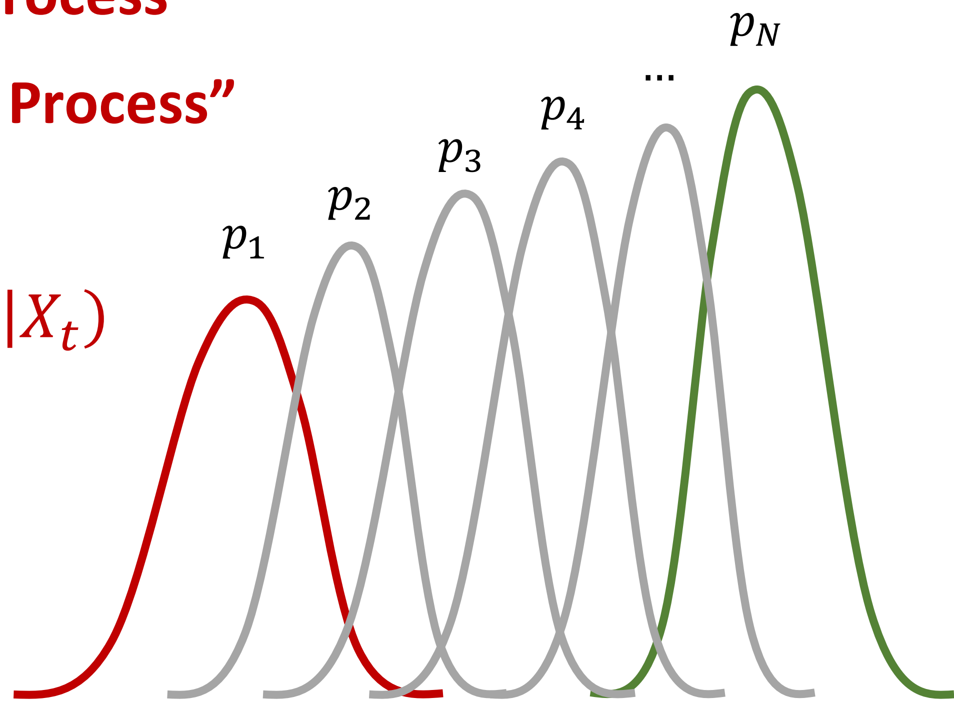

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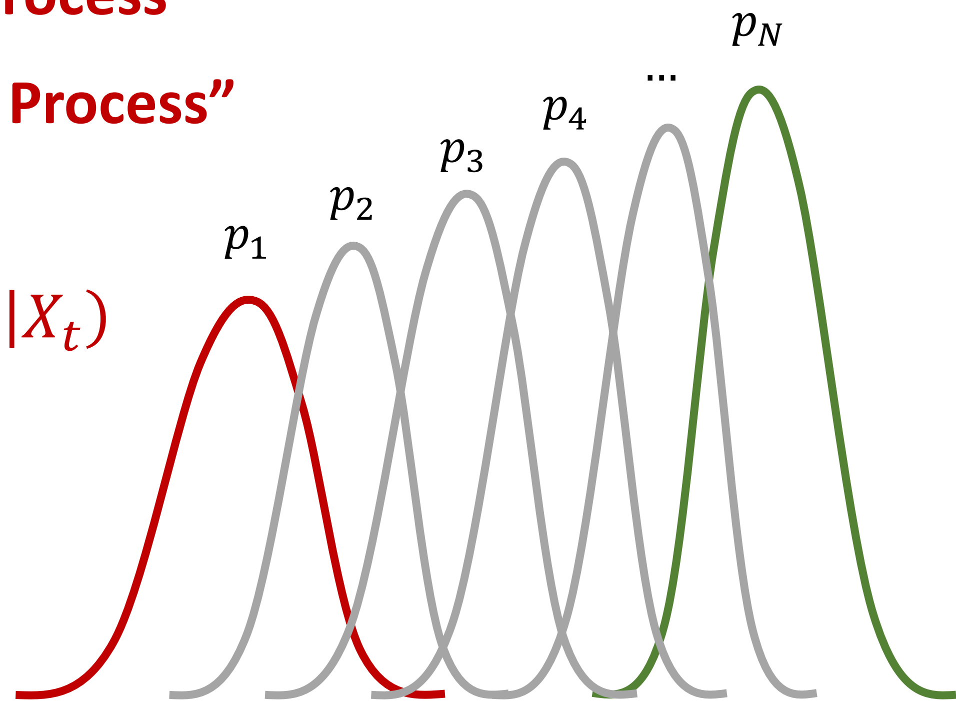

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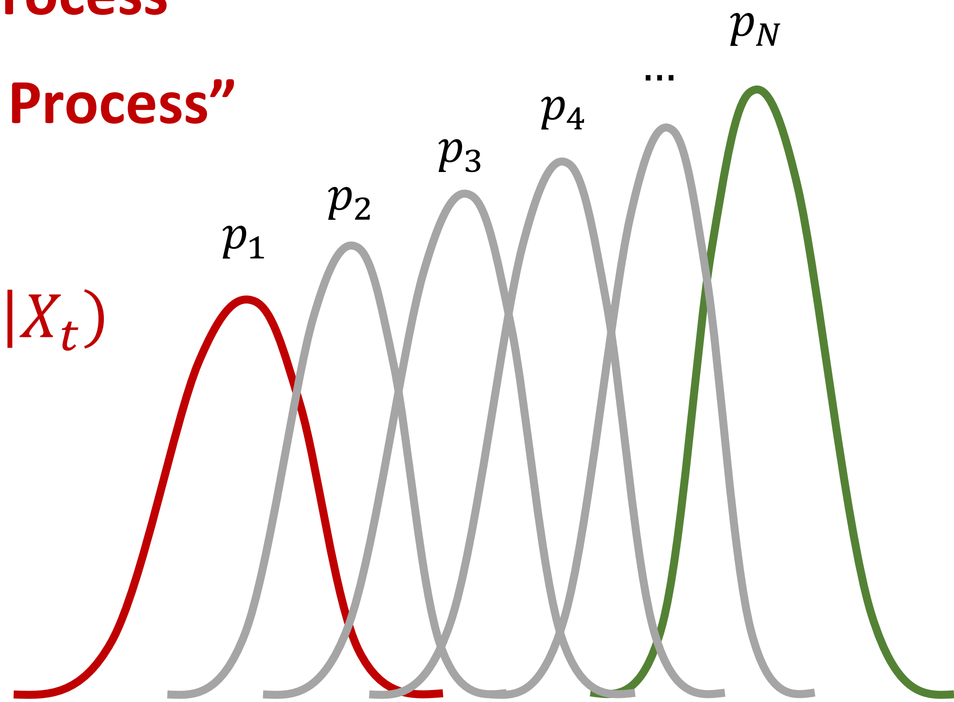

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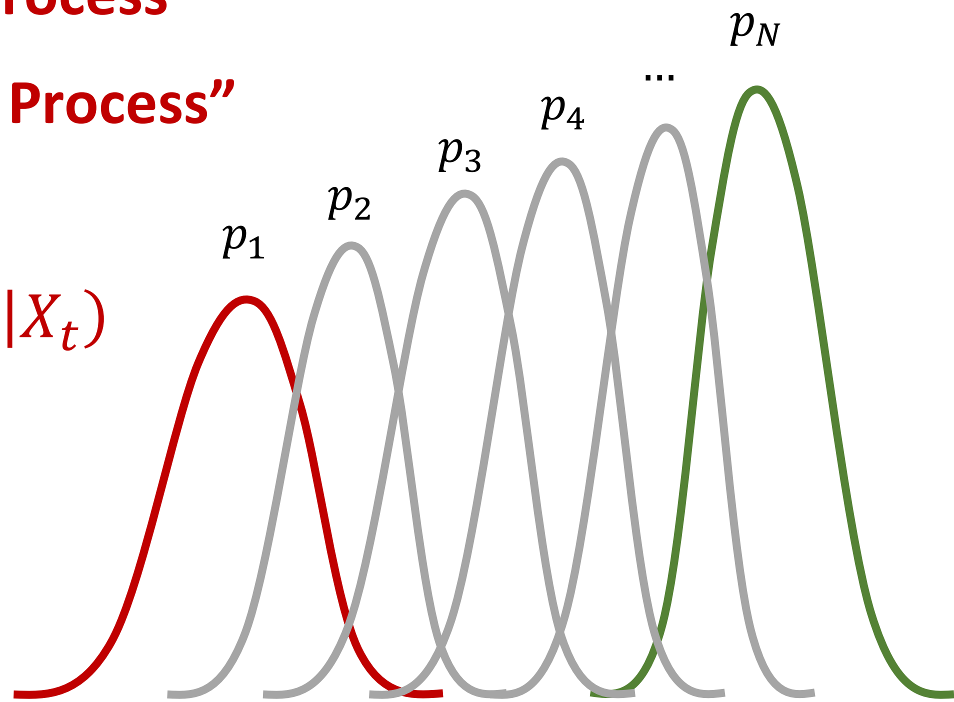

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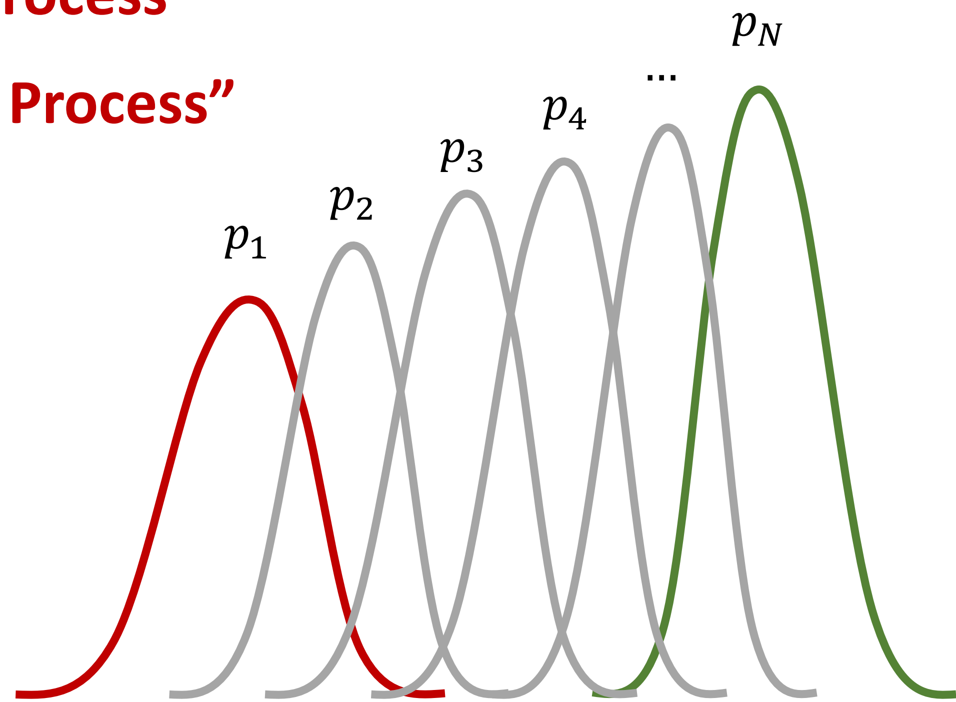

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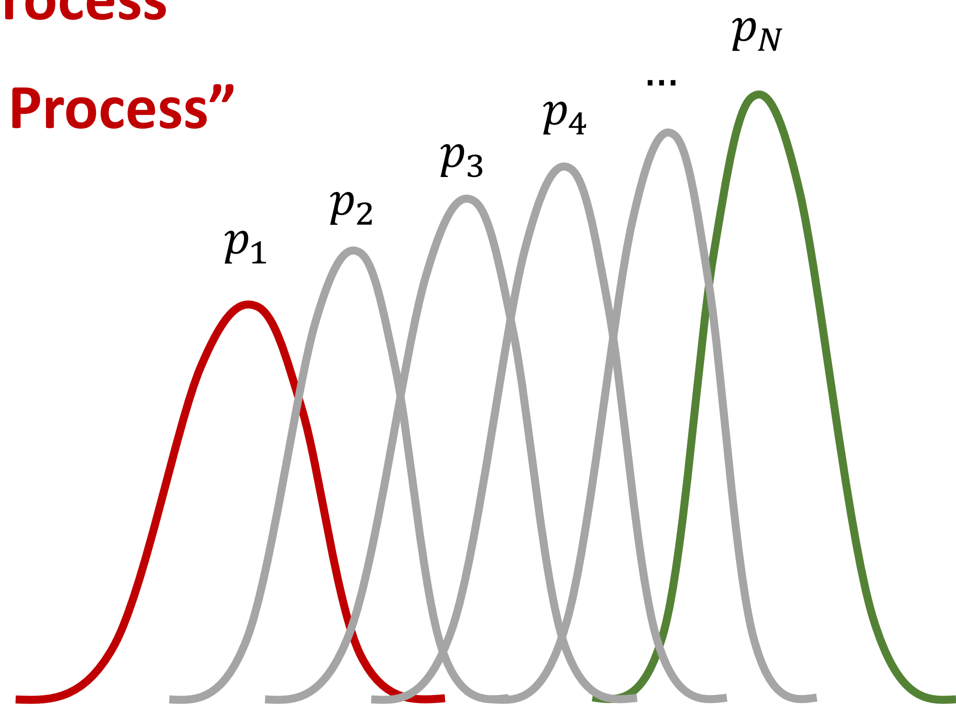
$$\log \frac{\tilde{P}_{1\to N}(X_{1:N})}{\tilde{P}_{N\to 1}(X_{1:N})} = \sum_{t=1}^{N-1} -U_t(X_t) + U_{t+1}(X_t)$$



Background - Methods

- **non-equilibrium approach:** Jarzynski Equality

$=$

Let's start by **Annealed Importance Sampling**

$X_1 \sim p_1$

$X_N \sim p_N$

$X_t \sim \mathrm{MCMC}_{p_t}(X_{t-1})$ **"Forward Process"**

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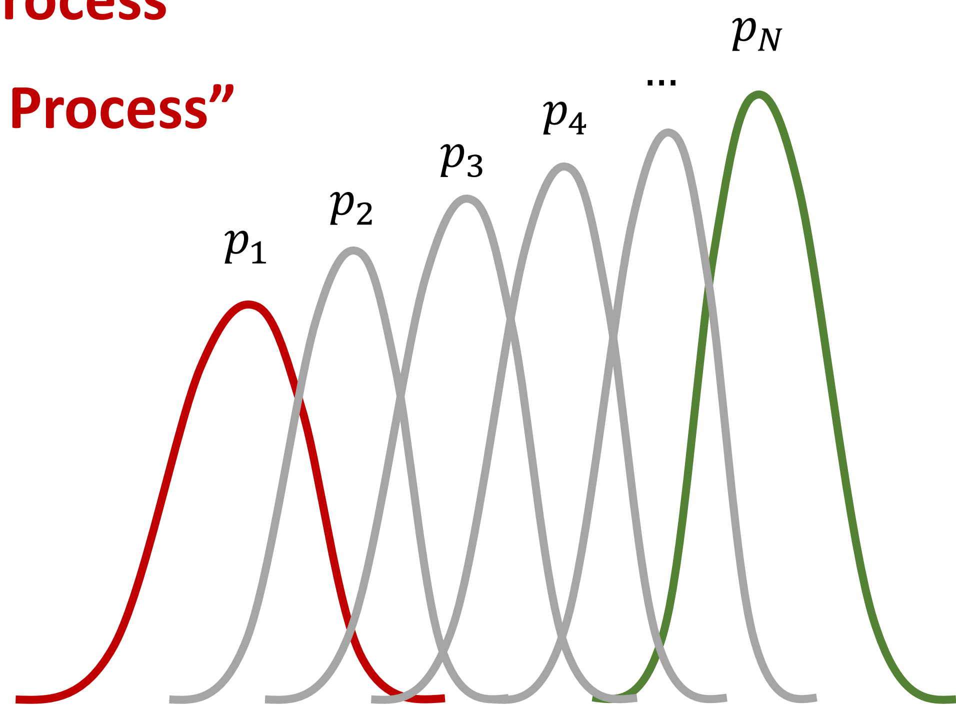
$$\log \frac{\tilde{P}_{1\to N}(X_{1:N})}{\tilde{P}_{N\to 1}(X_{1:N})} = \sum_{t=1}^{N-1} -U_t(X_t) + U_{t+1}(X_t)$$

How to use it to estimate Δf?



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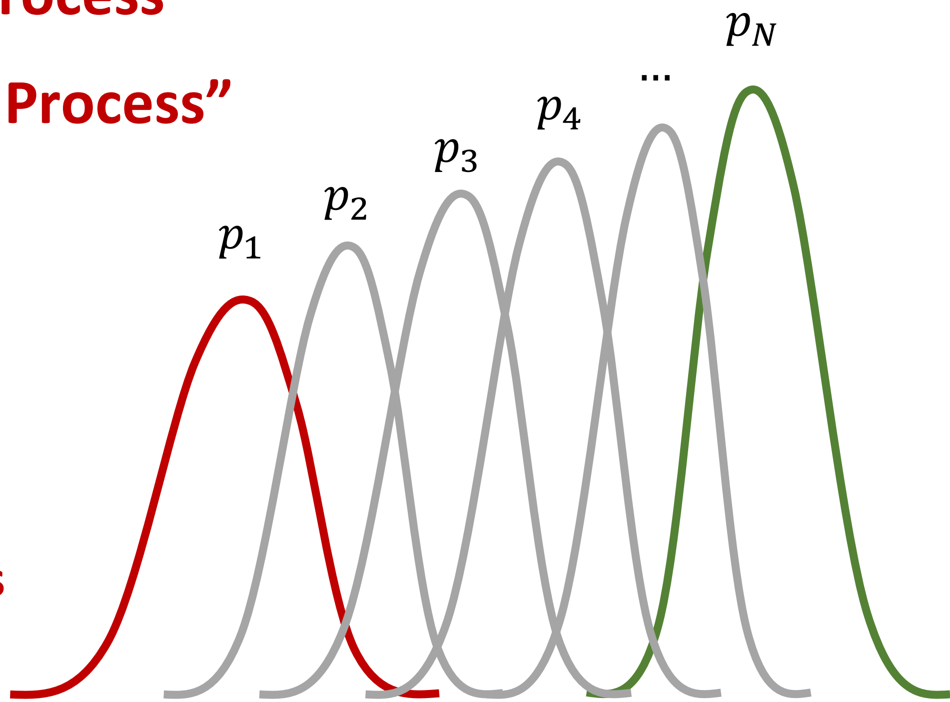
How to use it to estimate Δf?

$$\Delta f = -\log \frac{Z_N}{Z_1} = \log \frac{Z_{\tilde{P}_{1\to N}}}{Z_{\tilde{P}_{N\to 1}}}$$

The Transition kernels are normalized



Background - Methods

- **Annealed Importance Sampling**

$$X_1 \sim p_1 \qquad X_t \sim \mathrm{MCMC}_{p_t}(X_{t-1}); \qquad X_N \sim p_N \qquad X_{t-1} \sim \mathrm{MCMC}_{p_t}(X_t)$$

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- **Annealed Importance Sampling**

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$$= -\log \frac{\int \tilde{P}_{N\to 1}(X_{1:N}) \mathrm{d}X_{1:N}}{Z_{\tilde{P}_{1\to N}}}$$

Background - Methods

- **Annealed Importance Sampling**

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Background - Methods

- **Annealed Importance Sampling**

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$$= W(X_{1:N})$$

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Background - Methods

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$$= -\log \frac{\int \exp(-W(X_{1:N}))\tilde{P}_{1\to N}(X_{1:N})\mathrm{d}X_{1:N}}{Z_{\tilde{P}_{1\to N}}}$$

Background - Methods

- **Annealed Importance Sampling**

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$$= -\log \mathbf{E}_{P_{1\to N}}[\exp(-W)]$$

Background - Methods

- **Annealed Importance Sampling**

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$$\Delta f = -\log \mathbf{E}_{P_{1\to N}}[\exp(-W)], \qquad W(X_{1:N}) = \sum_{t=1}^{N-1} -U_t(X_t) + U_{t+1}(X_t)$$

Background - Methods

- **Annealed Importance Sampling**

$X_1 \sim p_1 \qquad X_t \sim \mathrm{MCMC}_{p_t}(X_{t-1});$

We do not use it in the final calculation

$X_N \sim p_N \qquad X_{t-1} \sim \mathrm{MCMC}_{p_t}(X_t)$

$$\Delta f = -\log \mathbf{E}_{P_{1\to N}}[\exp(-W)],$$

$$W(X_{1:N}) = \sum_{t=1}^{N-1} -U_t(X_t) + U_{t+1}(X_t)$$

Background - Methods

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Background - Methods

- **Annealed Importance Sampling**

$$X_1 \sim p_1 \qquad X_t \sim \mathrm{ULA}(X_{t-1});$$

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Background - Methods

- **Annealed Importance Sampling**

$X_1 \sim p_1 \qquad X_t \sim \mathrm{ULA}(X_{t-1});$

Taking the limit… (∞ intermediate distributions)

$$\Delta f = -\log \mathbf{E}_{P_{1\to N}}[\exp(-W)],$$

$$W(X_{1:N}) = \sum_{t=1}^{N-1} -U_t(X_t) + U_{t+1}(X_t)$$

Background - Methods

- **Annealed Importance Sampling**

$X_1 \sim p_1$ $\quad X_t \sim \mathrm{ULA}(X_{t-1});$ $\quad \mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},$

$$\Delta f = -\log \mathbf{E}_{P_{1\to N}}\left[\exp(-W)\right],$$

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$$\int \partial_t U_t(X_t)\mathrm{d}t$$

Background - Methods

- **Annealed Importance Sampling**

$$X_1 \sim p_1 \qquad \mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},$$

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Jarzynski Equality

Background - Methods

- Jarzynski Equality

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a$$

$$W(X) = \int_0^1 \partial_t U_t \mathrm{d}t$$

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Background - Methods

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“non-equilibrium”?

Background - Methods

- Jarzynski Equality

X_t does not follow $p_t \propto \exp(-U_t)$

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a$$

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Background - Methods

- Jarzynski Equality

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a$$

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$$\Delta f = -\log \mathbf{E}_{P_{1\to N}}\left[\exp(-W)\right],$$

Background - Methods

- Escorted Jarzynski Equality

X_t gets closer to $p_t \propto \exp(-U_t)$

$$\mathrm{d}X_t = u(X_t)\mathrm{d}t - \sigma^2 \nabla U_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t$$

$$\Delta f = -\log \mathbf{E}_{P_{1\to N}}\left[\exp(-W)\right],$$

Background - Methods

- Escorted Jarzynski and Controlled Crooks Fluctuation Theorem

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t(X_t)\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

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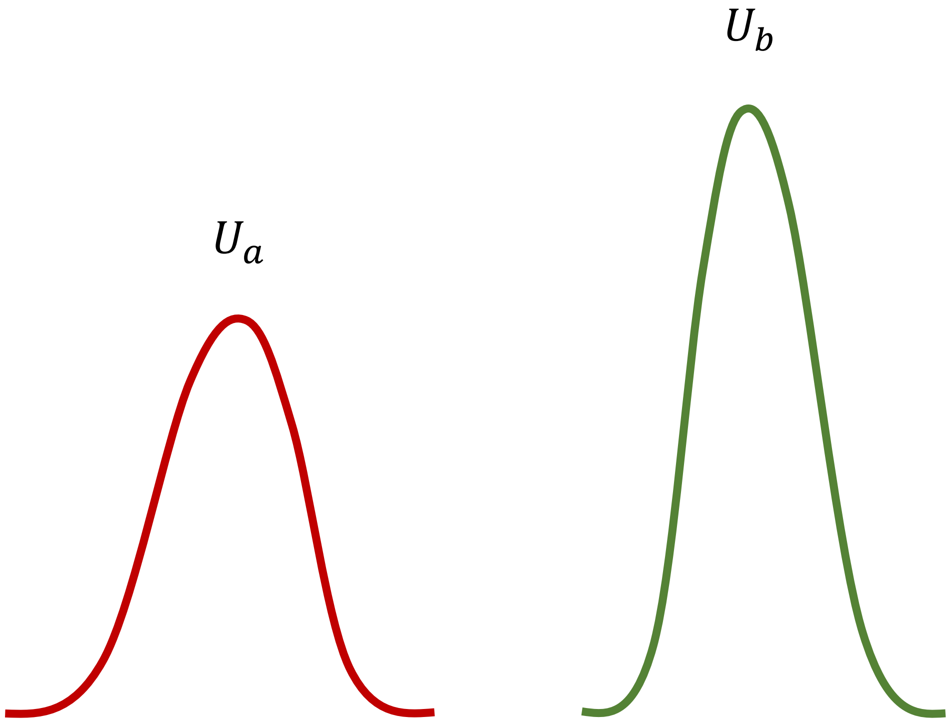
Methods

👉 Learn a transport between two states using their samples

👉 Estimate the free energy difference with escorted Jarzynski

Methods

Problem Setup



Methods

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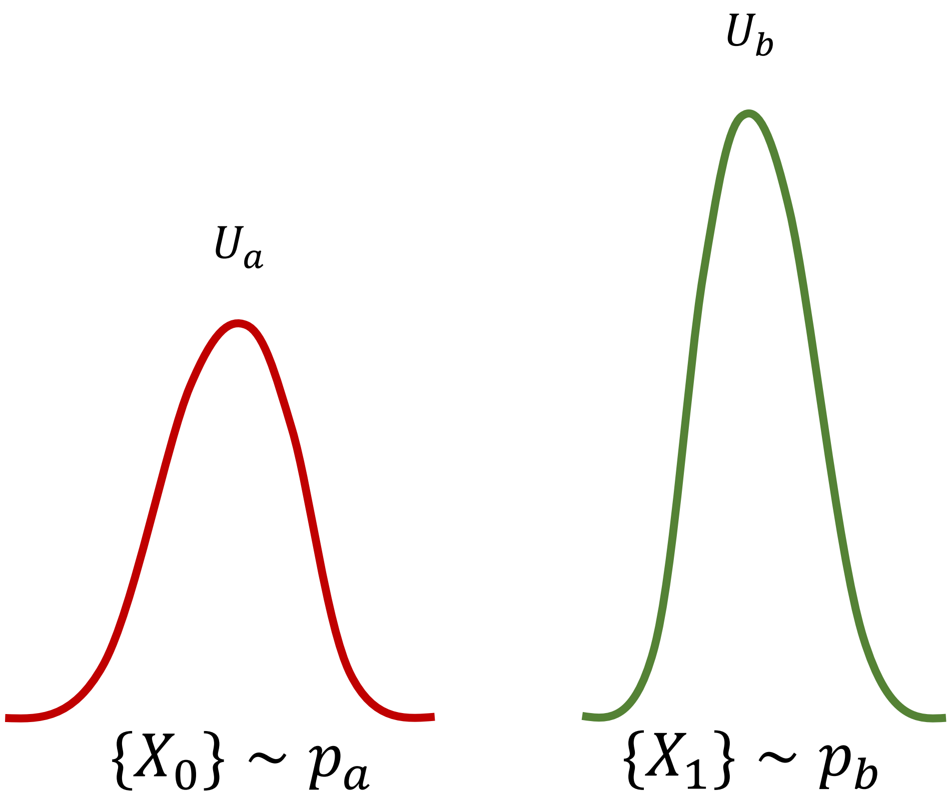
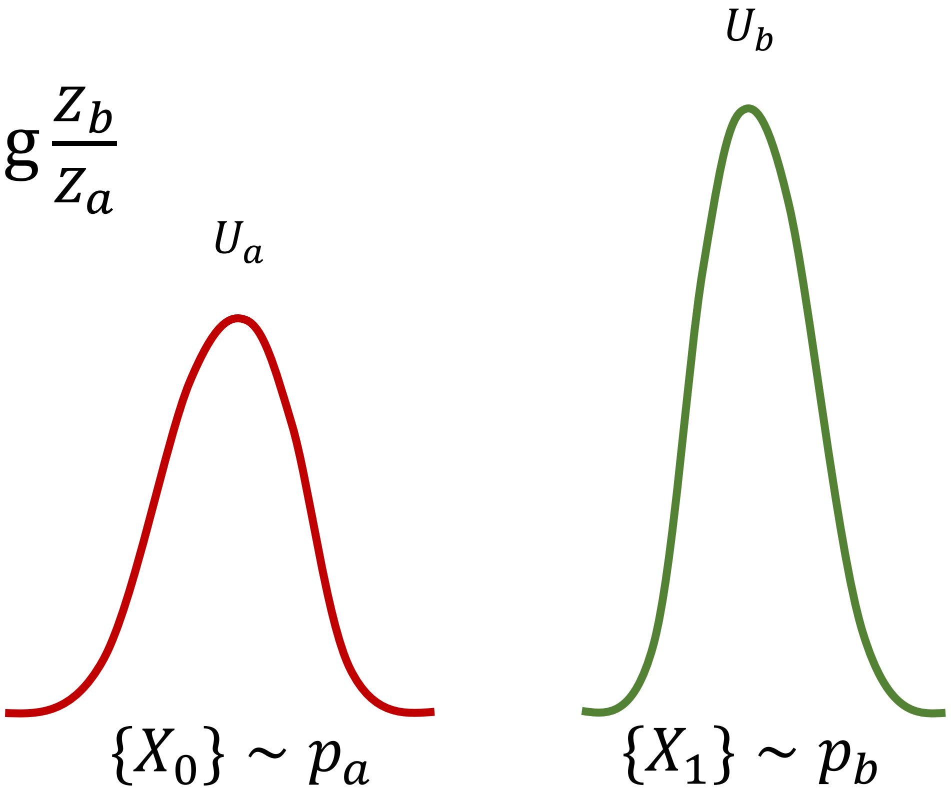


Methods

Problem Setup

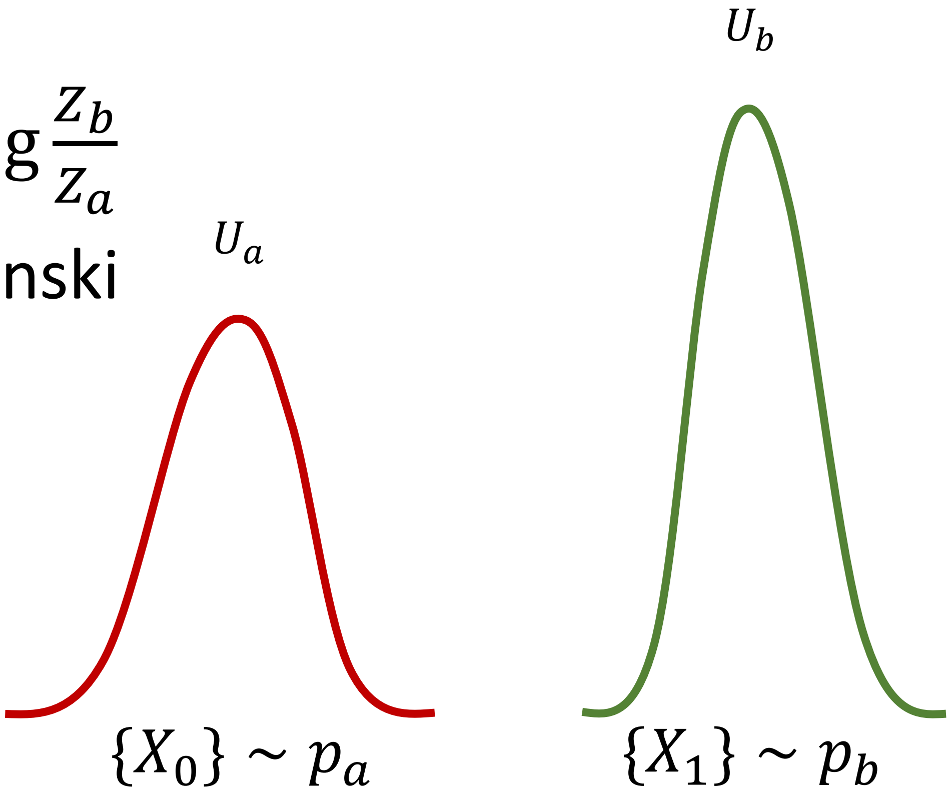
- Estimate $\Delta f = -\log \frac{Z_b}{Z_a}$



Methods

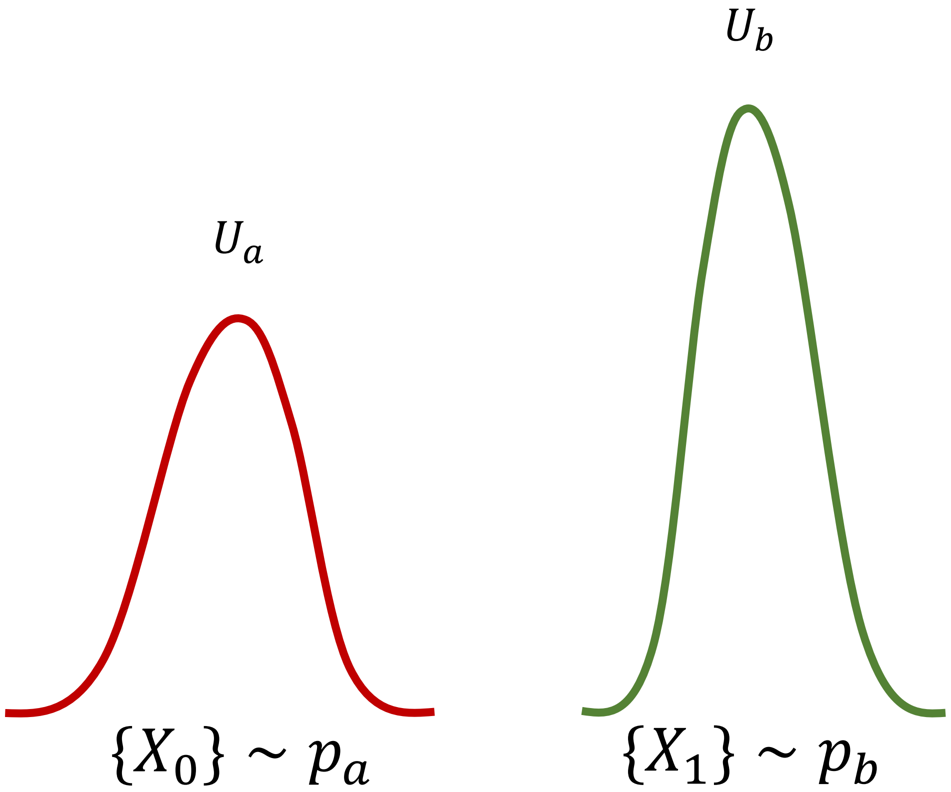
Problem Setup

- Estimate $\Delta f = -\log \frac{Z_b}{Z_a}$
- with escorted Jarzynski



Methods

How can we efficiently learn a transport (SDE) using data from two sides?



Methods

How can we efficiently learn a transport (SDE) using data from two sides?

Stochastic Interpolants

M. S. Albergo, N. M. Boffi, and E. Vanden-Eijnden. Stochastic interpolants: A unifying framework for flows and diffusions. *arXiv preprint arXiv:2303.08797*, 2023.

Introduction to SI

We want to learn $u_t, \nabla U_t$, so that

$$\mathrm{d}X_t = [u_t(X_t) - \sigma^2 \nabla U_t(X_t)]\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t}$$

maps between $\{X_0\}$ and $\{X_1\}$

We define a stochastic interpolant

$$x_t = (1-t)x_0 + tx_1 + \sqrt{t(1-t)}\epsilon, \quad x_0, x_1 \sim \{X_0\} \times \{X_1\}, \qquad \epsilon \sim N(0, \mathrm{Id})$$

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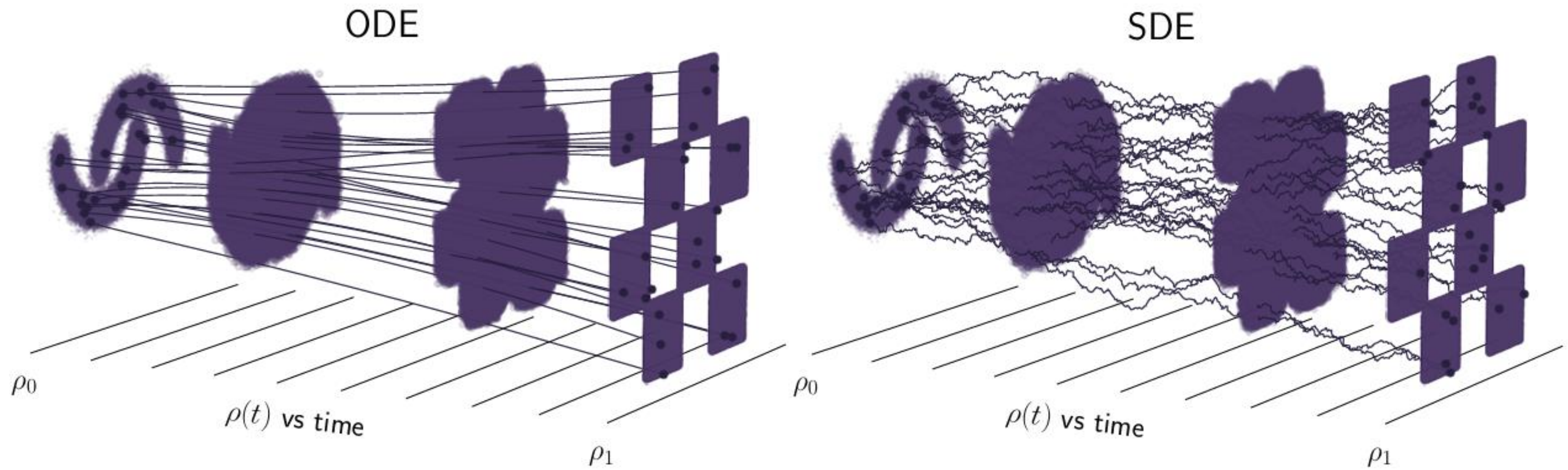
$$\min_u \mathbf{E}\left|\left|u_t(X_t) - \partial_t x_t\right|\right|^2$$

∇U_t learned by **score matching**

M. S. Albergo, N. M. Boffi, and E. Vanden-Eijnden. Stochastic interpolants: A unifying framework for flows and diffusions. *arXiv preprint arXiv:2303.08797*, 2023.

Introduction to SI



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Methods

Stochastic Interpolants:

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Methods

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Methods

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Recall Escorted Jarzynski & controlled Crooks:

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} + \Delta f$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

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Methods

Stochastic Interpolants:

Learn Stochastic Interpolant using data from both states

We learn $u_t, \nabla U_t$:

Calculate “generalized” work

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overrightarrow{B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

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Apply Escorted Jarzynski to estimate free energy

Recall Escorted Jarzynski & controlled Crooks:

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Methods

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Learn Stochastic Interpolant using data from both states

We learn $u_t, \nabla U_t$:

Calculate “generalized” work

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overrightarrow{B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overleftarrow{B_t},\ X_0 \sim p_b \Rightarrow \overleftarrow{\mathbf{P}}$$

Apply Escorted Jarzynski to estimate free energy

Recall Escorted Jarzynski & controlled Crooks:

Done?

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} + \Delta f$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

Recall Escorted Jarzynski & controlled Crooks:

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} + \Delta f$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

Recall Escorted Jarzynski & controlled Crooks:

"Forward-backward RND"

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} + \Delta f$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\ \mathrm{d}t + \sigma\sqrt{2}\ \overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad ➡ \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \quad \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\ \mathrm{d}t + \sigma\sqrt{2}\ \overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad ➡ \quad \overleftarrow{\mathbf{P}}$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} + \Delta f$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} - \log \frac{Z_b}{Z_a}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} - \log \frac{Z_b}{Z_a} \approx -\log \frac{Z_b p_b(X_T) \prod_1^T N(X_{t-1}|X_t)}{Z_a p_a(X_0) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\; X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\; X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} - \log \frac{Z_b}{Z_a} \approx -\log \frac{\boxed{Z_b p_b(X_T)} \prod_1^T N(X_{t-1}|X_t)}{Z_a p_a(X_0) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \quad \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} - \log \frac{Z_b}{Z_a} \approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_0 \sim p_b \Rightarrow \overleftarrow{\mathbf{P}}$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} - \log \frac{Z_b}{Z_a} \approx -\log \frac{\exp(-U_b(X_T))}{\exp(-U_a(X_0))} \frac{\prod_1^T N(X_{t-1}|X_t)}{\prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overrightarrow{B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overleftarrow{B_t},\ X_0 \sim p_b \Rightarrow \overleftarrow{\mathbf{P}}$$

$$N(X_t|X_{t-1}) = N(X_t| -\sigma^2 \nabla U_{t-1}(X_{t-1})\Delta t + u_{t-1}(X_{t-1})\Delta t, 2\sigma^2\Delta t)$$

$$W = -\log\frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} - \log\frac{Z_b}{Z_a} \approx -\log\frac{\exp(-U_b(X_T))}{\exp(-U_a(X_0))}\frac{\prod_1^T N(X_{t-1}|X_t)}{\prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overrightarrow{B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\mathrm{d}\overleftarrow{B_t},\ X_0 \sim p_b \Rightarrow \overleftarrow{\mathbf{P}}$$

$$N(X_t|X_{t-1}) = N(X_t| - \sigma^2 \nabla U_{t-1}(X_{t-1})\Delta t + u_{t-1}(X_{t-1})\Delta t, 2\sigma^2\Delta t)$$

$$W = -\log \frac{\mathrm{d}\overleftarrow{\mathbf{P}}}{\mathrm{d}\overrightarrow{\mathbf{P}}} = -\log \frac{Z_b}{Z_a} \approx -\log \frac{\exp(-U_b(X_T))}{\exp(-U_a(X_0))} \frac{\prod_1^T N(X_{t-1}|X_t)}{\prod_1^T N(X_t|X_{t-1})}$$

No need to learn Energy-parameterized network

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$dX_t = -\sigma^2 \nabla U_t(X_t)dt + u_t\, dt + \sigma\sqrt{2}\, d\overrightarrow{B_t},\ X_0 \sim p_a \Rightarrow \overrightarrow{\mathbf{P}}$$

$$dX_t = \sigma^2 \nabla U_t(X_t)dt + u_t\, dt + \sigma\sqrt{2}\, d\overleftarrow{B_t},\ X_0 \sim p_b \Rightarrow \overleftarrow{\mathbf{P}}$$

$$N(X_t | X_{t-1}) = N(X_t | -\sigma^2 \nabla U_{t-1}(X_{t-1})\Delta t + u_{t-1}(X_{t-1})\Delta t, 2\sigma^2 \Delta t)$$

$$W = -\log\frac{d\overleftarrow{\mathbf{P}}}{d\overrightarrow{\mathbf{P}}} = -\log\frac{Z_b}{Z_a} \approx -\log\frac{\exp(-U_b(X_T))}{\exp(-U_a(X_0))}$$

$$\frac{\prod_1^T N(X_{t-1} | X_t)}{\prod_1^T N(X_t | X_{t-1})}$$

No need to learn Energy-parameterized network

No need to calculate divergence

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W \approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods

Stochastic Interpolants:

We learn $u_t, \nabla U_t$:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W \approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \frac{\mathbf{E}_{\overrightarrow{\mathbf{P}}}[g(W-C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W+C)]} + C$$

👉 **Path-measure-based BAR**

Methods

$$\Delta f = -\log \frac{\mathbf{E}_{\overrightarrow{\mathbf{P}}}[g(W - C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W + C)]} + C$$

Methods

$$\Delta f = -\log \frac{\mathbf{E}_{\overrightarrow{\mathbf{P}}}[g(W - C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W + C)]} + C$$

A minimal-variance estimator

when $g(x) = \frac{1}{1+\exp(x)}, C = \Delta f$

Methods

$$\Delta f = -\log \frac{\mathbf{E}_{\overrightarrow{\mathbf{P}}}[g(W - C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W + C)]} + C$$

A minimal-variance estimator

when $g(x) = \frac{1}{1+\exp(x)}, C = \Delta f$

1. Initialize C;
2. Calculate Δf; Set $C \leftarrow \Delta f$;
3. Repeat (2) until converge.

Methods

$$\Delta f = -\log \frac{\mathbf{E}_{\overrightarrow{\mathbf{P}}}[g(W - C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W + C)]} + C$$

A minimal-variance estimator

when $g(x) = \frac{1}{1+\exp(x)}, C = \Delta f$

1. Initialize C;
2. Calculate Δf; Set $C \leftarrow \Delta f$;
3. Repeat (2) until converge.

Methods

Learn Stochastic Interpolant using data from both states

Calculate “generalized” work **with FB RND**

Apply Escorted Jarzynski + minimal-variance estimator

Any other practical consideration?

Methods – boundary conditions

Methods – boundary conditions

Let's recall again Escorted Jarzynski & controlled Crooks:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t \approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – boundary conditions

Requirement: $\exp(-U_0) \propto p_a, \exp(-U_1) \propto p_b$

Let's recall again Escorted Jarzynski & controlled Crooks:

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t \approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – boundary conditions

Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds:

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\, \mathrm{d}t + \sigma\sqrt{2}\, \overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\, \mathrm{d}t + \sigma\sqrt{2}\, \overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t \approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – boundary conditions

Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds:

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t + \log \frac{\exp(-U_a(X_0))\exp(-U_1(X_1))}{\exp(-U_b(X_1))\exp(-U_0(X_0))}$$

$$\approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – boundary conditions

Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds:

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t + \log \frac{\exp(-U_a(X_0))\exp(-U_1(X_1))}{\exp(-U_b(X_1))\exp(-U_0(X_0))}$$

$$\approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

Need a correction term 🥴

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – boundary conditions

Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds:

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t + \log \frac{\exp(-U_a(X_0))\exp(-U_1(X_1))}{\exp(-U_b(X_1))\exp(-U_0(X_0))}$$

$$\approx -\log \frac{\exp(-U_b(X_T)) \prod_1^T N(X_{t-1}|X_t)}{\exp(-U_a(X_0)) \prod_1^T N(X_t|X_{t-1})}$$

Do not need a correction term 😊

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – Discretization Error

Methods – Discretization Error

Discretized Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

$$\mathrm{d}X_t = -\sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overrightarrow{\mathrm{d}B_t},\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\mathrm{d}X_t = \sigma^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,\mathrm{d}t + \sigma\sqrt{2}\,\overleftarrow{\mathrm{d}B_t},\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

$$W = \int_0^1 \partial_t U_t \mathrm{d}t + \int_0^1 \nabla U_t \cdot u_t \mathrm{d}t - \int_0^1 \nabla \cdot u_t \mathrm{d}t + \log \frac{\exp(-U_a(X_0))\exp(-U_1(X_1))}{\exp(-U_b(X_1))\exp(-U_0(X_0))}$$

$$W \approx -\log \frac{\exp\left(-U_b(X_T)\right) \prod_1^T N\left(X_{t-1} \middle| X_t\right)}{\exp\left(-U_a(X_0)\right) \prod_1^T N\left(X_t \middle| X_{t-1}\right)}$$

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$$

Methods – Discretization Error

Discretized Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

$$\Delta X_t = -\sigma^2 \nabla U_t(X_t)\Delta t + u_t \Delta t + \sigma\sqrt{2\Delta t}\, \epsilon,\ X_0 \sim p_a \quad \Rightarrow \quad \overrightarrow{\mathbf{P}}$$

$$\Delta X_t = -\sigma^2 \nabla U_t(X_t)\Delta t - u_t \Delta t + \sigma\sqrt{2\Delta t}\epsilon,\ X_1 \sim p_b \quad \Rightarrow \quad \overleftarrow{\mathbf{P}}$$

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$$W_1 = \sum \partial_t U_t \Delta t + \nabla U_t \cdot u_t \Delta t + \nabla \cdot u_t \Delta t + \log \frac{\exp(-U_a(X_0))\exp(-U_1(X_1))}{\exp(-U_b(X_1))\exp(-U_0(X_0))}$$

$$W_2 = -\log \frac{\exp\left(-U_b(X_T)\right) \prod_1^T N\left(X_{t-1} \middle| X_t\right)}{\exp\left(-U_a(X_0)\right) \prod_1^T N\left(X_t \middle| X_{t-1}\right)}$$

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$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W_2)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W_2)]$$

Methods – Discretization Error

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$$\Delta f \approx -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W_1)] \approx \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W_1)]$$ **Biased!**

$$\Delta f = -\log \mathbf{E}_{\overrightarrow{\mathbf{P}}}[\exp(-W_2)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W_2)]$$

Methods – Discretization Error

Discretized Escorted Jarzynski & controlled Crooks with Imperfect boundary Conds

When $\exp(-U_0) \not\propto p_a, \exp(-U_1) \not\propto p_b$

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$$\Delta f = -\log \mathbf{E}_{\vec{\mathbf{P}}}[\exp(-W_2)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W_2)]$$ **asymptotically unbiased** 😊

Methods

Learn Stochastic Interpolant using data from both states

$$\Delta f = \log \frac{\mathbf{E}_{\vec{\mathbf{P}}}[g(W - C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W + C)]} + C$$

Calculate “generalized” work **with FB RND**

when $g(x) = \frac{1}{1+\exp(x)}$, $C = \Delta f$

1. Initialize C;
2. Calculate Δf; Set $C \leftarrow \Delta f$;
3. Repeat (2) until converge.

Apply Escorted Jarzynski + minimal-variance estimator

Methods

Learn Stochastic Interpolant using data from both states

Calculate “generalized” work **with FB RND**

1. No need to learn energy; no need to calculate divergence

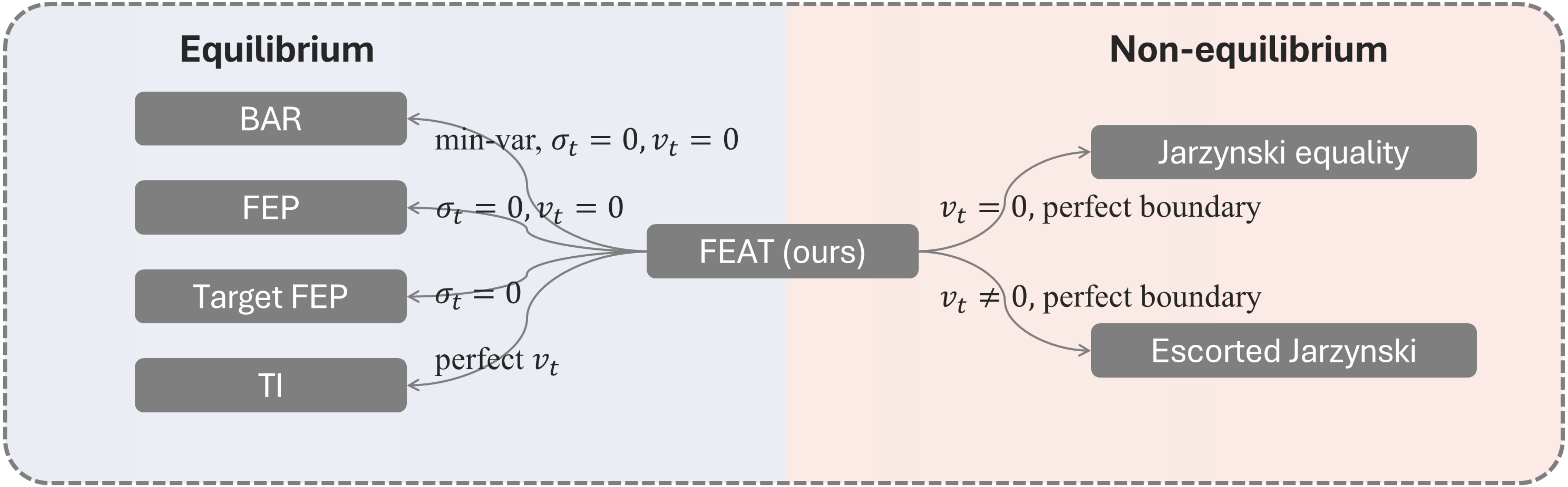
2. No need to have correction term;

3. No discretization bias.

Apply Escorted Jarzynski + minimal-variance estimator

Connection with Other Approaches

$$\mathrm{d}X_t = -\sigma_t^2 \nabla U_t(X_t)\mathrm{d}t + u_t\,(X_t)\mathrm{d}t + \sigma_t \sqrt{2}\,\overrightarrow{\mathrm{d}B_t}$$



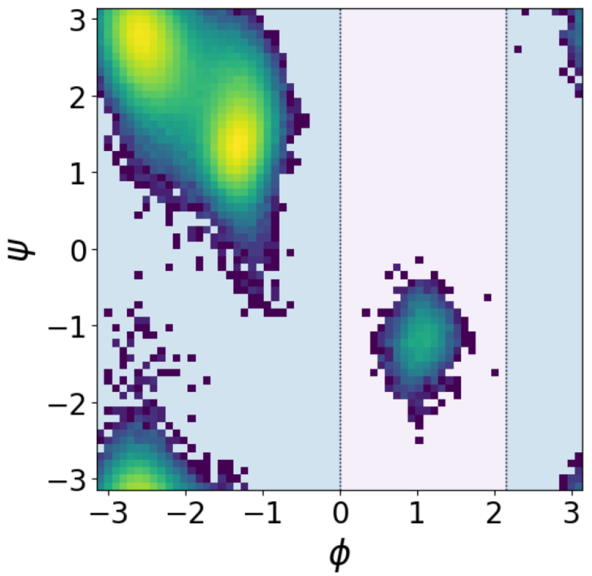
Results

⭐ GMM:
Between a **16-mode GMM** and a **40-mode GMM**

⭐ LJ system:
Between system **without LJ potential** and system **with LJ potential**

⭐ Alanine dipeptide – Solvation (ALDP-S):
Between ALDP in **vacuum** and ALDP in **implicit solvent**

⭐ Alanine dipeptide – Transition (ALDP-T):
Between ALDP in **two meta-stable states**



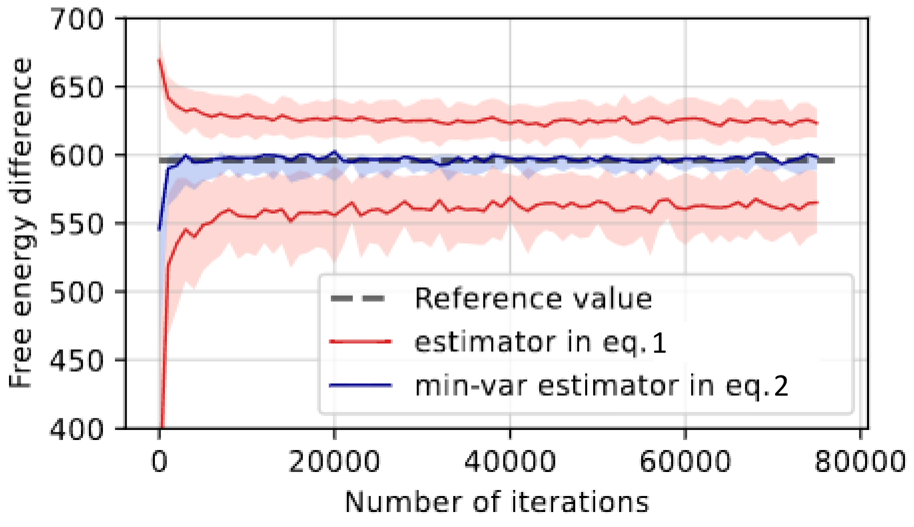
Results

Method	GMM		LJ			ALDP-S	ALDP-T
	$d = 40$	$d = 100$	$d = 55 \times 3$	$d = 79 \times 3$	$d = 128 \times 3$	$d = 22 \times 3$	$d = 22 \times 3$
Reference	0	0	234.77 ± 0.09	357.43 ± 3.43	595.98 ± 0.58	29.43 ± 0.01	-4.25 ± 0.05
Target FEP w. FM	0.09 ± 0.26	-17.96 ± 1.49	232.06 ± 0.03	*	*	29.47 ± 0.22	-4.78 ± 0.32
Neural TI	-181.63 ± 6.65	-402.93 ± 283.75	328.55 ± 336.39	468.76 ± 391.16	N/A	24.93 ± 3.13	-4.11 ± 2.56
Ours	0.04 ± 0.04	-5.34 ± 1.52	232.47 ± 0.15	356.74 ± 0.79	595.04 ± 6.52	29.38 ± 0.04	-4.56 ± 0.08

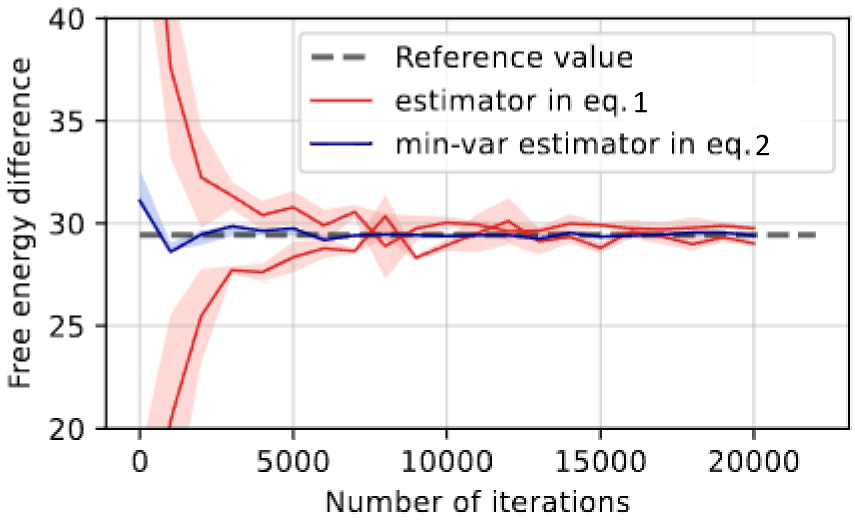
Results

Eq 1: $\Delta f = -\log \mathbf{E}_{\vec{\mathbf{P}}}[\exp(-W)] = \log \mathbf{E}_{\overleftarrow{\mathbf{P}}}[\exp(W)]$

Eq 2: $\Delta f = -\log \frac{\mathbf{E}_{\vec{\mathbf{P}}}[g(W-C)]}{\mathbf{E}_{\overleftarrow{\mathbf{P}}}[g(-W+C)]} + C$



(b) LJ-128.



(c) ALDP-S.

Summary:

- 👉 Non-equilibrium approach to calculate free energy difference
- 👉 Learn transport with Stochastic Interpolants
- 👉 Using FB RND to calculate work
- 👉 Estimate with Minimal variance estimator with Escorted Jarzynski equality

Summary:

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Compared to other baselines:

Neural TI: non-equilibrium for higher flexibility

Neural target FEP: easier calculation with FB RND

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Neural network is generalizable -> future work 😊

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MBAR: we do not need intermediate distributions 😊

Neural network is generalizable -> future work 😊

Need some training time 😔

Neural networks are still limited to handle very large systems 😔

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Thank you!

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