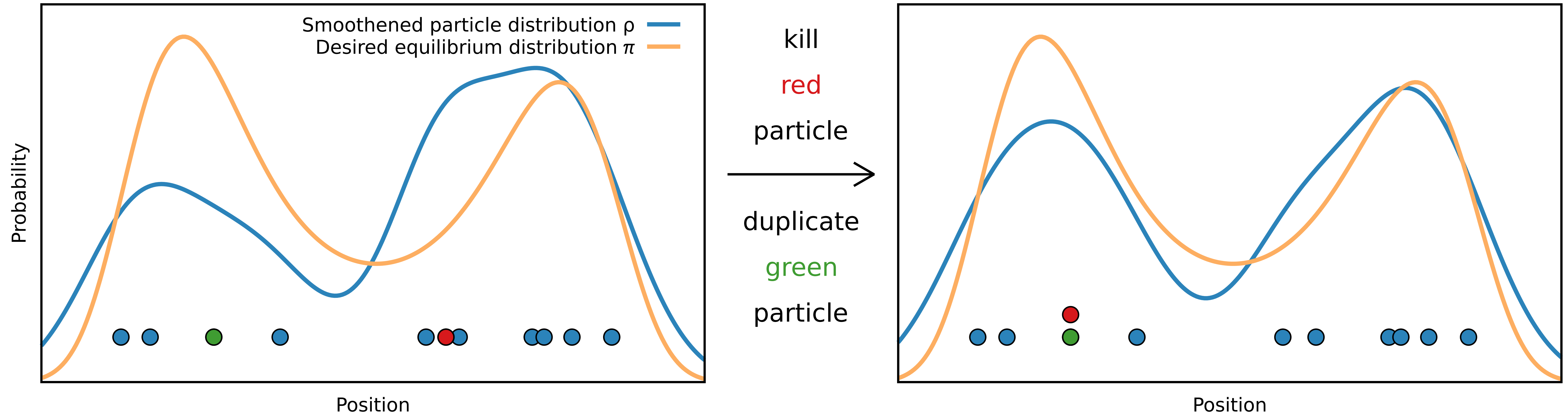
Sampling Rare Event Energy Landscapes via a Birth-Death Process Augmented Langevin Dynamics



Omar Valsson

Work with Benjamin Pampel, Simon Holbach, and Lisa Hartung

UMD Brin MRC — Rare Event
March 2, 2023

University of North Texas, Denton, TX, USA

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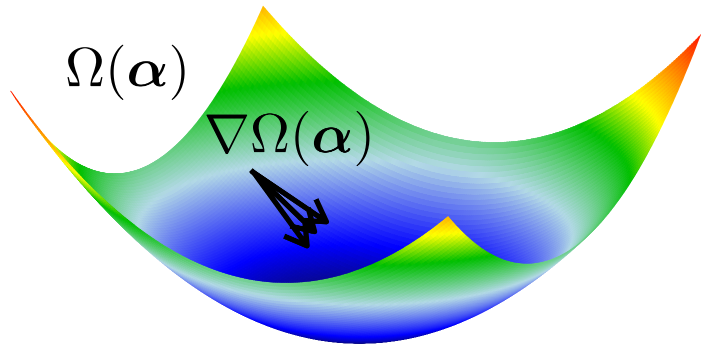
Method Development

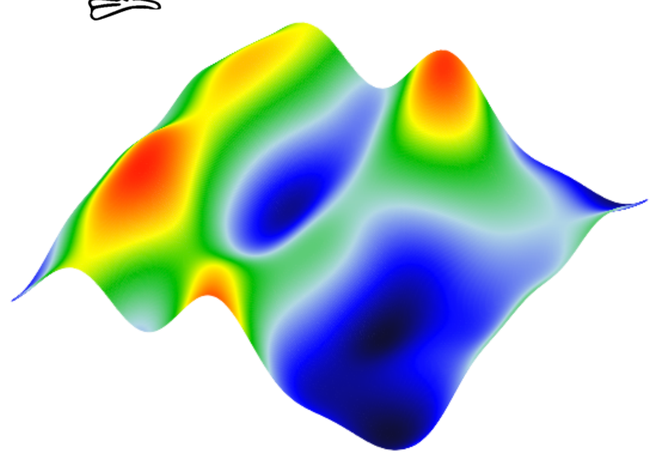
Enhanced Sampling Methods

$$\Omega[V] = \frac{1}{\beta}\log\frac{\int d\mathbf{s}\, e^{-\beta[F(\mathbf{s})+V(\mathbf{s})]}}{\int d\mathbf{s}\, e^{-\beta F(\mathbf{s})}} + \int d\mathbf{s}\, p(\mathbf{s}) V(\mathbf{s})$$

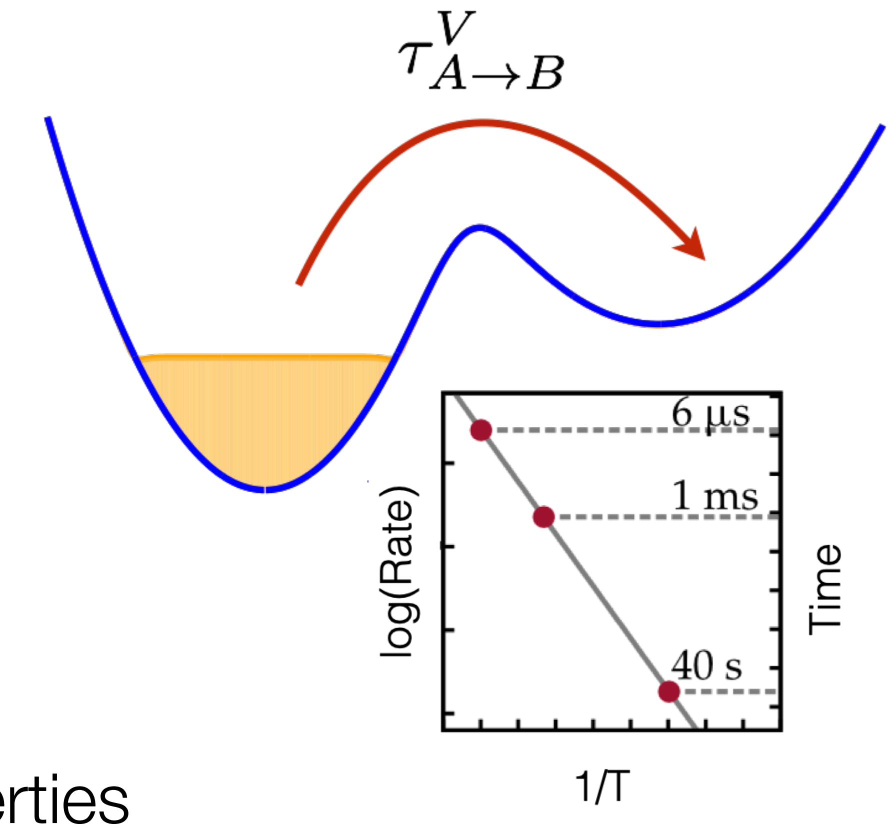


Variationally Enhanced Sampling

PLUMED

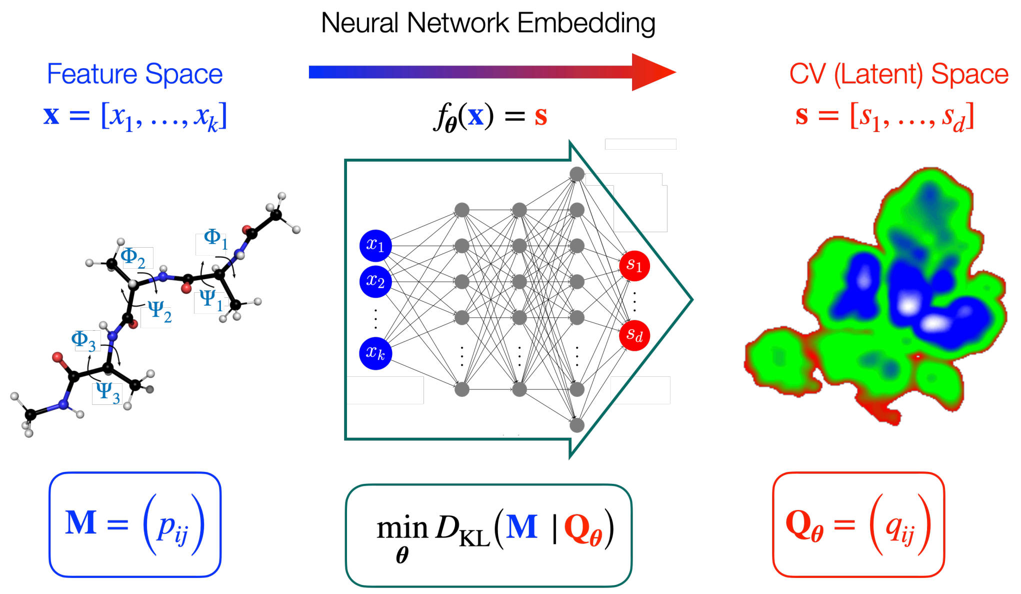


Thermodynamic Properties
Free Energy Landscapes



Kinetic Rates

Machine Learning

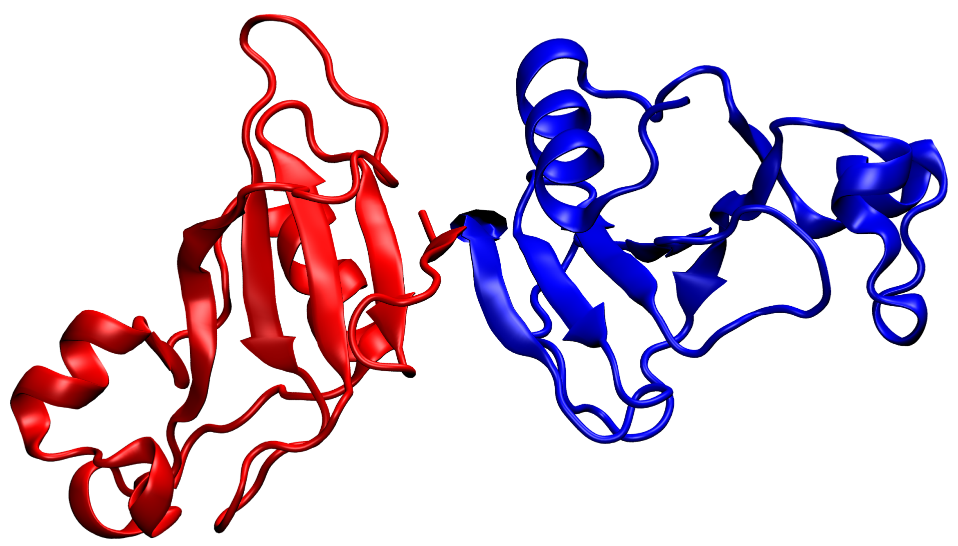


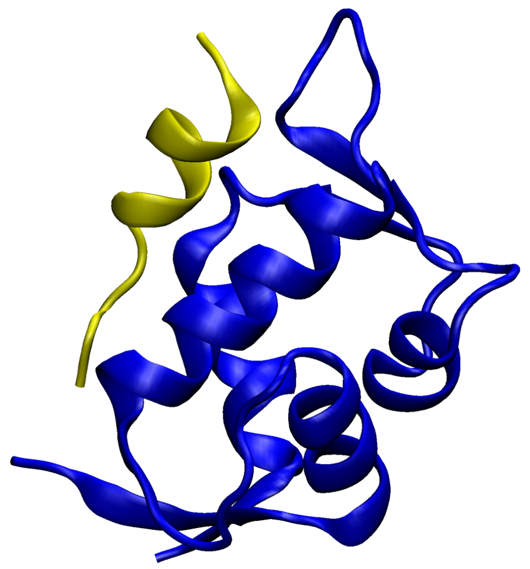
Multiscale Reweighted
Stochastic Embedding

Application Domains

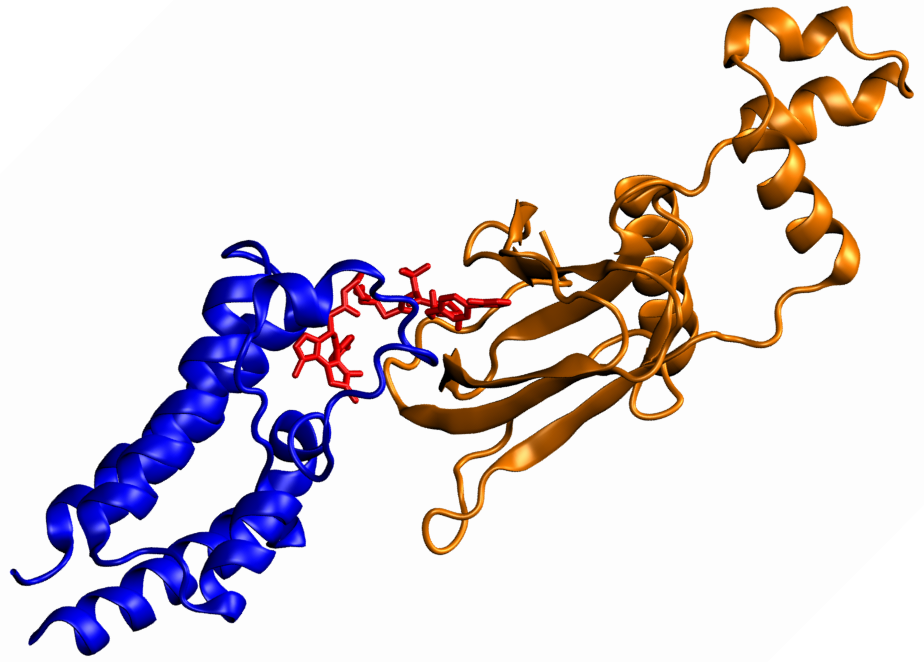
Biomolecular Systems

Protein-Protein Interactions



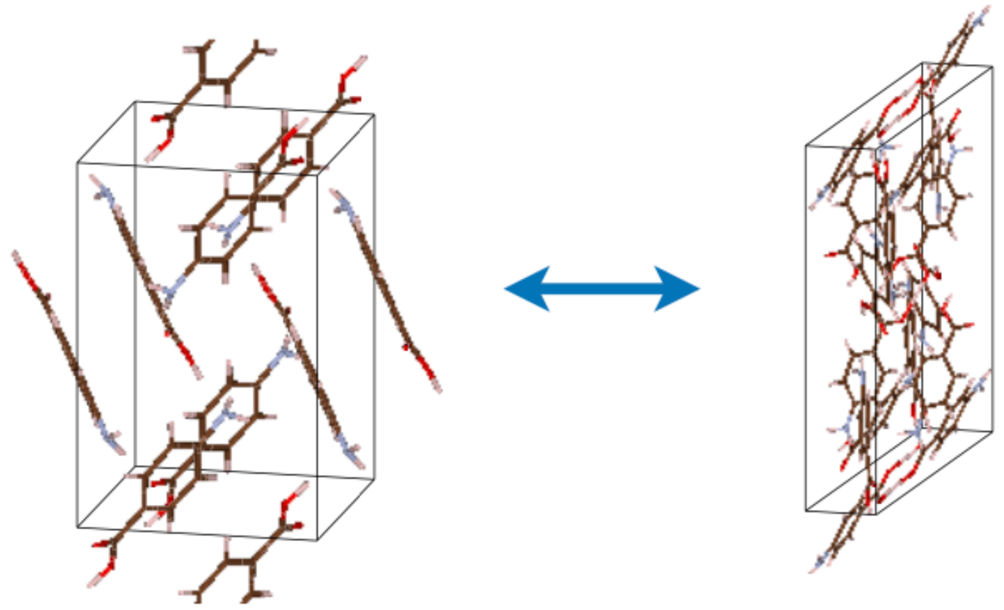


Protein Degradation (PROTACs)



Molecular Crystals

Polymorphic transitions



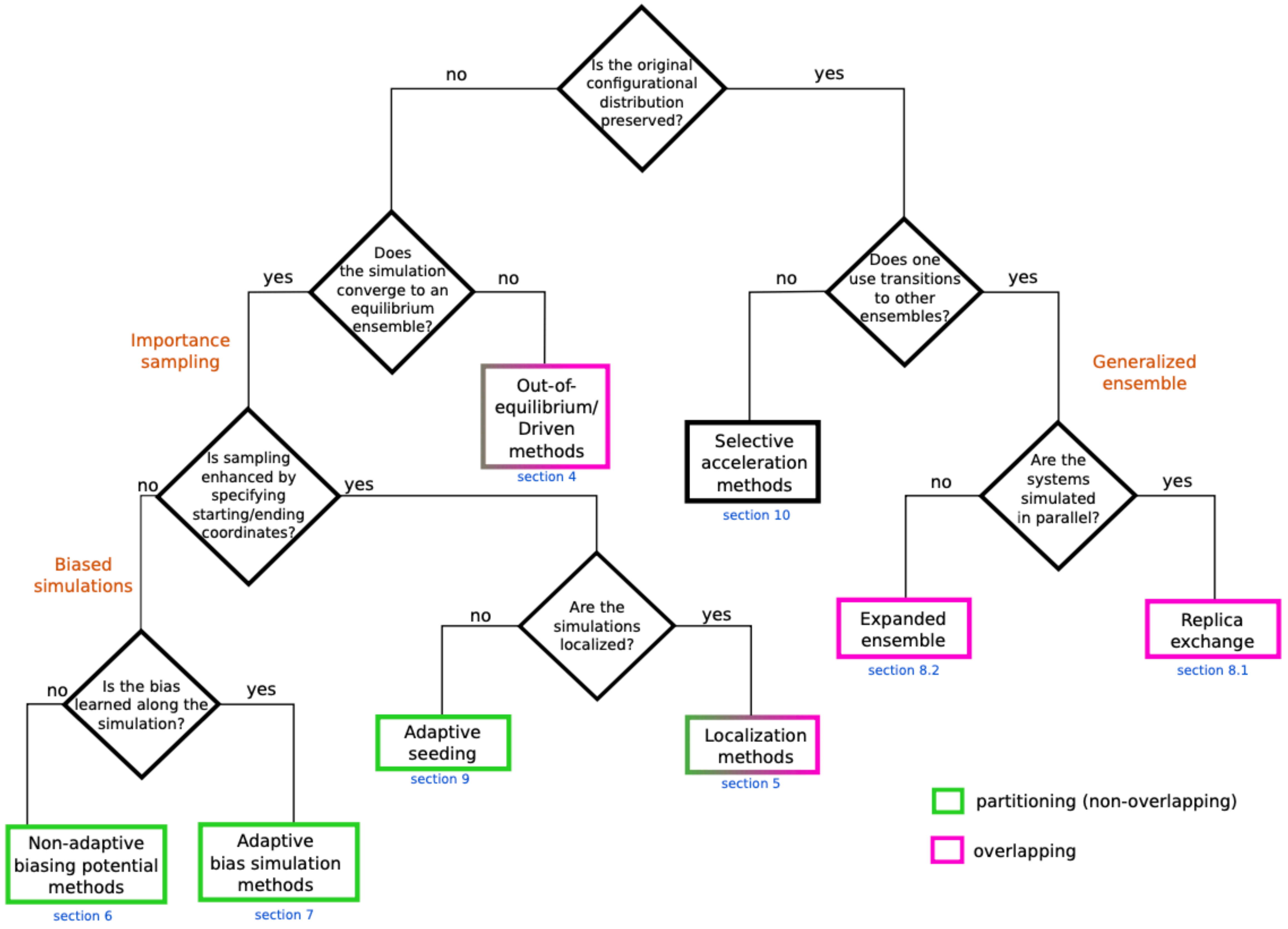
Review of Enhanced Sampling Methods

Enhanced Sampling Methods for Molecular Dynamics Simulations [Article v1.0]

Jérôme Hénin[1*], Tony Lelièvre[2*], Michael R. Shirts[3*], Omar Valsson[4,5*], Lucie Delemotte[6*]

[1]Université Paris Cité, Laboratoire de Biochimie Théorique, CNRS UPR 9080, Paris, France; [2]CERMICS, Ecole des Ponts ParisTech, INRIA, Marne-la-Vallée, France; [3]Department of Chemical and Biological Engineering, University of Colorado Boulder, Boulder, CO, USA, 80309; [4]University of North Texas, Department of Chemistry, Denton, TX, USA; [5]Max Planck Institute for Polymer Research, Mainz, Germany; [6]KTH Royal Institute of Technology, Science for Life Laboratory, Stockholm, Sweden

Abstract Enhanced sampling algorithms have emerged as powerful methods to extend the utility of molecular dynamics simulations and allow the sampling of larger portions of the configuration space of complex systems in a given amount of simulation time. This review aims to present the unifying principles of and differences between many of the computational methods currently used for enhanced sampling in molecular simulations of biomolecules, soft matter and molecular crystals. In fact, despite the apparent abundance and divergence of such methods, the principles at their core can be boiled down to a relatively limited number of statistical and physical concepts. To enable comparisons, the various methods are introduced using similar terminology and notation. We then illustrate in which ways many different methods combine features of a relatively small number of the same enhanced sampling concepts. This review is intended for scientists with an understanding of the basics of molecular dynamics simulations and statistical physics who want a deeper understanding of the ideas that underlie various enhanced sampling methods and the relationships between them. This living review is intended to be updated to continue to reflect the wealth of sampling methods as they continue to emerge in the literature.



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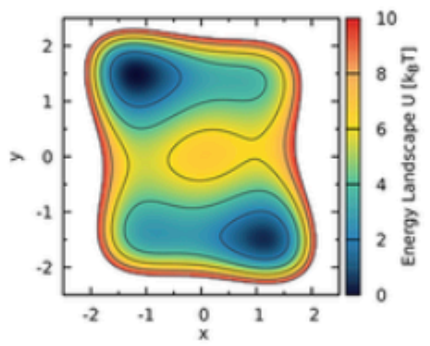
Editors' Suggestion

Sampling rare event energy landscapes via birth-death augmented dynamics

Benjamin Pampel, Simon Holbach, Lisa Hartung, and Omar Valsson

Phys. Rev. E **107**, 024141 (2023) – Published 28 February 2023



A common problem in simulations of complex systems is the separation of metastable states by high barriers that hinder transitions between the states. The authors address this by adapting a sampling algorithm that includes a birth-death process, and show that this scheme can efficiently sample energy landscapes with such barriers.

Show Abstract +

Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

Numerical Implementation

Mathematical analysis

Dr. Benjamin Pampel

Max Planck Institute for Polymer Research

Dr. Lisa Hartung

Dr. Simon Holbach

University of Mainz

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Funded by DFG Deutsche Forschungsgemeinschaft German Research Foundation

Overdamped Langevin Dynamics

Overdamped Langevin equation that describe the time evolution of the motion of a particle in an energy landscape $U(x): \mathbb{R}^d \to \mathbb{R}$ that we want to sample

$$\mathrm{d}x(t) = -D\beta \nabla U(x(t))\,\mathrm{d}t + \sqrt{2D}\,\mathrm{d}W(t)$$

$D > 0$: diffusion coefficient

$\beta = 1/k_\mathrm{B}T$

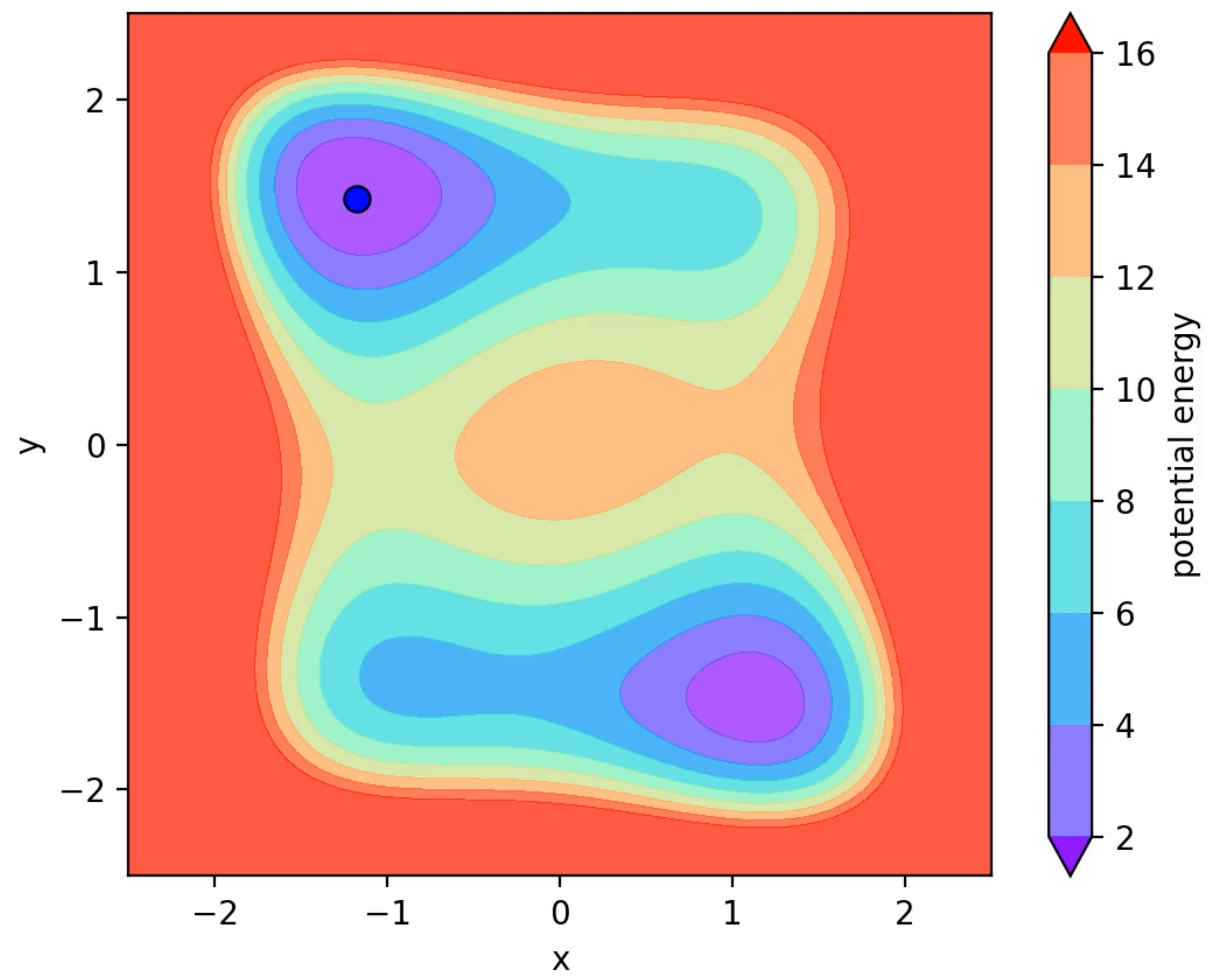
W: standard Brownian motion on $\mathbb{R}$

$x(0) \in \mathbb{R}^d$: initial conditions

The solution $X = (x(t))_{t\geq 0}$ is a Markov process that has a unique stationary (Boltzmann) distribution

$$\pi(x) = Z^{-1}e^{-\beta U(x)}$$

Normalization constant Z generally unknown



Can simulate in practice using the Euler-Maruyama algorithm

Gives a trajectory that samples $\pi(x)$ (given infinite time)

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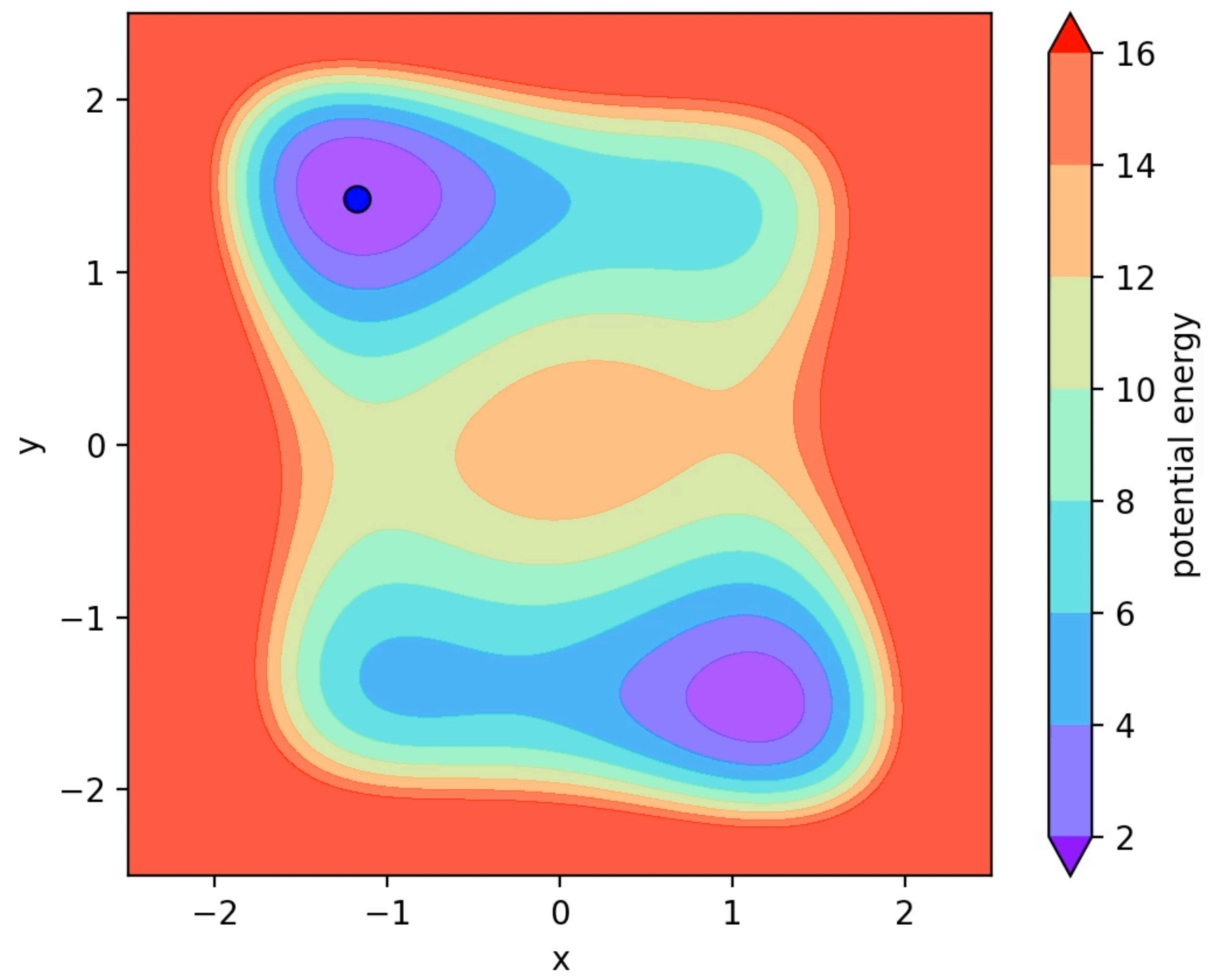

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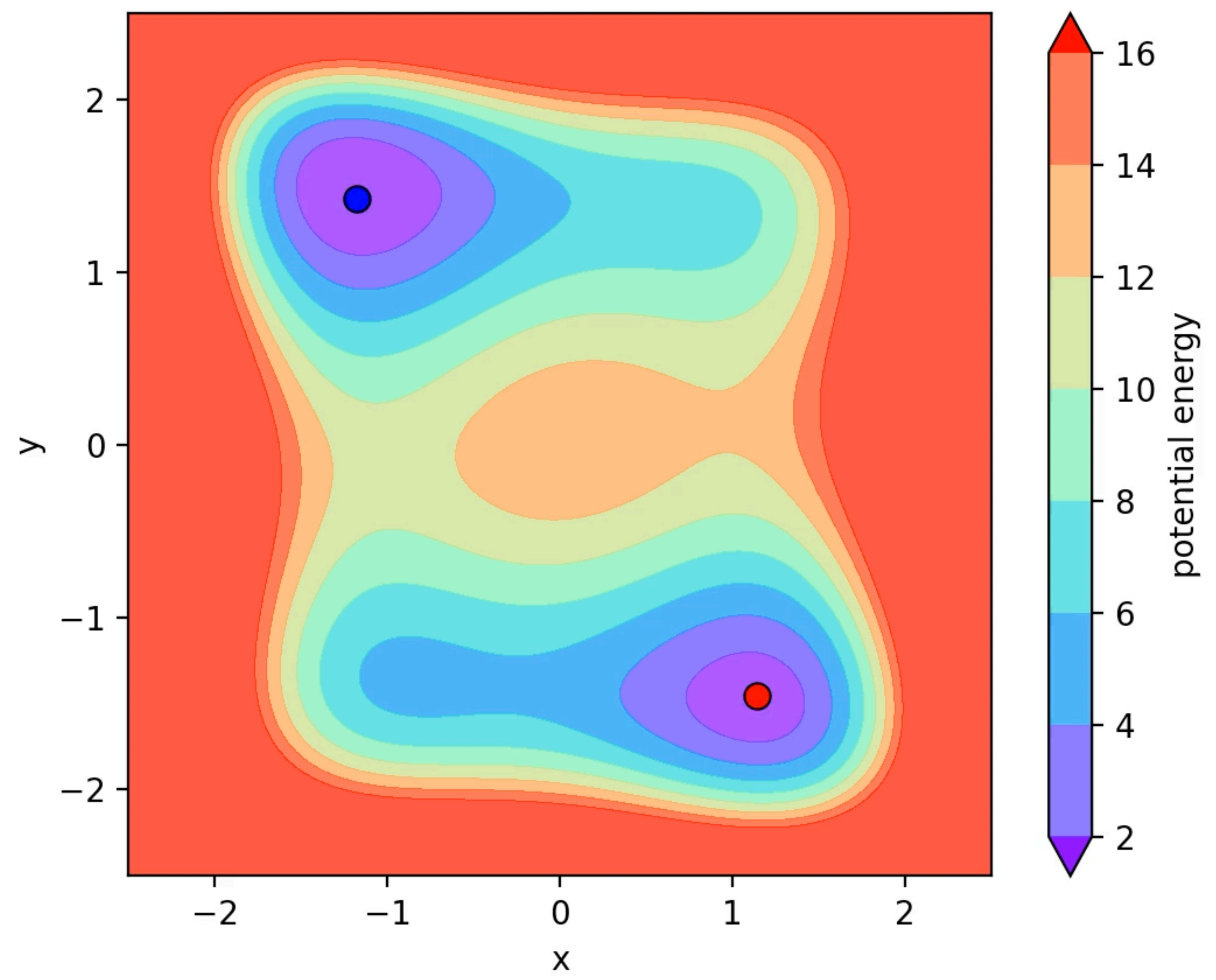

Can simulate in practice using the Euler-Maruyama algorithm

Gives a trajectory that samples $\pi(x)$ (given infinite time)

Can use multiple independent simulations to improve sampling statistics

Fokker-Planck Equation

The overdamped Langevin equation is the probabilistic counterpart of the Fokker-Planck equation that describes the time evolution of probability density $\rho_t(x)$

$$\partial_t \rho_t(x) = L^* \rho_t(x) \quad \text{with} \quad L^* \rho_t(x) = D \nabla \cdot \left(\nabla \rho_t(x) + \beta \rho_t(x) \nabla U(x) \right)$$

With the distribution $\pi(x)$ as the stationary solution, $L^* \pi(x) = 0$

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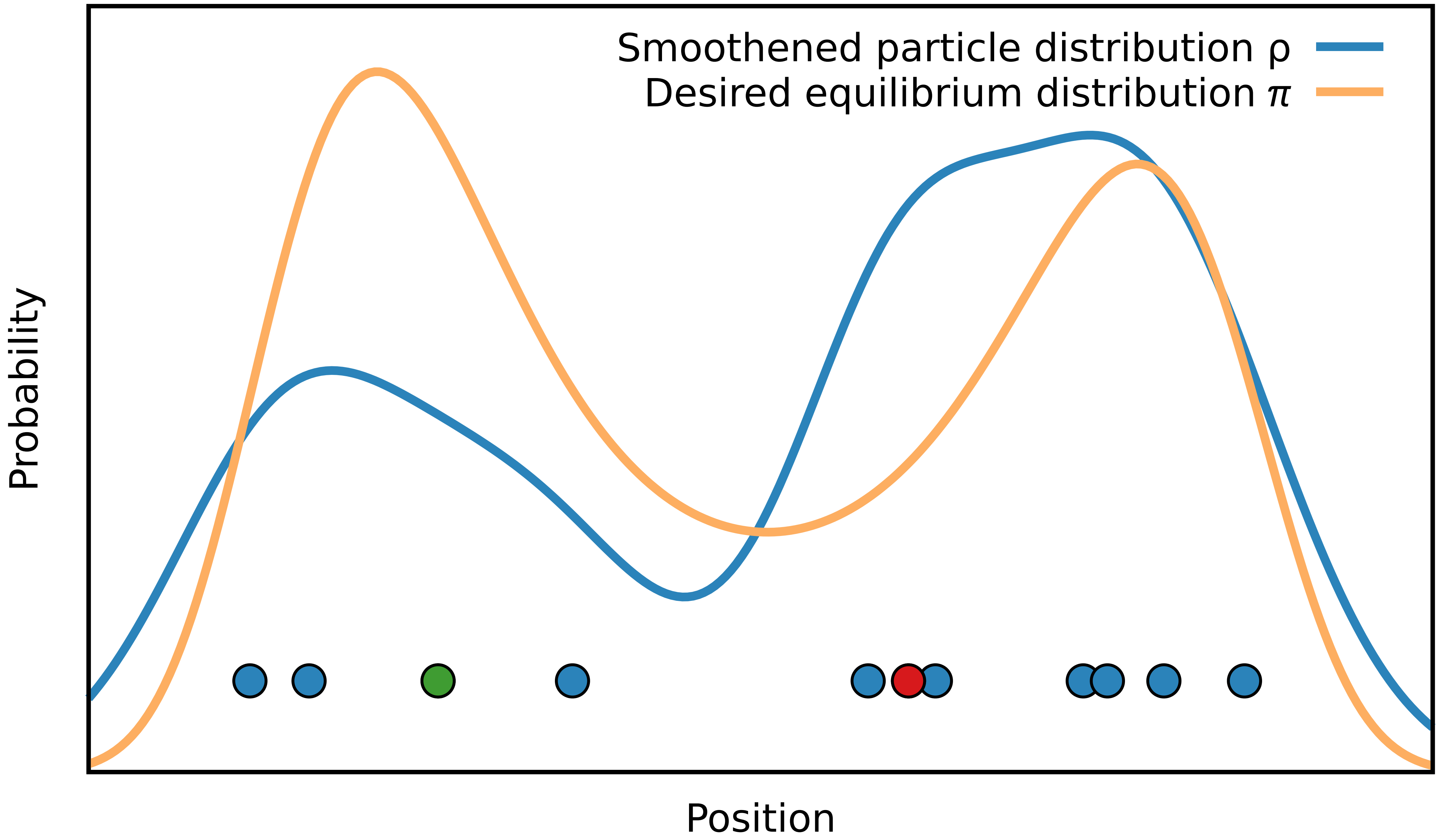
Particle picture to solve the Fokker-Planck: consider an ensemble of N independent Langevin dynamics simulations

Empirical particle distribution $\mu_t^N(x) = \frac{1}{N} \sum_k^N \delta_{x_k(t)}$

Smoothed estimate by employing a convolution with a (Gaussian) kernel, i.e., kernel density estimation

$$K * \mu_t^N(x) = \frac{1}{N} \sum_k^N K(x - x_k(t))$$

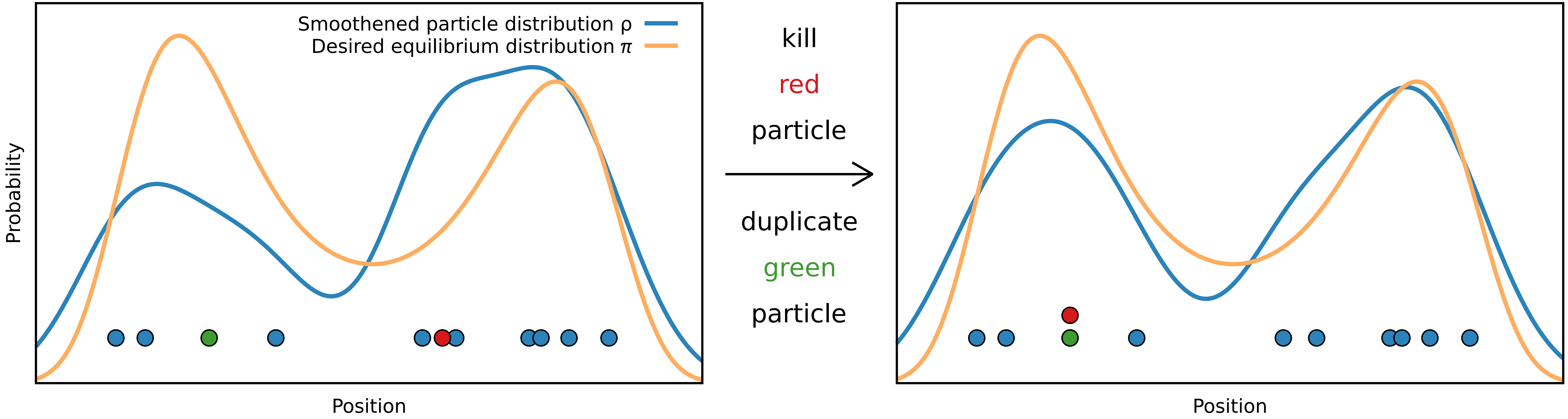
Should approximate the stationary distribution in the long time limit $\lim_{t \to \infty} K * \mu_t^N \approx \pi(x)$



Ad-Hoc Birth-Death Events

Can we do better?

Idea: Improve the agreement with the desired equilibrium distribution by killing and duplicating particle (i.e. simulations)



We address here how we can do this in a theoretically sound way

Original idea from [1], but an issue with obtaining correct sampling that we fix in [2]

[1] Lu, Lu, and Nolen, arXiv:1905.09863

[2] Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

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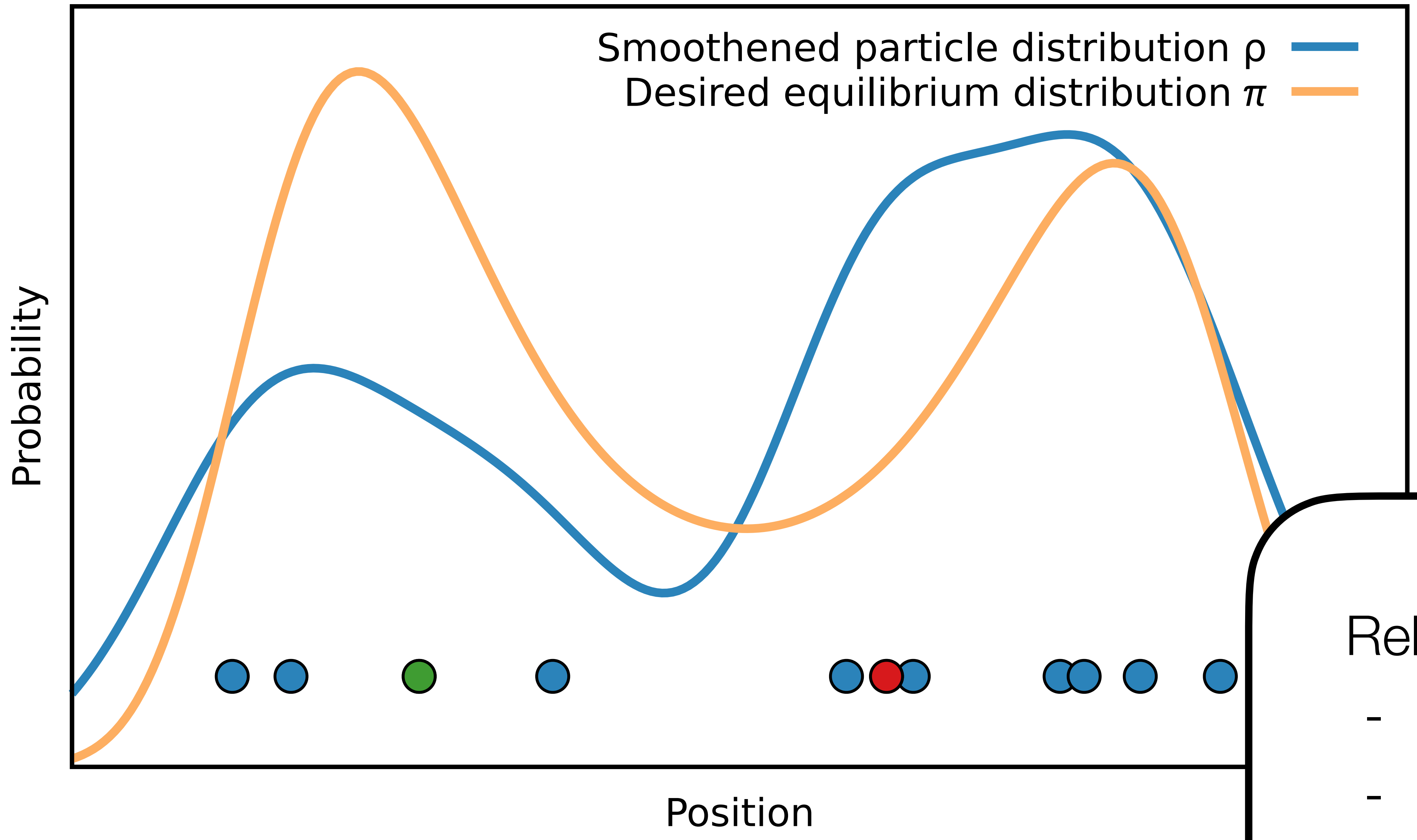

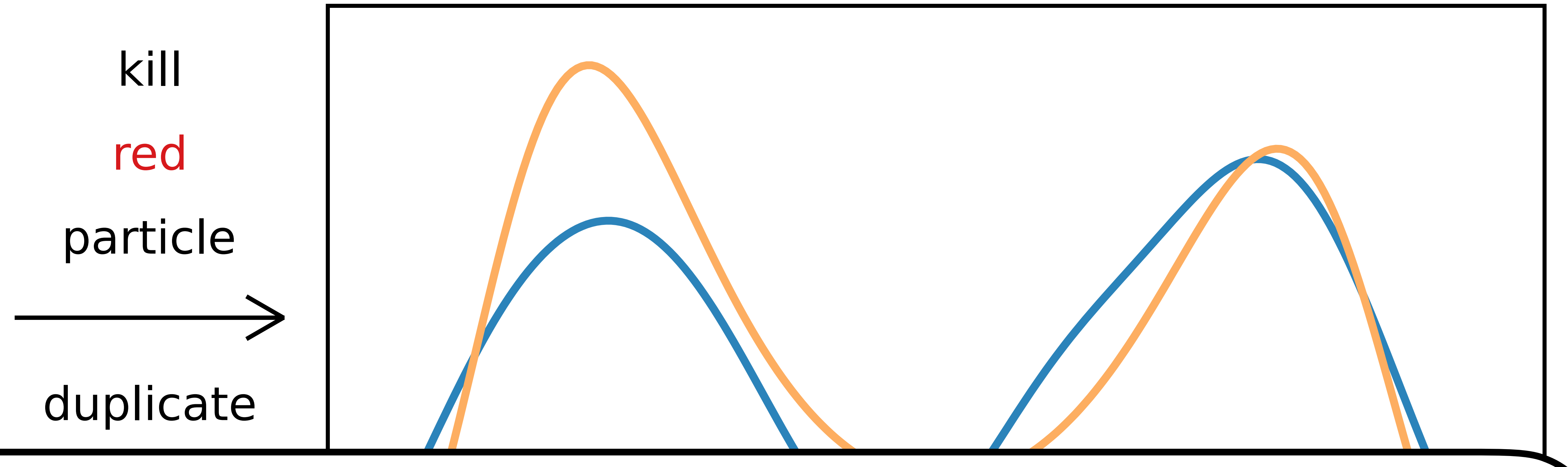

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Related works

- Lindsey, Weare, & Zhang, SIAM ASA J Uncertain Quantification 2022
- Rotskoff, Jelassi, Bruna, and Vanden-Eijnden, ICML/PMLR 2019
- Goodman & Weare, Comm. App. Math. And Comp. Sci. 2010
- Grassberger CPC 2002
- …..

[1] Lu, Lu, and Nolen, arXiv:1905.09863

[2] Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

Fokker-Planck-Birth-Death Equation

Consider a non-linear and non-local Fokker-Planck-Birth-Death (FP-BD) equation [1]

$$\partial_t \rho_t(x) = L^* \rho_t(x) - \tau_\alpha \alpha_\pi(\rho_t)\, \rho_t$$

$\tau_\alpha > 0:$ birth-death rate with units 1/time, can assume $\tau_\alpha = 1$

Where we have added a so-called **birth-death term** $\alpha_\pi(\rho_t)$

$$\alpha_\pi(\rho_t) = \log \frac{\rho_t(x)}{\pi(x)} - \int \log\left(\frac{\rho_t(x)}{\pi(y)}\right) \rho_t(x)\, \mathrm{d}y$$

First term: Increase $\rho_t(x)$ at x if smaller than $\pi(x)$, decrease if larger

Second term: Preserves normalization

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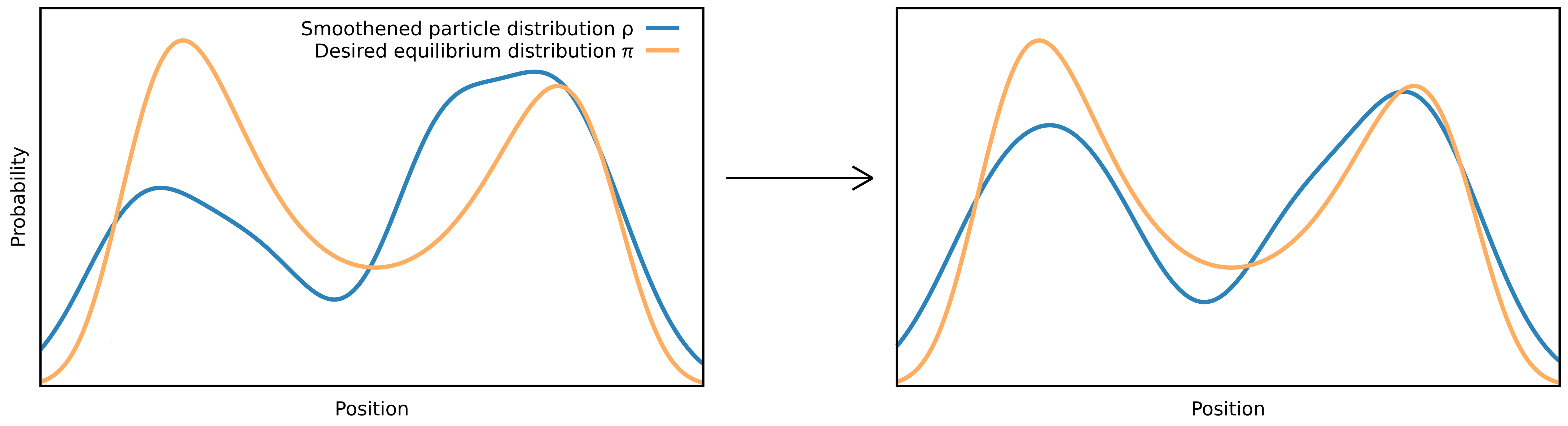
Second term: Preserves normalization

Where $\alpha_\pi(\pi) = 0$ so $\pi(x)$ remains the stationary solution,
i.e., adding the birth-death terms does not change the equilibrium

The effect of the birth-death term is to allow for non-local moves of the probability density (with normalization preserved)

Can be shown that the speed of convergence is independent of barrier heights

Now, the question is, how can we solve this equation? Can we define a probabilistic counterpart to this FB-BD equation?



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Interacting Particle Picture of the Fokker-Planck-Birth-Death Equation

Assume N particles with positions $x_1(t), \ldots, x_N(t) \in \mathbb{R}^d$ at time $t \geq 0$ and empirical particle distribution $\mu_t^N(x) = \frac{1}{N}\sum_k^N \delta_{x_k(t)}$

Replace the birth-death term $\alpha_\pi(\rho_t)$ with a smoothened approximation $\Lambda_\pi(\rho_t)$

$$\partial_t \rho_t(x) = L^* \rho_t(x) - \tau_\alpha \Lambda_\pi(\rho_t)\, \rho_t$$

Leads to the following dynamics:

Each particle diffuses independently according to the overdamped Langevin dynamics

Each particle has an independent exponential clock that strikes with rate $\tau_\alpha \, | \Lambda(\mu_t^N)(x_i(t)) \, |$

- $\Lambda(\mu_t^N)(x_i(t)) > 0$: kill particle i (and duplicate random selected other)
- $\Lambda(\mu_t^N)(x_i(t)) < 0$, duplicate particle i (and kill random selected other)

total particle number N is preserved

Thus, this birth-death dynamics will help distribute the particles according to $\pi(x)$ and speed up convergence of $\mu_t^N(x)$ to $\pi(x)$

We are left with selecting the smoothened approximation $\Lambda_\pi(\rho_t)$

[1] Lu, Lu, and Nolen, arXiv:1905.09863
[2] Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

Interacting Particle Picture of the Fokker-Planck-Birth-Death-Equation

Few possible choices for the smoothened approximation $\Lambda_\pi(\rho_t)$

All feature a convolution with a Gaussian kernel $K(x)$ with covariance matrix $\boldsymbol{\Sigma}$

$$K * f(x) = \int K(x-y) f(y)\, dy \qquad \text{with} \qquad K(x) = \frac{1}{(2\pi)^{d/2}|\boldsymbol{\Sigma}|^{1/2}} \exp\left(-\frac{x^\top \boldsymbol{\Sigma}^{-1} x}{2}\right), \quad x \in \mathbb{R}^d,$$

The original choice from [1]

$$\Lambda^0(\mu_t^N) = \log \frac{K * \mu_t^N(x)}{\pi(x)} - \int \log\left(\frac{K * \mu_t^N(y)}{\pi(y)}\right) \mu_t^N(y)\, \mathrm{d}y$$

Compare the smoothed particle density with $\pi(x)$

But, one crucial shortcoming, $\Lambda^0(\pi) \neq 0$, so $\pi(x)$ is not a stationary solution to approximate FP-BD equation
In practice: converges to the wrong distribution

Could solve this by adding a correction term [2]: $\Lambda^{\mathrm{ad}}(f) = \Lambda^0(f) - \Lambda^0(\pi)$, but not convenient for mathematical analysis

[1] Lu, Lu, and Nolen, arXiv:1905.09863
[2] Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

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Our choice, a multiplicative term (new contribution introduced in [2])

$$\Lambda^{\mathrm{mu}}(\mu_t^N) = \log \frac{K * \mu_t^N(x)}{K * \pi(x)} - \int \log\left(\frac{K * \mu_t^N(y)}{K * \pi(y)}\right) \mu_t^N(y)\, \mathrm{d}y$$

Compare the smoothed particle density with $K * \pi(x)$, the convoluted $\pi(x)$

Cleary, $\Lambda^{\mathrm{mu}}(\pi) = 0$

Work with $\Lambda^{\mathrm{mu}}(\mu_t^N)$, unless stated otherwise

[1] Lu, Lu, and Nolen, arXiv:1905.09863
[2] Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

Interacting Particle Picture: Mathematical Properties

If we formally take $\mathbf{\Sigma} = \mathbf{0}$ and interpret $K(x)$ as a Dirac delta function
=> all approximation $\Lambda^{0}(\pi)$, $\Lambda^{\mathrm{ad}}(\pi)$, and $\Lambda^{\mathrm{mu}}(\pi)$ correspond to the exact term $\alpha(\pi)$

Can proof that empirical particle distribution $\mu_t^N(x)$ convergences weakly to the solution $\rho_t(x)$ of the approximate Fokker-Planck-Birth-Death equation when $N \to \infty$

Gives proper meaning to the idea that this interacting particle system is the probabilistic counter-part of the Fokker-Planck-Birth-Death equation.

If we increase the magnitude of the Gaussian covariance matrix, $|\Sigma| \to \infty$, we turn off the effect of the birth-death term

See [1] and [2] for further mathematical properties and proofs

[1] Lu, Lu, and Nolen, arXiv:1905.09863
[2] Pampel, Holbach, Hartung, Valsson, Phys Rev E 107, 024141 (2023)

Interacting Particle Picture: Implementation

Can write out the explicit birth-death term in the particle-based picture

$$\Lambda^{\text{mu}}(\mu_t^N)(x_i) = \log\left(\frac{1}{N}\sum_{j=1}^{N} K(x_i - x_j)\right) - \log(K * \pi(x_i)) - \frac{1}{N}\sum_{k=1}^{N}\left[\log\left(\frac{1}{N}\sum_{j=1}^{N} K(x_k - x_j)\right) - \log(K * \pi(x_k))\right].$$

Employ diagonal Gaussian kernels with bandwidths $\boldsymbol{\sigma} = (\sigma_1, \ldots, \sigma_d)$

Note: do not need to know the normalization of $\pi(x)$

$$K(x) = \frac{1}{(2\pi)^{d/2}\prod_{i=1}^{d}\sigma_i}\exp\left(-\sum_{i=1}^{d}\left(\frac{x^{(i)}}{\sqrt{2}\sigma_i}\right)^2\right)$$

Duplicate/kill particles with probability

$$q_i = 1 - \exp\left(-\tau_\alpha|\Lambda_i|M\theta\right)$$

$\Lambda_i := \Lambda^{\text{mu}}(\mu_t^N)(x_i)$ Langevin time step

M : Number of Langevin steps between attempting birth/death moves

θ : Langevin time step

Interacting Particle Picture: Implementation

Algorithm 1: Birth-death augmented Langevin dynamics

Input:

- Potential U (and temperature T) corresponding to the equilibrium distribution π
- Langevin solver $L(X, P, U, \theta)$ with corresponding parameters
- Calculation rule for smoothed birth-death term Λ using Gaussian kernel K with bandwidths $\boldsymbol{\sigma}$
- Rate factor τ_α
- Langevin time step θ
- Number of Langevin steps J
- Number of Langevin steps between birth-death attempts M
- N particles with initial positions $X = \{x_i\}_{i=1}^N$ and momenta $P = \{p_i\}_{i=1}^N$

Output:

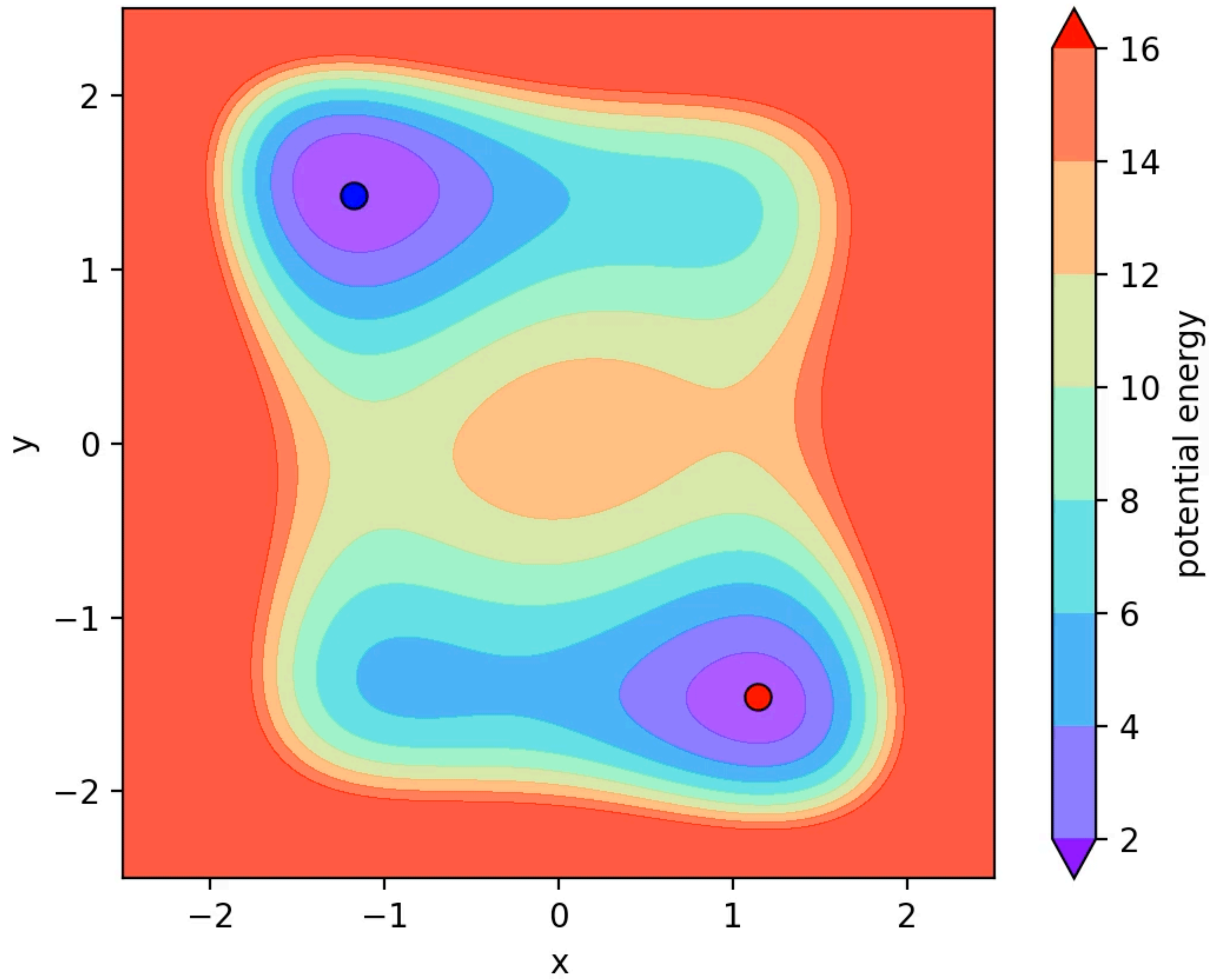
- Set of particles whose empirical measure approximates π

for $t \leftarrow 1$ **to** J **do**
  update X and P by Langevin solver $L(X, P, U, \theta)$
  if $(t \mod M) = 0$ **then**
    Calculate Λ for all particles
    Draw N independent random numbers $\{r_i\}_{i=1}^N$ uniformly from $[0, 1)$
    Make list ζ of indices i for which $r_i \leq q_i = 1 - \exp(-\tau_\alpha |\Lambda_i| M\theta)$
    Shuffle ζ randomly
    foreach $i \in \zeta$ [a] **do**
      Select particle j uniformly from all other particles
      if $\Lambda_i > 0$ **then**
        $x_i \leftarrow x_j;\ p_i \leftarrow p_j$
      else if $\Lambda_i < 0$ **then**
        $x_j \leftarrow x_i;\ p_j \leftarrow p_i$
      end if
    end foreach
  end if
end for

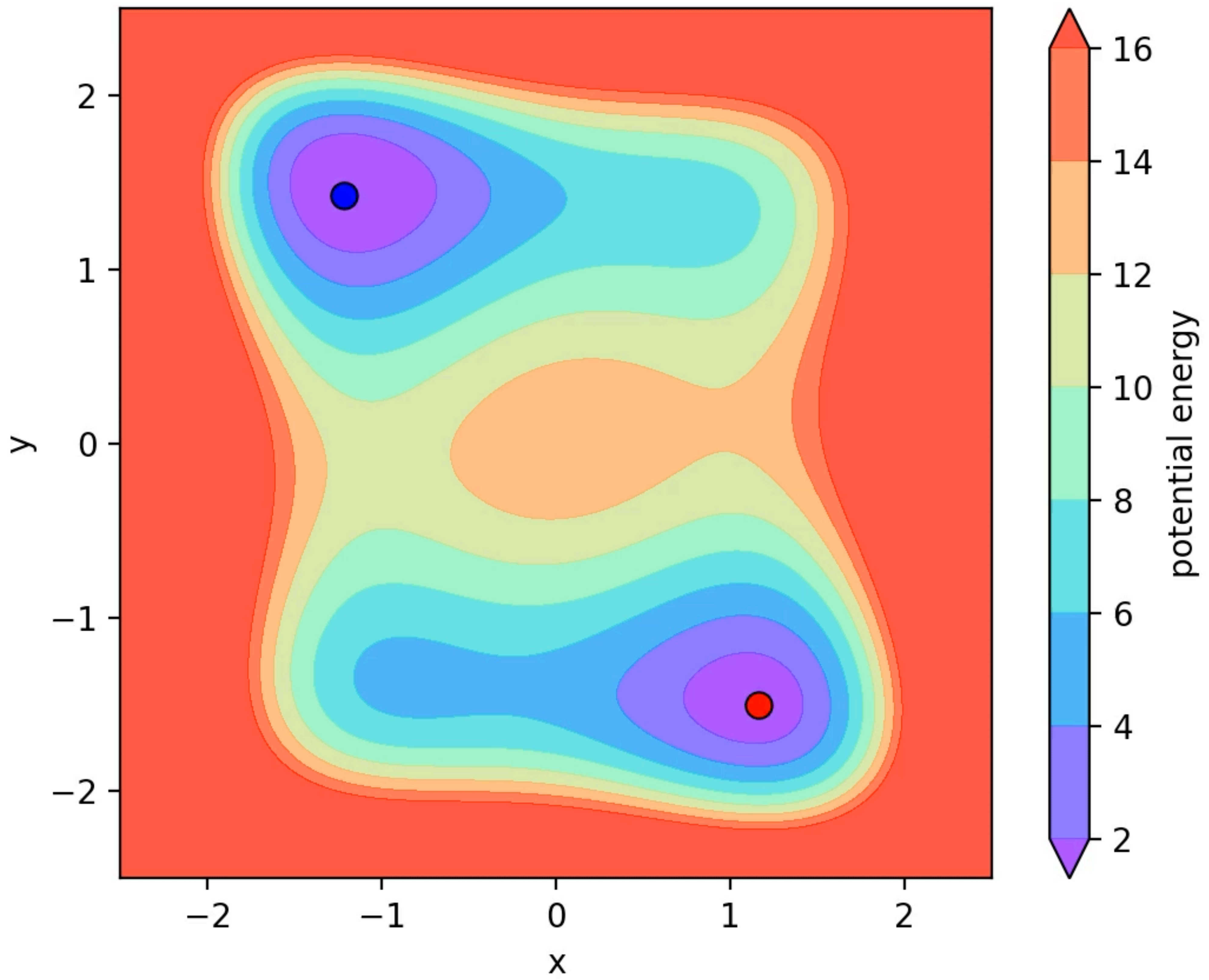
Implemented in a Python code
Available on Github: github.com/bpampel/bdld

Example of Behavior

Without birth/death moves (i.e., pure Langevin dynamics)



With birth/death moves



$N = 100$ particles in both cases, only show two

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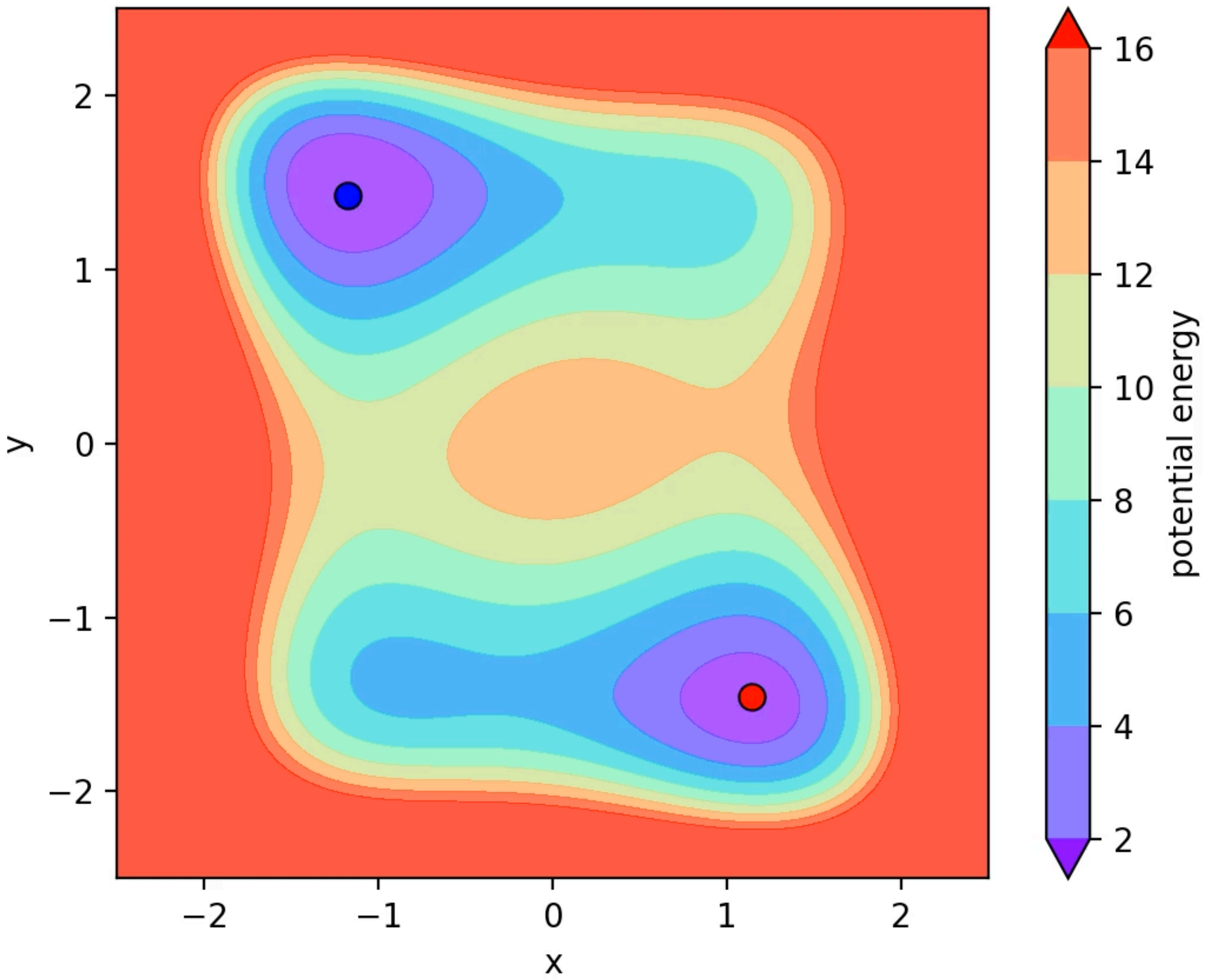

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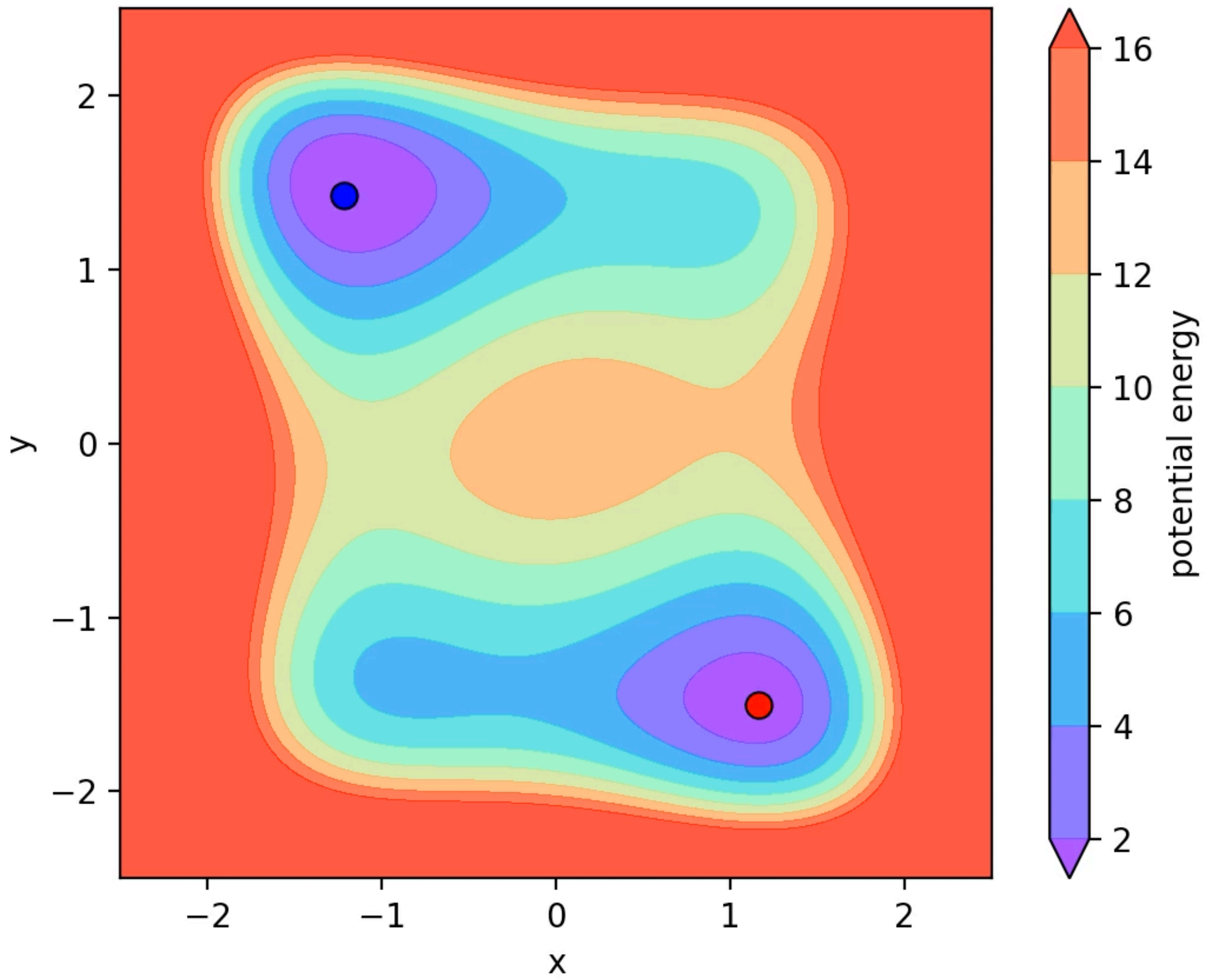
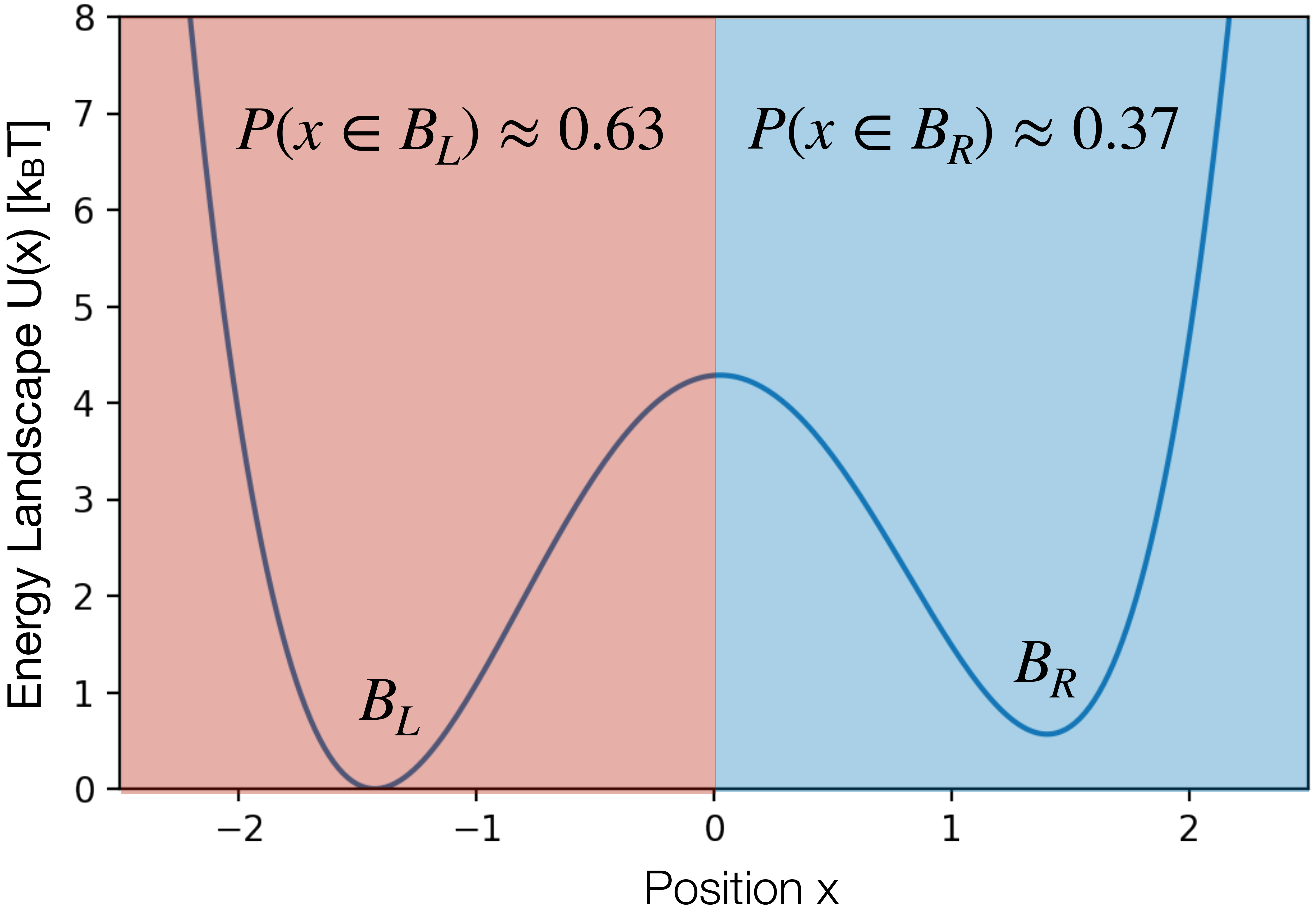


$N = 100$ particles in both cases, only show two

Applications

Will explore the performance of this birth/death augmented Langevin dynamics scheme and the impact of various parameters by using prototypical rare event energy landscapes

Start with a two state model with a moderately high barrier (~ 4 $k_B T$)



Unless otherwise stated

Employ $N = 100$ particles

Euler-Maruyama algorithm to solve the overdamped Langevin dynamics

$M = 100$ Langevin steps between trying birth/death moves

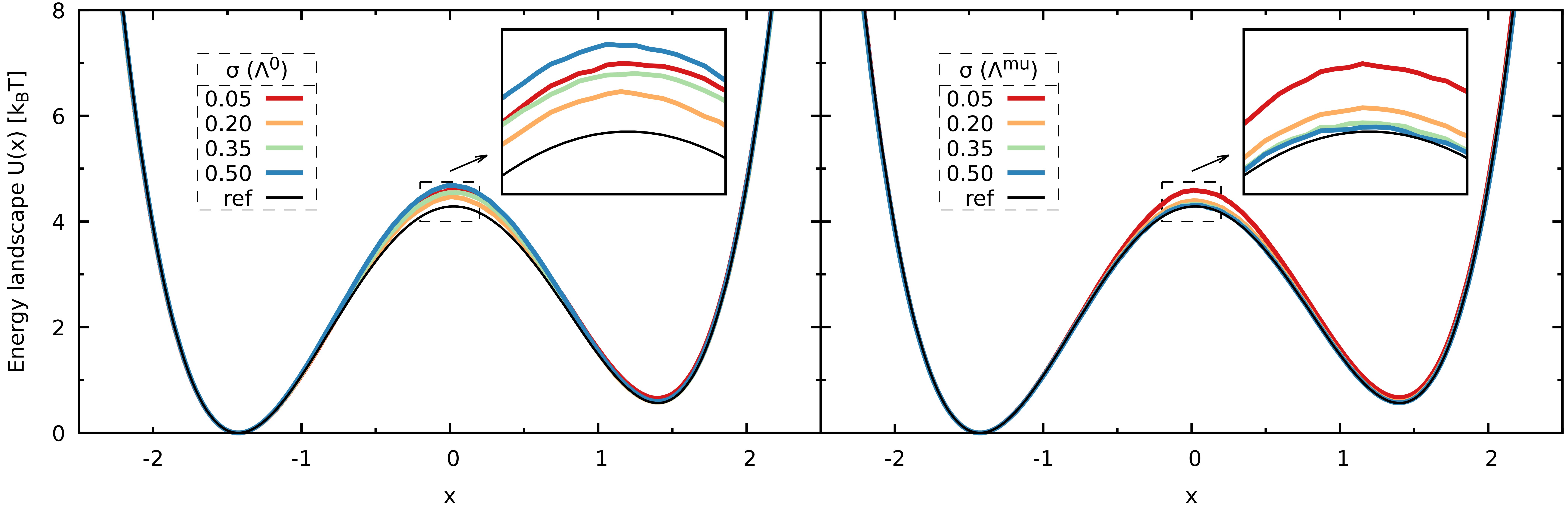
Choice of the Approximation

Original approximation from [1]

$$\Lambda^0(\mu_t^N) = \log \frac{K * \mu_t^N(x)}{\pi(x)} - \int \log\left(\frac{K * \mu_t^N(y)}{\pi(y)}\right) \mu_t^N(y)\,\mathrm{d}y$$

Multiplicative approximation from our work [2]

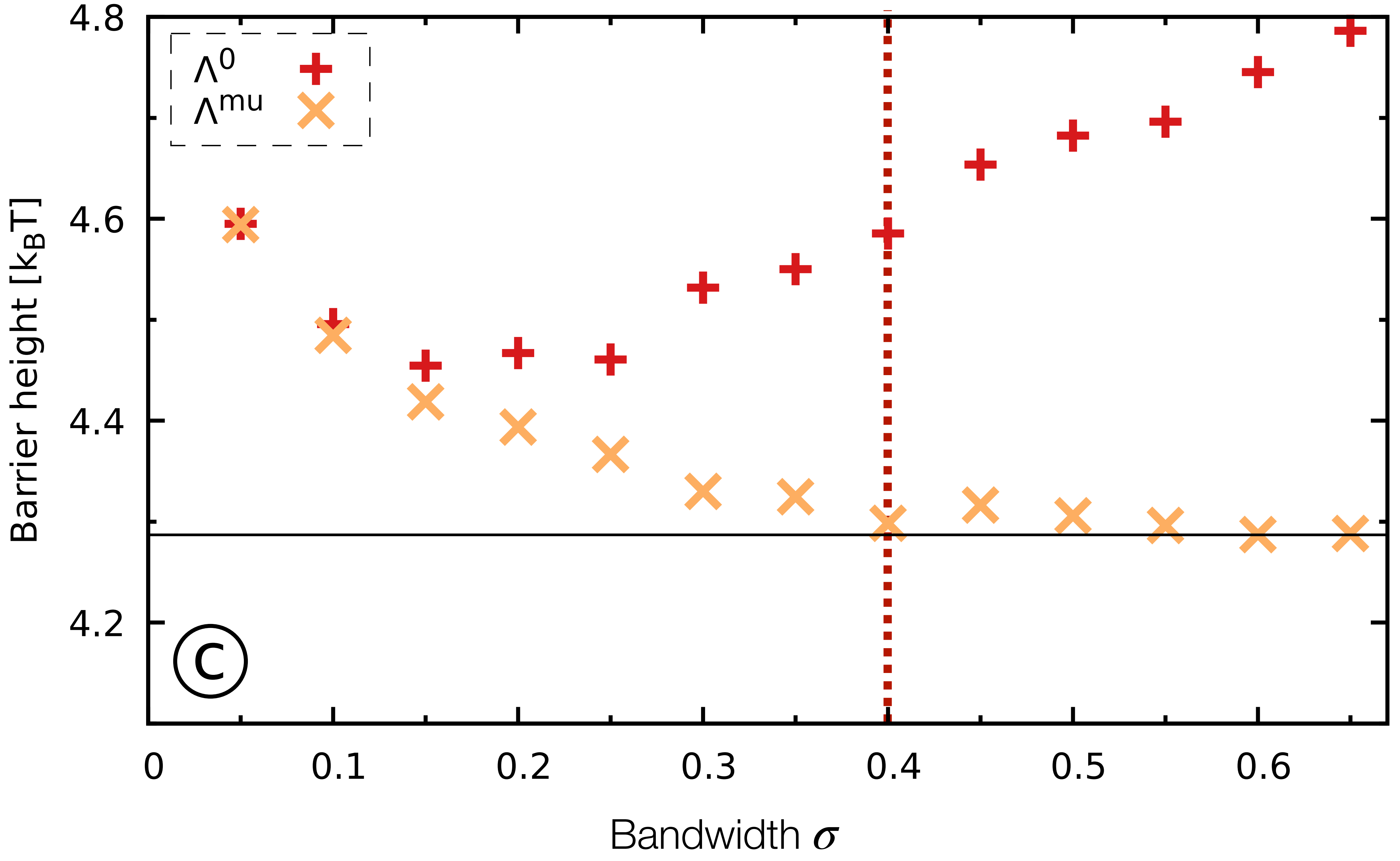
$$\Lambda^{\mathrm{mu}}(\mu_t^N) = \log \frac{K * \mu_t^N(x)}{K * \pi(x)} - \int \log\left(\frac{K * \mu_t^N(y)}{K * \pi(y)}\right) \mu_t^N(y)\,\mathrm{d}y$$



Original approximation leads to incorrect sampling and results as expected

100 Particles - overdamped Langevin Dynamics

Choice of the Approximation



Original approximation leads to under-sampling of barrier region and too high barrier estimates

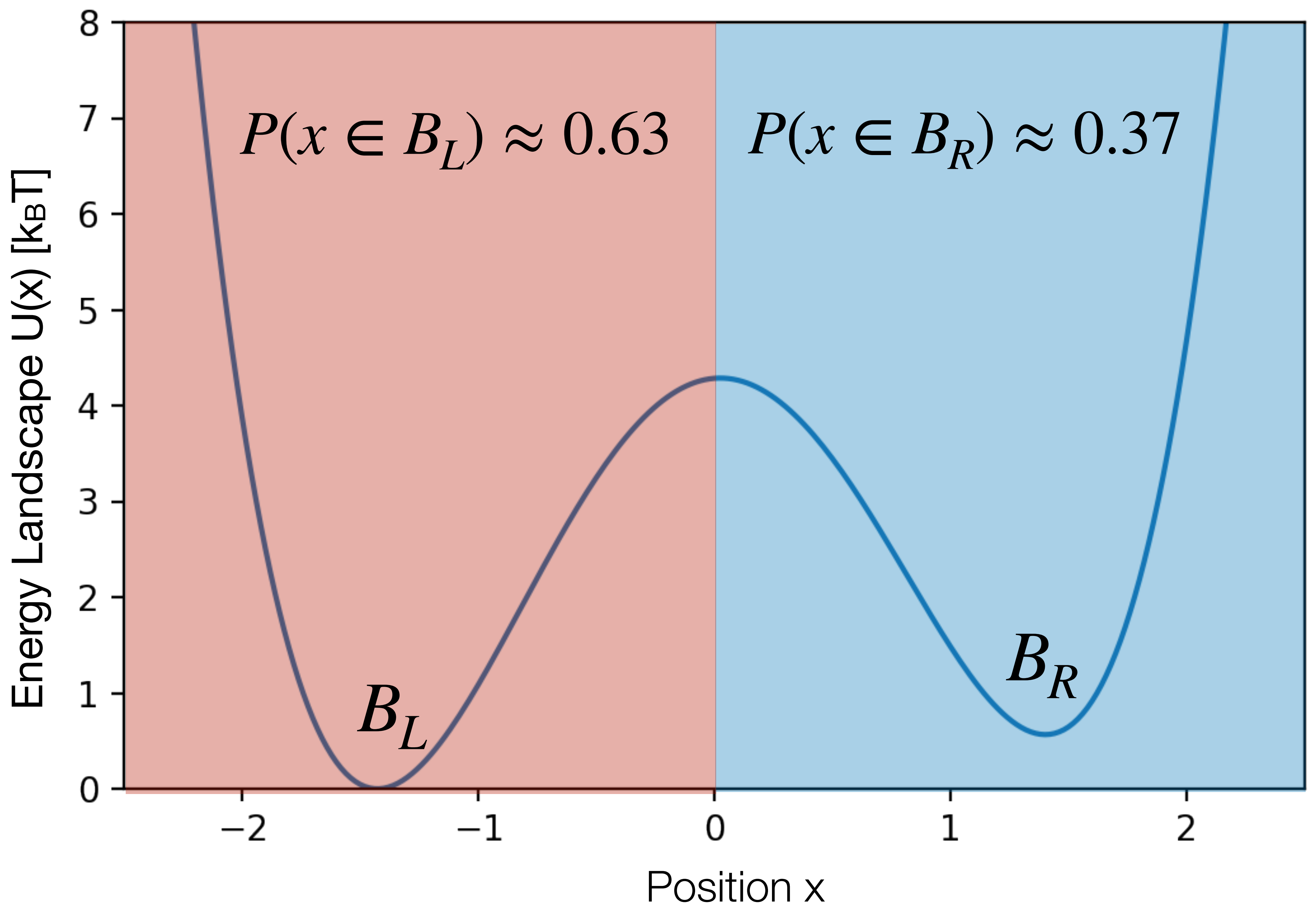
Obtain good sampling with new multiplicative birth/death term $\Lambda^{\mathrm{mu}}(\mu_t^N)$ as long as above a certain critical bandwidth

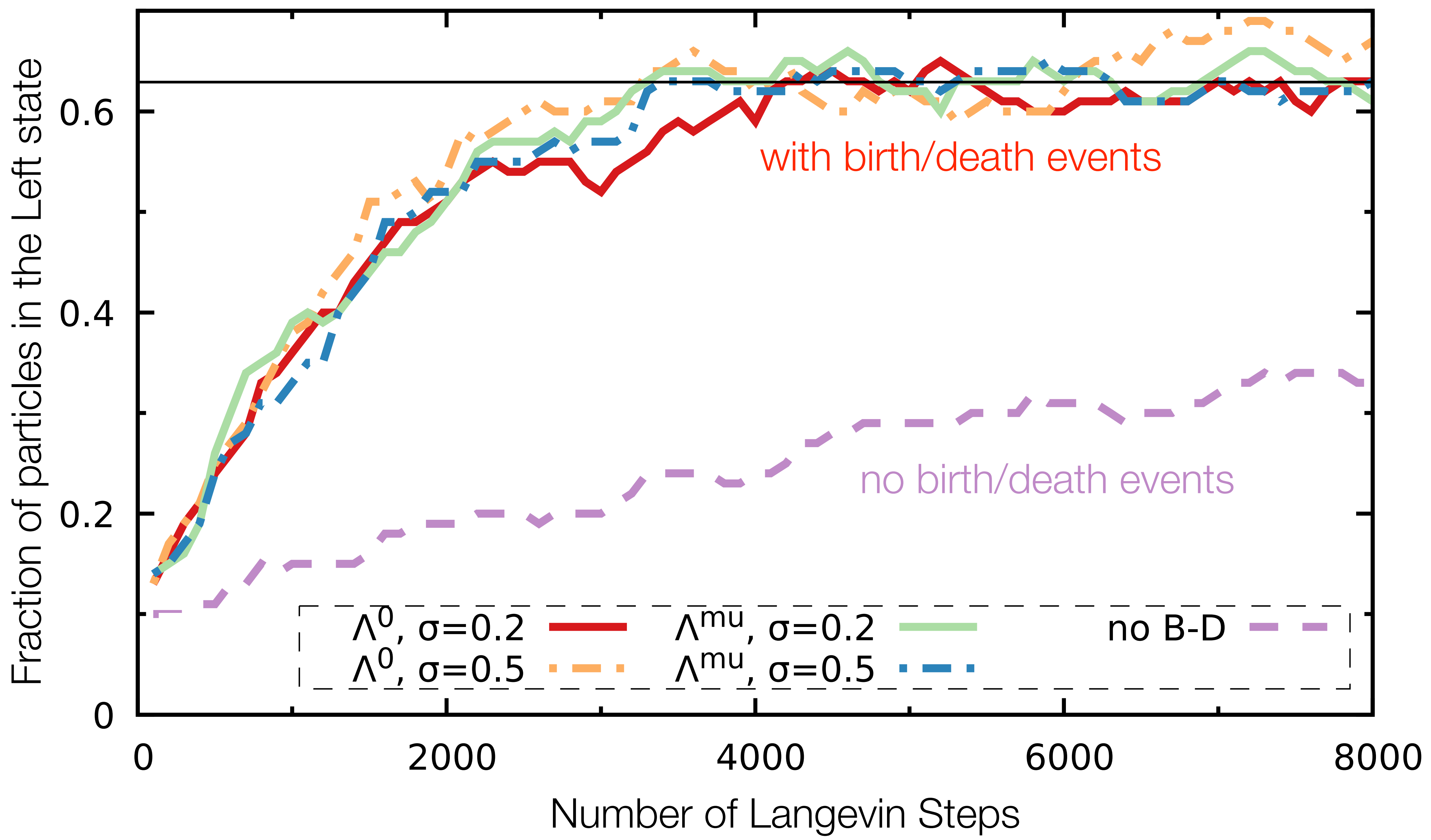
100 Particles - overdamped Langevin Dynamics

Speed of Equilibration

100 Particles

- Start far from equilibrium with 10 in left state and 90 in right state
- Should be 63 in left state and 37 in right state on average in equilibrium



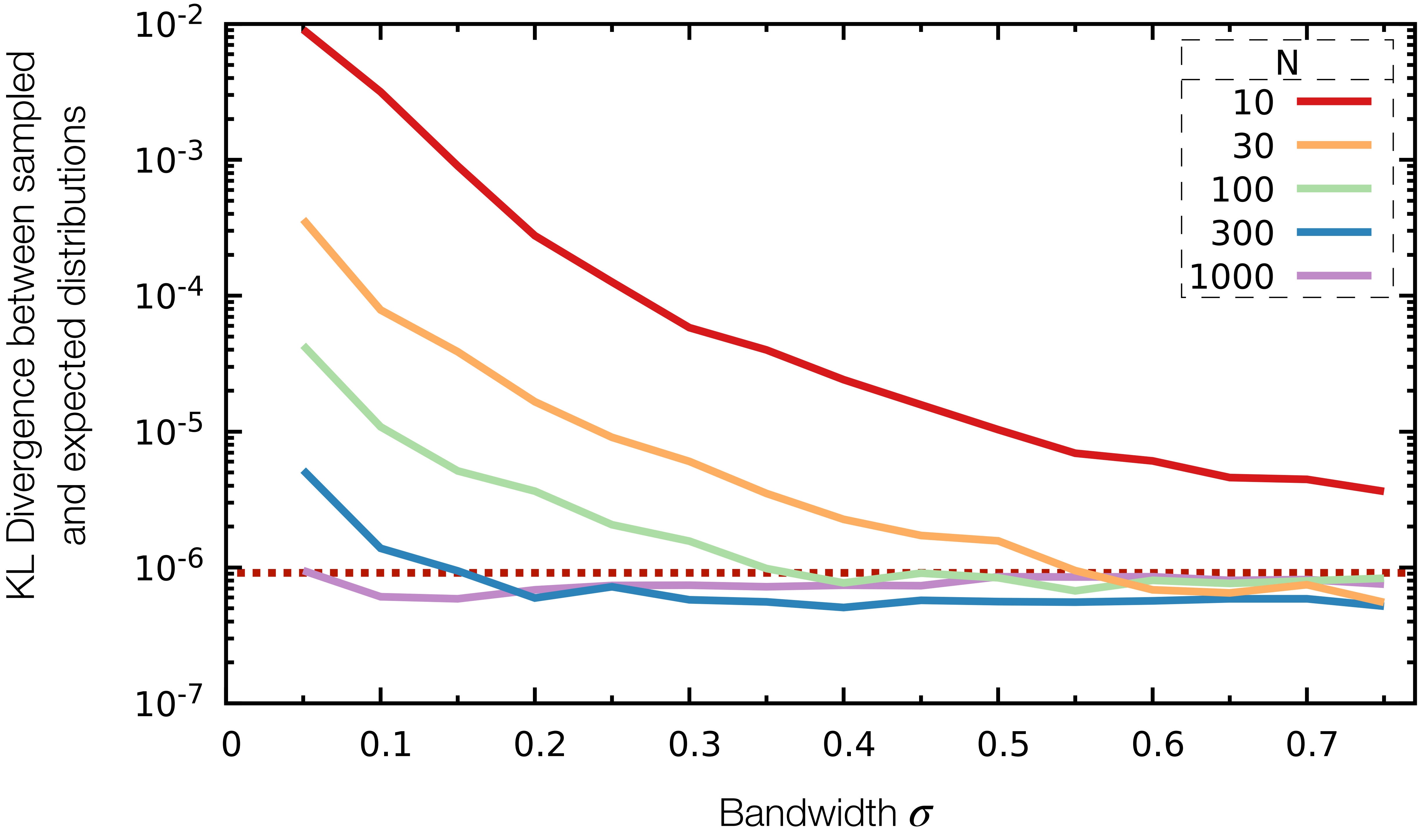


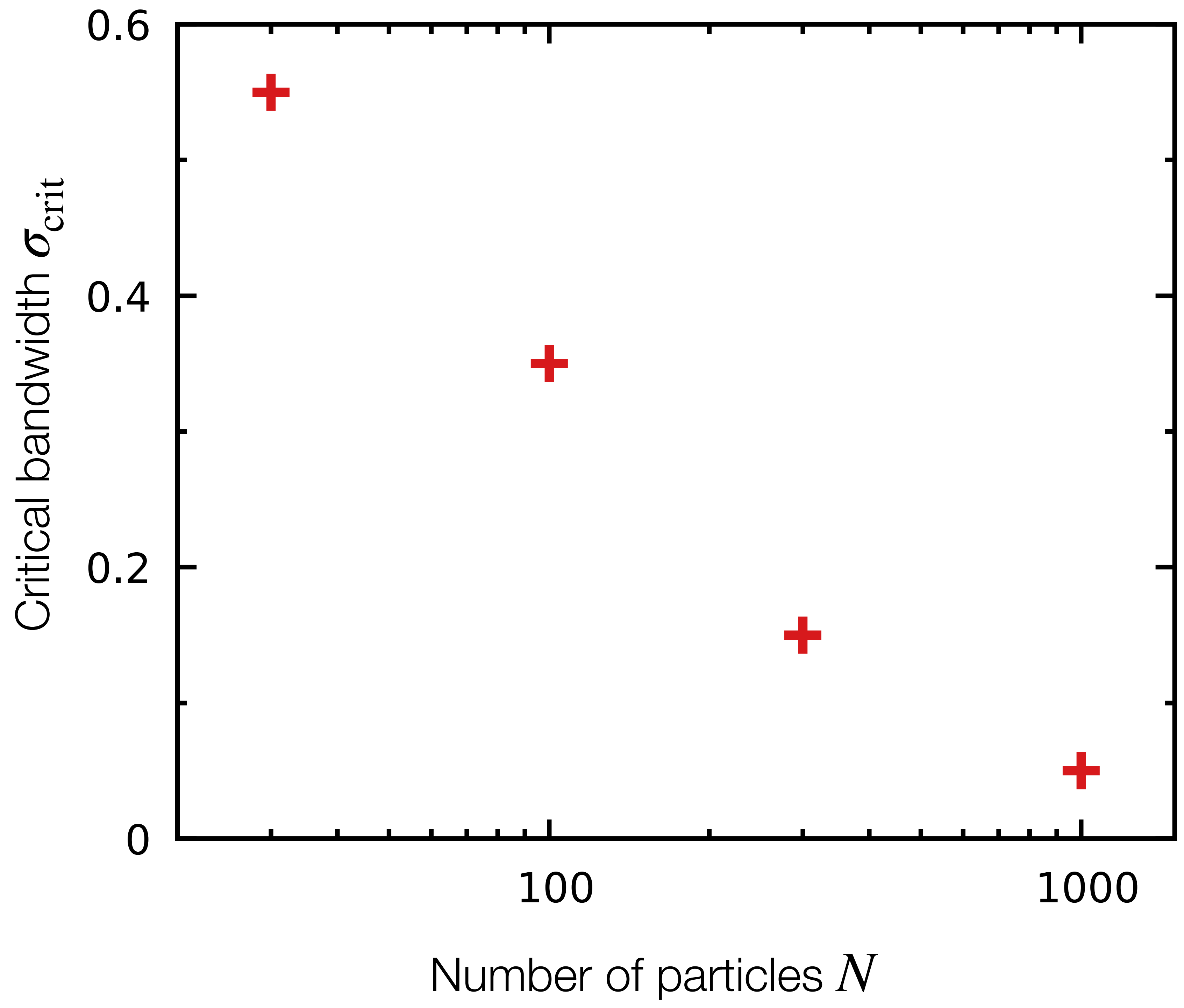
Reach equilibrium orders of magnitude faster with the birth/death scheme

Choice of approximation has very little effect on the equilibrium properties

100 Particles - Underdamped Langevin Dynamics with $\gamma = 10$

Number of Particles and the Critical Bandwidth

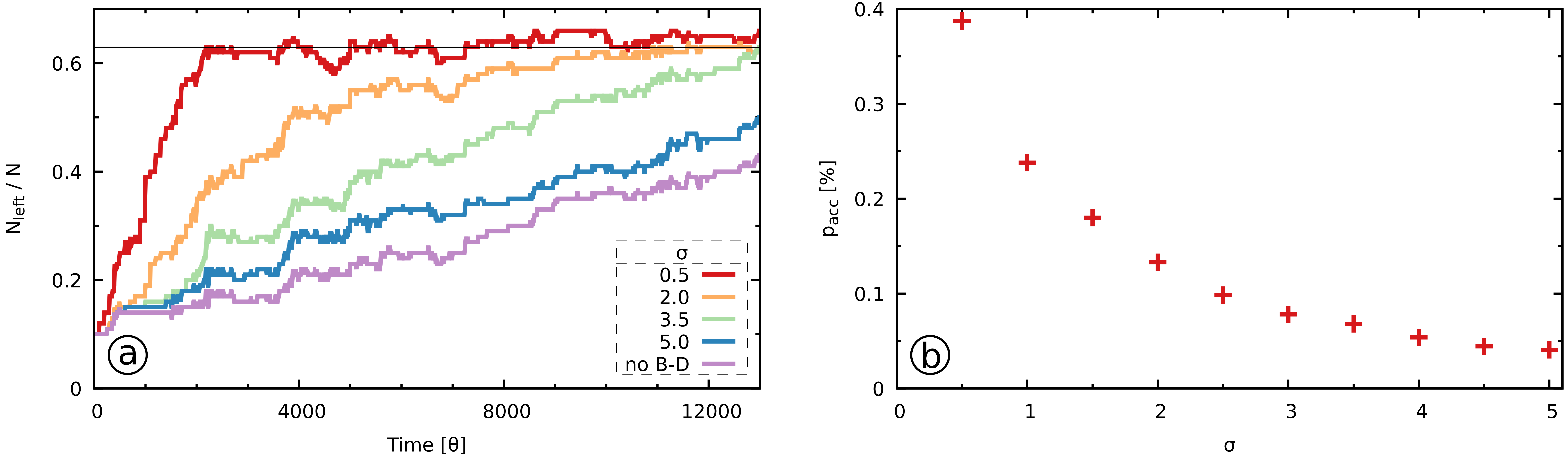




Critical bandwidth: the lowest value of for which the KL divergence is below 10^{-6}

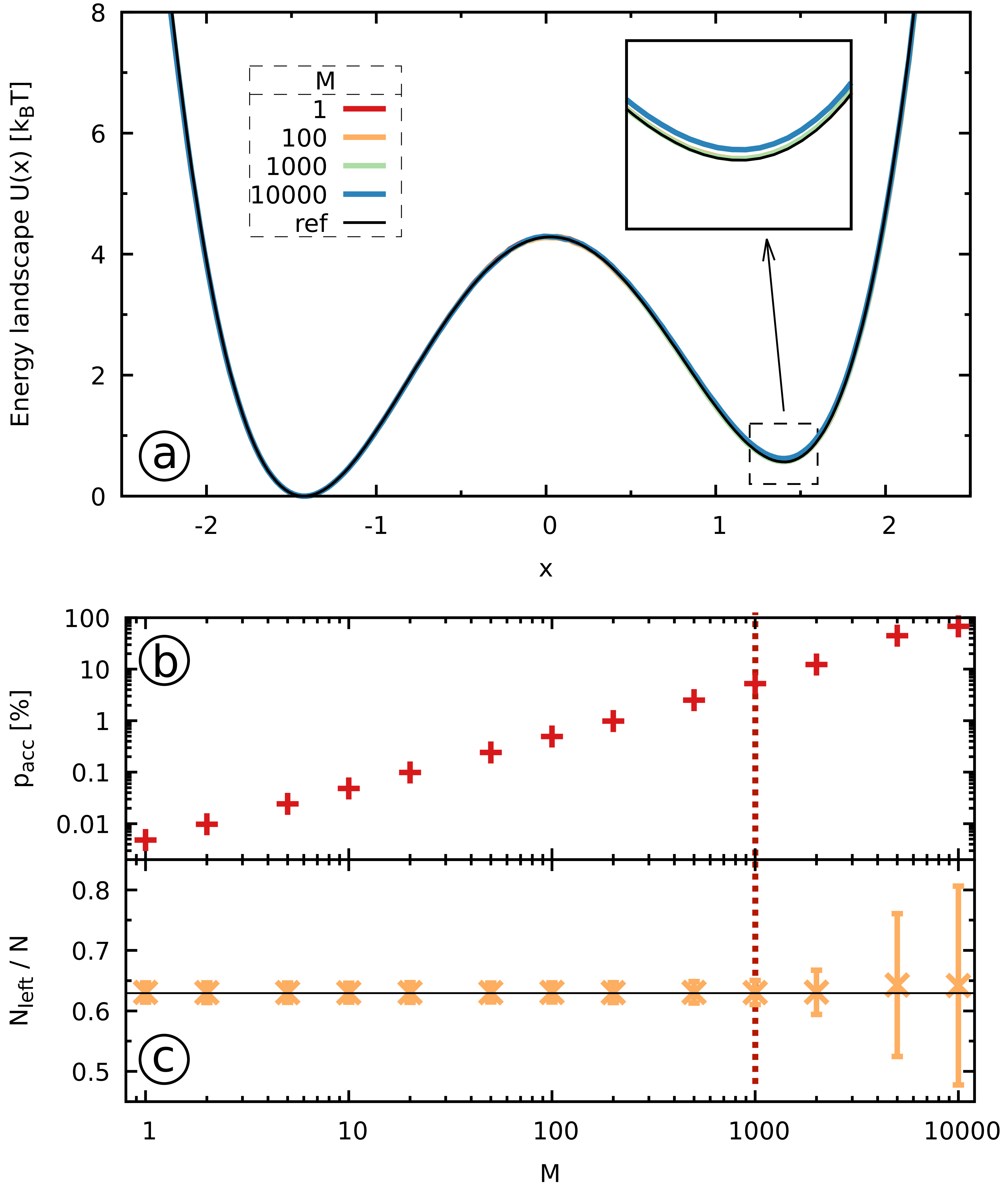
Increasing the number of particles leads to lower value of the critical bandwidth

Effect of Increasing the Bandwidth

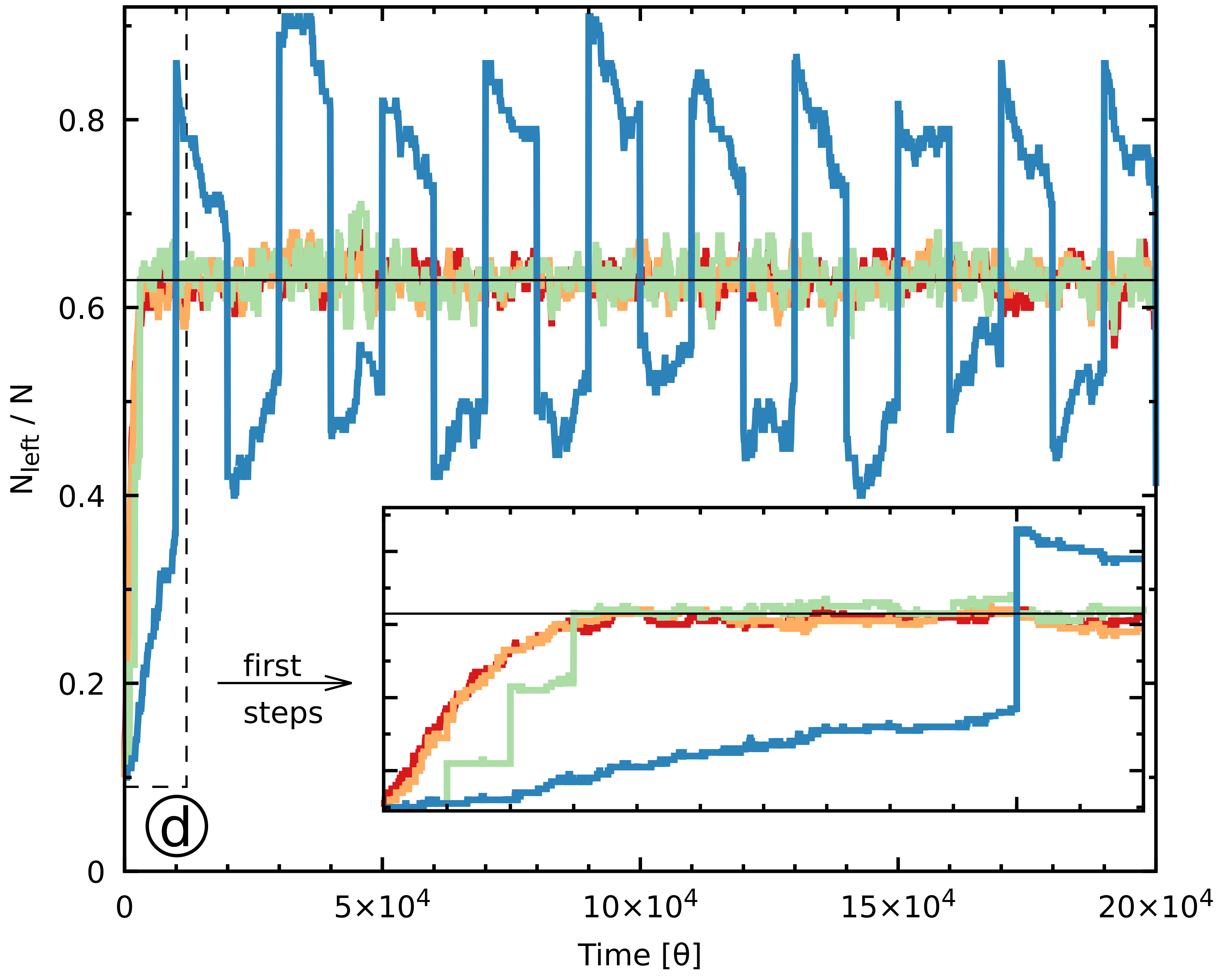


Gradually turns off the birth/death moves

Effect of the Birth-Death Stride M



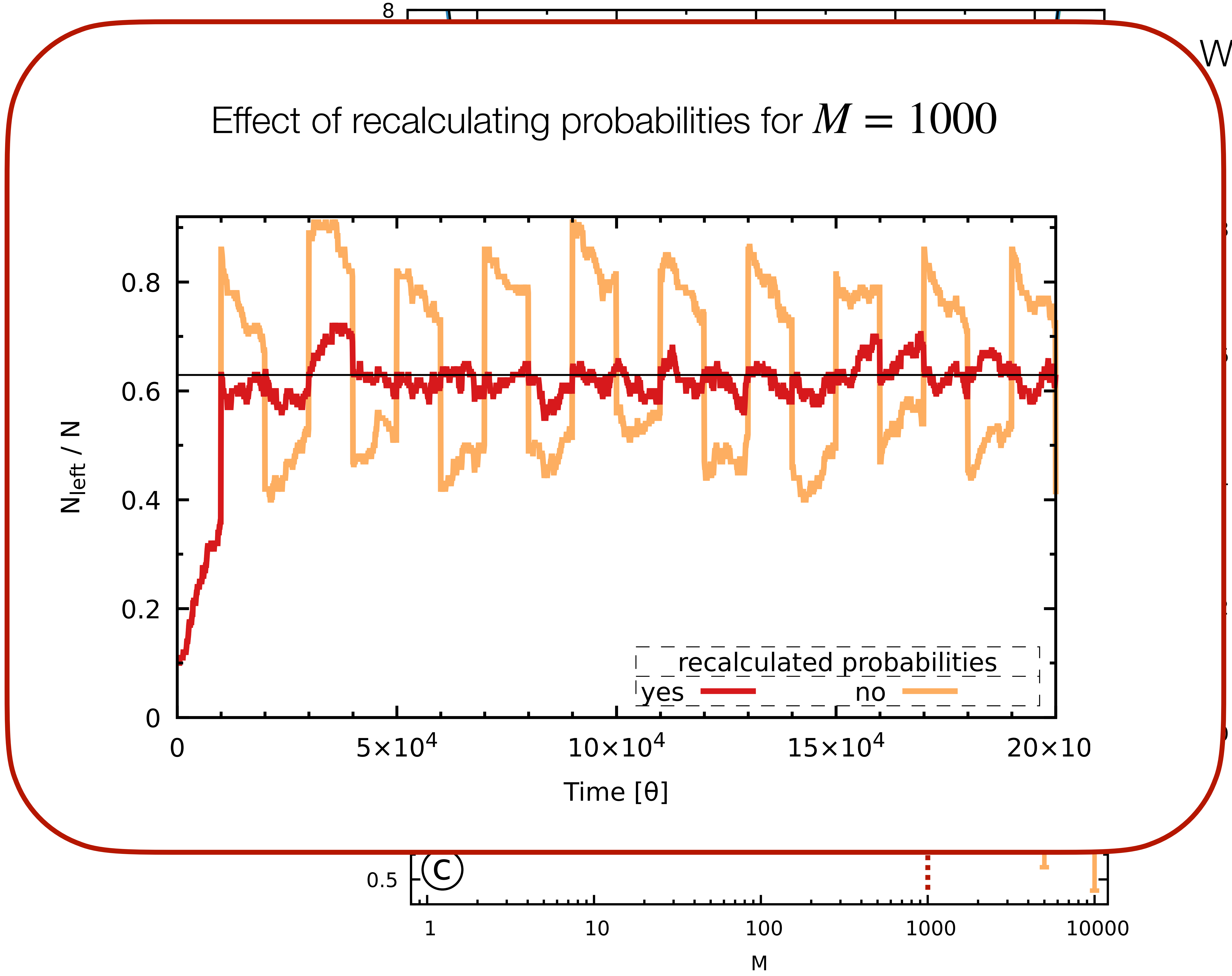
Want to avoid doing the birth/death step at every Langevin step

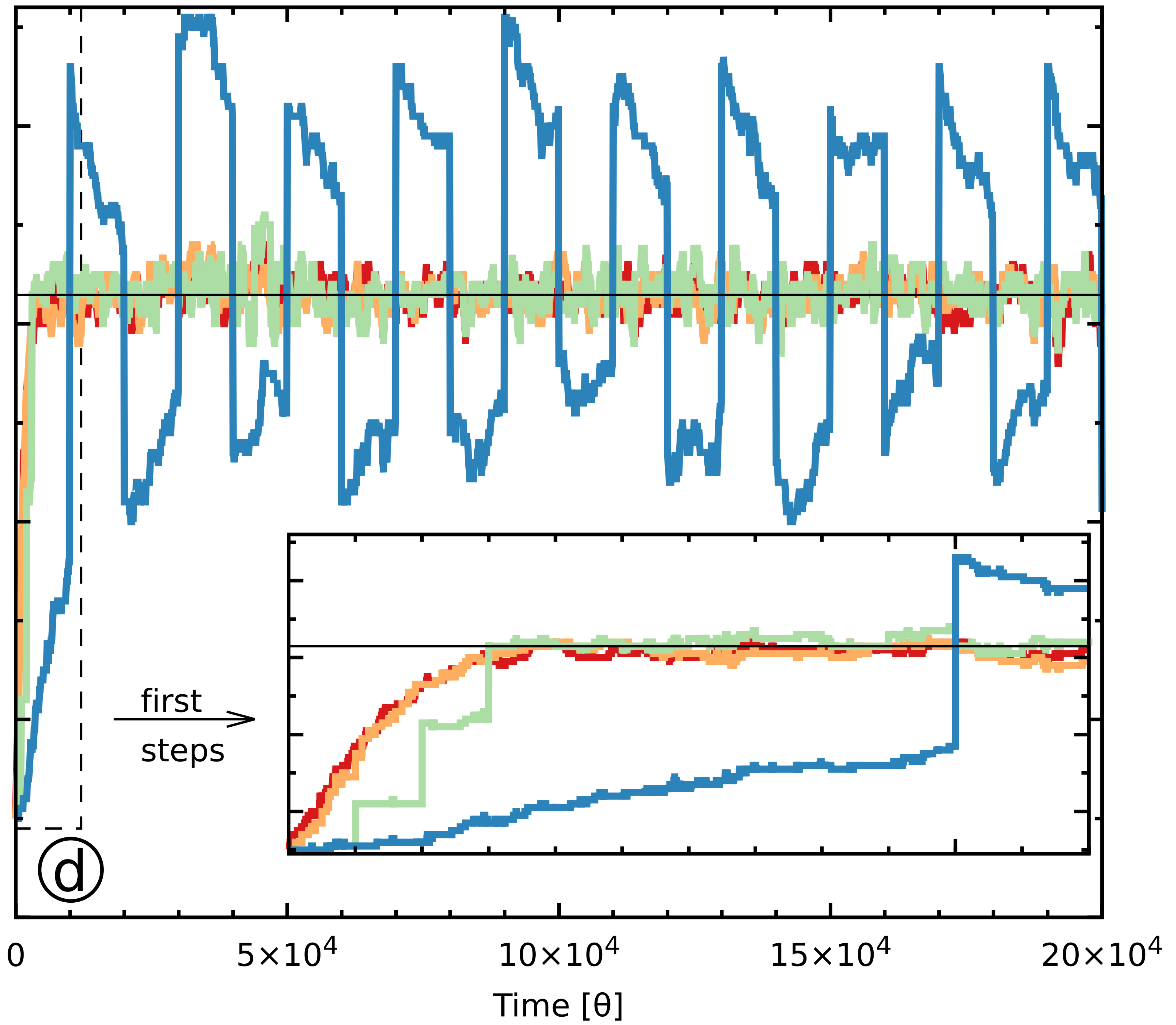


No significant difference in results as long as the percentage of accepted birth/death moves below 5-10% ($M = 1000$ in this case)

Effect of the Birth-Death Stride M

Want to avoid doing the birth/death step at every Langevin step





 No significant difference in results as long as the percentage of accepted birth/death moves below 5-10% ($M = 1000$ in this case)

More General Dynamics

Normally interested in the more general case of underdamped Langevin dynamics (or other stochastic dynamics)

$$\mathrm{d}x(t) = \frac{p(t)}{m}\,\mathrm{d}t$$

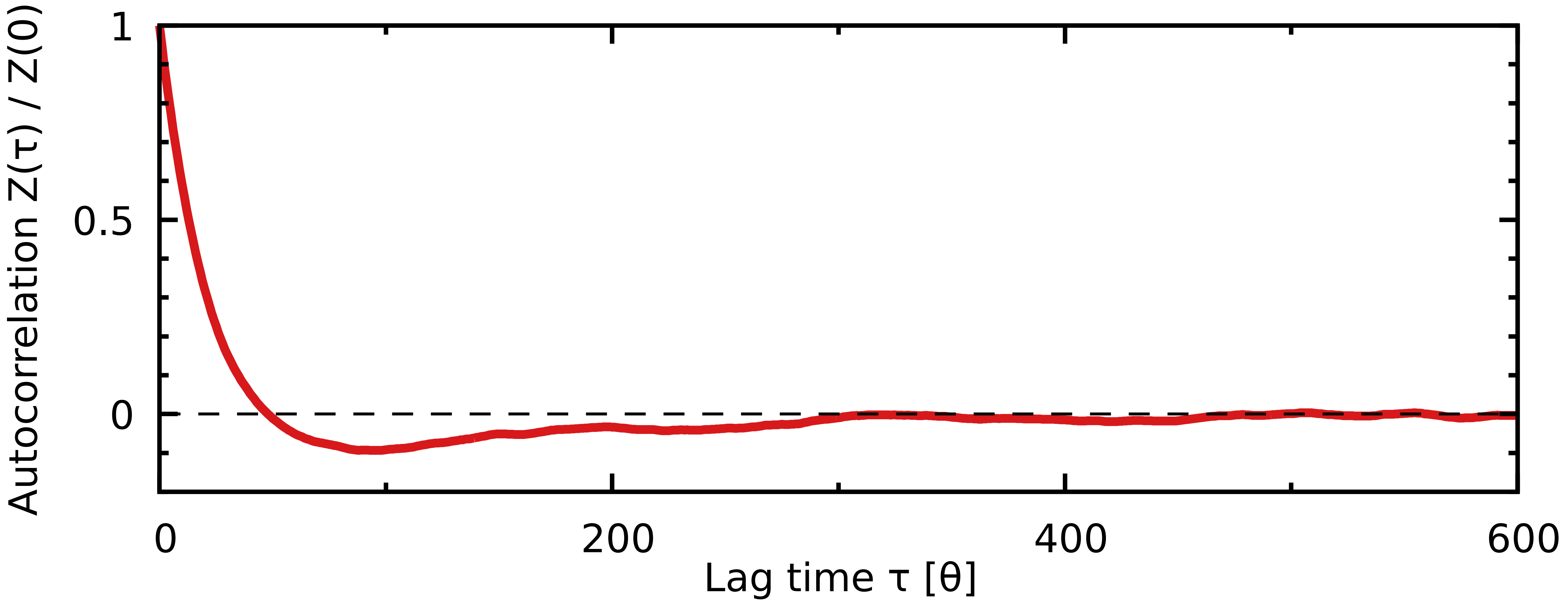
$$\mathrm{d}p(t) = -\nabla U(x(t))\mathrm{d}t - \gamma p(t)\mathrm{d}t + \sqrt{\frac{2m\gamma}{\beta}}\mathrm{d}W(t),$$

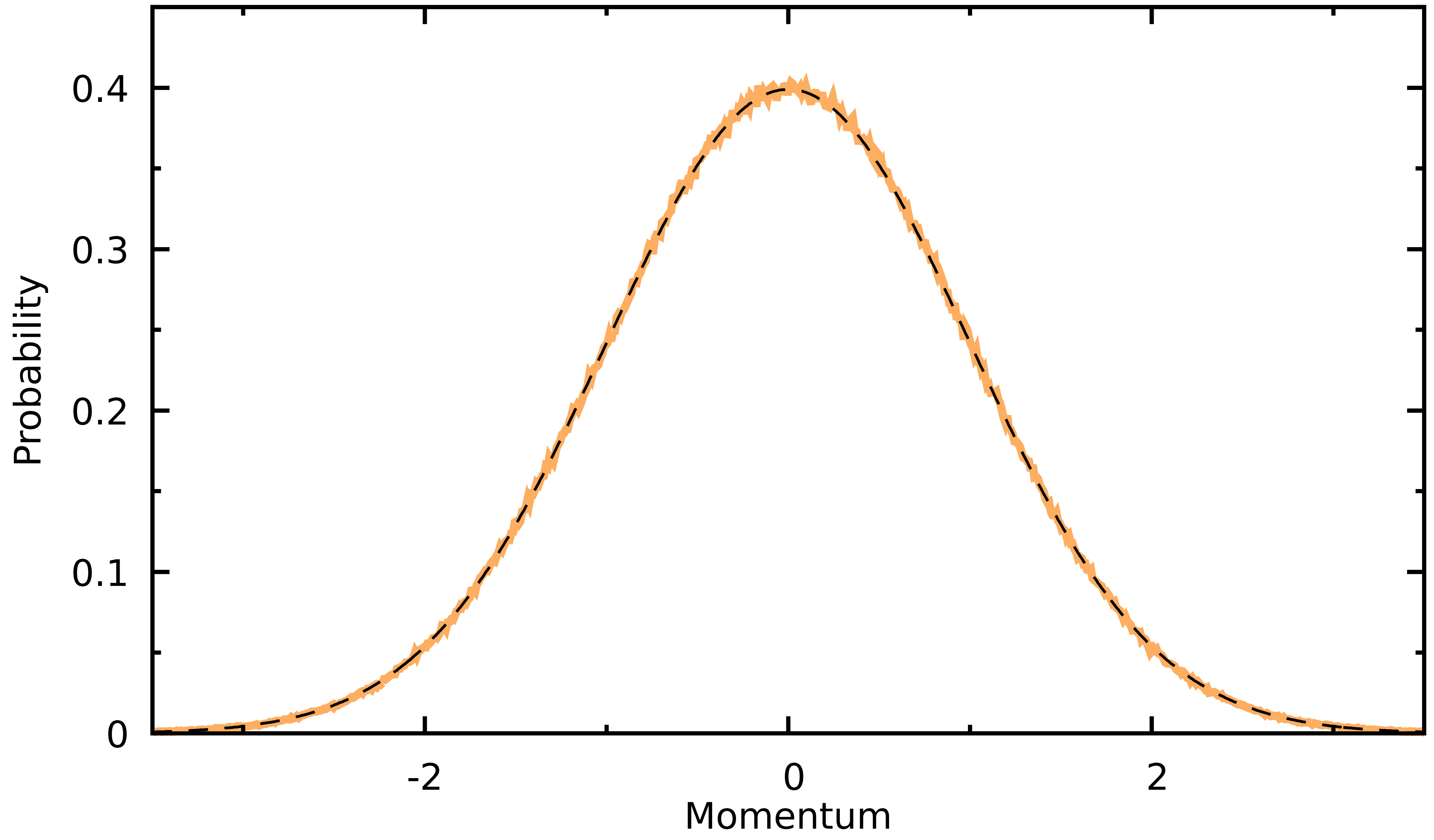
The corresponding Fokker-Planck equation depends on both position x and momentum p

$$\rho_t(x,p) \neq \rho_t(x)\cdot\rho_t(p)$$

Can be simulated using the Langevin Algorithm from Bussi and Parrinello, PRE 2007 with $\gamma = 10$

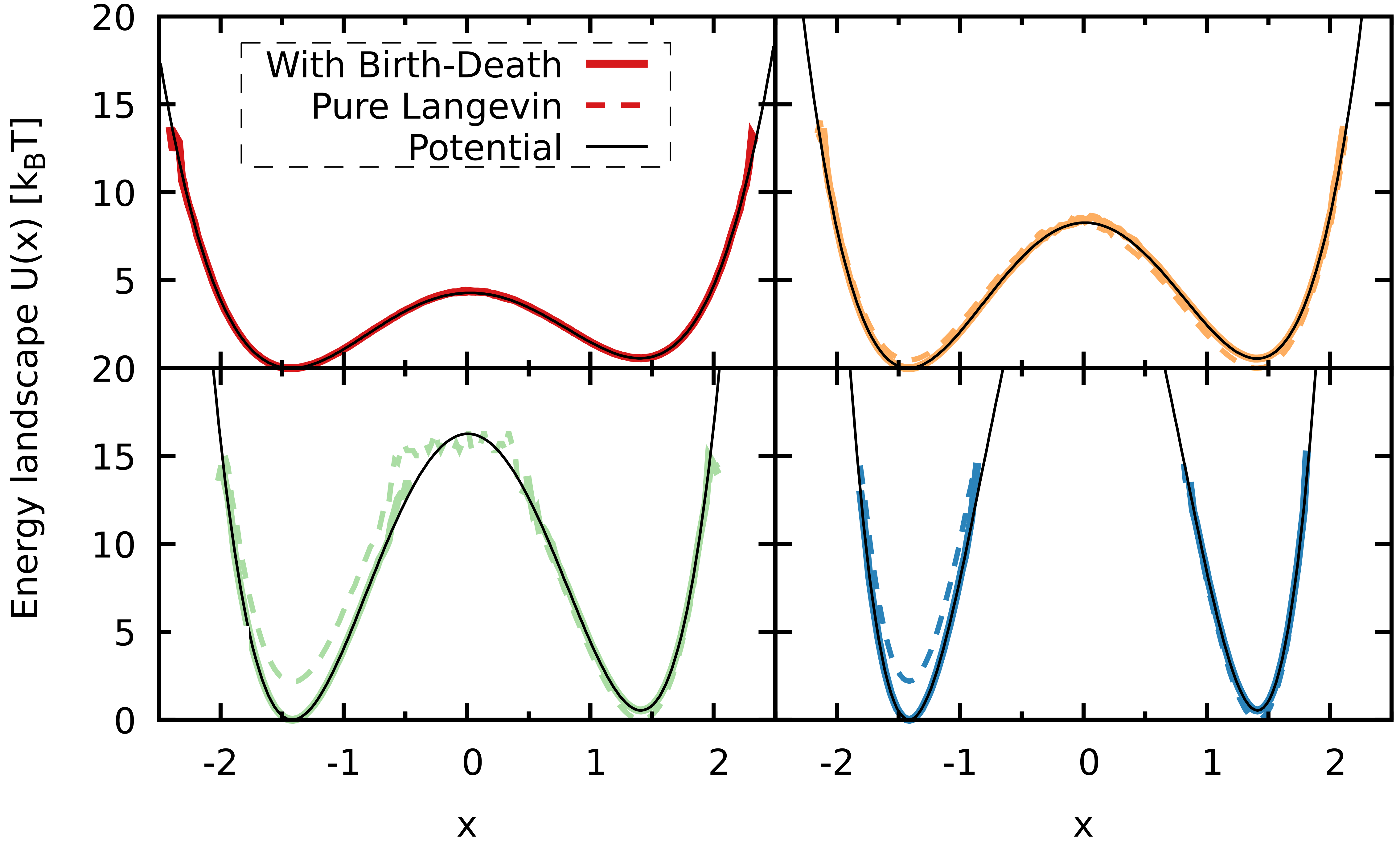
Do the same as before and a birth/death term that depends only on the position: works fine



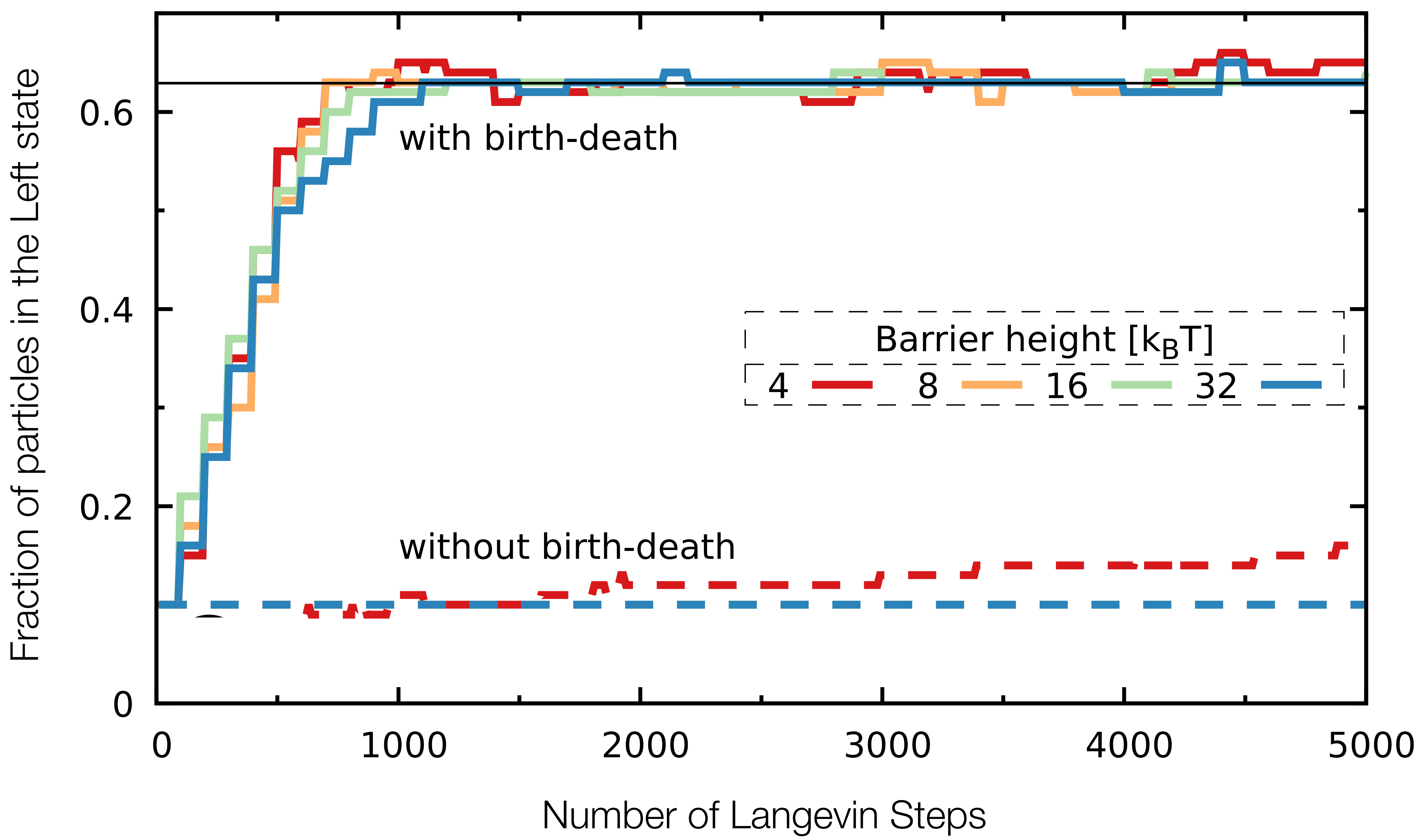


The average time between birth-death moves is 6000 Langevin steps, or 10 times the decorrelation time of the momentum

Speed of Equilibration is Independent of Barrier Height

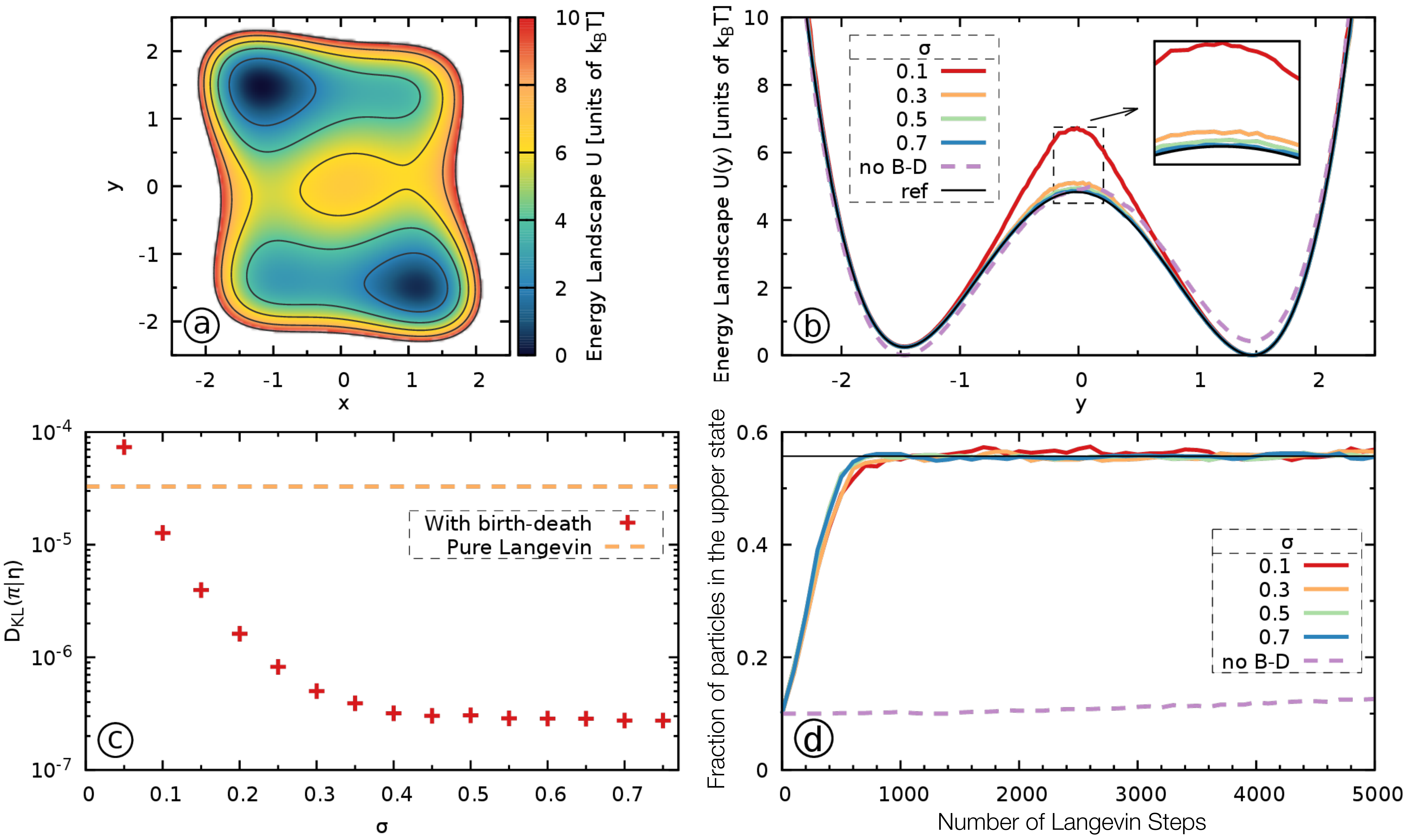


Potentials with increased barrier height, but preserved population of left/right states



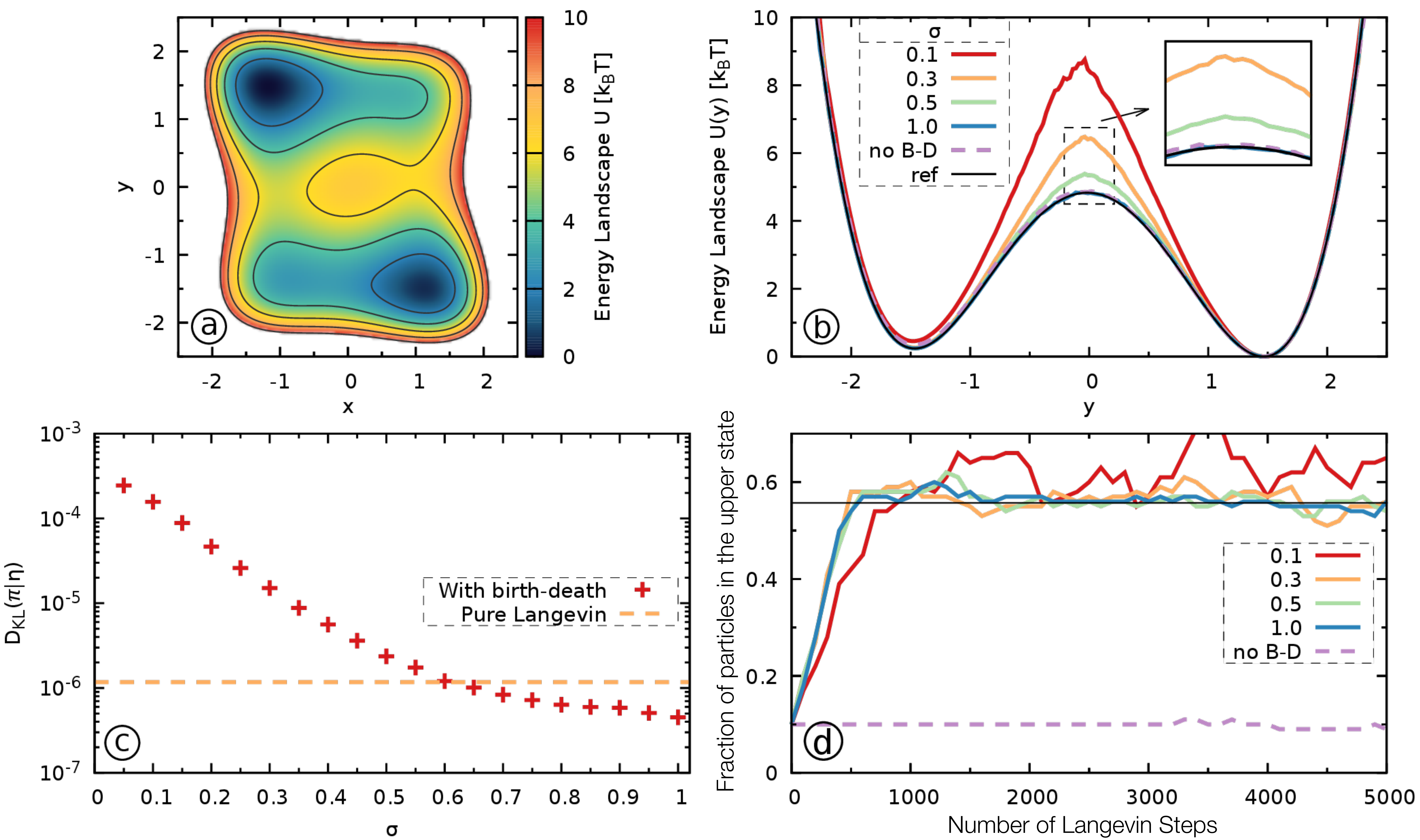
100 Particles - Underdamped Langevin Dynamics with $\gamma = 10$

Higher-Dimensions: 2D Wolfe-Quapp Potential



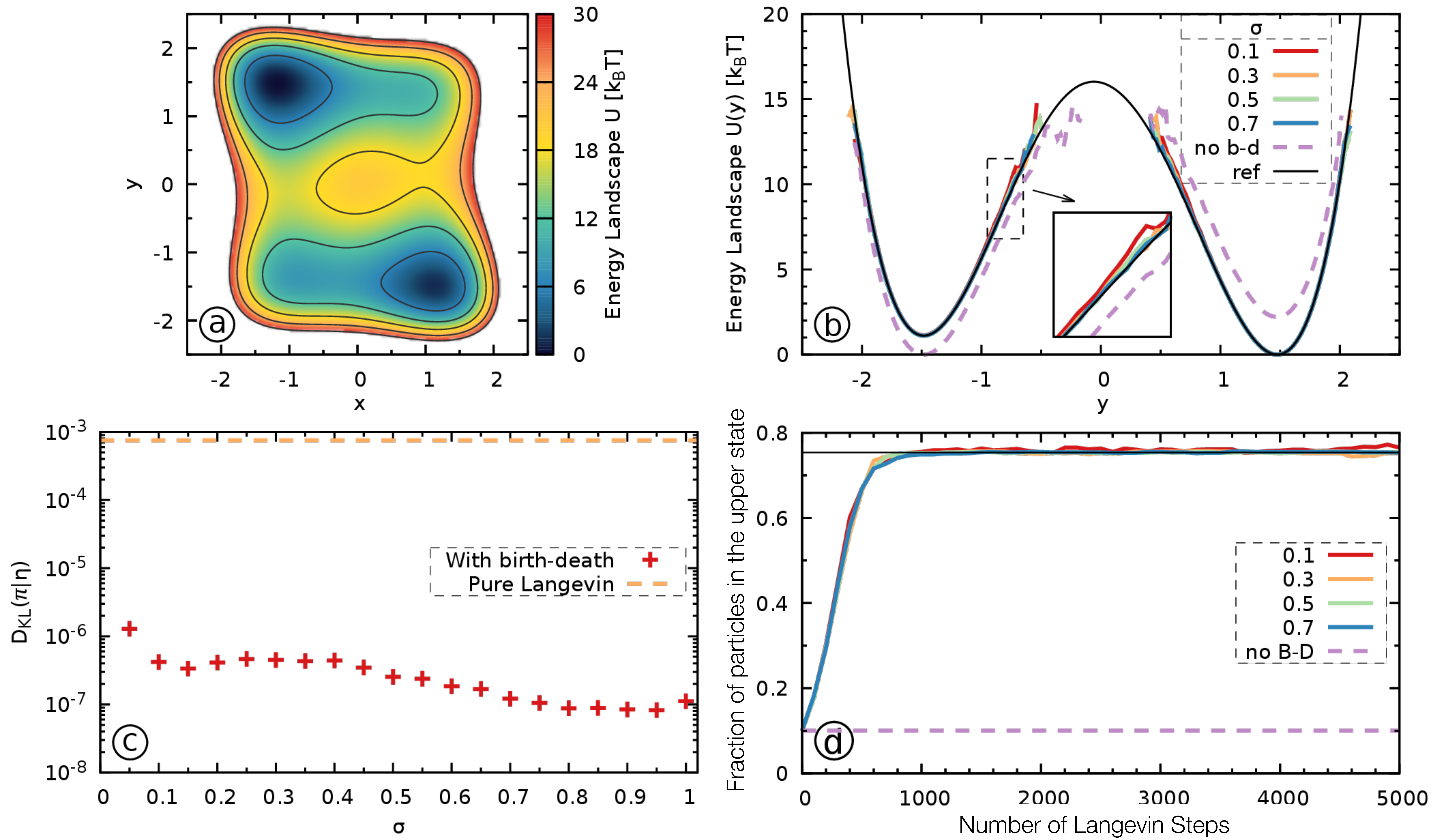
1000 Particles - Underdamped Langevin Dynamics with $\gamma = 10$

Higher-Dimensions: 2D Wolfe-Quapp Potential



100 Particles - Underdamped Langevin Dynamics with $\gamma = 10$

Higher-Dimensions: Scaled 2D Wolfe-Quapp Potential

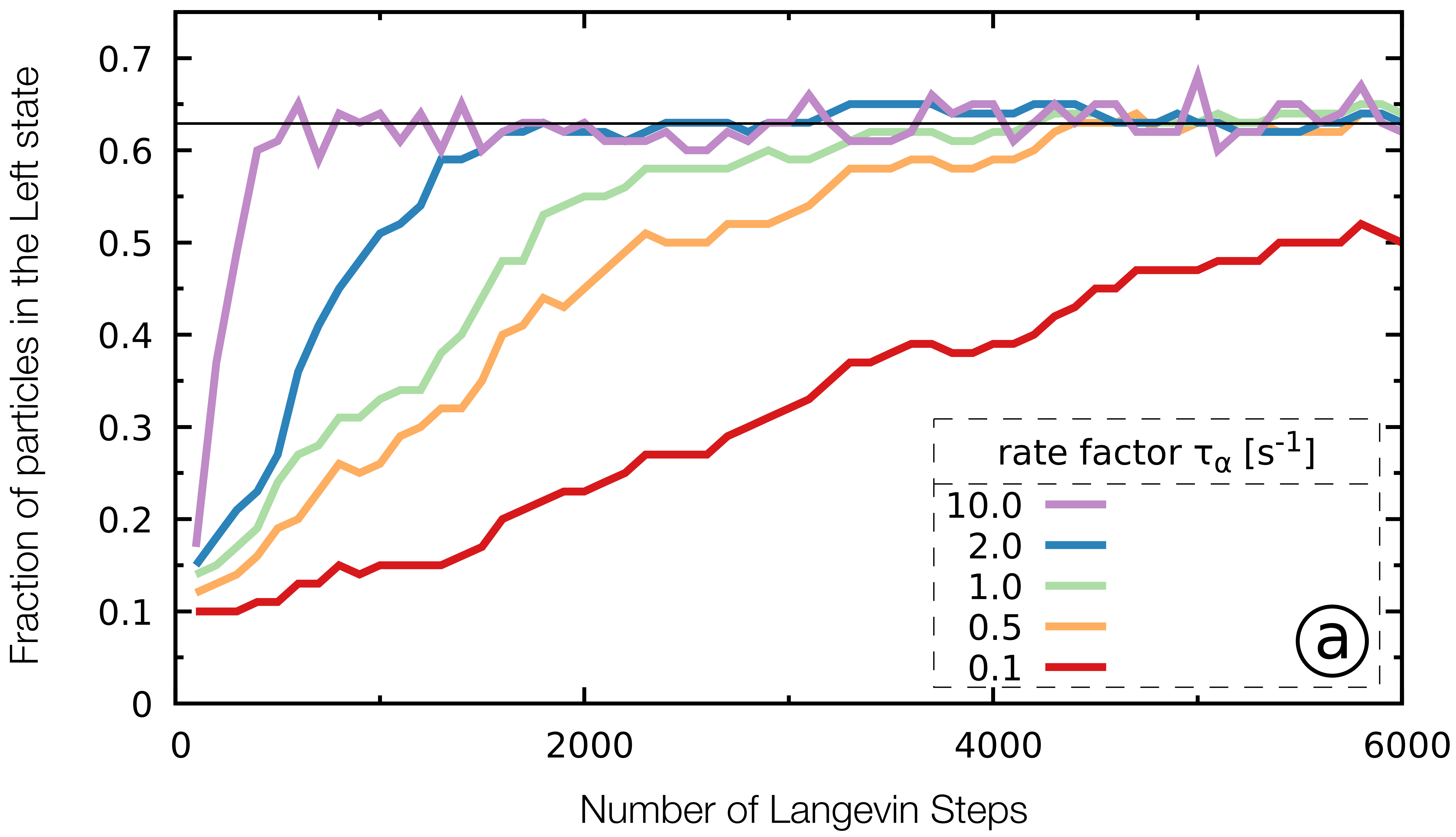


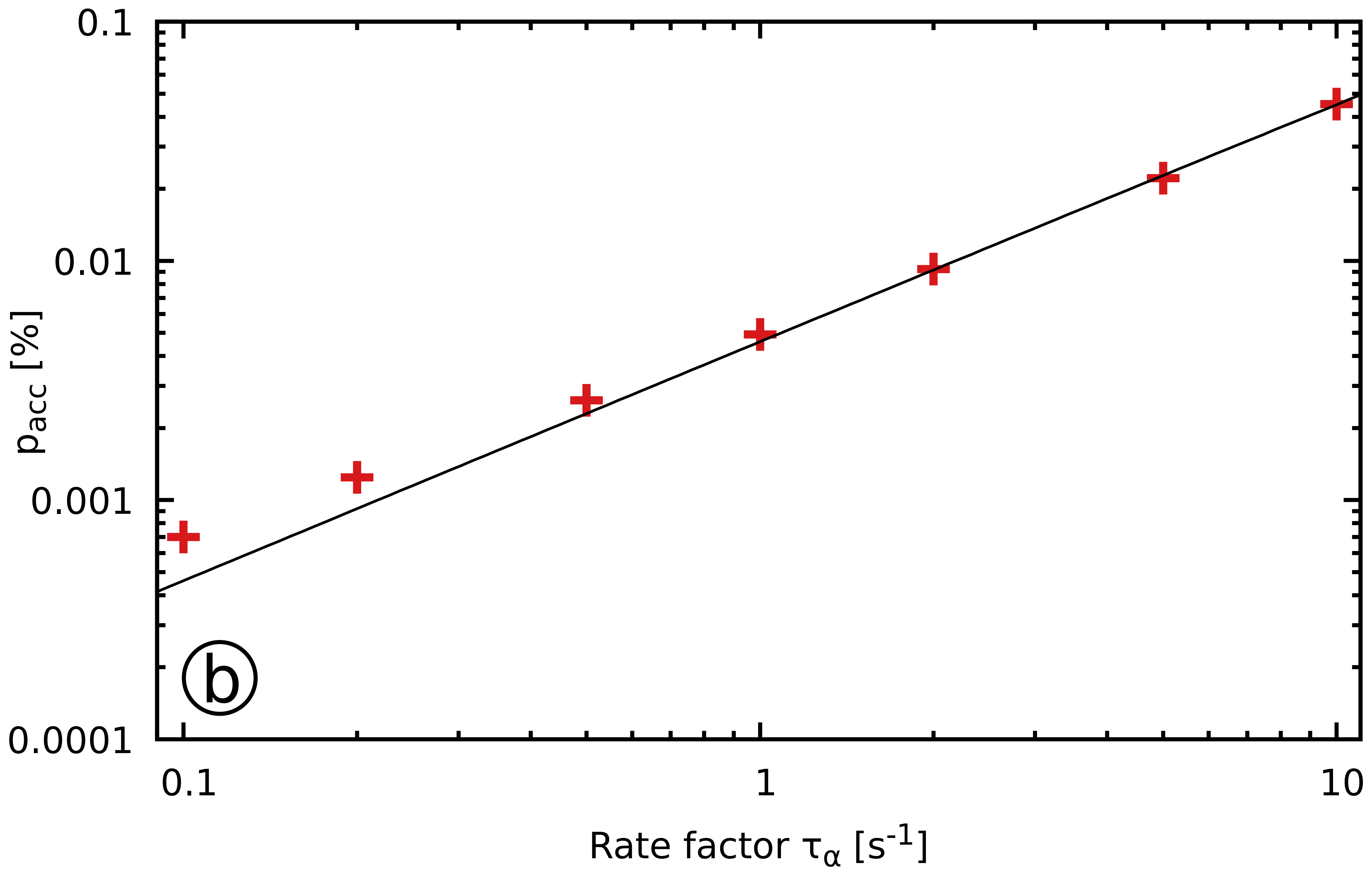
1000 Particles - Underdamped Langevin Dynamics with $\gamma = 10$

Effect of the Rate Factor τ_α

Fokker-Planck-Brith-Death equation $\partial_t \rho_t = L^* \rho_t - \tau_\alpha \alpha_\pi(\rho_t)\rho_t,$

Brith-Death probabilities $q_i = 1 - \exp\left(-\tau_\alpha |\Lambda_i| M\theta\right),$





The rate factor modulates the speed of equilibration, as expected

Still Very Early On: Issues

What about higher-dimensional cases and atomistic simulations? How far can we push this?

- Main issue is the estimation of the particle density
- Can we use some approximations?
- Probably not the way to go!
- => Perform the birth/death in a lower-dimensional subspace (i.e., CVs)

Samples the equilibrium Boltzmann distribution, similar as parallel-tempering

- Per se not an issue
- But, can be difficult to describe transition states and low populated states
- Can lose particles from a metastable state

Algorithm can only populate metastable states that have a walker

- Only “exploitation” mode and not “exploration” mode
- Need to know states in advance

Still Very Early On: Outlook and Next Steps

Perform the birth/death step only a subspace of some CVs

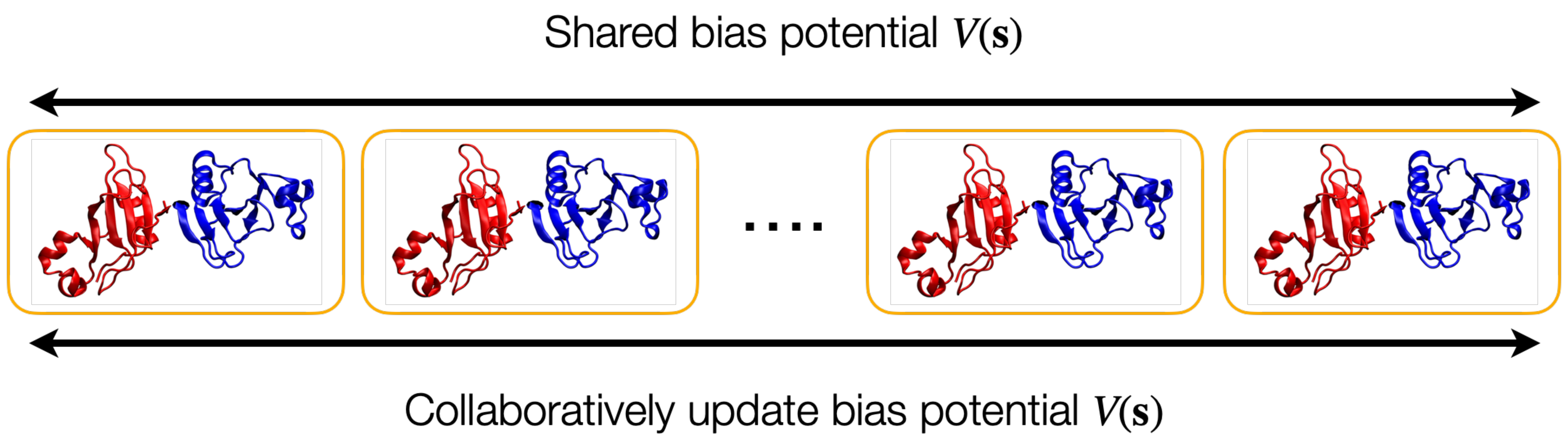
- How does the method work in this case?
- Birth/death dynamics on a free energy landscape that is a-priori unknown
- Need to estimate the energy landscape on the fly

Combine with a CV-based enhanced sampling method => the long time goal

- Should help with many of the issues
    - Add “exploration” mode to the combined method
    - Better sample transition states and higher lying regions

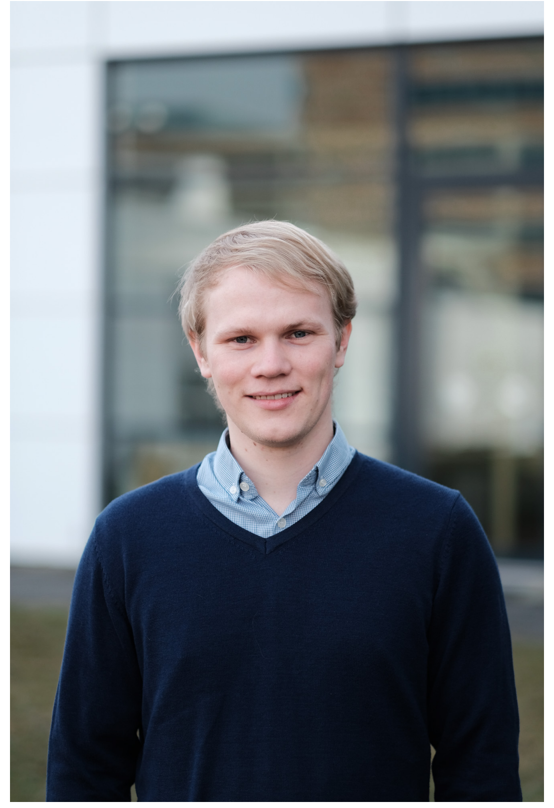
Improve performance of multiple walker simulations — Our initial motivation

- Related Idea: Lelièvre, Rousset, & Stoltz, JCP 2007



Acknowledgements

Numerical Implementation



Dr. Benjamin Pampel

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TRR 146

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MAX PLANCK INSTITUTE FOR POLYMER RESEARCH

JG|U JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Other Recent Publications

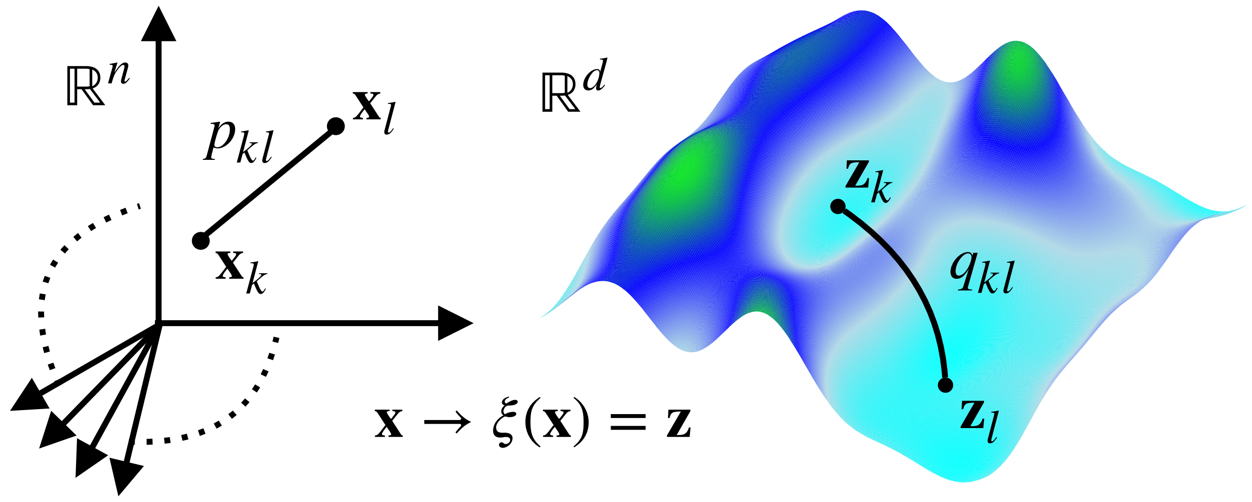
Multiscale Reweighted Stochastic Embedding[A]

and

Reweighted Manifold Learning[B]

For Learning CV from Biased Simulation Data

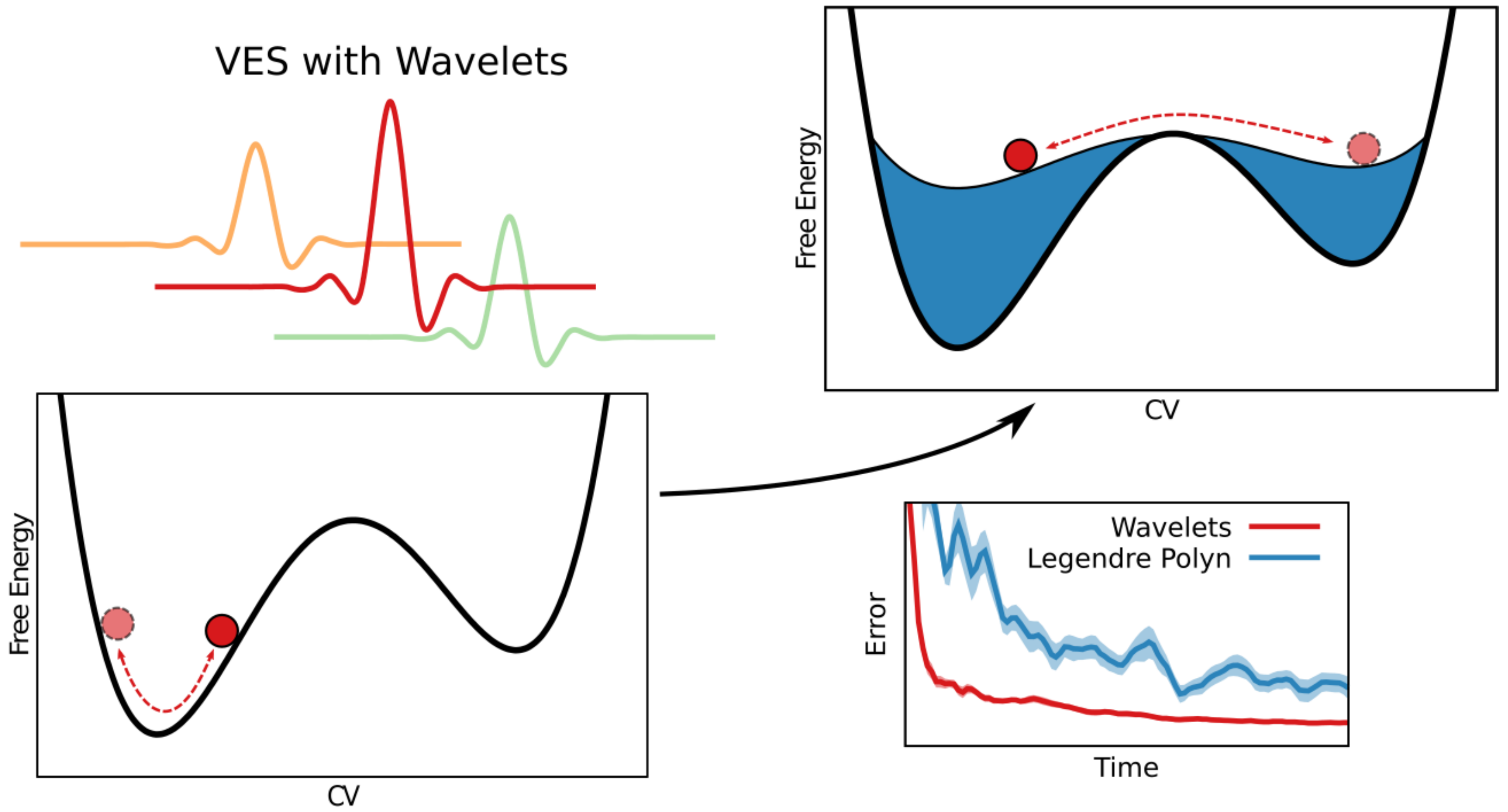
[A] J. Phys. Chem. A, 125, 6286 (2021)
[B] J. Chem. Theory Comput. 18, 7179 (2022)

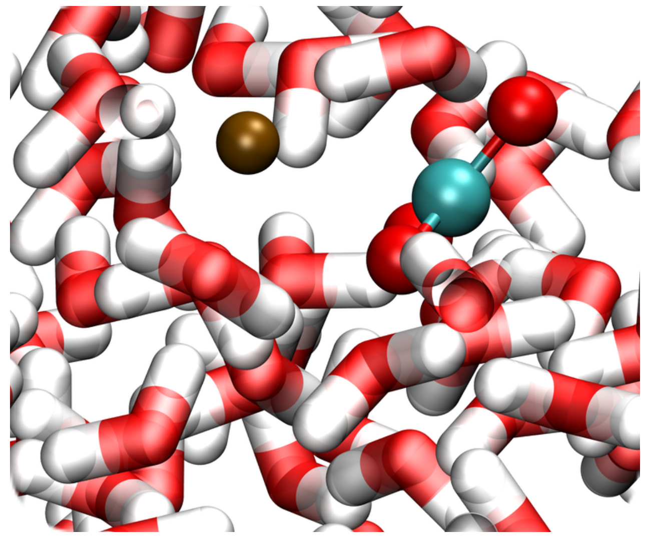


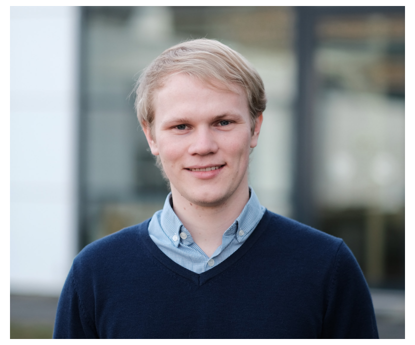
With Jakub Rydzewski, Nicolaus Copernicus University, Poland

Wavelet (Localized) Based Bias Potentials for Variationally Enhanced Sampling

J. Chem. Theory Comput. 18, 4127-4141 (2022)



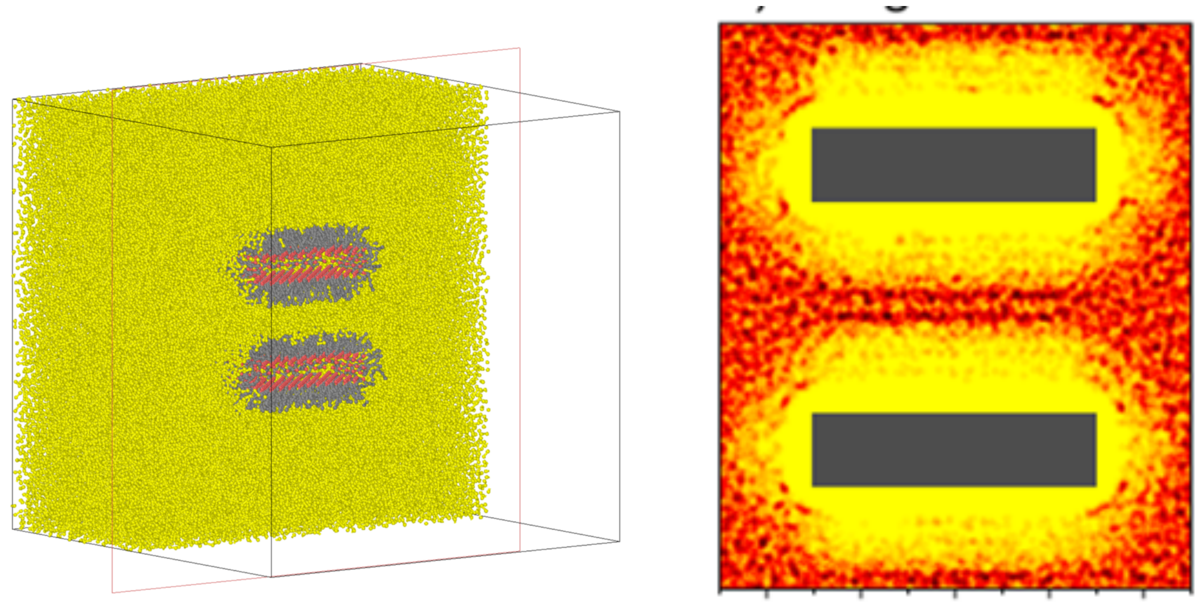


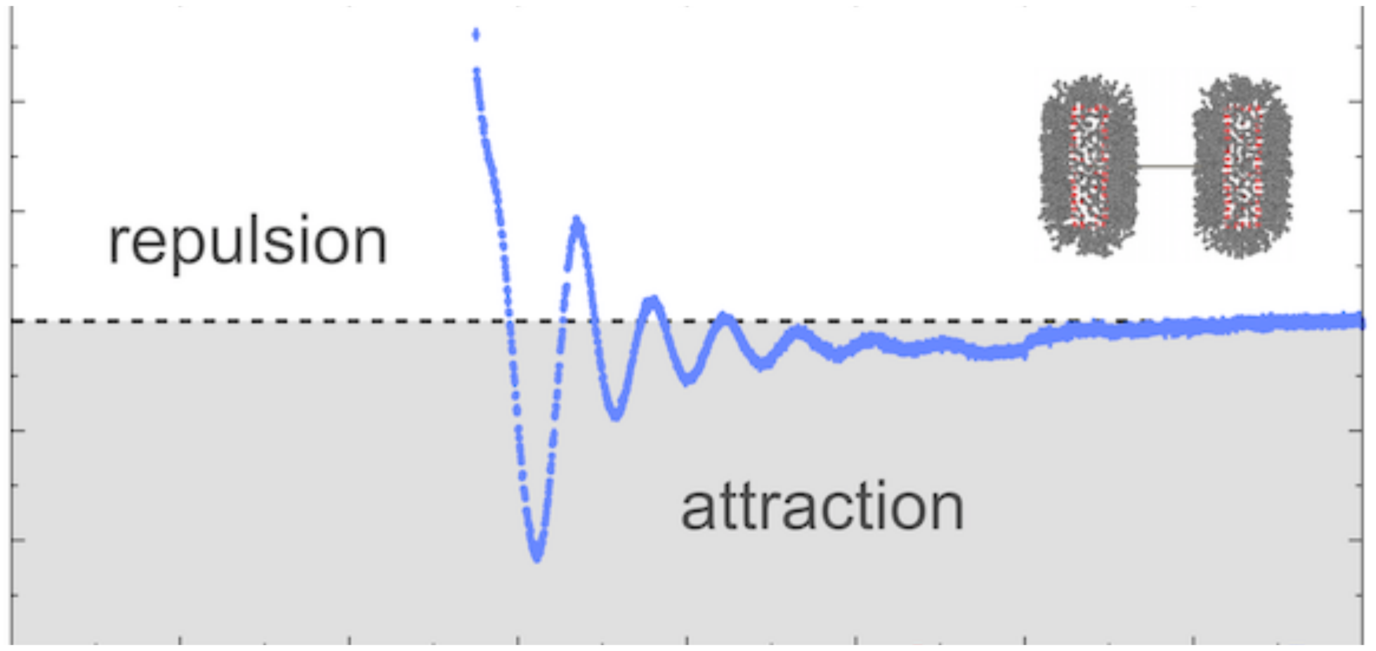


Benjamin Pampel

The Crucial Role of Solvation Forces in the Steric Stabilization of Nanoplatelets

Nano Lett. 22, 9847–9853 (2022)





Nanning Petersen