“RARE CONFORMATIONAL TRANSITIONS IN BIOMOLECULAR SYSTEMS”

Brin MRC Workshop on Rare Events: Analysis, Numerics, and Applications
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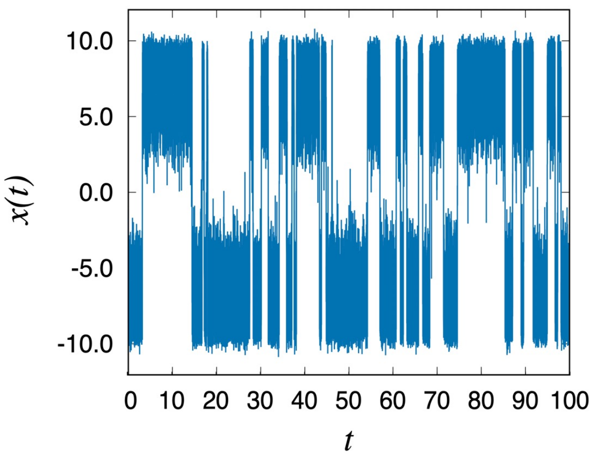
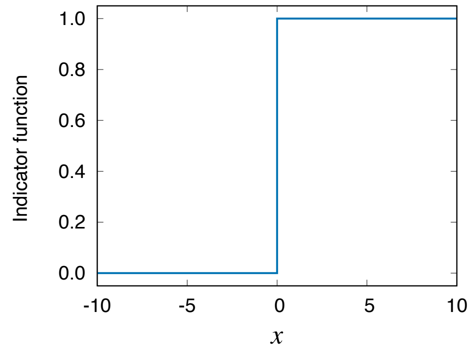
Reactive flux formalism (Chandler 1978)

$$\mathrm{A} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{B}$$





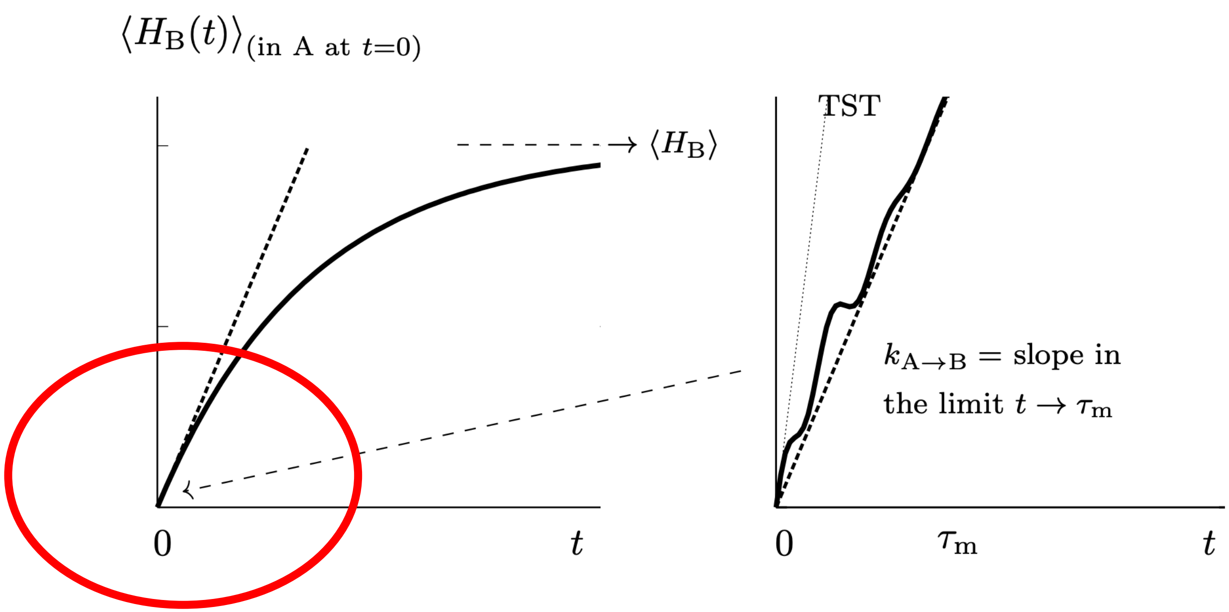
Indicator functions

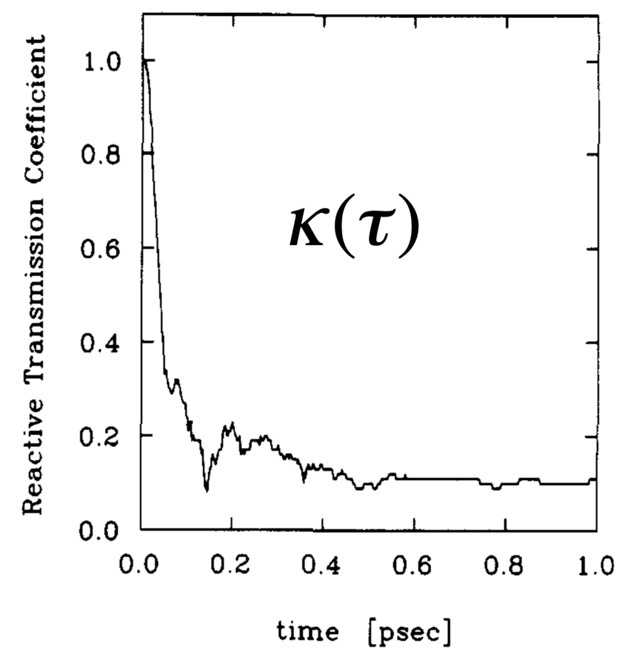
$H_A(x)$ = 1 if in state A, = 0 otherwise
$H_B(x)$ = 1 if in state B, = 0 otherwise

$$k_{\mathrm{A}\to\mathrm{B}} = \lim_{t\to\tau_{\mathrm{m}}} \frac{d}{dt} \frac{\langle H_{\mathrm{A}}(0) H_{\mathrm{B}}(t)\rangle}{\langle H_{\mathrm{A}}\rangle}$$

$$= \lim_{t\to\tau_{\mathrm{m}}} \frac{1}{\langle H_{\mathrm{A}}\rangle} \left\langle H_{\mathrm{A}}(0) \dot{H}_{\mathrm{B}}(t) \right\rangle$$

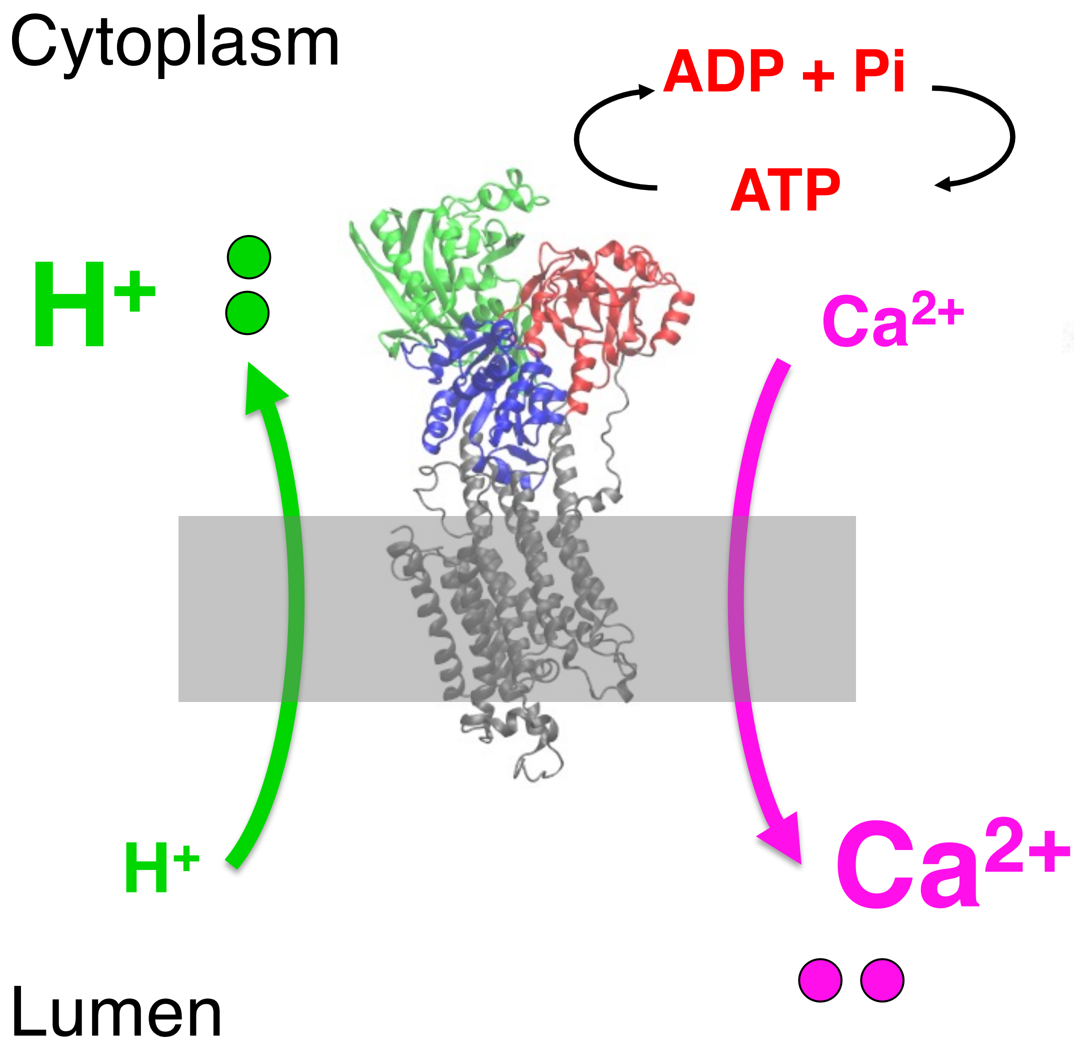
$$= k_{\mathrm{TST}}\, \kappa(\tau)$$



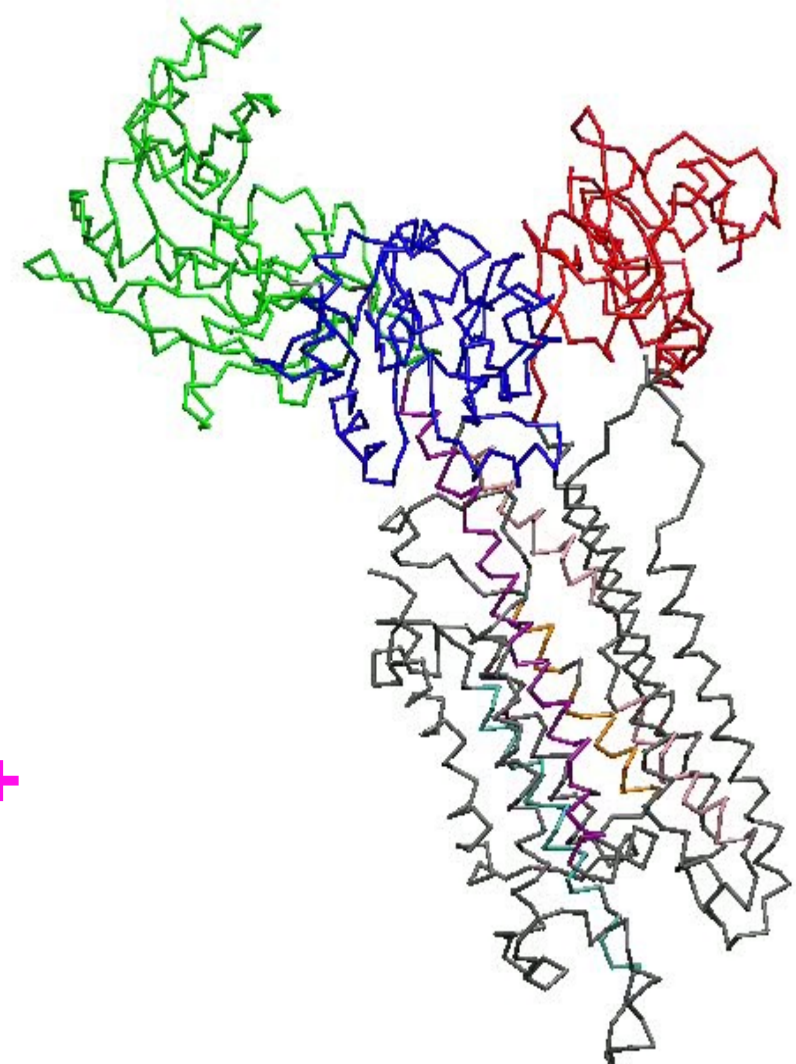


Chandler. “Statistical mechanics of isomerization dynamics in liquids and the transition state approximation” *J. Chem. Phys.* **68**, 2959–2970 (1978).
Northrup et al, “Dynamical theory of activated processes in globular proteins.” *Proc. Natl. Acad. Sci. USA* **79**, 4035-4039 (1982).

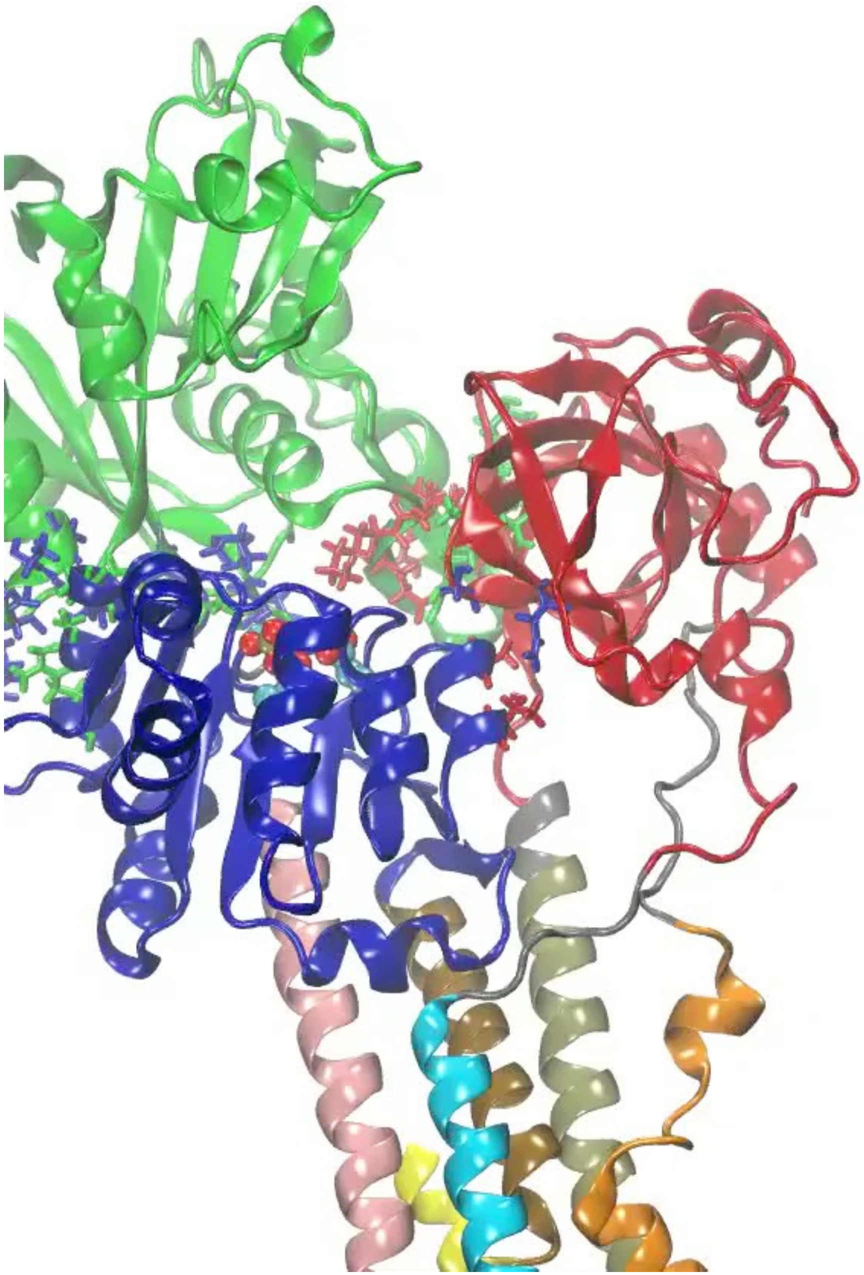
Calcium pump SERCA
(sarco/endoplasmic reticulum Ca^{2+}-ATPase)



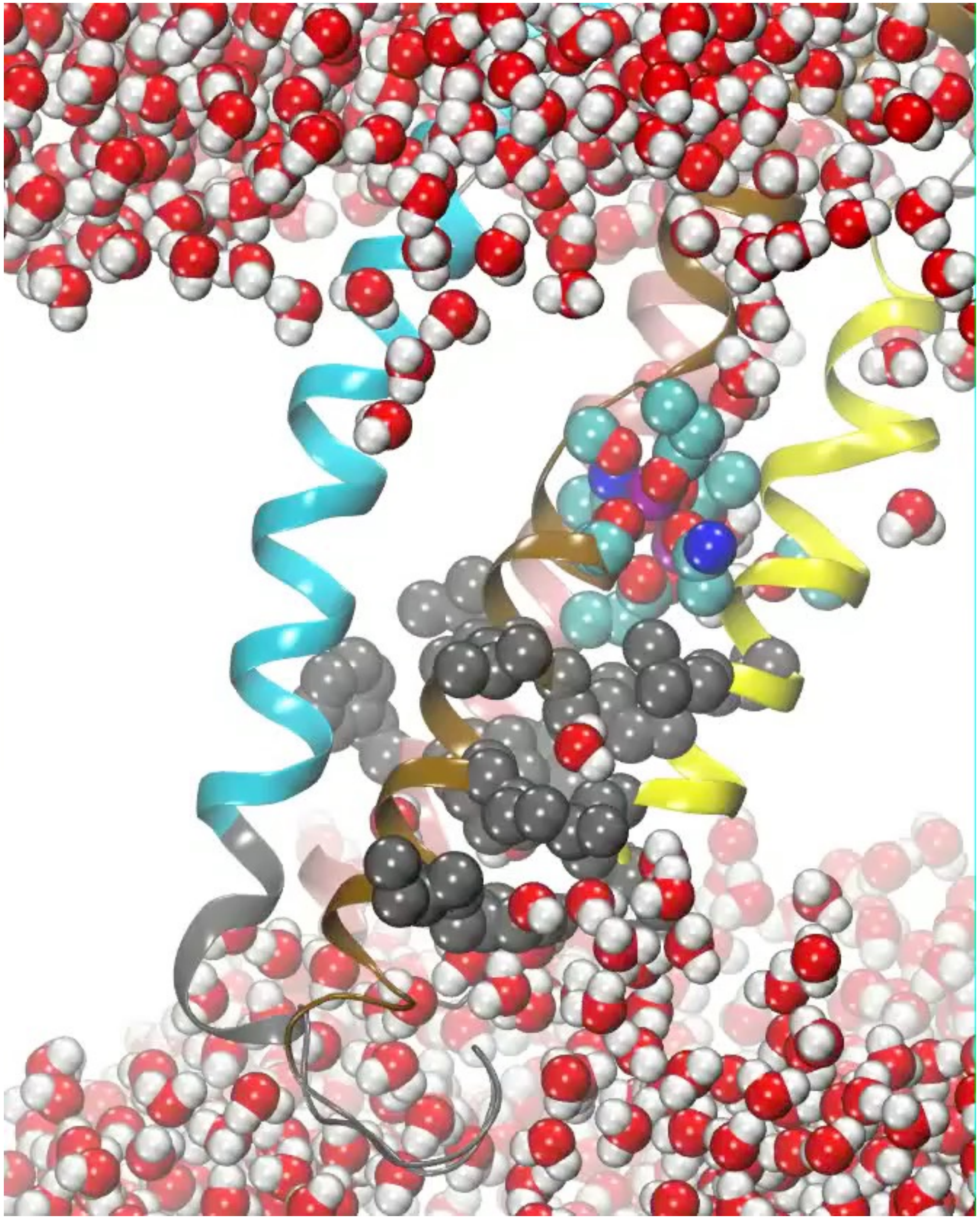
E1–2Ca (1SU4)



Opening the Luminal Access



Interacting residues on P and A domains shield the phosphorylated Asp351 from back reaction



Hydrophobic residues on M6 and M4 are shown in space filling

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String Method with Swarms-of-Trajectories, Mean Drifts, Lag Time, and Committor

Published as part of The Journal of Physical Chemistry virtual special issue "125 Years of The Journal of Physical Chemistry".

Benoît Roux*

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Benoît Roux[a)]

THE JOURNAL OF PHYSICAL CHEMISTRY LETTERS
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Committor-Consistent Variational String Method

Ziwei He, Christophe Chipot, and Benoît Roux*

Cite This: *J. Phys. Chem. Lett.* 2022, 13, 9263–9271 Read Online

Discovering reaction pathways, slow variables, and committor probabilities with machine learning

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Manuscript ID	ct-2023-00028r
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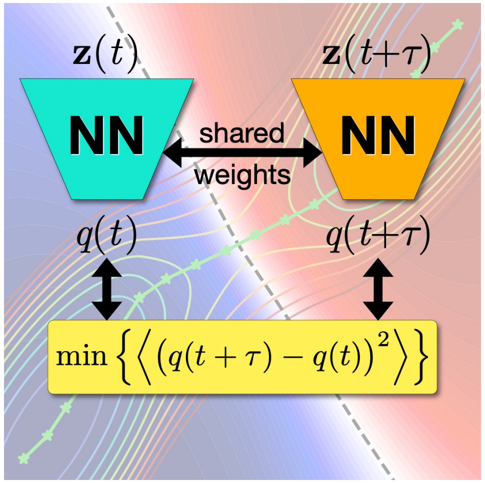
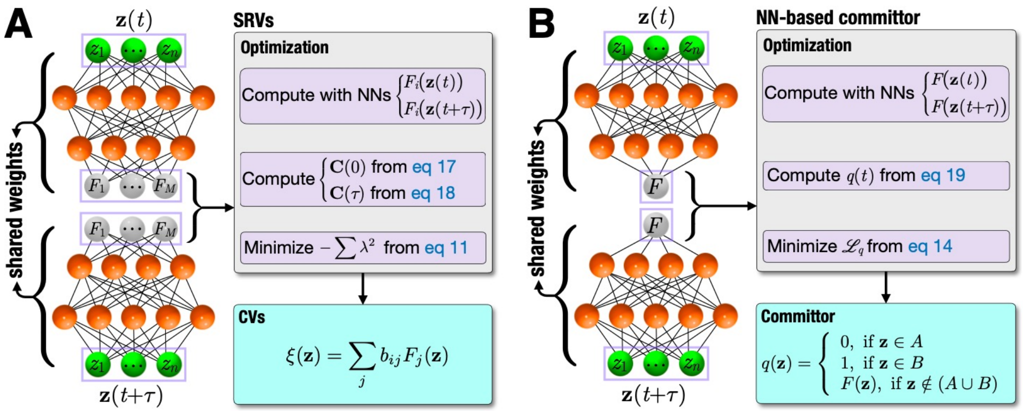




Propagator

$$\rho(\mathbf{z}'; t+\tau) \;=\; \int d\mathbf{z}\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\, \rho(\mathbf{z}; t)$$

forward propagation step $(\mathbf{z} \to \mathbf{z}')$ from the time t to the time $t+\tau$

Markovian dynamics

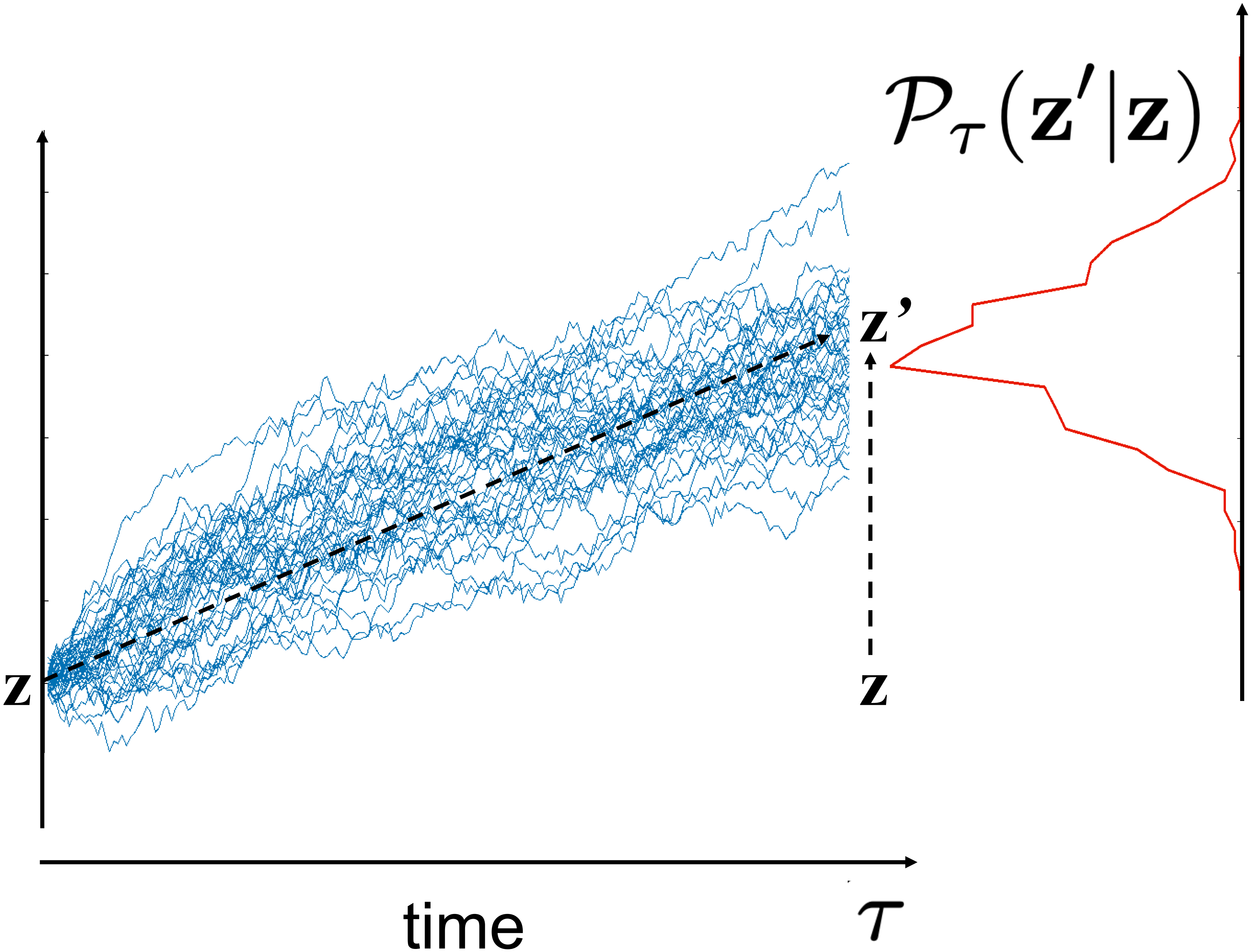
$$\boldsymbol{\rho}(t+n\tau) = \boldsymbol{\mathcal{P}}_{n\tau} \cdot \boldsymbol{\rho}(t),$$

$$\boldsymbol{\mathcal{P}}_{n\tau} \;=\; (\boldsymbol{\mathcal{P}}_\tau)^n.$$

Microscopic detailed balance

$$\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\, \rho_{\mathrm{eq}}(\mathbf{z}) \;=\; \mathcal{P}_\tau(\mathbf{z}|\mathbf{z}')\, \rho_{\mathrm{eq}}(\mathbf{z}')$$

Forward propagation step z to z'



Spectral decomposition

$$\lambda_k(\tau)\,\psi_k^{\mathrm{R}}(\mathbf{z}') = \int d\mathbf{z}\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\,\psi_k^{\mathrm{R}}(\mathbf{z})$$

$$\psi_1^{\mathrm{R}}(\mathbf{z}) = \rho_{\mathrm{eq}}(\mathbf{z})$$

$$\lambda_k(\tau)\,\psi_k^{\mathrm{L}}(\mathbf{z}) = \int d\mathbf{z}'\psi_k^{\mathrm{L}}(\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})$$

$$\psi_1^{\mathrm{L}}(\mathbf{z}) = 1$$

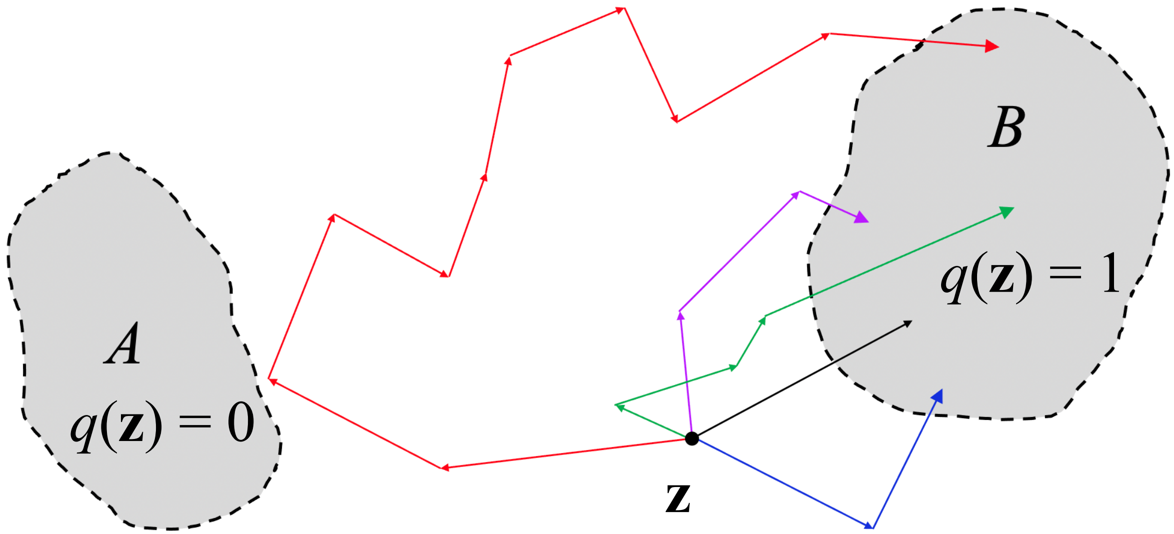
$$\delta_{kl} = \int d\mathbf{z}\,\psi_k^{\mathrm{L}}(\mathbf{z})\,\psi_l^{\mathrm{R}}(\mathbf{z}) = (\psi_k^{\mathrm{L}} \cdot \psi_l^{\mathrm{R}})$$

$$\delta_{kl} = \int d\mathbf{z}\,\psi_k^{\mathrm{L}}(\mathbf{z})\,\psi_l^{\mathrm{L}}(\mathbf{z})\,\rho_{\mathrm{eq}}(\mathbf{z})$$

Time correlation functions

$$\begin{aligned}\langle v(\tau)\,v(0)\rangle &= \int d\mathbf{z} \int d\mathbf{z}'\,v(\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\,v(\mathbf{z})\,\rho_{\mathrm{eq}}(\mathbf{z}) \\ &= \sum_k (v \cdot \psi_k^{\mathrm{R}})^2\,e^{-\mu_k \tau}\end{aligned}$$

TPT: Committor probability



$$\begin{aligned}
q(\mathbf{z}) &= \int_{\in B} d\mathbf{z}'\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) + \int_{\notin A,B} d\mathbf{z}' \int_{\in B} d\mathbf{z}''\,\mathcal{P}_\tau(\mathbf{z}''|\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) \\
&\quad + \int_{\notin A,B} d\mathbf{z}' \int_{\notin A,B} d\mathbf{z}'' \int_{\in B} d\mathbf{z}'''\,\mathcal{P}_\tau(\mathbf{z}'''|\mathbf{z}'')\,\mathcal{P}_\tau(\mathbf{z}''|\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) \quad + \ldots \\
&= \int_{\in B} d\mathbf{z} \ldots \mathbf{z}''|\mathbf{z}') + \ldots \Big\}\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) \\
&= 0 + \int_{\in} \ldots \\
&= \int_{\in A} d\mathbf{z} \ldots \\
&= \int_{\in A} d\mathbf{z}'\,q(\mathbf{z}') + \int_{\in B} d\mathbf{z}'\,q(\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) + \int_{\notin A,B} d\mathbf{z}'\,q(\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) \\
&= \int d\mathbf{z}'\,q(\mathbf{z}')\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})
\end{aligned}$$

$$q(\mathbf{z}'') = \int d\mathbf{z}\,q(\mathbf{z})\,\mathcal{P}_\tau(\mathbf{z}|\mathbf{z}'')$$

The reactive flux from A to B

$$J_{AB} = \frac{1}{2\tau}\left\langle \left(q(\tau) - q(0)\right)^2 \right\rangle$$

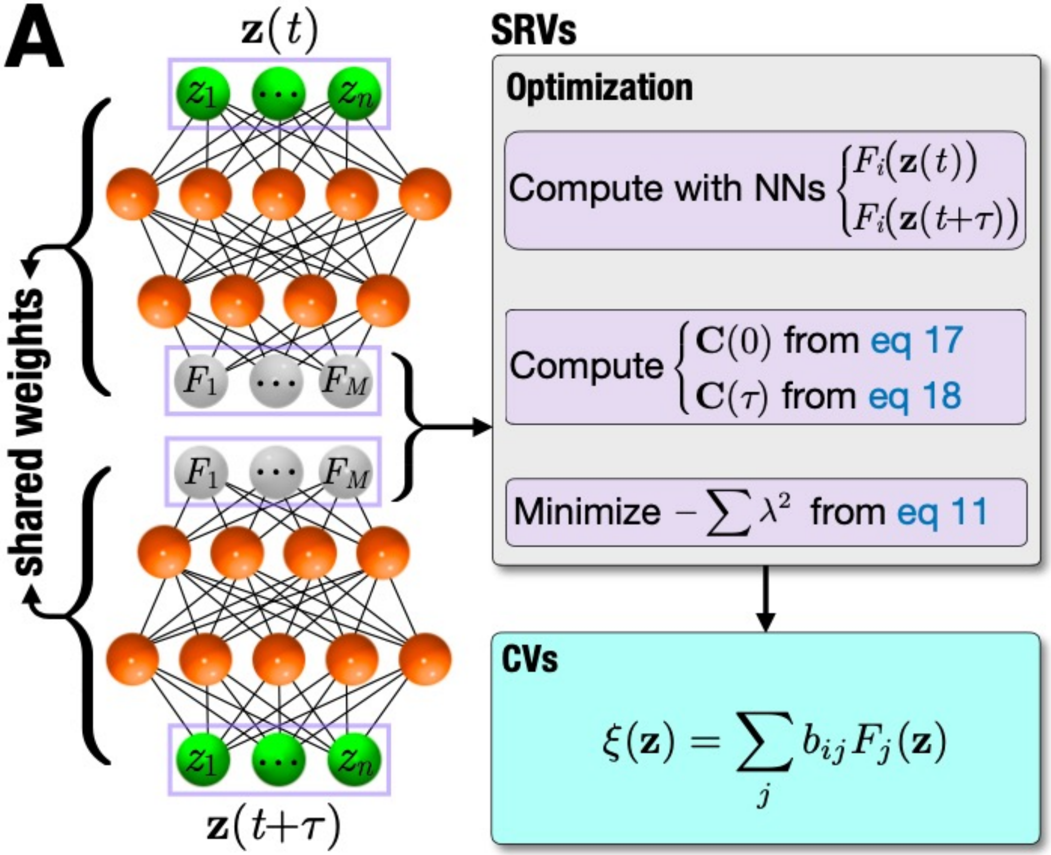
Minimizing the steady-state flux J_{AB} with respect to a trial function $q(\mathbf{z})$ yields,

$$\begin{aligned}
0 &= \frac{\delta J_{AB}[q]}{\delta q(\mathbf{z}'')} \\
0 &= \frac{1}{2\tau}\int d\mathbf{z}\int d\mathbf{z}'\,\Big(q(\mathbf{z}') - q(\mathbf{z})\Big)\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\,\rho_{\mathrm{eq}}(\mathbf{z})\,\Big(\delta(\mathbf{z}'-\mathbf{z}'') - \delta(\mathbf{z}-\mathbf{z}'')\Big) \\
0 &= \int d\mathbf{z}\,\Big(q(\mathbf{z}'') - q(\mathbf{z})\Big)\,\mathcal{P}_\tau(\mathbf{z}''|\mathbf{z})\,\rho_{\mathrm{eq}}(\mathbf{z}) - \int d\mathbf{z}'\,\Big(q(\mathbf{z}') - q(\mathbf{z}'')\Big)\,\mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}'')\,\rho_{\mathrm{eq}}(\mathbf{z}'') \\
0 &= 2\,\rho_{\mathrm{eq}}(\mathbf{z}'')\int d\mathbf{z}\,\Big(q(\mathbf{z}'') - q(\mathbf{z})\Big)\,\mathcal{P}_\tau(\mathbf{z}|\mathbf{z}'') \\
0 &= \int d\mathbf{z}\,\Big(q(\mathbf{z}'') - q(\mathbf{z})\Big)\,\mathcal{P}_\tau(\mathbf{z}|\mathbf{z}'')
\end{aligned}$$

can serve as a variational principle

$$q(\mathbf{z}'') = \int d\mathbf{z}\,q(\mathbf{z})\,\mathcal{P}_\tau(\mathbf{z}|\mathbf{z}'')$$

Spectral decomposition and ML

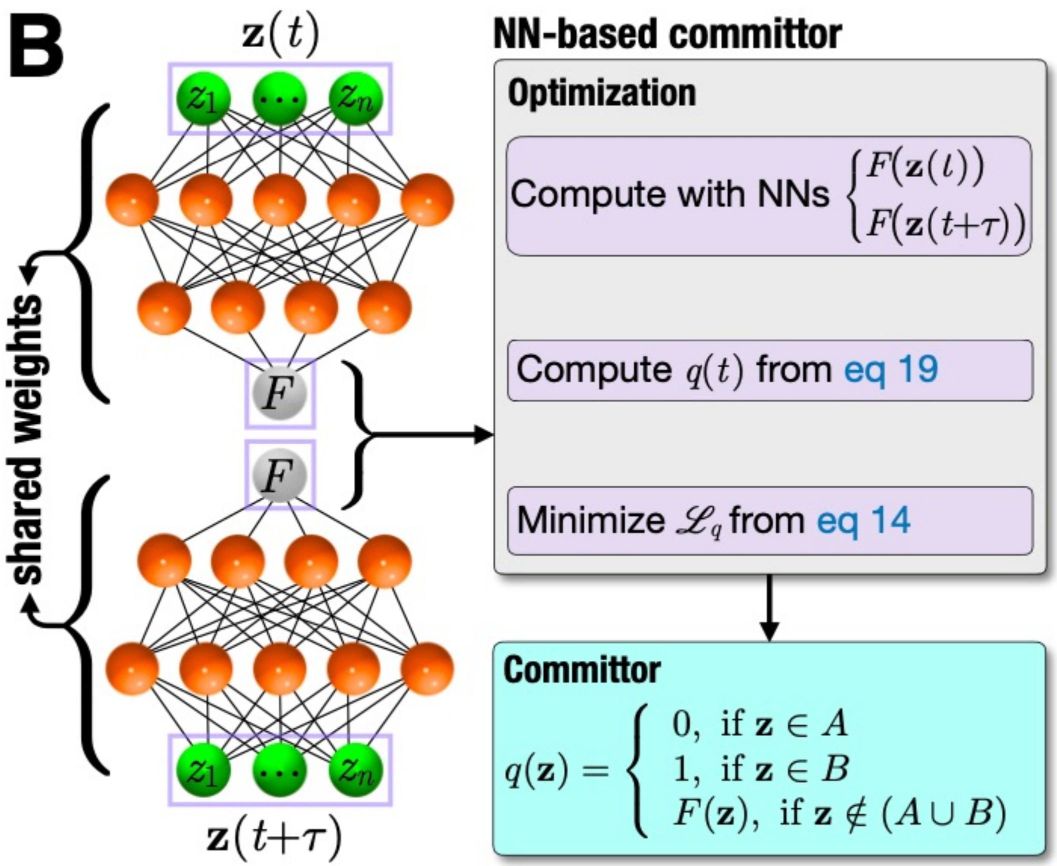


$$\mathscr{L}_v = -\frac{\langle v(\tau)\, v(0) \rangle}{\langle v(0)\, v(0) \rangle}$$

$$v(\mathbf{z}) = \sum_{i=1}^{M} b_i F_i(\mathbf{z})$$

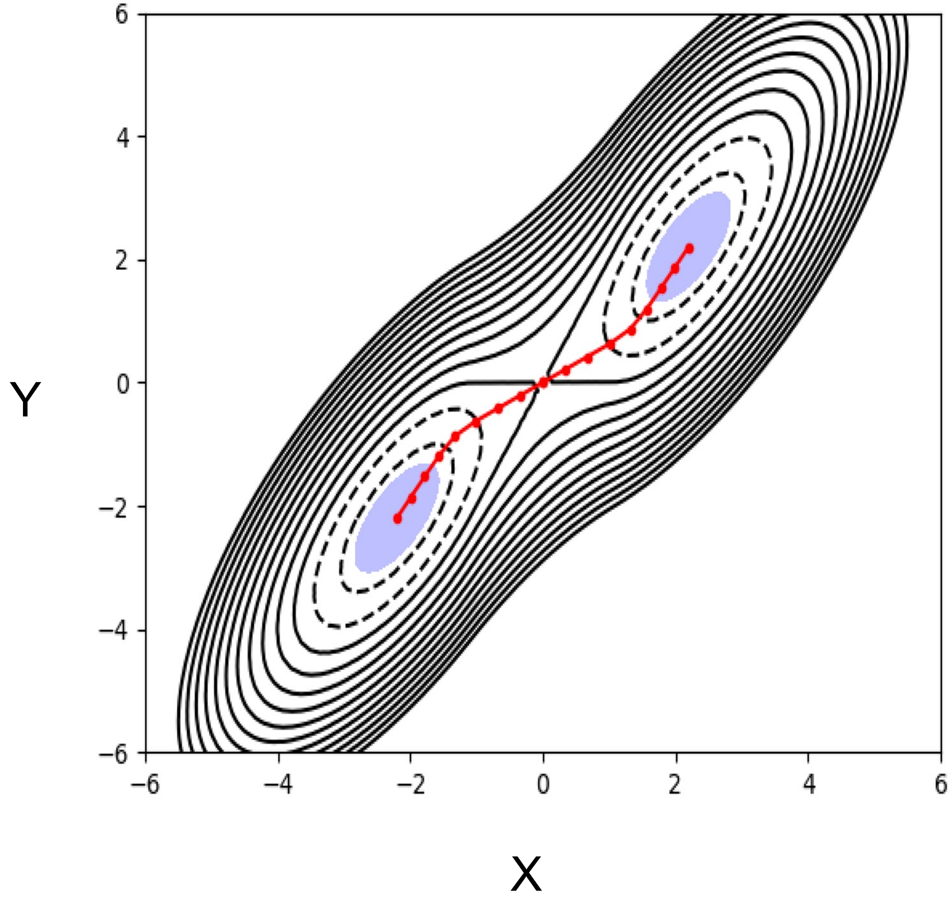
$$\mathbf{C}(\tau)\mathbf{B} = \mathbf{C}(0)\mathbf{B}\boldsymbol{\Lambda}$$

Committor probability and ML



$$\mathscr{L}_q = 2\tau J_{\mathrm{AB}} = \left\langle \left(q(\tau) - q(0) \right)^2 \right\rangle$$

Berezhkovskii-Szabo 2D potential



$$\beta V(x, y) = \beta V(x) + 1.01\omega^2(x - y)^2/2$$

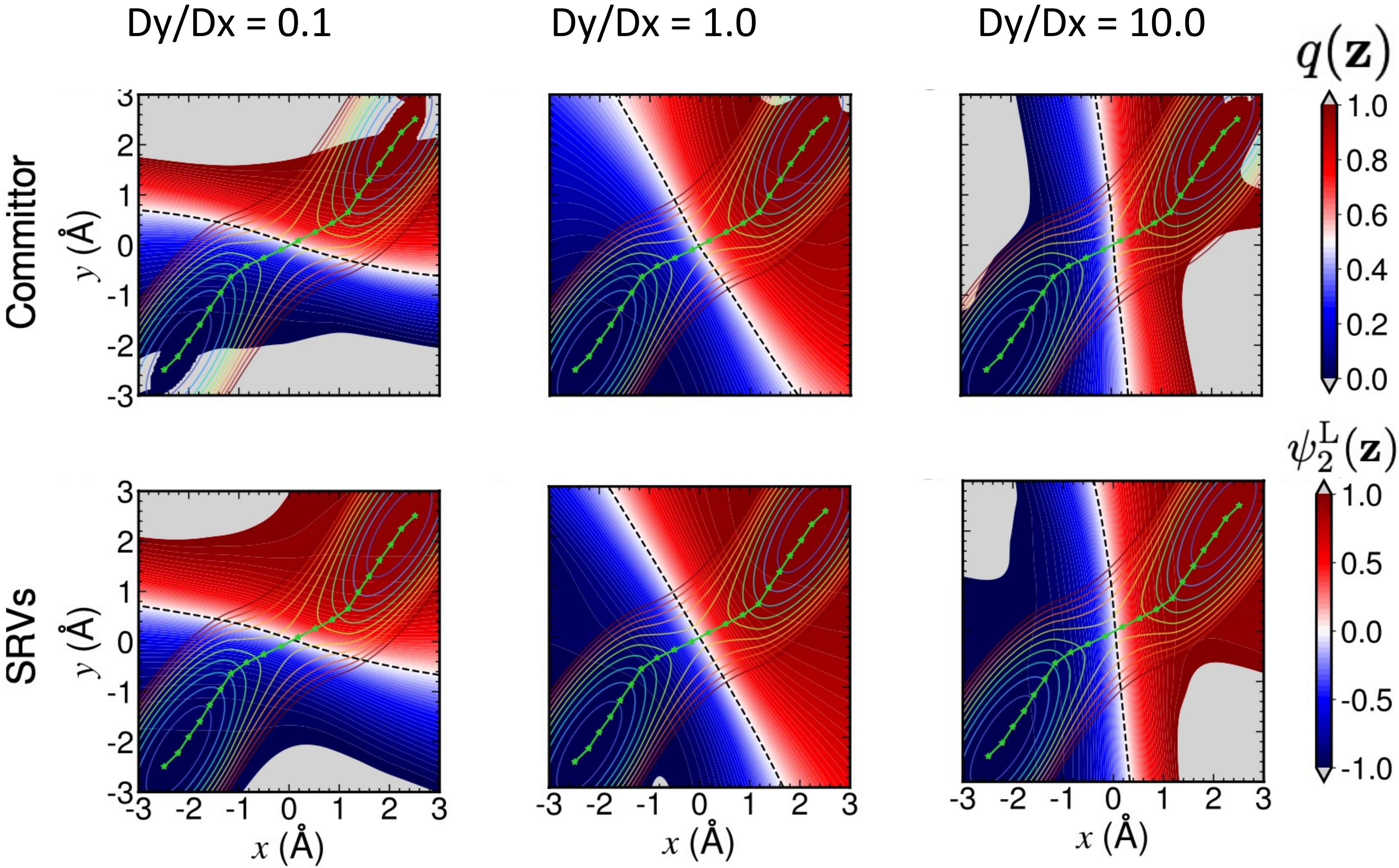
$V(x)$ is calculated from,

$$\beta V(x) = \begin{cases} -\omega^2 x_0^2/4 + \omega^2(x + x_0)^2/2, & x < -x_0/2 \\ -\omega^2 x^2/2, & -x_0/2 \le x \le x_0/2 \\ -\omega^2 x_0^2/4 + \omega^2(x - x_0)^2/2, & x_0/2 < x \end{cases}$$

Dy/Dx = 0.1 Dy/Dx = 1.0 Dy/Dx = 10.0

A. Berezhkovskii, S. Szabo, *J. Chem. Phys.,* 122 014503 (2005)
P. Tiwary, B. J. Berne, *J. Chem. Phys*., 147 152701 (2017)

Committor and slowest eigenvector

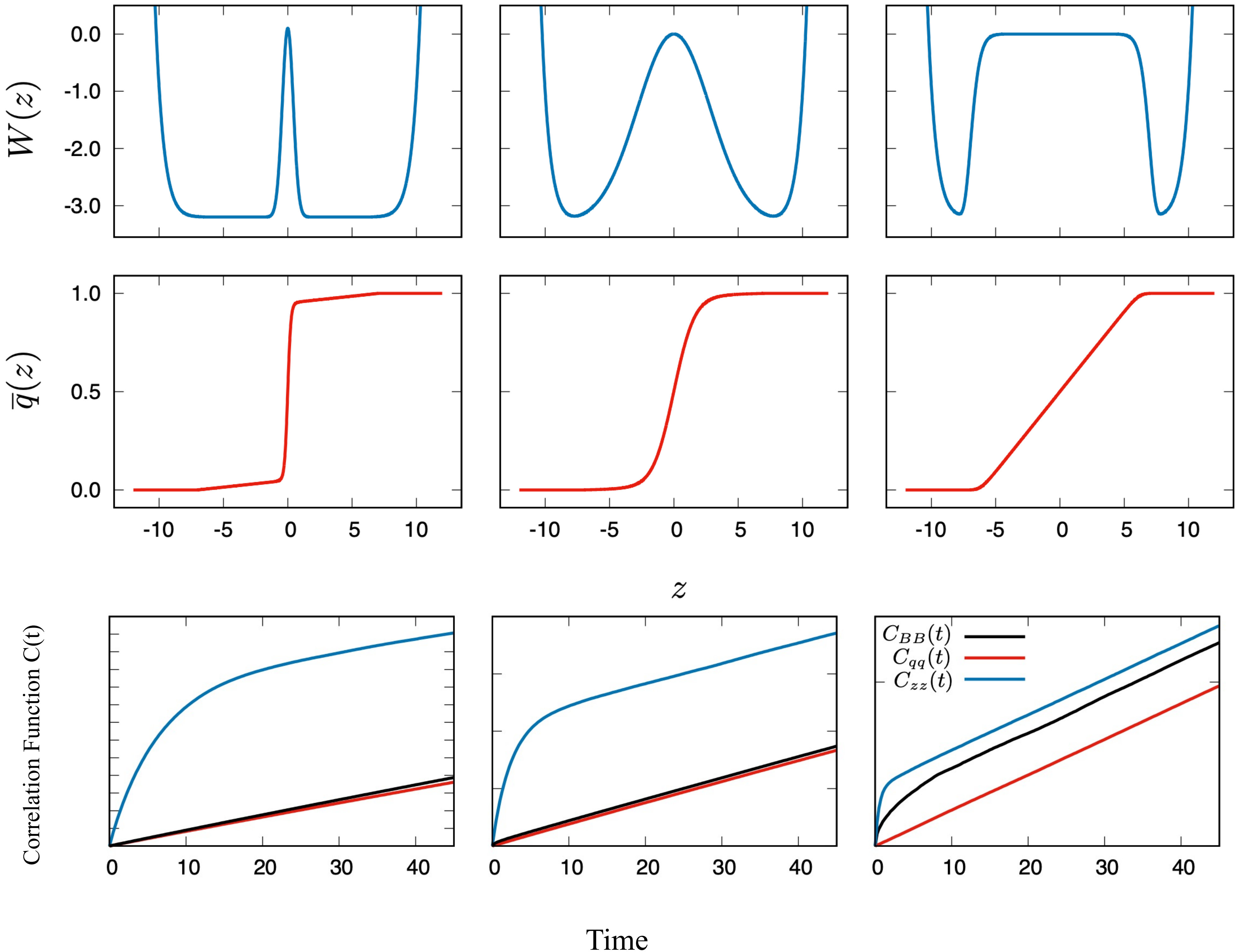


Committor and slowest eigenvector

$$q(\mathbf{z}) \approx -\left(\frac{a}{b-a}\right) \psi_1^{\mathrm{L}}(\mathbf{z}) + \left(\frac{1}{b-a}\right) \psi_2^{\mathrm{L}}(\mathbf{z})$$

$$\begin{aligned}
\int d\mathbf{z}'\, q(\mathbf{z}')\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) &= -\left(\frac{a}{b-a}\right) \int d\mathbf{z}'\, \psi_1^{\mathrm{L}}(\mathbf{z}')\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) \\
&\quad + \left(\frac{1}{b-a}\right) \int d\mathbf{z}'\, \psi_2^{\mathrm{L}}(\mathbf{z}')\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z}) \\
&= -\left(\frac{a}{b-a}\right) \psi_1^{\mathrm{L}}(\mathbf{z}) + \left(\frac{1}{b-a}\right) \lambda_2\, \psi_2^{\mathrm{L}}(\mathbf{z}) \\
&= q(\mathbf{z}) + \left(\frac{\lambda_2 - 1}{b-a}\right) \psi_2^{\mathrm{L}}(\mathbf{z}) \\
&\approx q(\mathbf{z})
\end{aligned}$$

$$|(\lambda_2 - 1)/(b-a)| \ll 1$$



W(z)
0.0
-1.0
-2.0
-3.0
q̄(z)
1.0
0.5
0.0
-10
-5
0
5
10
z
Correlation Function C(t)
0
10
20
30
40
Time
$C_{BB}(t)$
$C_{qq}(t)$
$C_{zz}(t)$

Reactive flux formalism

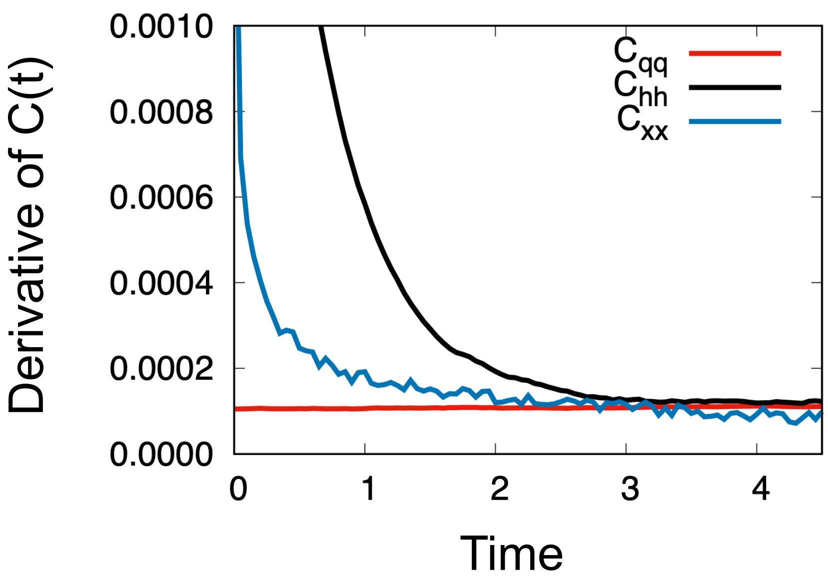
$$k_{AB} = \lim_{t \to \tau_m} -\frac{1}{p_A} \langle H_B(0)\, \dot{H}_B(t) \rangle$$

$$H_B(x) = \theta\Big((\mathbf{z} - \mathbf{z}^\dagger) \cdot \boldsymbol{n} \Big)$$

n must be parallel to $\nabla q(\mathbf{z})$

Transition path theory

$$k_{AB} = \lim_{t \to \tau} -\frac{1}{p_A} \langle q(0)\, \dot{q}(t) \rangle$$



Using a less-than-perfect committor?

$$\langle q_\star(0)\, q_\star(\tau)\rangle = \int d\mathbf{z} \int d\mathbf{z}'\, q_\star(\mathbf{z})\, q_\star(\mathbf{z}')\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\, \rho_{\mathrm{eq}}(\mathbf{z})$$
$$= \sum_k \left(q_\star \cdot \psi_k^{\mathrm{R}}\right)^2 e^{-\mu_k \tau}$$

$$\left(q_\star \cdot \psi_k^{\mathrm{R}}\right) = \int d\mathbf{z}\, q_\star(\mathbf{z})\, \psi_k^{\mathrm{R}}(\mathbf{z})$$

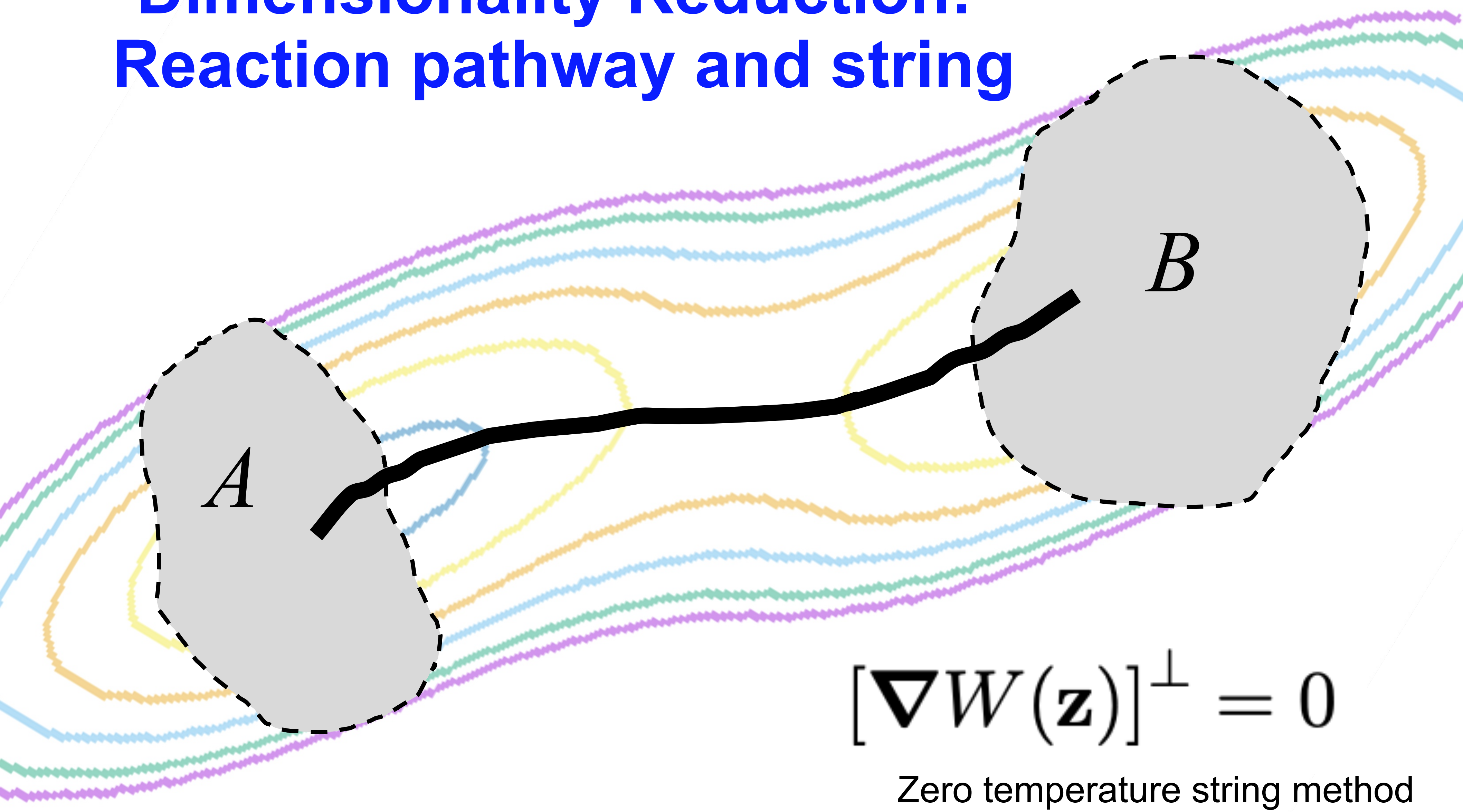
An approximate committor overlaps with higher order eigenvectors $\psi_k^{\mathrm{L}}(\mathbf{z})$

The committor time-correlation function is not linear at short time even if the dynamics within the subspace **z** is Markovian

As t increases to some lag-time τ_{m} then $C_{qq}(t)$ becomes linear

M. Ruiz-Montero, D. Frenkel, and J. Brey, “Efficient schemes to compute diffusive barrier crossing rates,” Mol. Phys. 90(6), 925–941 (1997).

Dimensionality Reduction: Reaction pathway and string

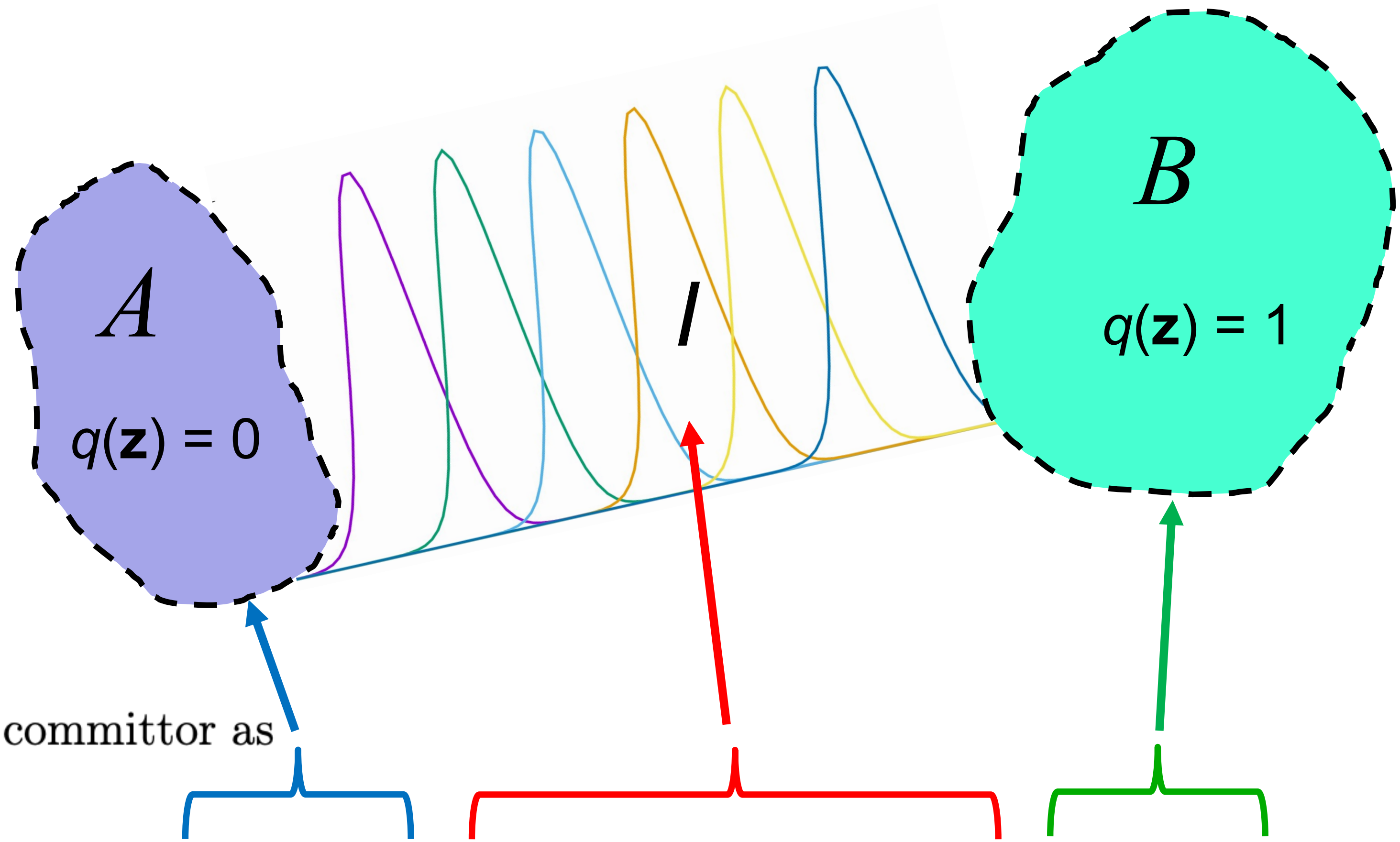


$$[\nabla W(\mathbf{z})]^{\perp} = 0$$

Zero temperature string method

Elber & Karplus. *Chem. Phys. Letts.* 139:375 (1987).
Jónsson et a; Eds. B. J. Berne, G. Ciccotti and D. F. Coker (World Scientific, 1998).
Maragliano et al ,*J. Chem. Phys.* 2006, **125**, 24106.
Pan et al, *J. Phys. Chem. B* 2008, **112**, 3432–3440.

Basis set expansion for the committor



We write the committor as

$$q(\tilde{\mathbf{z}}(\mathbf{x})) = h_A(\tilde{\mathbf{z}}(\mathbf{x}))\, q_A + h_I(\tilde{\mathbf{z}}(\mathbf{x})) \left(\sum_i b_i\, f_i(\tilde{\mathbf{z}}(\mathbf{x})) \right) + h_B(\tilde{\mathbf{z}}(\mathbf{x}))\, q_B$$

He, Z.; Chipot, C.; Roux, B. Committor-consistent variational string method. *J. Phys. Chem. Letters* 2022, *13*, 9263–9271.

The committor time-correlation function

$$\langle q(\tau)q(0)\rangle = \left\langle \left(h_A(\tau)q_A + h_I(\tau)\left(\sum_i b_i f_i(\tau)\right) + h_B(\tau)\right)\left(h_A(\tau)q_A + h_I(0)\left(\sum_j b_j f_j(0)\right) + h_B(0)\right)\right\rangle$$

$$\left\langle \left(q(\tau) - q(0)\right)^2 \right\rangle = \frac{1}{2}\mathbf{b}^t\left(\mathbf{D}(0) - \mathbf{D}(\tau)\right)\mathbf{b} + \left(\mathbf{g}(0) - \mathbf{g}(\tau)\right)\cdot\mathbf{b}$$

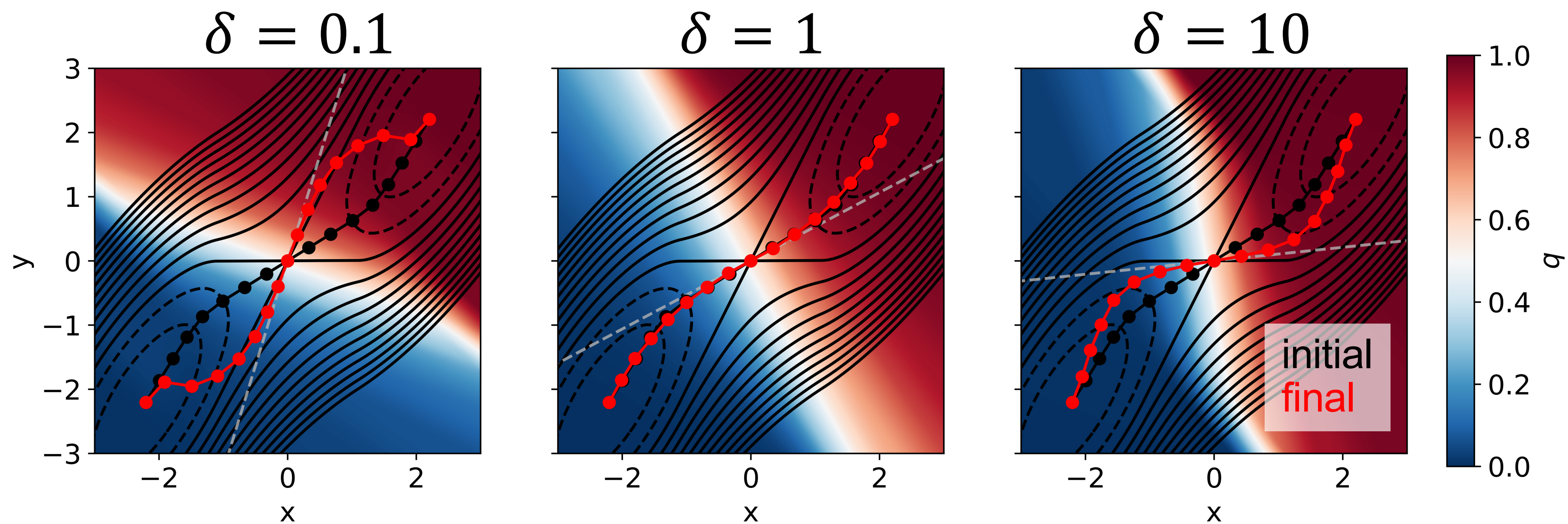
Minimization of this simple quadratic form:

$$\mathbf{b} = -\left(\mathbf{D}(0) - \mathbf{D}(\tau)\right)^{-1}\left(\mathbf{g}(0) - \mathbf{g}(\tau)\right)$$

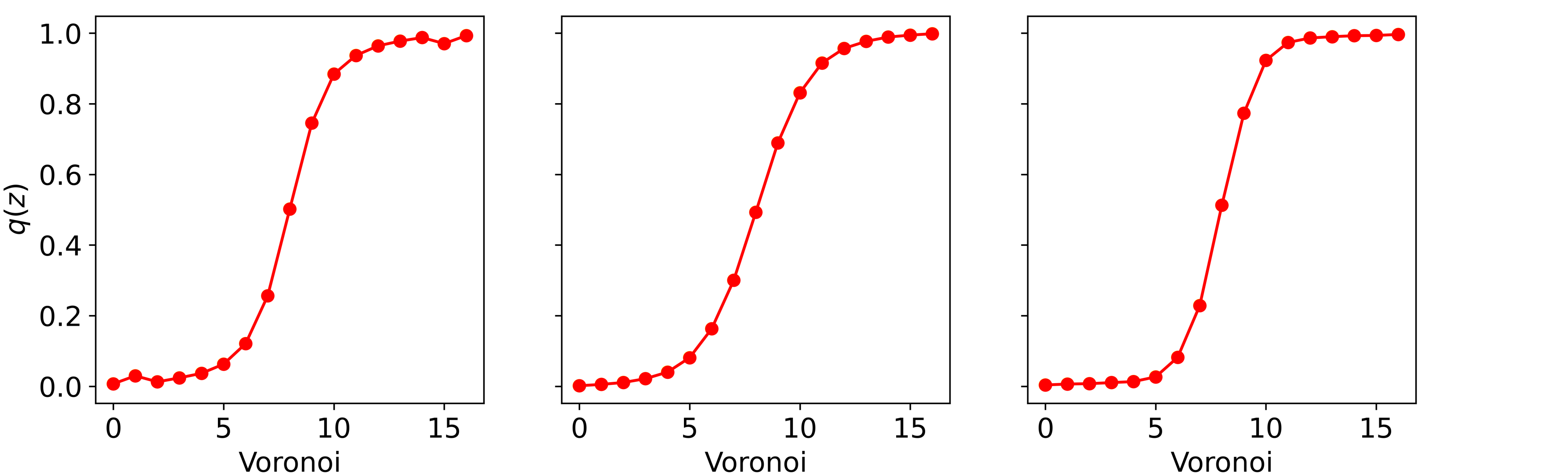
He, Z.; Chipot, C.; Roux, B. Committor-consistent variational string method. *J. Phys. Chem. Letters* 2022, *13*, 9263–9271.

2D model: Berezhkovskii-Szabo potential

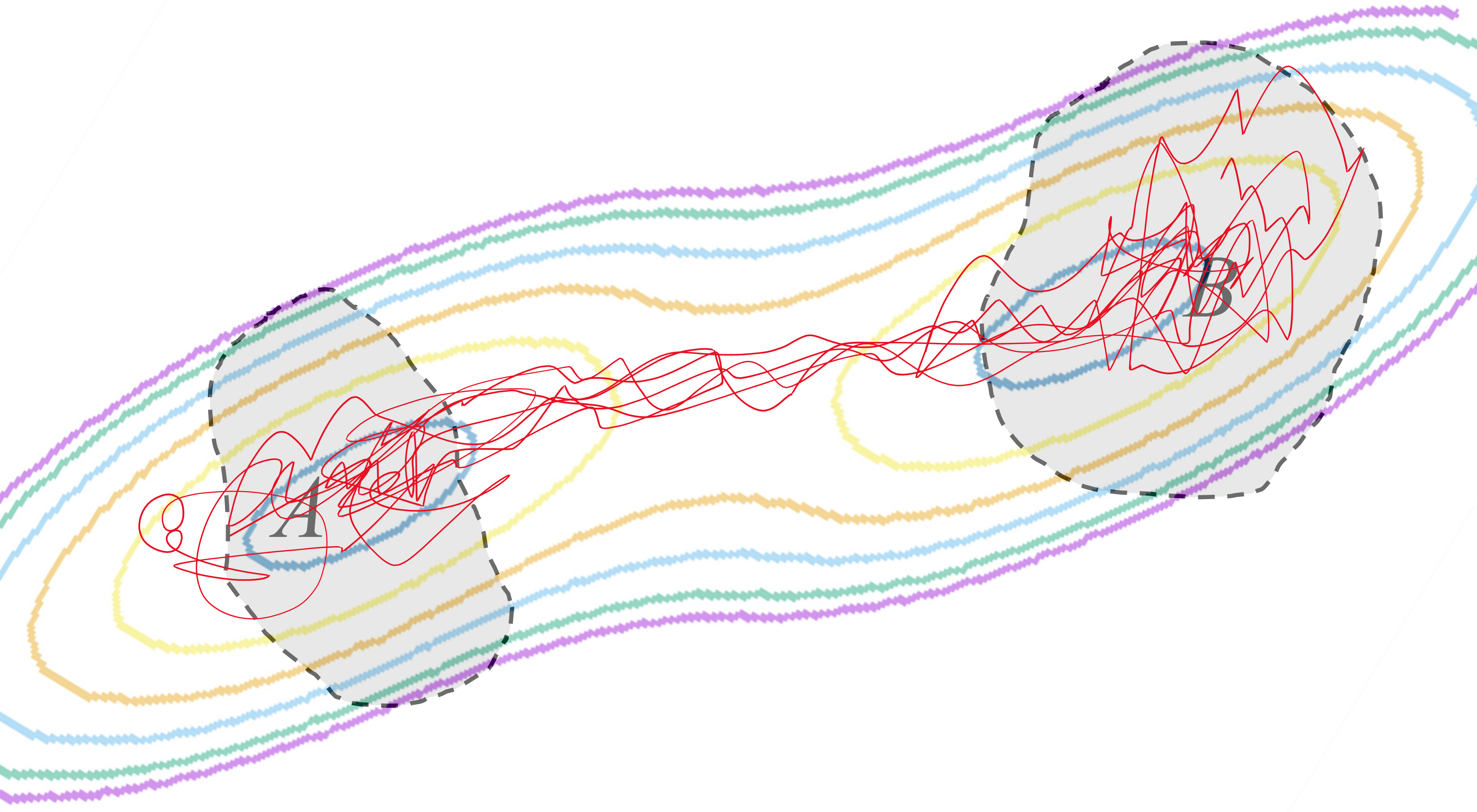
String



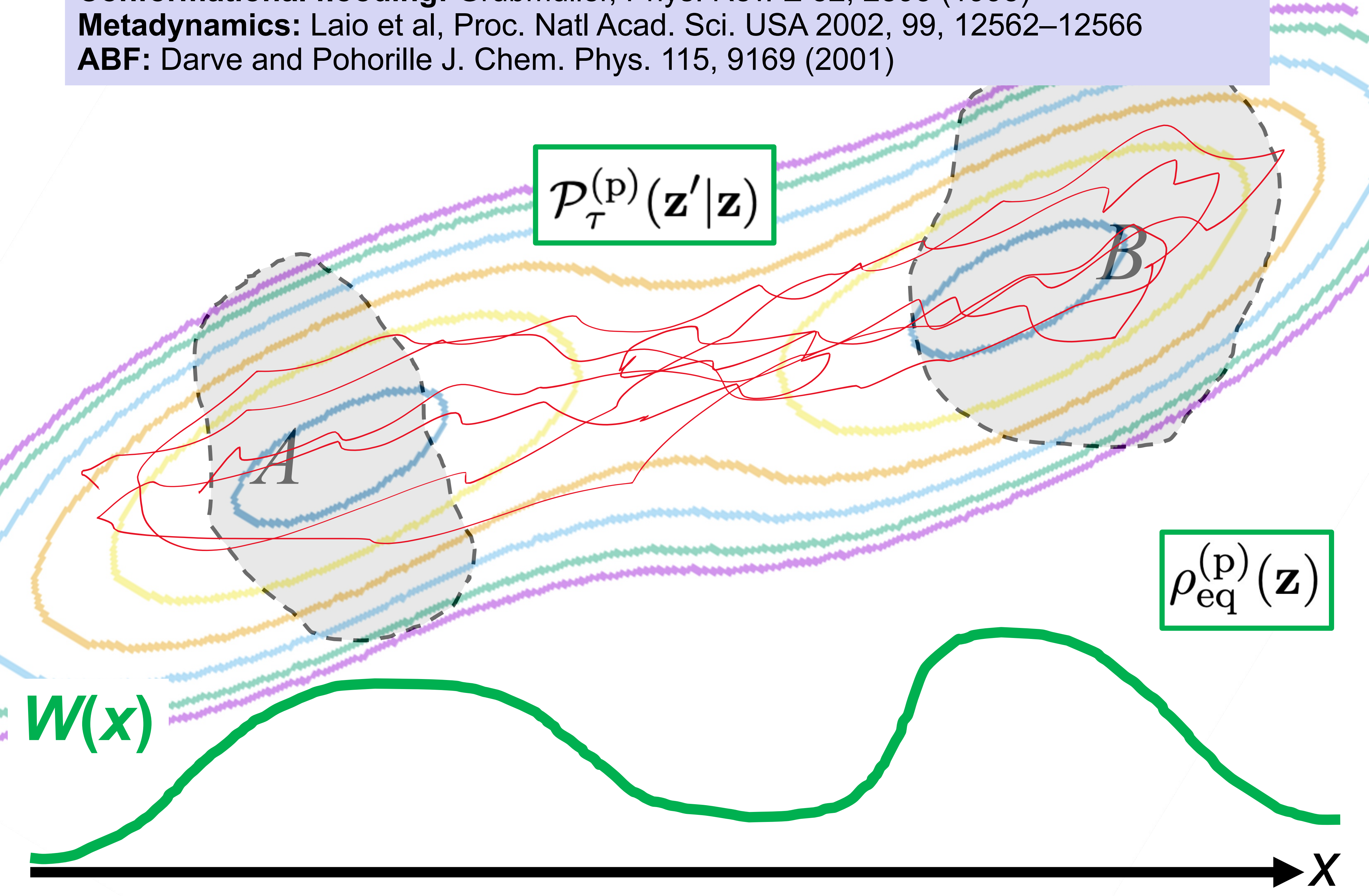
Committor



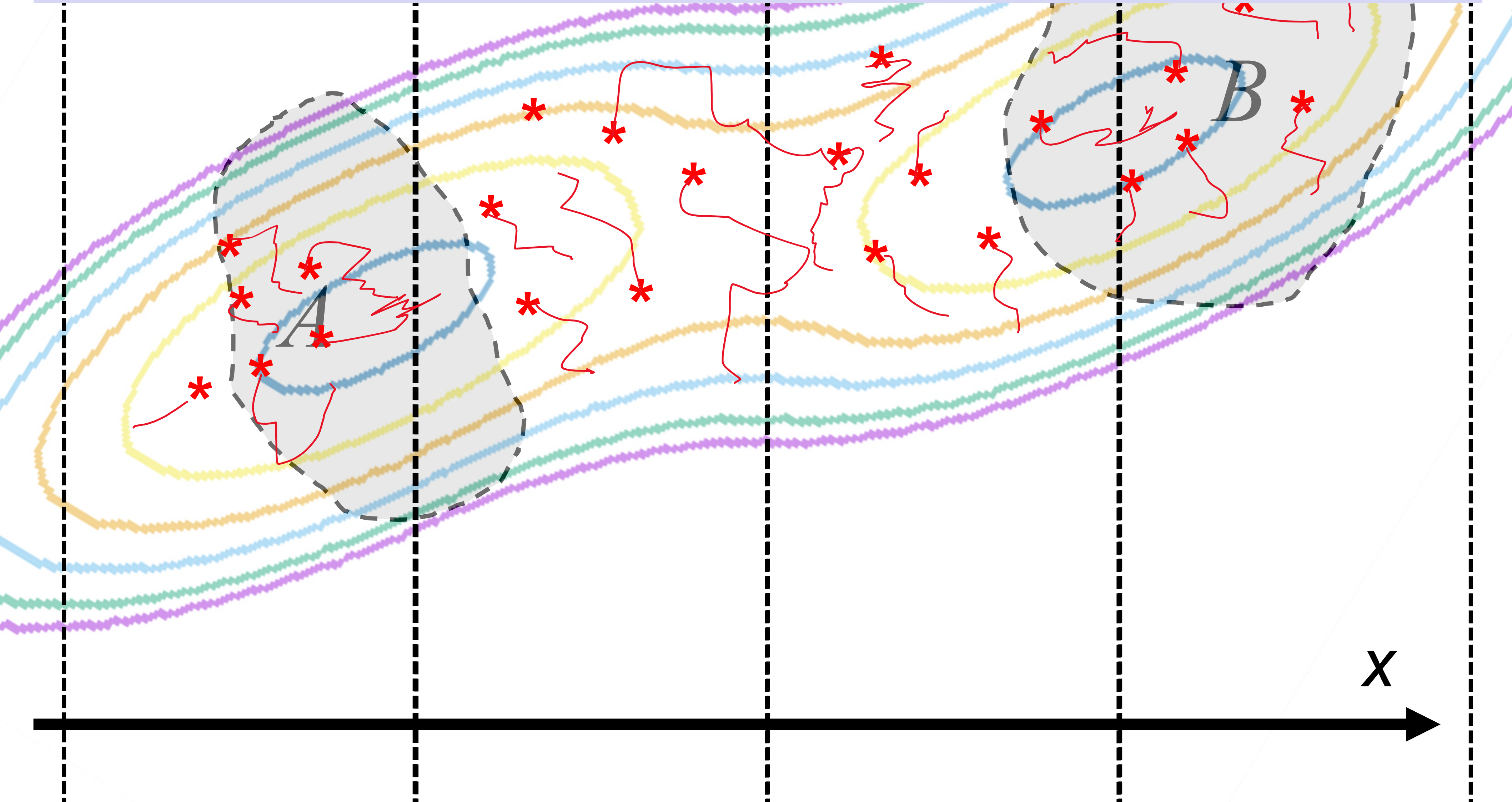
What about sampling?

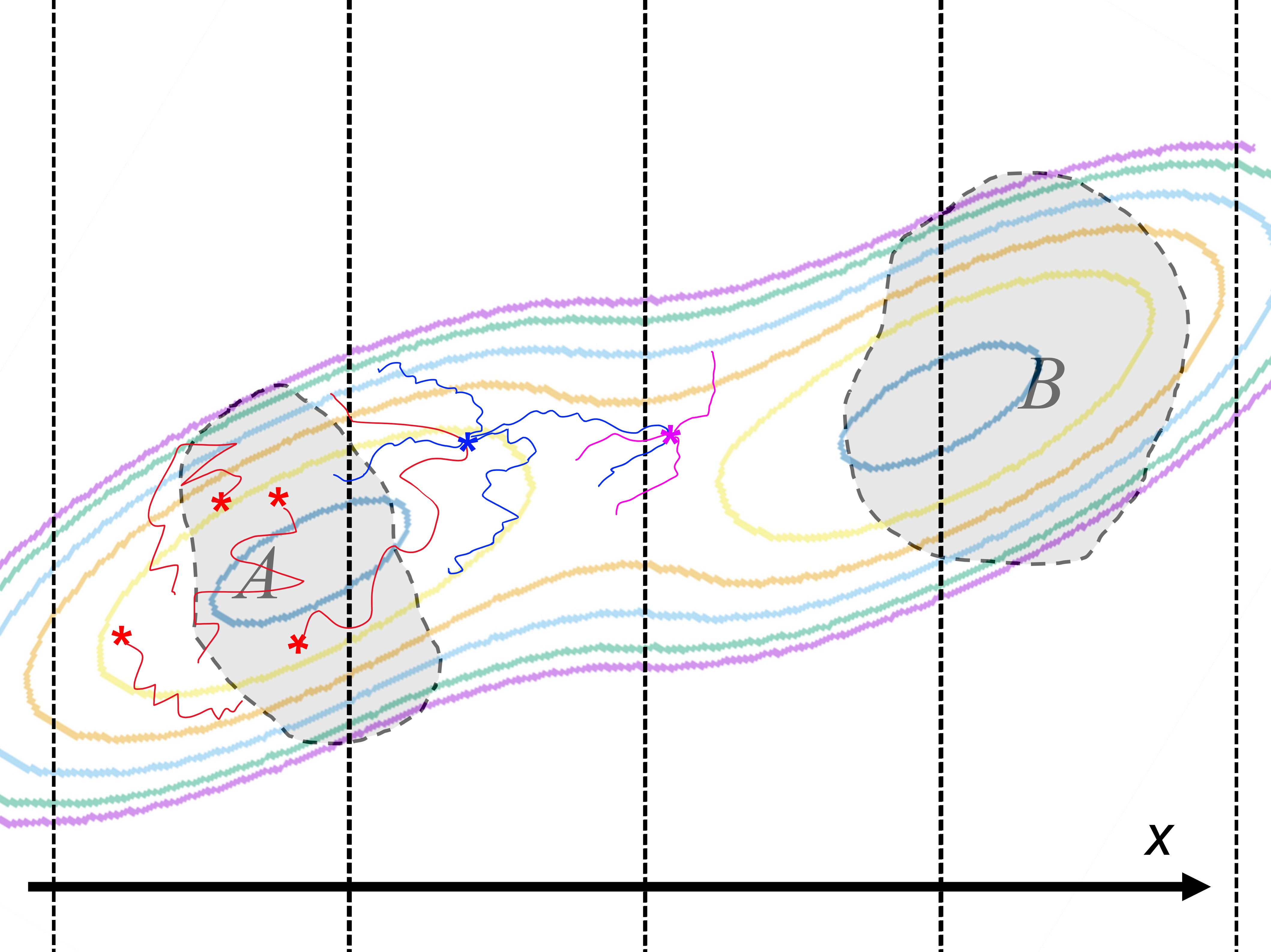


Umbrella sampling: Torrie and Valleau, J. Comp. Phys. 23, 187-199 (1977)
Conformational flooding: Grubmüller, Phys. Rev. E 52, 2893 (1995)
Metadynamics: Laio et al, Proc. Natl Acad. Sci. USA 2002, 99, 12562–12566
ABF: Darve and Pohorille J. Chem. Phys. 115, 9169 (2001)



Weighted Ensemble: Huber and Kim, Biophys. J. 70 97-110 (1996); Zuckerman1 and Chong, Annual Review of Biophysics 46, 43-57 (2017).
Milestoning: Faradjian and Elber, J. Chem. Phys. 120, 10880 (2004)
Transition interface sampling: Moroni et al, Physica A 340, 395-401 (2004)
Forward flux sampling: Allena et al J. Chem. Phys. 124, 194111 (2006)
Nonequilibrium umbrella sampling: Dickson et al, J. Chem. Phys. 130, 074104 (2009)
Adaptive multilevel splitting: Cérou et al, J. Chem. Phys. 134, 054108 (2011)





A
B
x

Enhanced Sampling?

Unbiased trajectories

- Picking initial conditions
- Non-ergodic sampling
- Reconstruct equilibrium
- Natural unbiased dynamics
  - Reweights based on initial conditions
- Generate rare configurations?

Biased trajectories

- Run dynamics with biasing potential
- Ergodic sampling
- Equilibrium from Boltzmann reweighting
- Can populate top of free energy barriers
- Dynamics corrupted by biasing potential
  - Run unbiased trajectories & reweight?
  - Unbiasing the dynamics?

Transition-based reweighting analysis method (TRAM) : Wu et al, *Proc. Natl. Acad. Sci. U.S.A.* 113, E3221–E3230 (2016).

Galerkin approximation: Thiede et al, *J. Chem. Phys.* 150, 244111 (2019)

$$\langle f(\tau)\, g(0)\rangle = \int d\mathbf{z} \int d\mathbf{z}'\, f(\mathbf{z}')\, g(\mathbf{z})\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\; \rho_{\mathrm{eq}}(\mathbf{z})$$

$\mathcal{P}_\tau^{(\mathrm{p})}(\mathbf{z}'|\mathbf{z})$ $\rho_{\mathrm{eq}}^{(\mathrm{p})}(\mathbf{z})$

GLE & memory function: Berne et al, *J. Chem. Phys.* 93, 5084-5095 (1990).

Diffusion constant: Woolf and Roux, *J. Am. Chem. Soc.* 116, 5916 (1994); Lee et al, *J. Chem. Inf. Model.* 56, 721–733 (2016)

Arrhenius reweighting: Tiwary and Parrinello, *Phys. Rev. Lett.* 111, 230602 (2013)

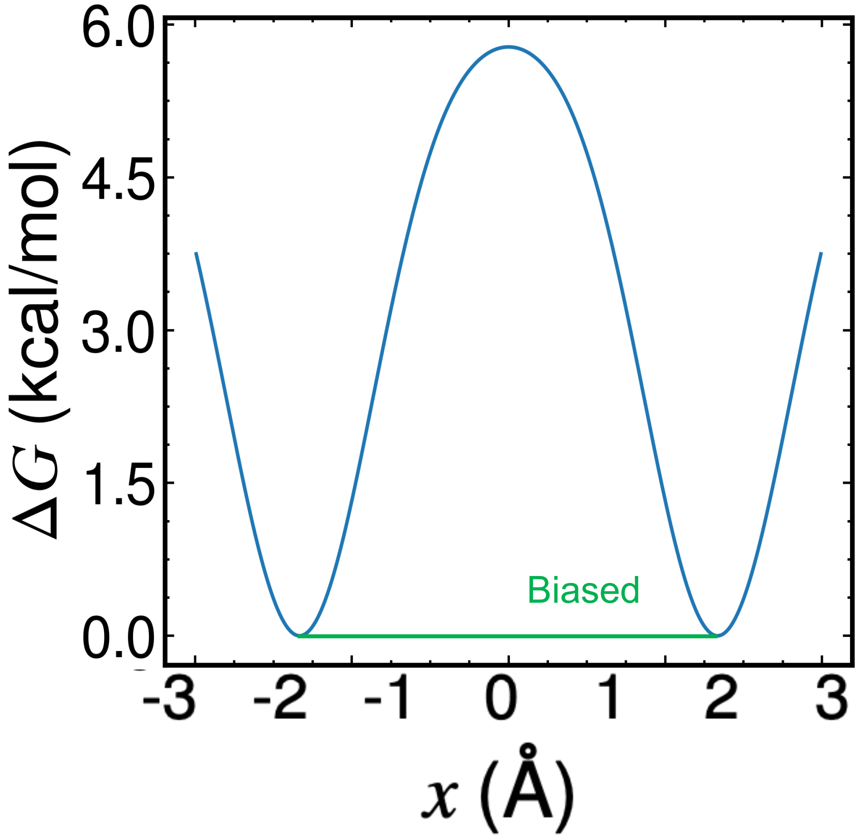
DHAM: Rosta and Hummer, *J Chem. Theory Comput.* 11, 276-85 (2015)

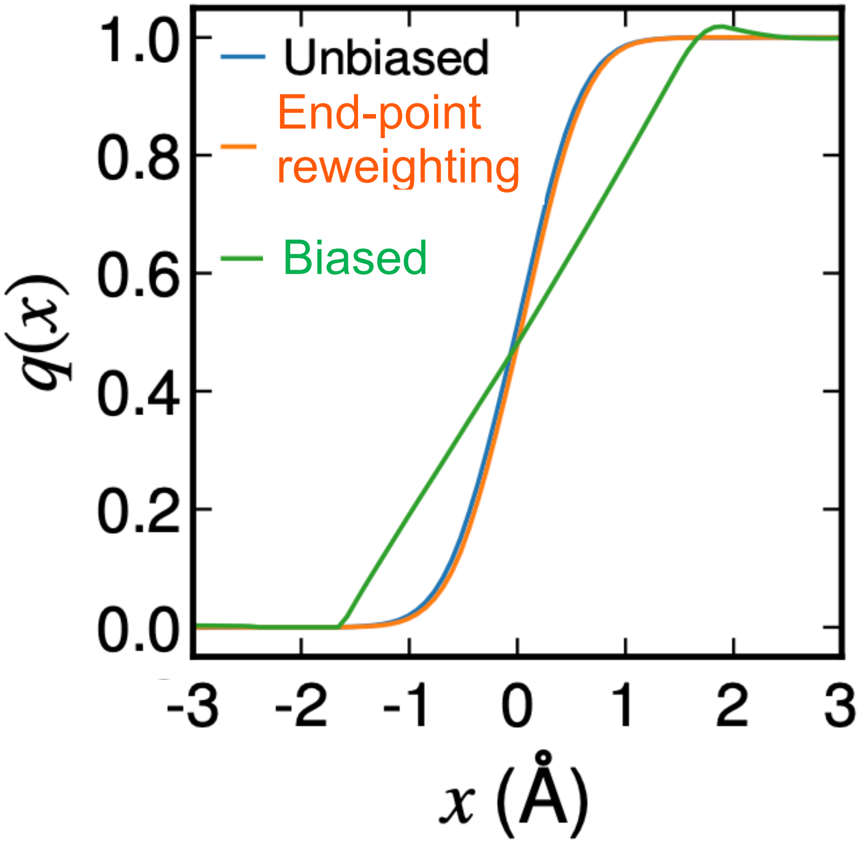
End-point reweighting: Tiwary and Berne, *J. Chem. Phys.* 147, 152701 (2017); Wang and Tiwary, *J. Chem. Phys.* 152, 144102 (2020)

$$\mathcal{P}_\tau^{(\mathrm{p})}(\mathbf{z}'|\mathbf{z}) \approx e^{-\delta W(\mathbf{z}')/2k_{\mathrm{B}}T}\, \mathcal{P}_\tau(\mathbf{z}'|\mathbf{z})\, e^{\delta W(\mathbf{z})/2k_{\mathrm{B}}T}$$

End-point reweighting

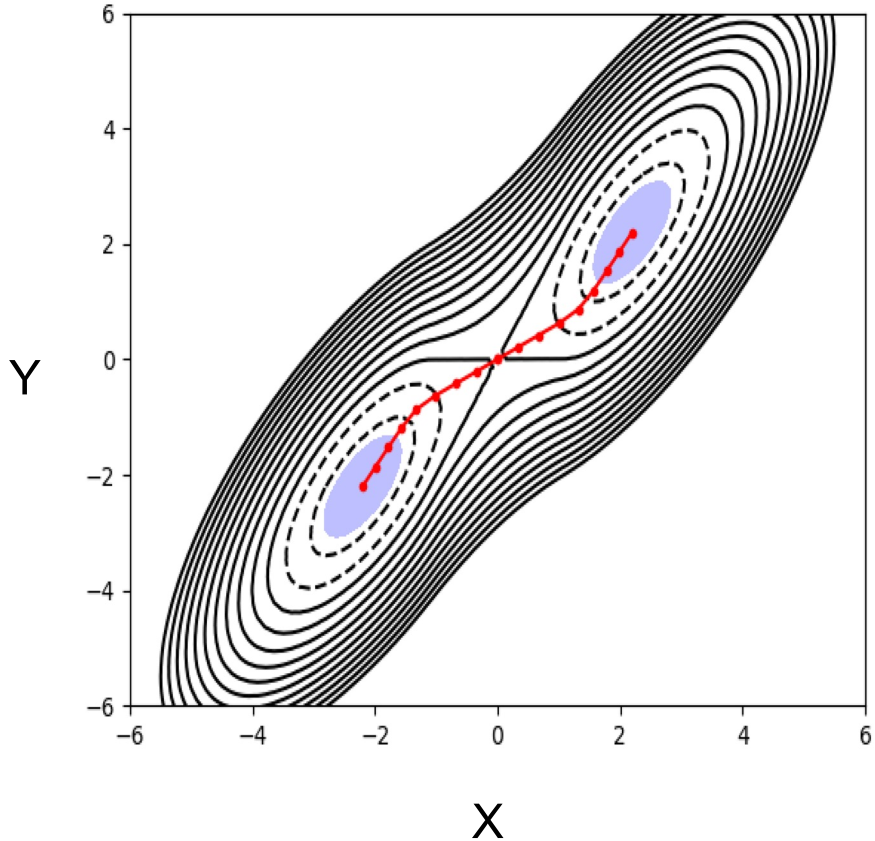
Using WTM-eABF biased simulation:





$$J^{AB} = \frac{1}{2\tau}\left\langle (q(\tau) - q(0))^2 e^{\frac{w(\tau)+w(0)}{2k_bT}} \right\rangle$$

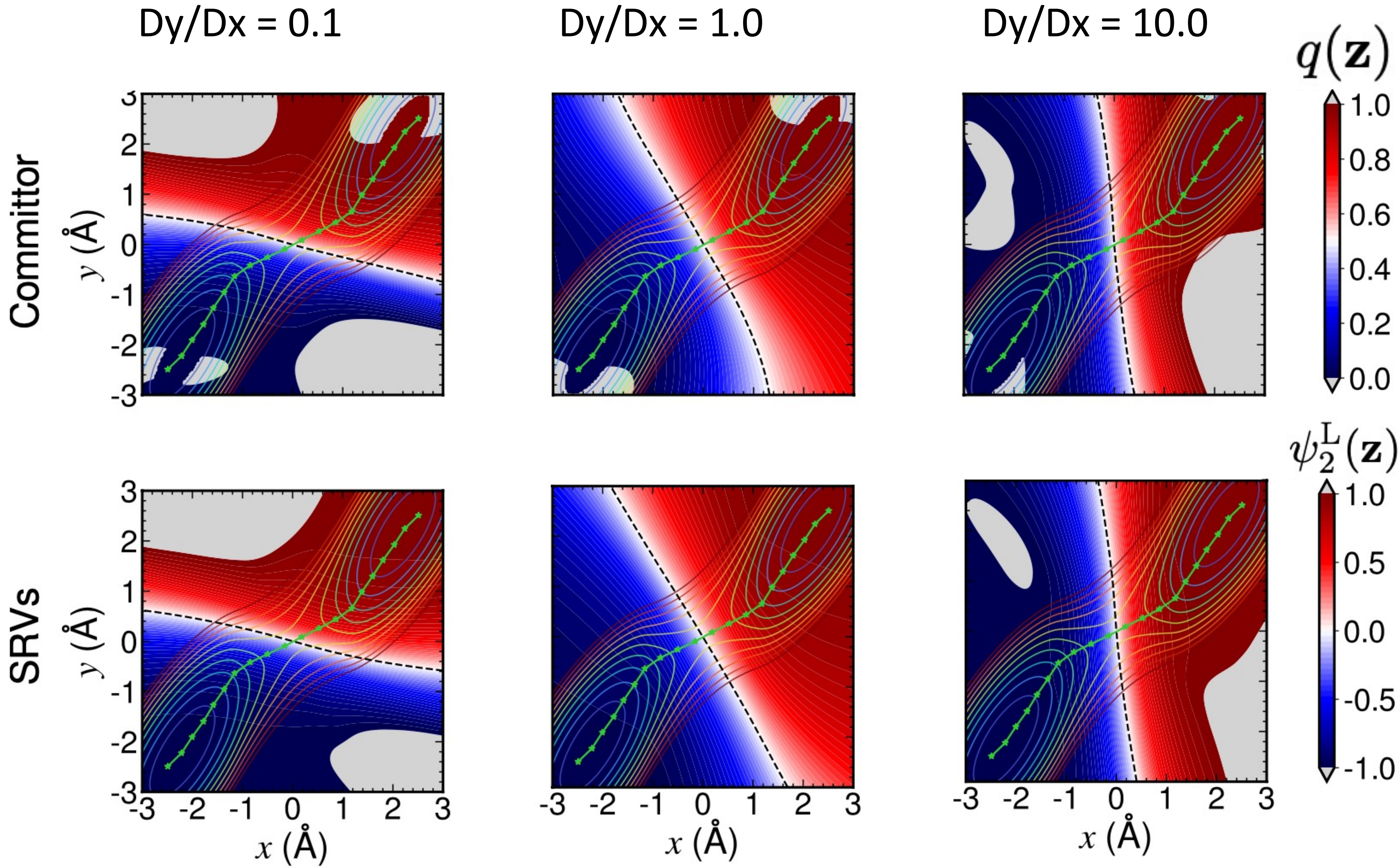
Adaptive Biasing Force (ABF) based on the Path Coordinate Variable (PCV) along String



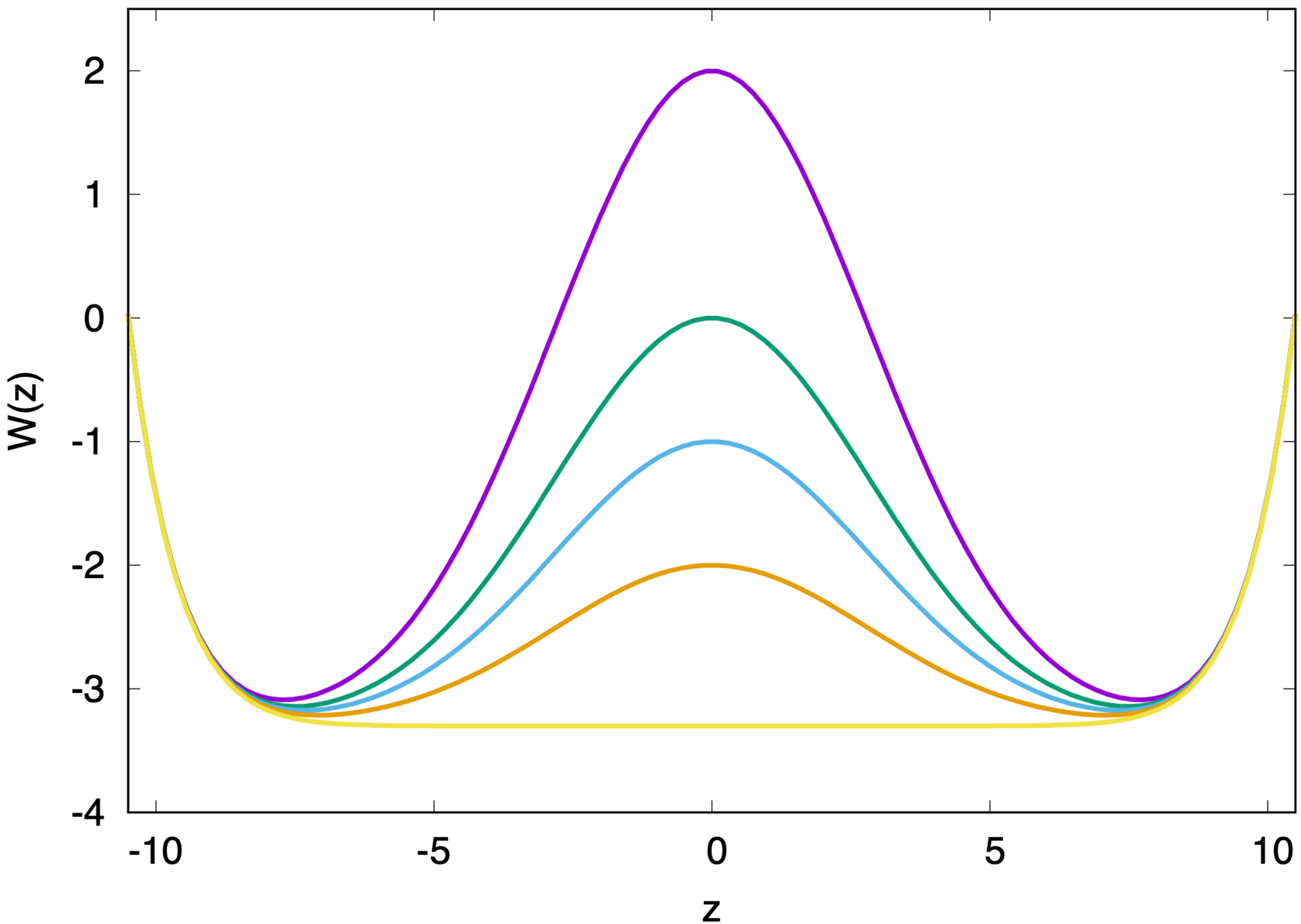
$$s(\mathbf{z}) = \frac{\sum_{k=0}^{K} \left(\frac{k}{K}\right) e^{-\lambda(\mathbf{z}-\mathbf{z}^{(k)})^2}}{\sum_{k=0}^{K} e^{-\lambda(\mathbf{z}-\mathbf{z}^{(k)})^2}}$$

Branduardi, D.; Gervasio, F. L.; Parrinello, M. From A to B in Free Energy Space. *J. Chem. Phys.* 2007, *126*, 054103.

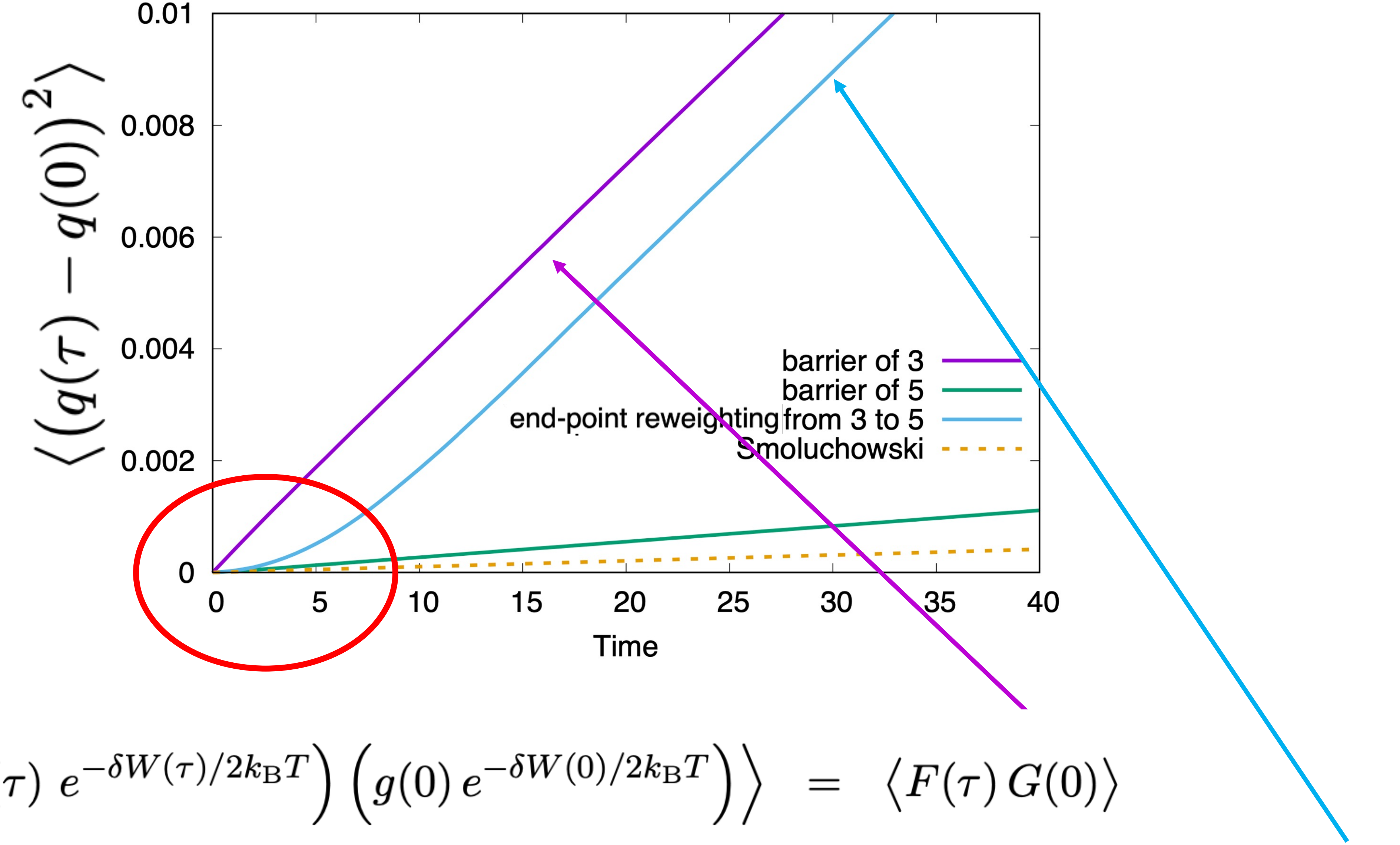
ABF sampling along PCV and re-weighting



Unbiasing biased simulations?



End-point reweighting leaves the dynamics biased



$$\left\langle \left(f(\tau)\, e^{-\delta W(\tau)/2k_{\mathrm{B}}T} \right) \left(g(0)\, e^{-\delta W(0)/2k_{\mathrm{B}}T} \right) \right\rangle = \langle F(\tau)\, G(0) \rangle$$

$$= \sum_k (F \cdot \psi_k^{\mathrm{R}})\, (G \cdot \psi_k^{\mathrm{R}})\, e^{-\mu_k \tau}$$

Unbiasing biased simulations?

$$\mathcal{P}_{\Delta t}(z'|z) = \left(\frac{e^{-\Delta z^2/4D\Delta t}}{\sqrt{4\pi D\Delta t}}\right) e^{-[W(z')-W(z)]/2k_\mathrm{B}T} e^{-\langle\Delta z\rangle_{(z)}F/4k_\mathrm{B}T}$$

$$\mathcal{P}^p_{\Delta t}(z'|z) = \left(\frac{e^{-\Delta z^2/4D\Delta t}}{\sqrt{4\pi D\Delta t}}\right) e^{-[W^p(z')-W^p(z)]/2k_\mathrm{B}T} e^{-\langle\Delta z\rangle^p_{(z)}F^p/4k_\mathrm{B}T}$$

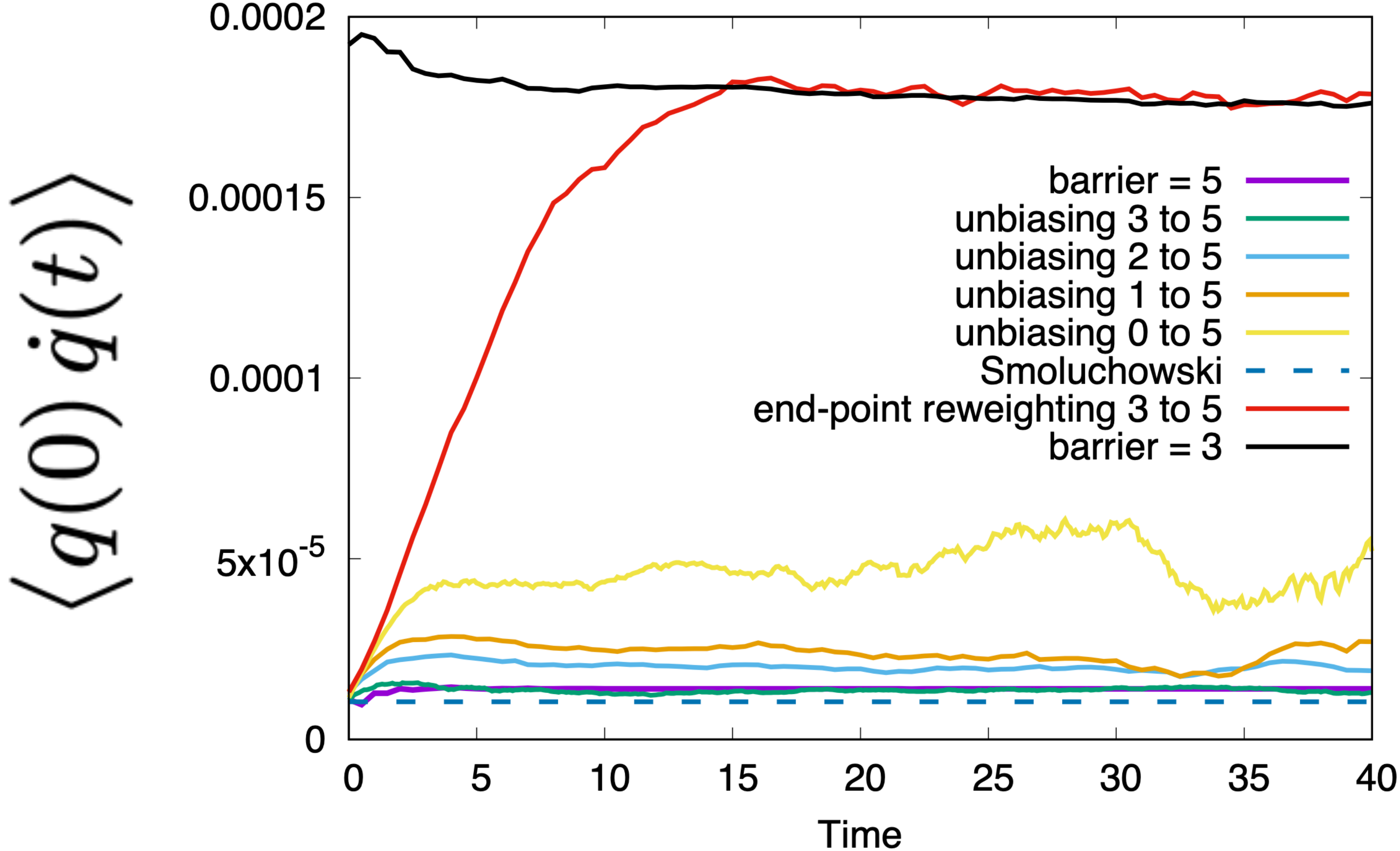
$$\frac{\mathcal{P}^p_{\Delta t}(z'|z)}{\mathcal{P}_{\Delta t}(z'|z)} = \frac{e^{-[W^p(z')-W^p(z)]/2k_\mathrm{B}T} e^{-\langle\Delta z\rangle^p_{(z)}F^p/4k_\mathrm{B}T}}{e^{-[W(z')-W(z)]/2k_\mathrm{B}T} e^{-\langle\Delta z\rangle_{(z)}F/4k_\mathrm{B}T}}$$

$$\frac{\mathcal{P}^p_{\tau}(z'|z)}{\mathcal{P}_{\tau}(z'|z)} = e^{-[\delta W(z')-\delta W(z)]/2k_\mathrm{B}T} e^{-\mathcal{A}_\tau(z',z)/4k_\mathrm{B}T}$$

$$\mathcal{A}_\tau(z',z) = \frac{1}{4k_\mathrm{B}T}\sum_{n=0}^{N}\left(\langle\Delta z\rangle^p_{z(n\Delta t)}F^p(z(n\Delta t)) - \langle\Delta z\rangle_{z(n\Delta t)}F(z(n\Delta t))\right)$$

Onsager and Machlup, "Fluctuations and Irreversible Processes" *Physical Review* **91**, 1505-1512 (1953)
Woolf, *Chemical Physics Letters* **289,** 433–441 (1998)
Zuckerman and Woolf, *J. Chem. Phys.* **111**, 9475-9484 (1999).

Unbiasing biased simulations?



$$\frac{\mathcal{P}^p_\tau(z'|z)}{\mathcal{P}_\tau(z'|z)} = e^{-[\delta W(z')-\delta W(z)]/2k_\mathrm{B}T}\, e^{-\mathcal{A}_\tau(z',z)/4k_\mathrm{B}T}$$

Conclusions

- Build on a formal Markovian propagator of the dynamics in configurational space
- Spectral analysis offers a rich but open-ended perspective
- TPT formulation can focus on a given transition of interest between two metastable sates
- Time correlation function from biased simulations (various options)
- Leverage new machine learning technologies
- Enable iterative strategies to discover and refine a guess reaction coordinate