TRANSITION-PATH SAMPLING AND FREE-ENERGY CALCULATIONS

Chris Chipot

Laboratoire International Associé CNRS-UIUC,
Unité Mixte de Recherche n° 7565, Université de Lorraine

Beckman Institute for Advanced Science and Technology,
Department of Physics
University of Illinois at Urbana-Champaign

INTRODUCTION

Why do we need reaction coordinates?

WHAT IS A GOOD REACTION-COORDINATE MODEL ?

- Reaction coordinate versus order parameter
- Committor distributions

THE STRING METHOD

- The basic string method
- The string method with swarms of trajectories

EXTRACTING THE FREE ENERGY FROM THE MINIMUM-ACTION PATH

- Path-collective variables
- Perturbative approach

APPLICATIONS

- Transition path of activation loop in c-Src kinase
- Chemomechanical coupling in V_1-ATPase

RECONCILING THERMODYNAMICS AND KINETICS

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RECONCILING THERMODYNAMICS AND KINETICS

Why do we need reaction coordinates?

Capture both the kinetics and the thermodynamics of complex chemical and biological processes

Intricate transitions between metastable states often mirror substantial collectivity and rugged free-energy landscapes

De Donder, T. L'affinité. Gauthier-Villars: Paris, **1927**

Kirkwood, J. G. *J. Chem. Phys.* **1935**, *3*, 300–313

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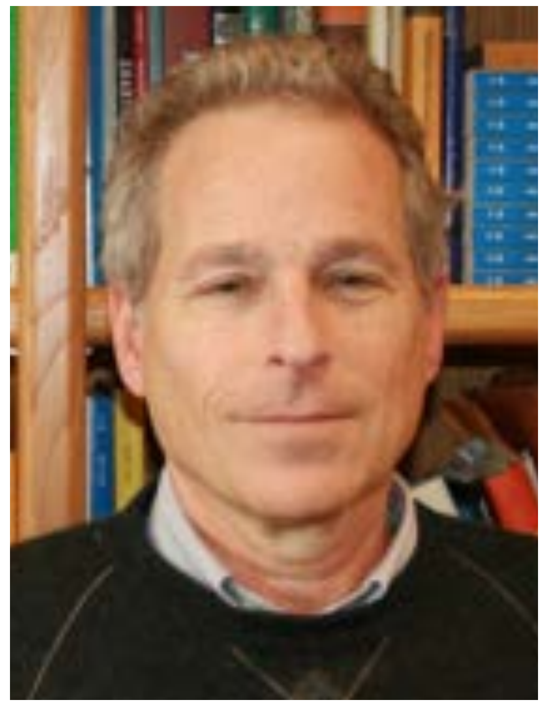
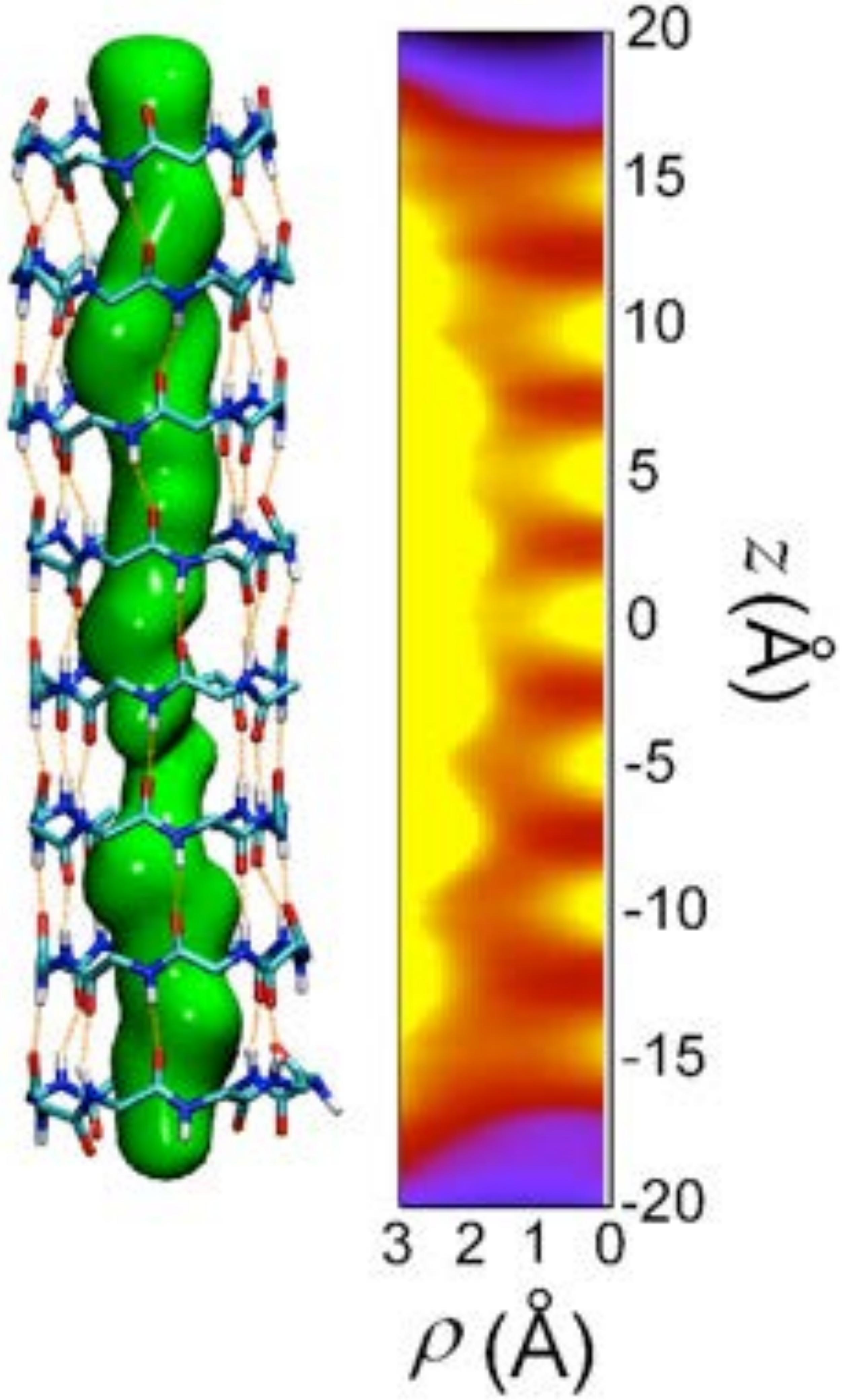
RECONCILING THERMODYNAMICS AND KINETICS

WHAT IS A GOOD REACTION-COORDINATE MODEL ?



The *true* reaction coordinate generally refers to a unique mathematical object on $\mathbb{R}^{3N}$.

It defines the minimum free-energy pathway connecting the reference state to the target state of the transformation.



In practice, we coarse-grain the atomic detail: $\{x_1, x_2, \ldots, x_N\} \longrightarrow \{z_1, z_2, \ldots, z_n\}$, where $n << N$

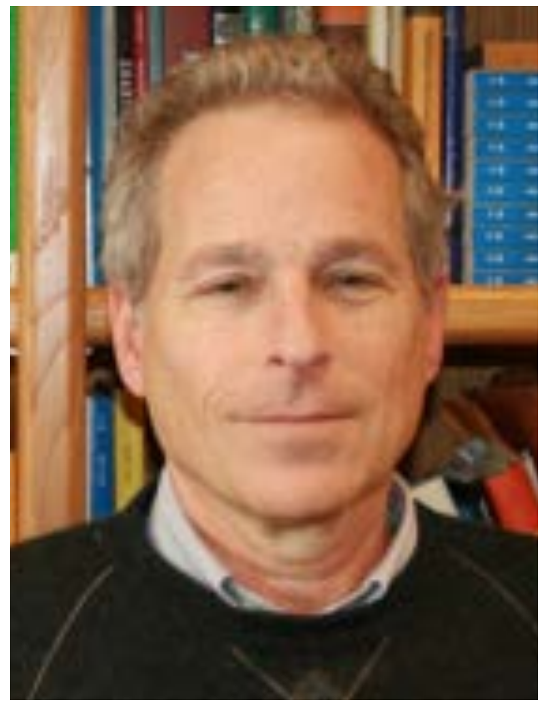
Cartesian coordinates

collective variables

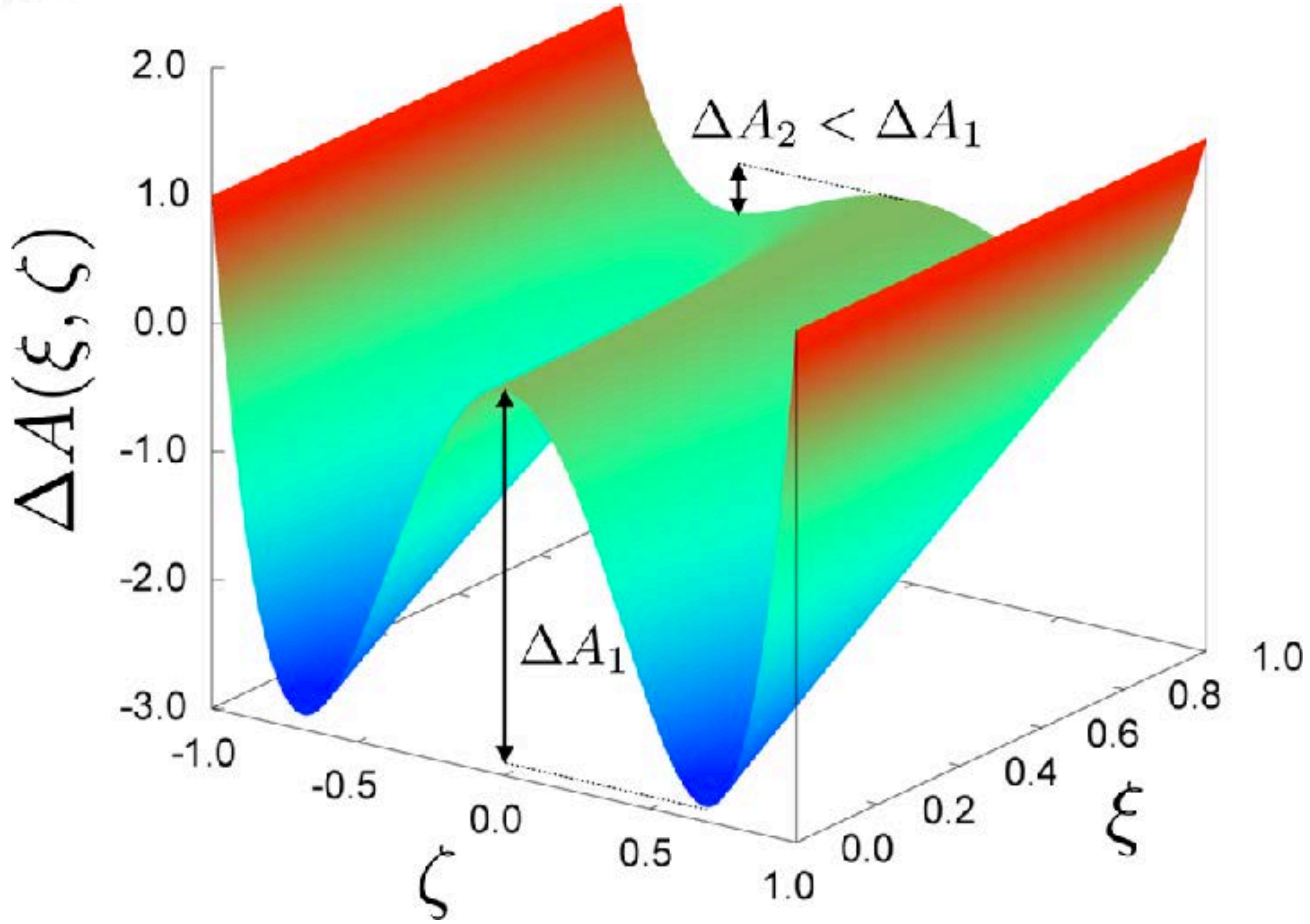
Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

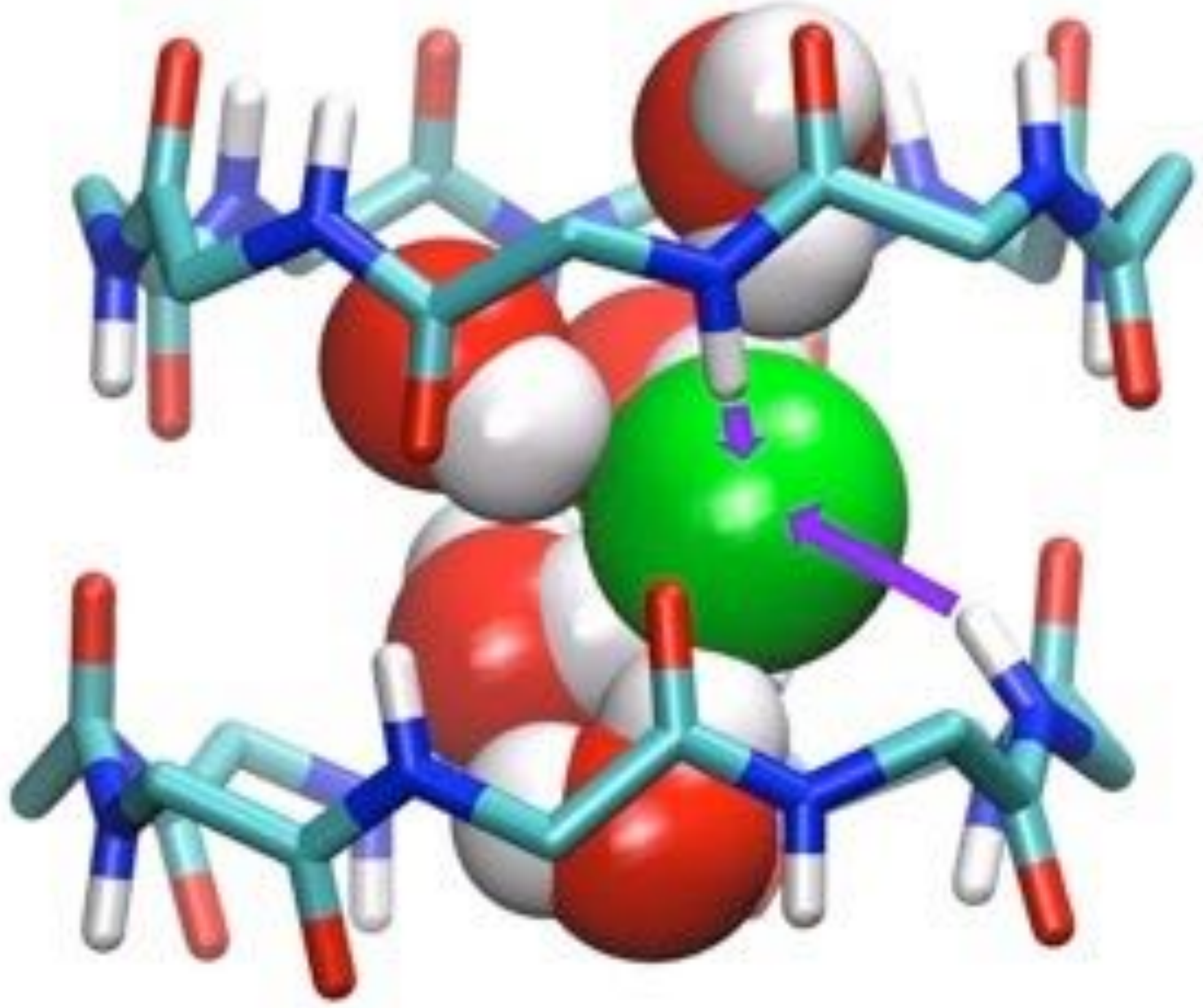
Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. *Ann. Rev. Phys. Chem.* **2002**, *59*, 291-318

WHAT IS A GOOD REACTION-COORDINATE MODEL ?



A one-dimensional order parameter, namely the long axis of the cavity, is not enough to describe ion conduction in a synthetic channel.





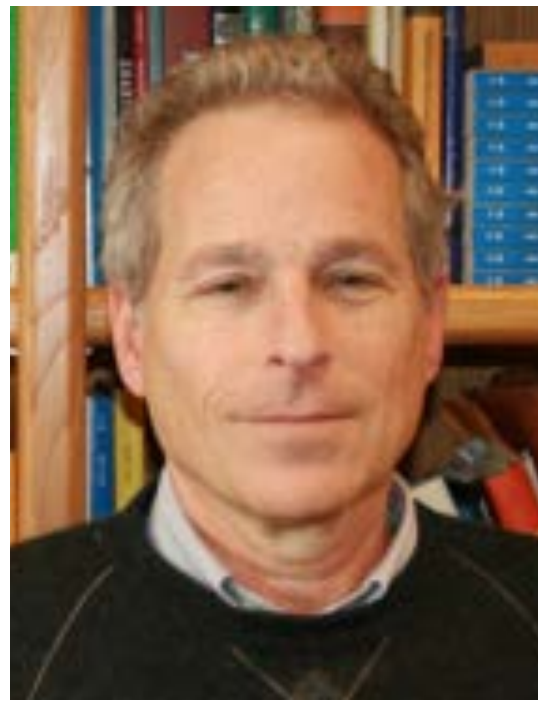
Stringent assumption of a one-dimensional geometric variable: Averaging of all other, fast and slow, degrees of freedom, which could not be further from the truth.

Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. *Ann. Rev. Phys. Chem.* **2002**, *59*, 291-318

Chipot, C.; Lelièvre, T. *SIAM J. Appl. Math.* **2011**, *71*, 1673-1695

WHAT IS A GOOD REACTION-COORDINATE MODEL ?

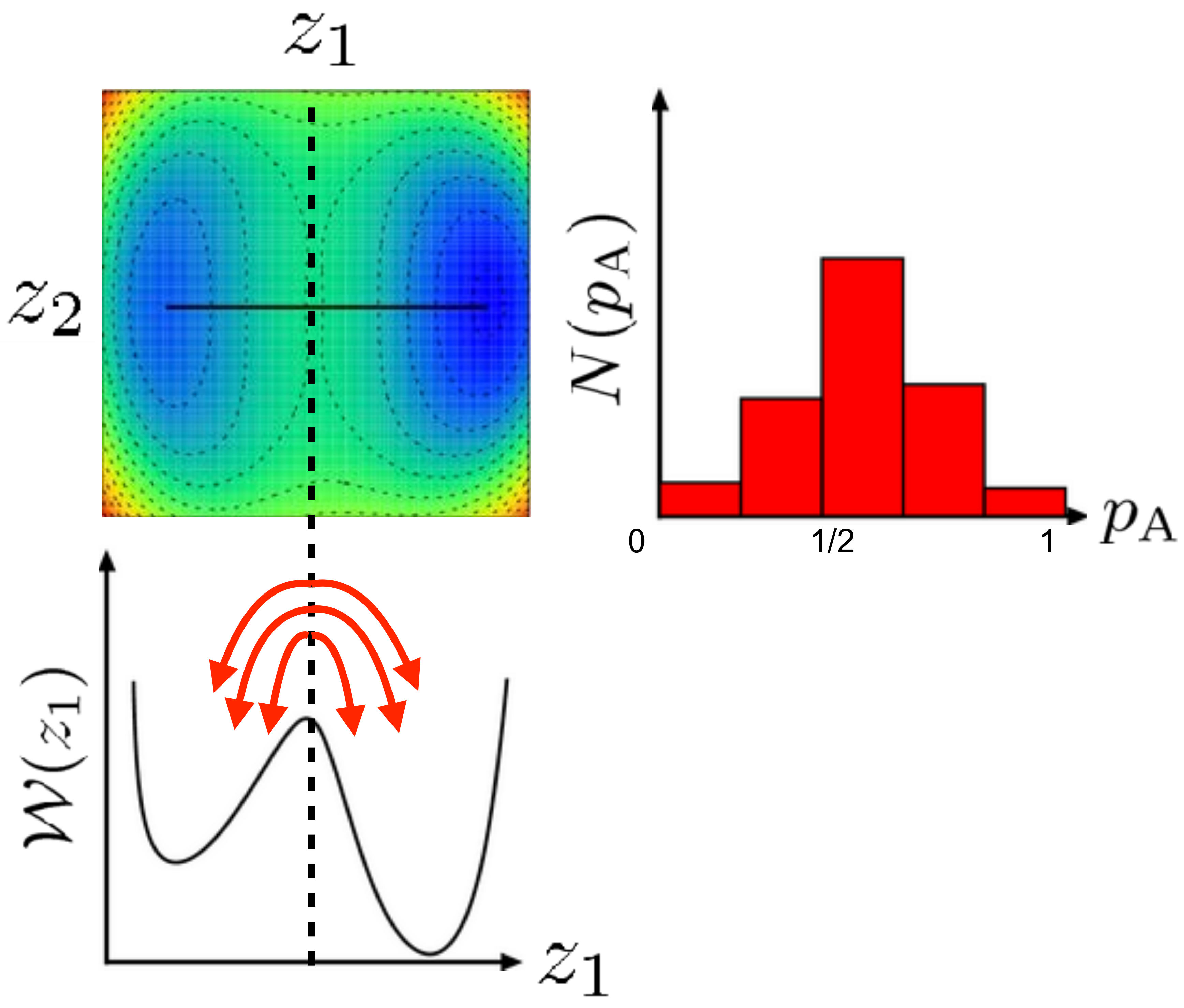


Including relevant collective variables is absolutely crucial for finding true dynamical pathways.

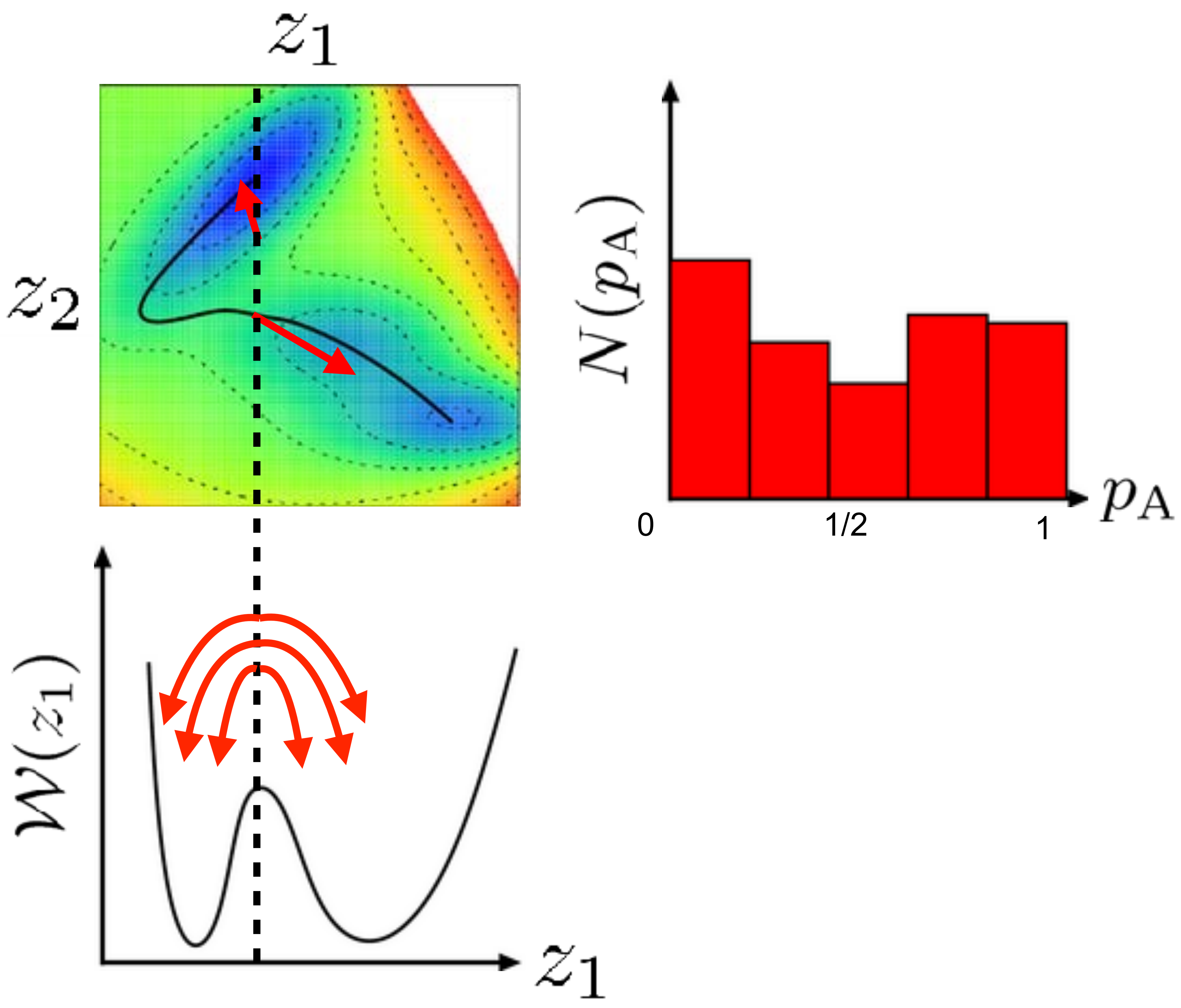
Committor — The probability to reach the target state before returning to the reference state.

The transition state surface for A → B transitions is formed of configurations where $p_B = p_A = 1/2$.

Case 1:



Case 2:



Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

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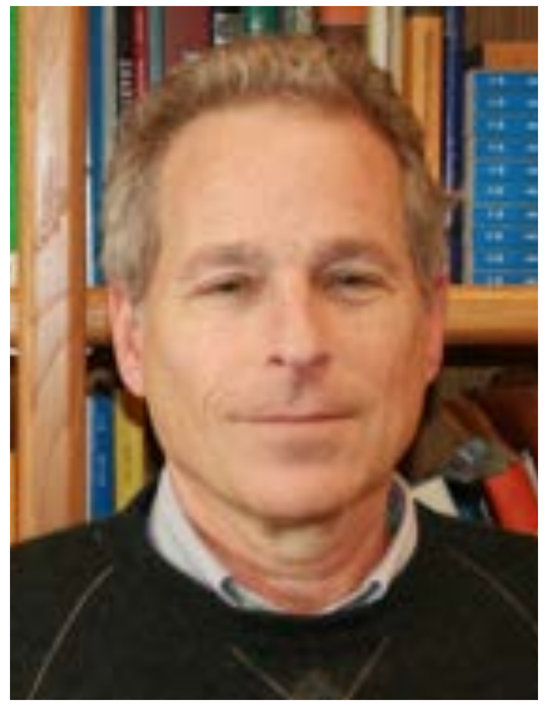
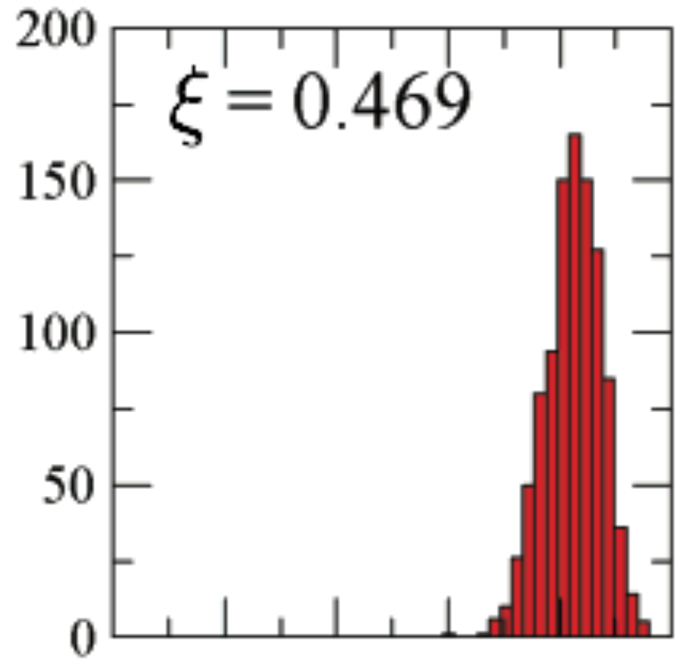
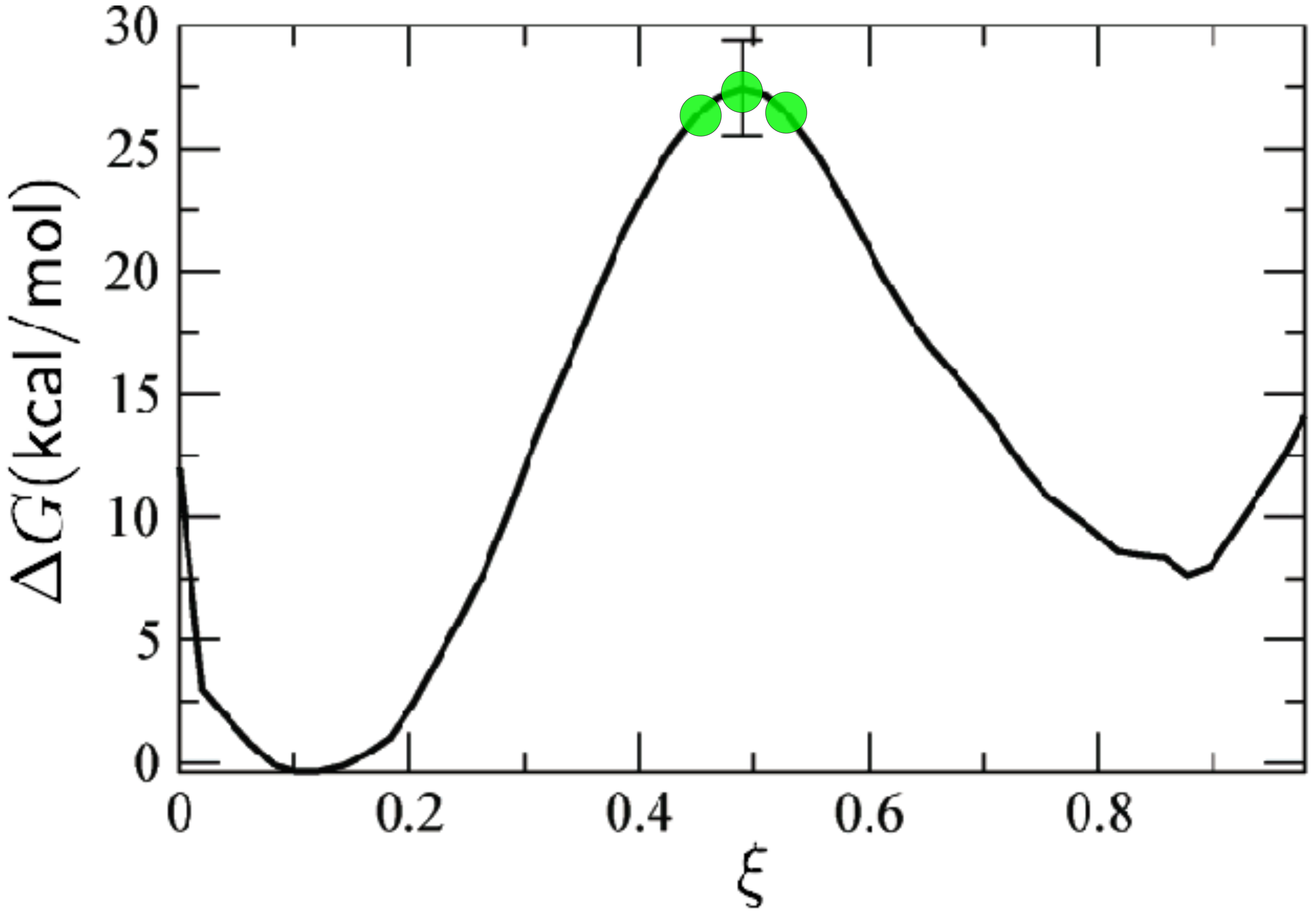


While the choice of the reaction-coordinate model does not impact the thermodynamics of the process at hand, it modulates its kinetics.

Option: Determine $N(p_A)$, the distribution of the committor probability, p_A, for the model of the reaction coordinate, ξ.





Run a series of molecular dynamics simulations from the putative maximum of the free-energy barrier and infer $N(p_A)$.

Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. *Ann. Rev. Phys. Chem.* **2002**, *59*, 291-318

What is a good reaction-coordinate model ?

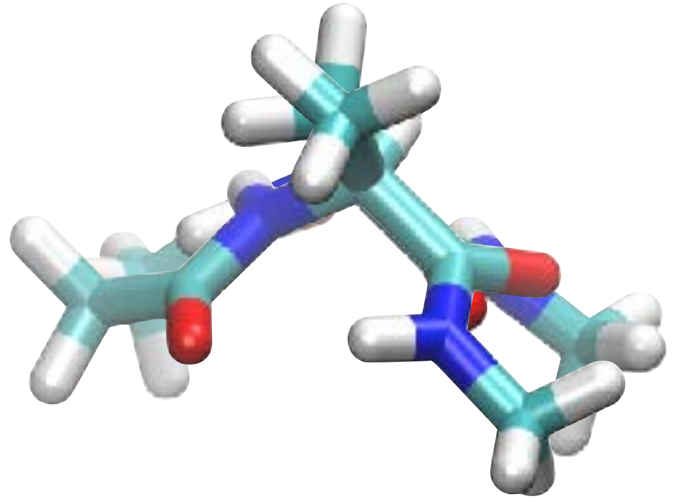
low collectivity

`distance`
`distanceZ`
`distanceXY`

Possible linear combination of variables

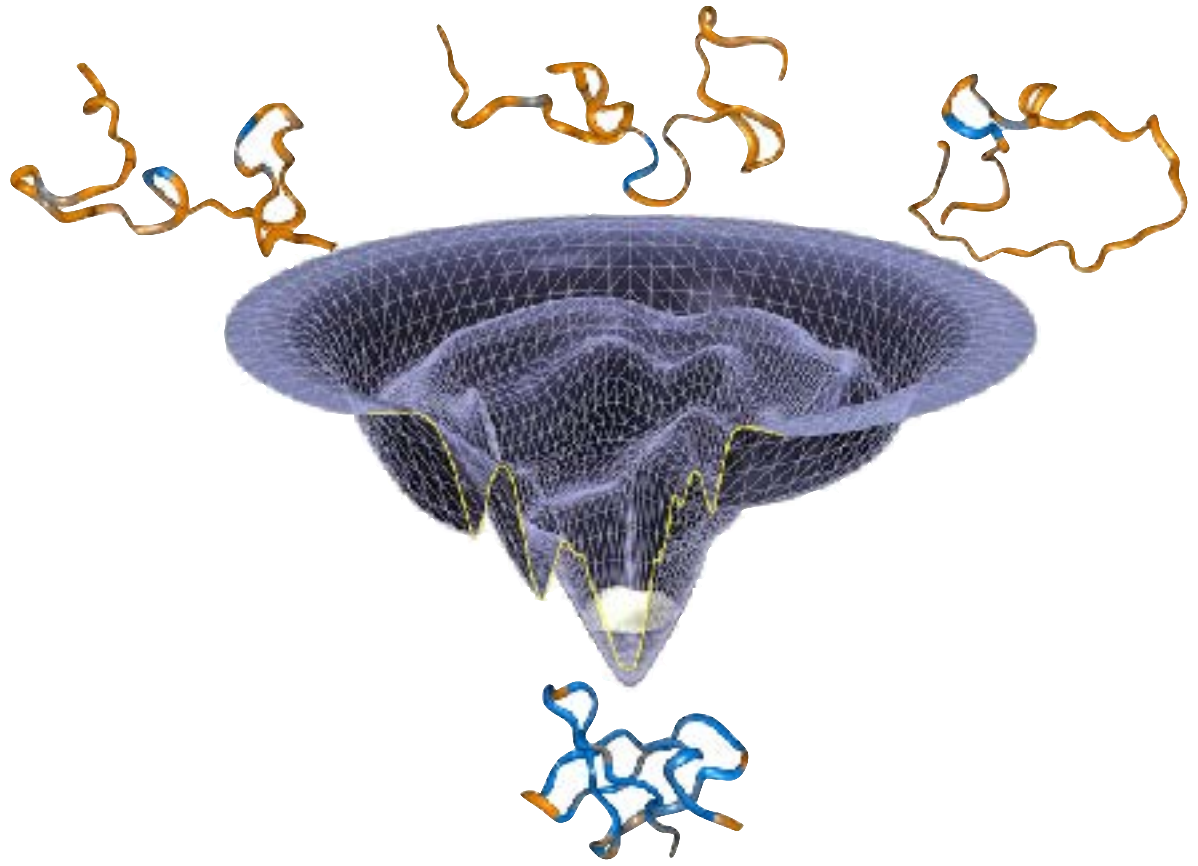
`angle`

`dihedral`

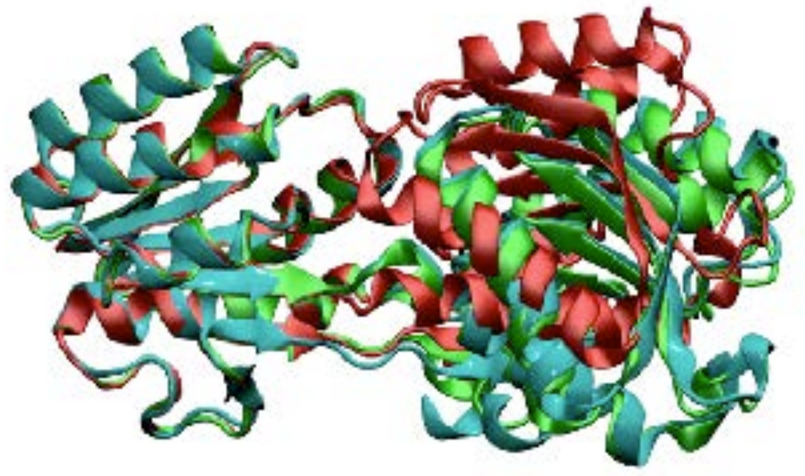


`rmsd`
`gyration`

Degenerate variable



`eigenvector`



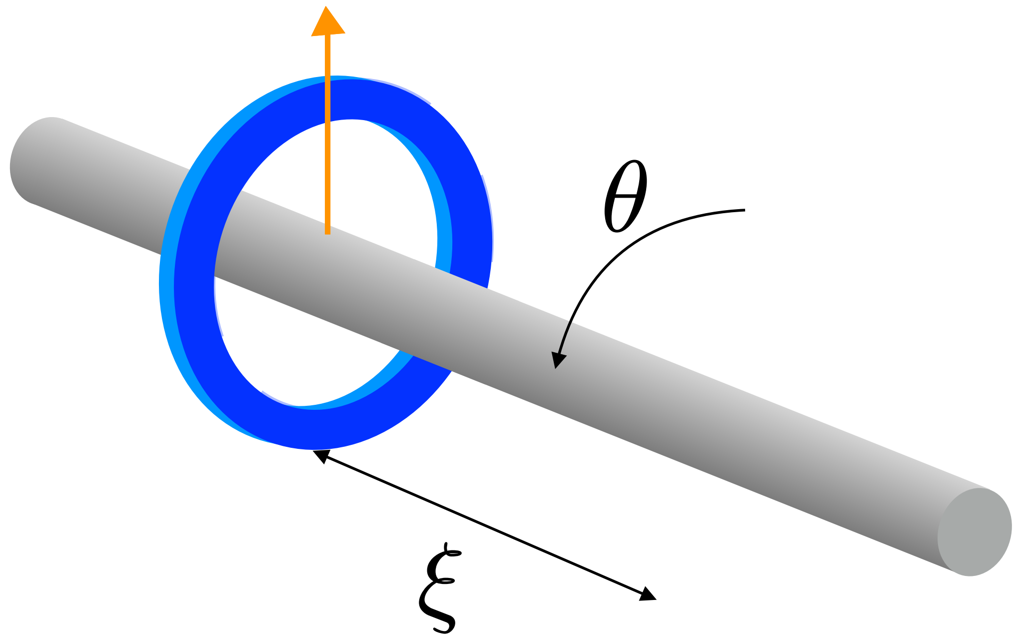
From normal mode or principal component analysis

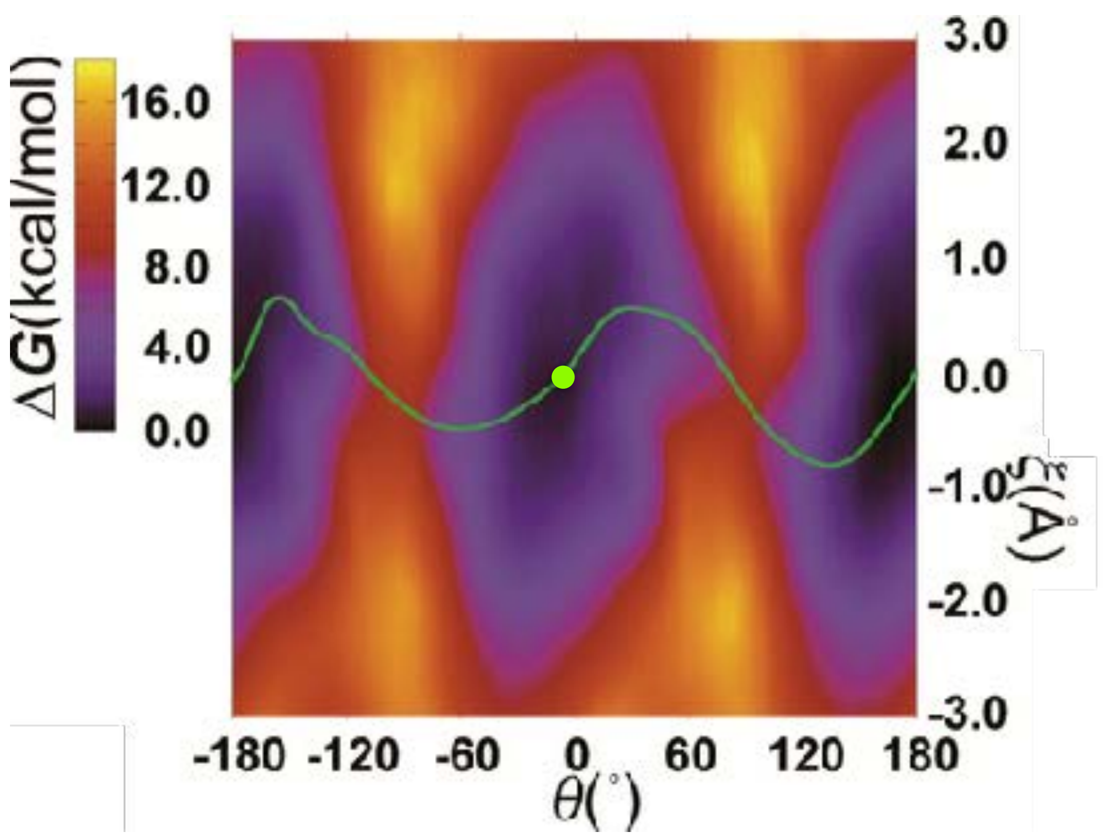
high collectivity

Hénin, J.; Forin, G.; Chipot, C.; Klein, M. L. *J. Chem. Theor. Comput.* **2010**, *6*, 35-47

Fiorin, G.; Klein, M. L.; Hénin, J. *Mol. Phys.* **2013**, *111*, 3345-3362

WHAT IS A GOOD REACTION-COORDINATE MODEL ?

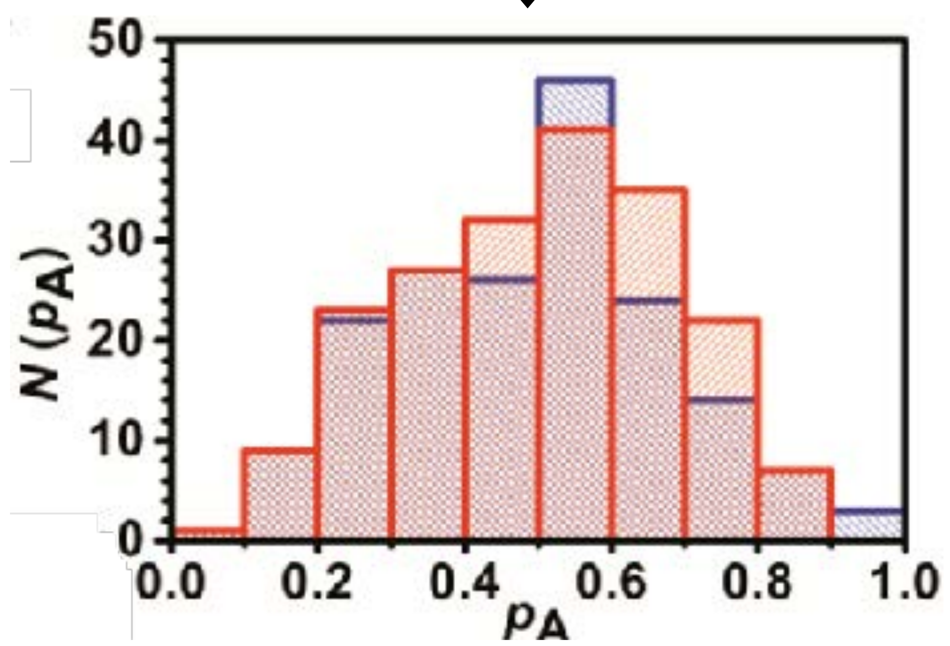




Movements in molecular objects can be more complex than suggested by chemical intuition.

Define reaction coordinate model based on chemical intuition

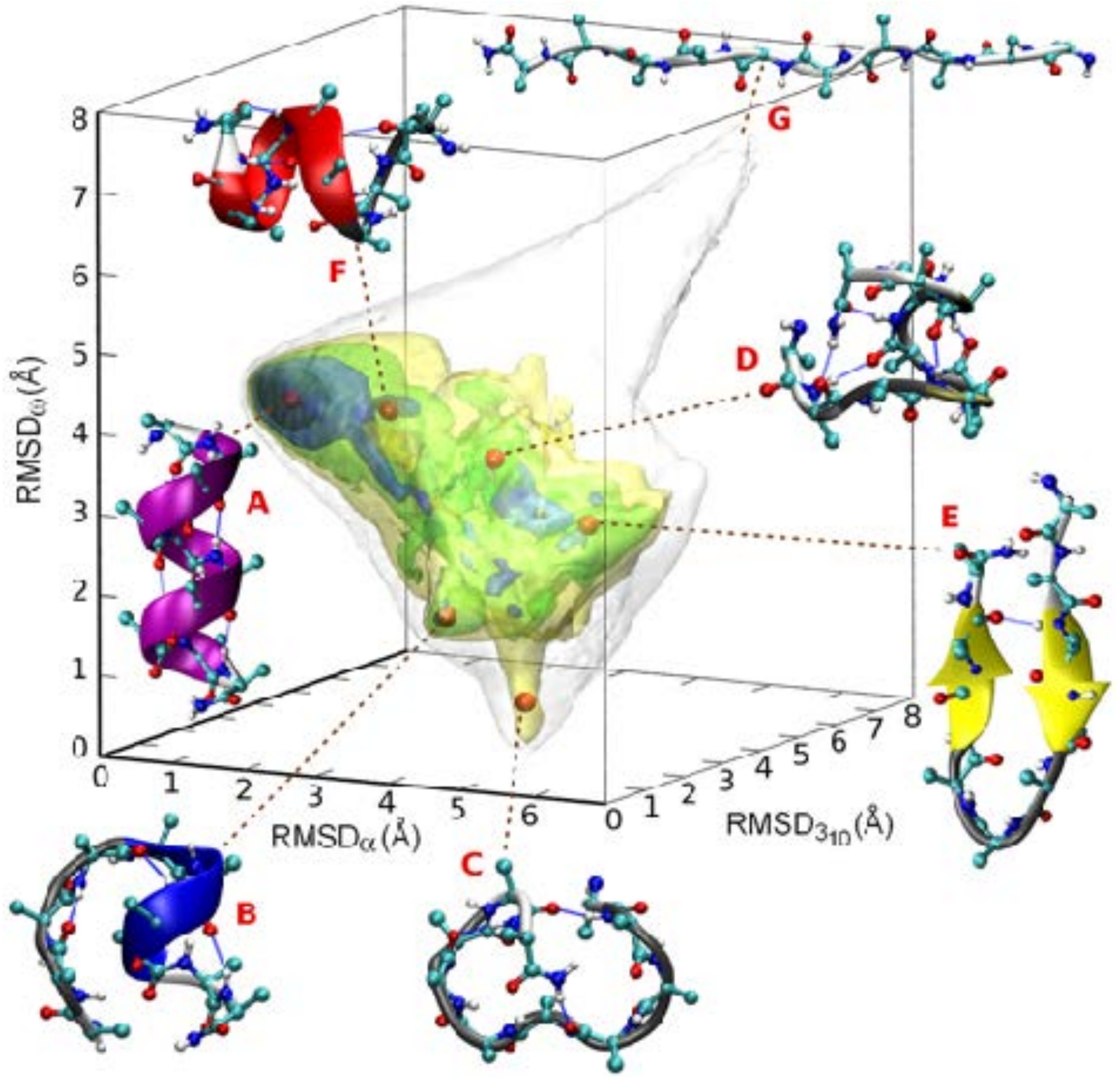
Ascertain that the reaction coordinate model is a committor function



Increase dimensionality of the model

Turn to ergodic-sampling algorithms

Search for a minimum-action path



Liu, P.; Shao, X.; Chipot, C.; Cai, W. *Chem. Sci.* **2015**

Bolhuis, P. G.; Dellago, C.; Chandler, D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5877-5882

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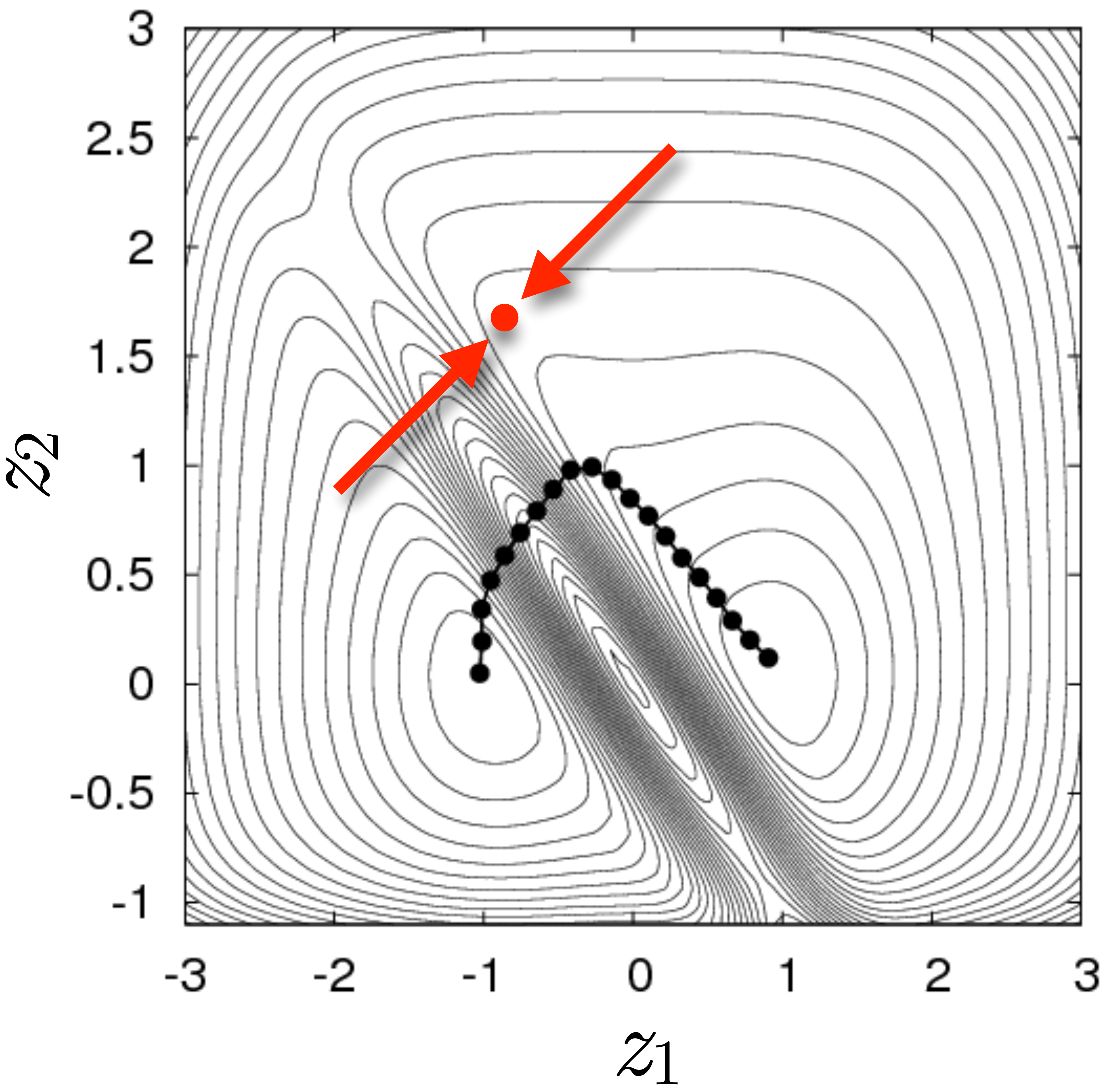
RECONCILING THERMODYNAMICS AND KINETICS

THE BASIC STRING METHOD

Let us assume some minimum-action (most probable) transition path connecting two basins of a free-energy landscape defined by a set of collective variables **z**. Let us also consider the potential of mean force along this path,

$$\exp[-\beta w(z)] = \frac{\int \mathrm{dx}\ \delta[\mathbf{z} - \mathbf{z}'(\mathbf{x})]\ \exp[-\beta U(\mathbf{x})]}{\int \mathrm{dx}\ \exp[-\beta U(\mathbf{x})]}$$

$$\mathbf{F} = -\boldsymbol{\nabla}_z w(z)$$



Evolve the string of images until:

$$\boxed{(\mathbf{DF})^{\perp} = 0}$$

Maragliano, L.; Fischer, A.; Vanden-Eijnden, E.; Ciccotti, G. *J. Chem. Phys.* **2006**, *125*, 024106

THE STRING METHOD WITH SWARMS OF TRAJECTORIES

Let us assume that the collective variables evolve on the free-energy landscape according to non-inertial Brownian dynamics,

$$z_i(\delta t) = z_i(0) + \sum_j \left\{ \beta D_{ij}[\mathbf{z}(0)] F_j[\mathbf{z}(0)] + \nabla_{z_j} D_{ij}[\mathbf{z}(0)] \right\} \delta t + R_i(0) \qquad \text{where} \qquad F_i = -\nabla_i w(\mathbf{z})$$

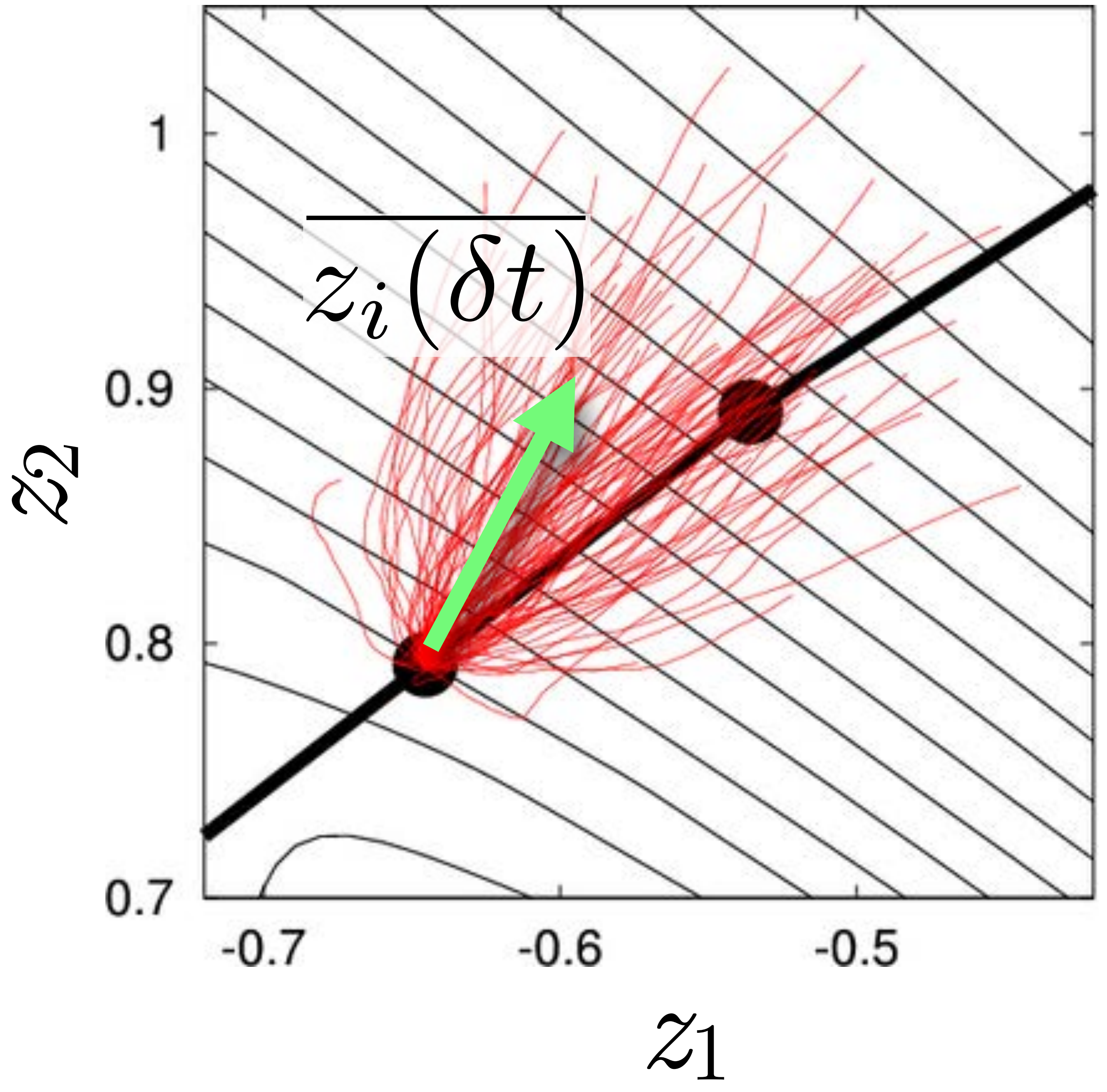
$$\langle R_i(0) R_i(\delta t) \rangle = 2 D_{ij} \delta t$$

Let us consider a path $\mathbf{z}(\alpha)$ connecting the two basins, such that α varies between 0 and 1,

$$z_i(\alpha) = z_i(\alpha') + \sum_j \left\{ \beta D_{ij}[\mathbf{z}(0)] F_j[\mathbf{z}(0)] + \nabla_{z_j} D_{ij}[\mathbf{z}(0)] \right\} \delta t$$

Average drift from an ensemble of unbiased trajectories of length δt,

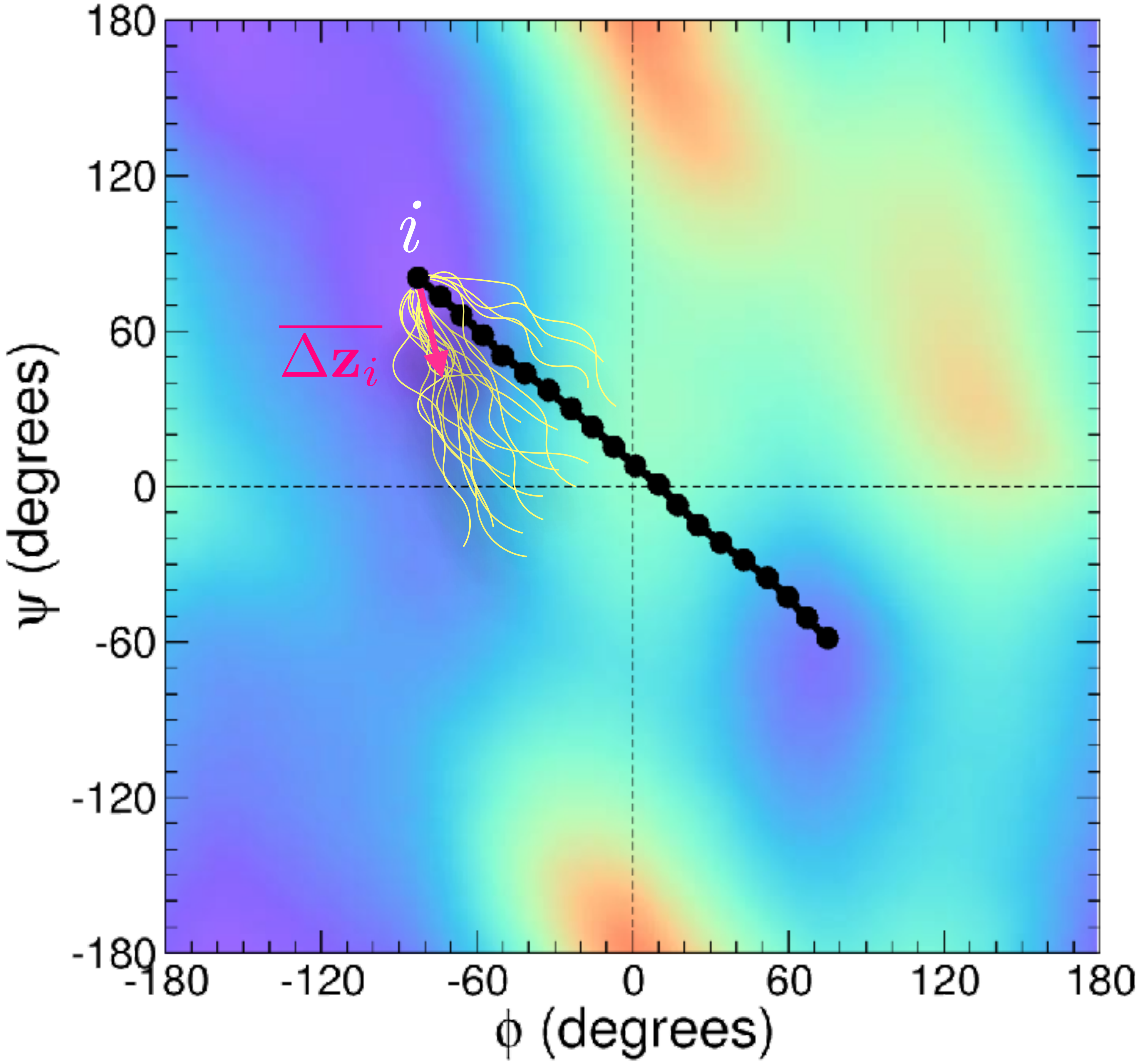
$$\overline{z_i(\delta t)} = \overline{z_i(\delta t) - z_i(0)} = \sum_j \left\{ \beta D_{ij}[\mathbf{z}(0)] F_j[\mathbf{z}(0)] + \nabla_{z_j} D_{ij}[\mathbf{z}(0)] \right\} \delta t$$



Pan, A. C.; Sezer, D.; Roux, B. *J. Phys. Chem. B* **2008**, *112*, 3432-3440

Ren, W.; Vanden-Eijnden, E.; Maragakis, P.; E, W. *J. Chem. Phys.* **2005**, *123*, 134109

THE STRING METHOD WITH SWARMS OF TRAJECTORIES



Prepare a configuration for each one of the P images of the string, the corresponding collective variables of which are close to $\mathbf{z}_i$, for $i = 1,\ldots, P$.

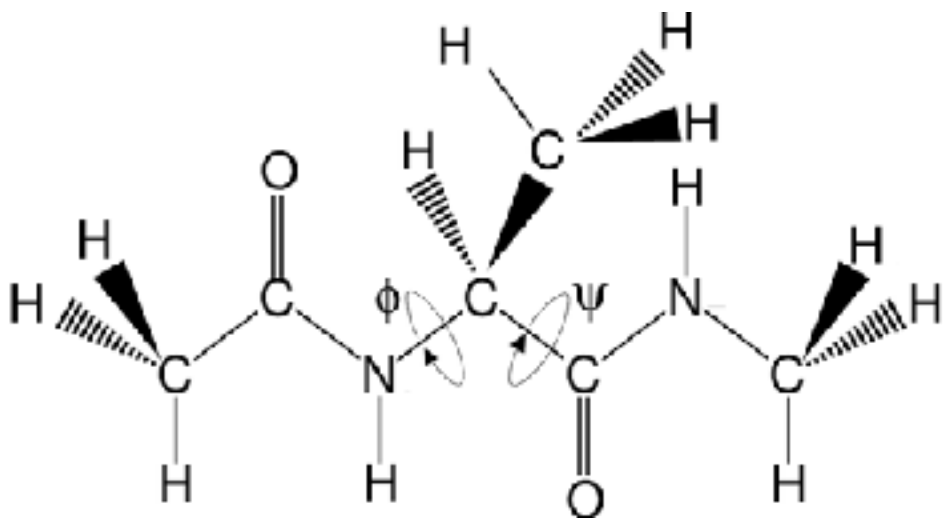
Generate an equilibrium trajectory for each image with $\mathbf{z}$ restrained around $\mathbf{z}_i$.

From the equilibrium trajectory, generate a large number of short, unbiased trajectories for each image.

Use the resulting average displacement, $\overline{\Delta \mathbf{z}_i}$, to determine the position of the P images.

Parameterize the string to ensure that the images are equidistant in collective-variable space.

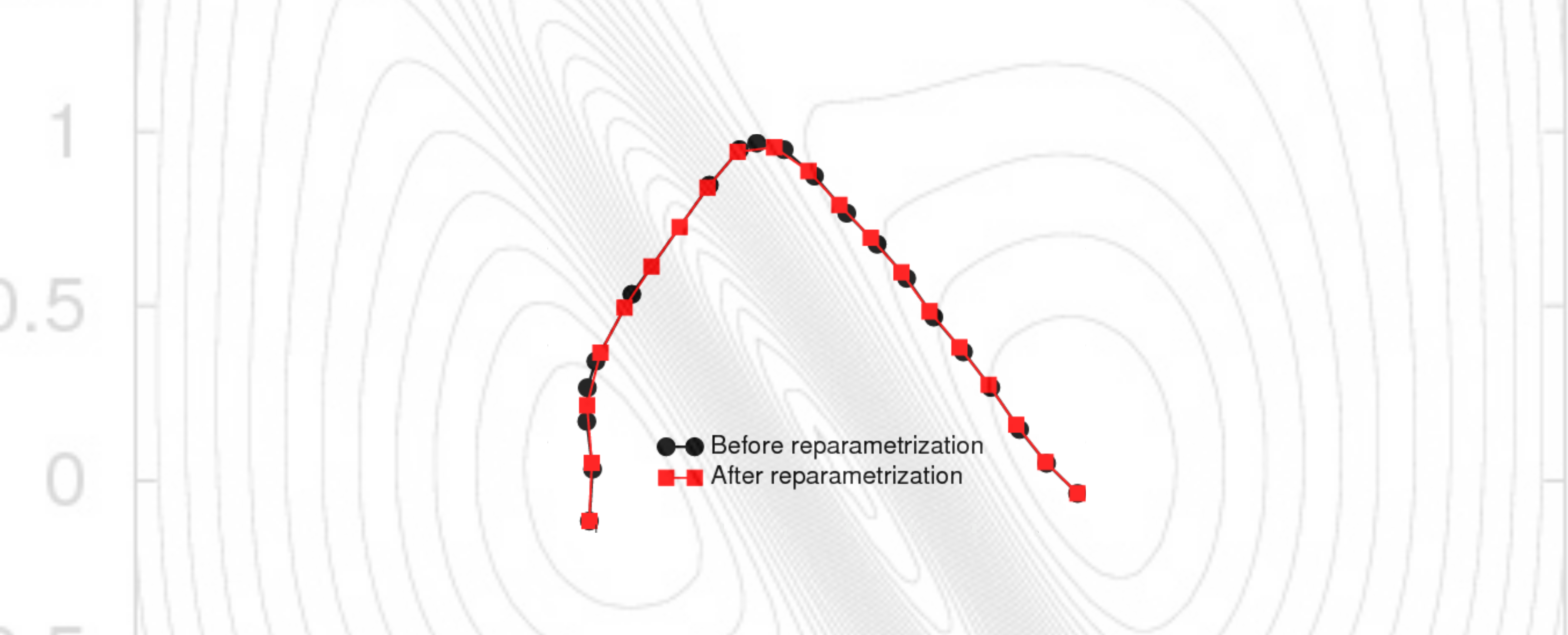
$$\begin{cases} C_{7\text{eq}} : -81°, +81° \\ C_{7\text{ax}} : +63°, -81° \end{cases}$$



Pan, A. C.; Sezer, D.; Roux, B. *J. Phys. Chem. B* **2008**, *112*, 3432-3440

The string method with swarms of trajectories

Reparametrization prevents the path from becoming under-resolved, especially near free energy barriers



E, W.; Ren, W.; Vanden-Eijnden, E. *Phys. Rev. B* **2002**, *66*, 052301

Maragliano, L.; Fischer, A.; Vanden-Eijnden, E.; Ciccotti, G. *J. Chem. Phys.* **2006**, *125*, 024106

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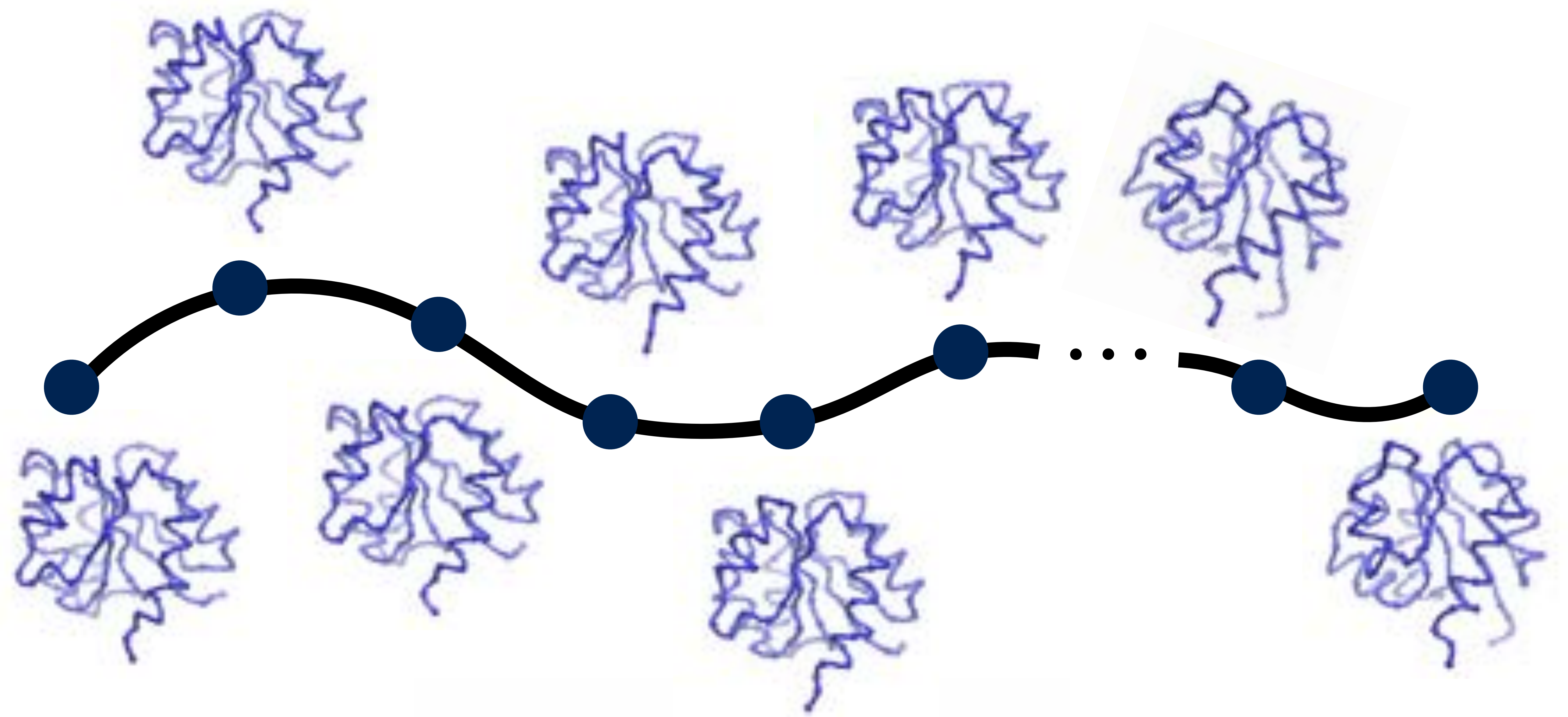
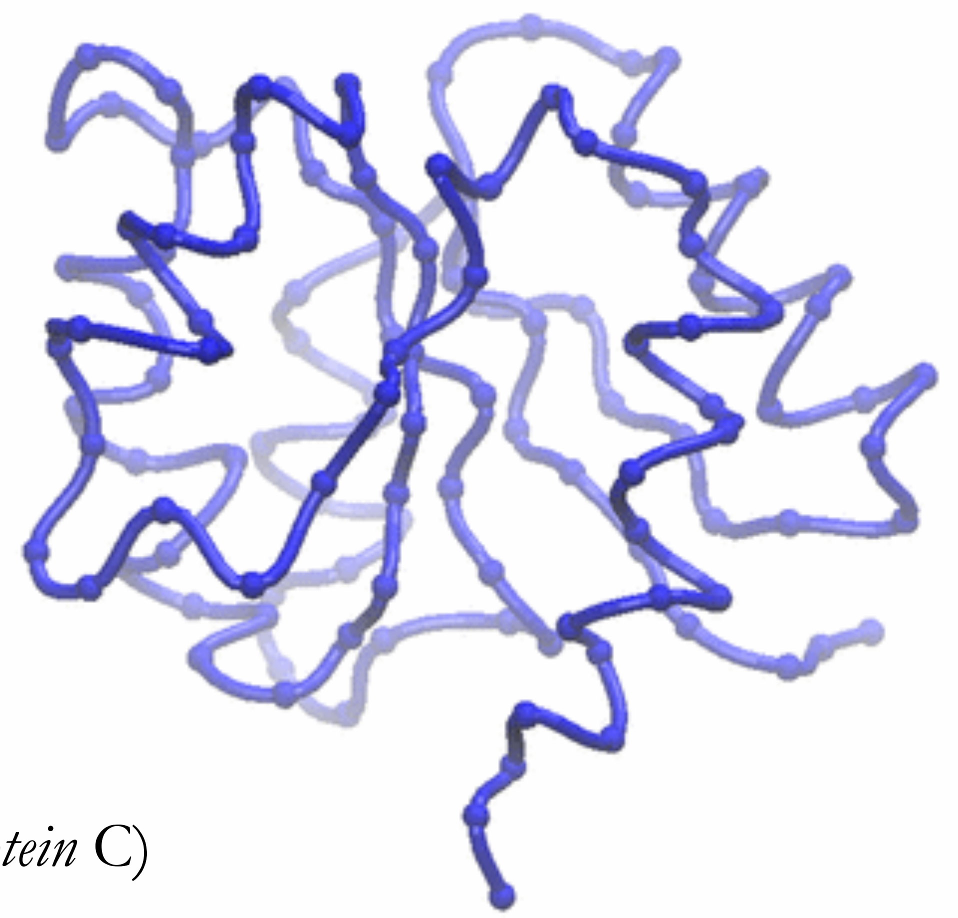
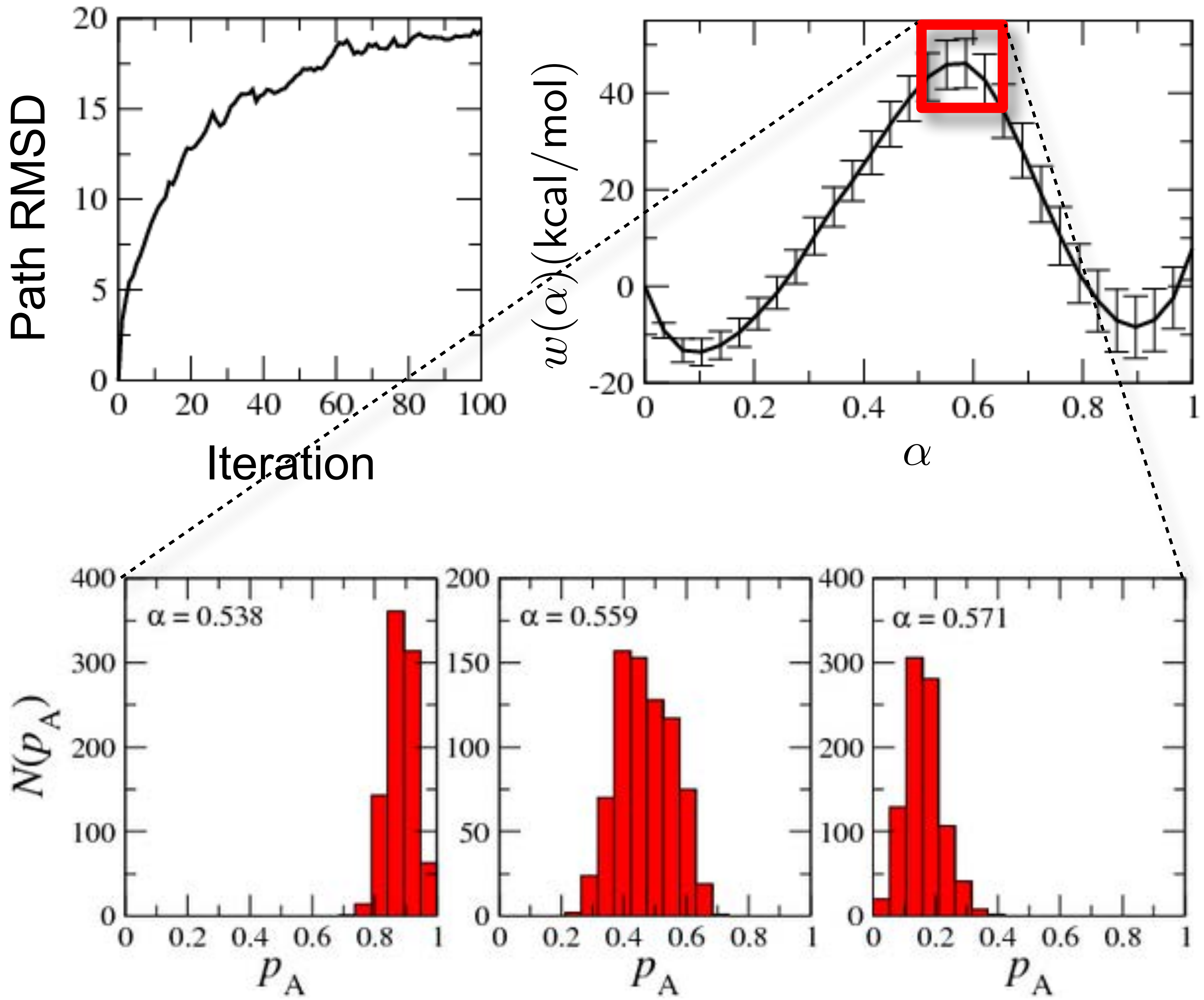




NtrC (Nitrogen regulatory *protein* C)



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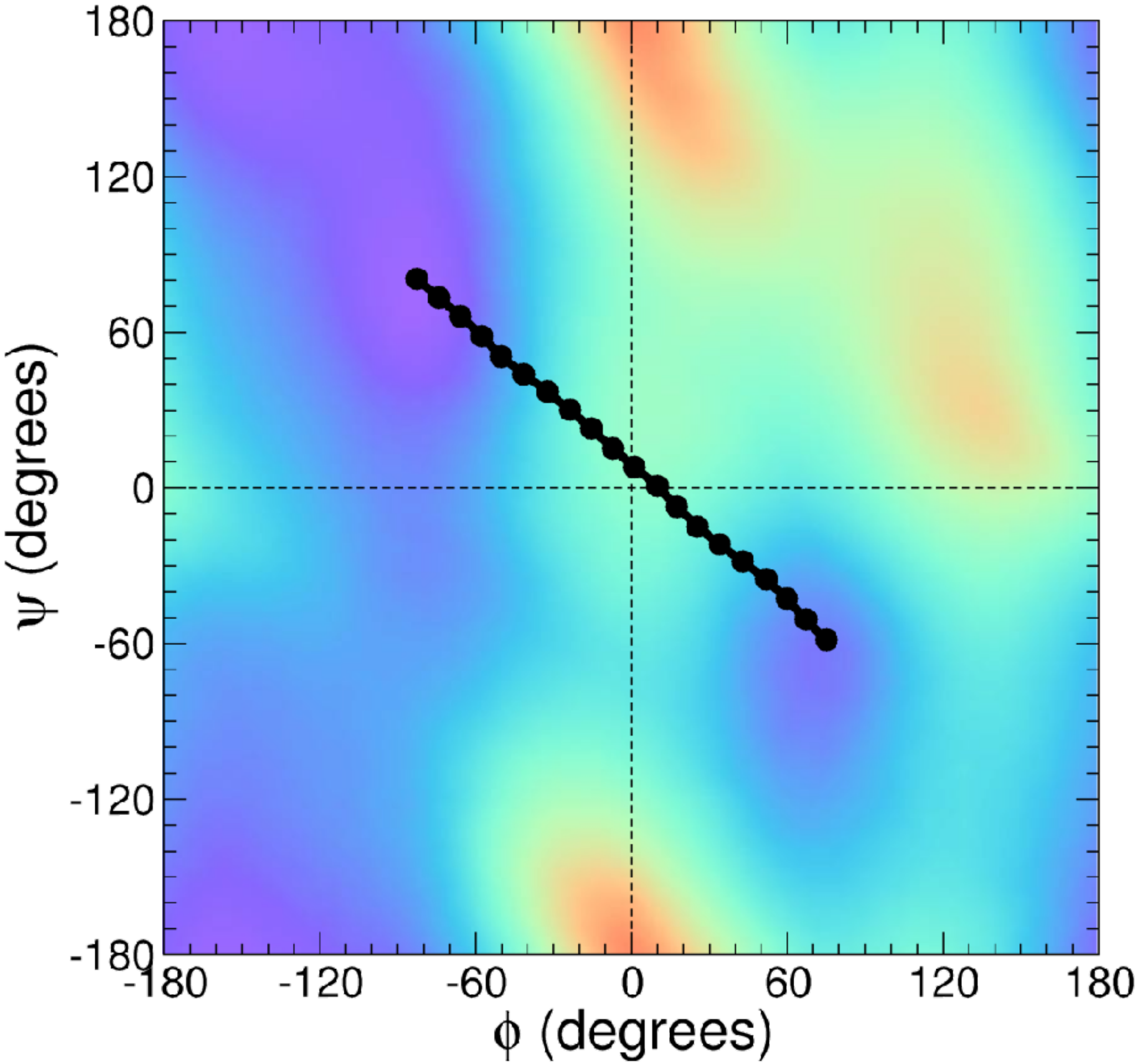
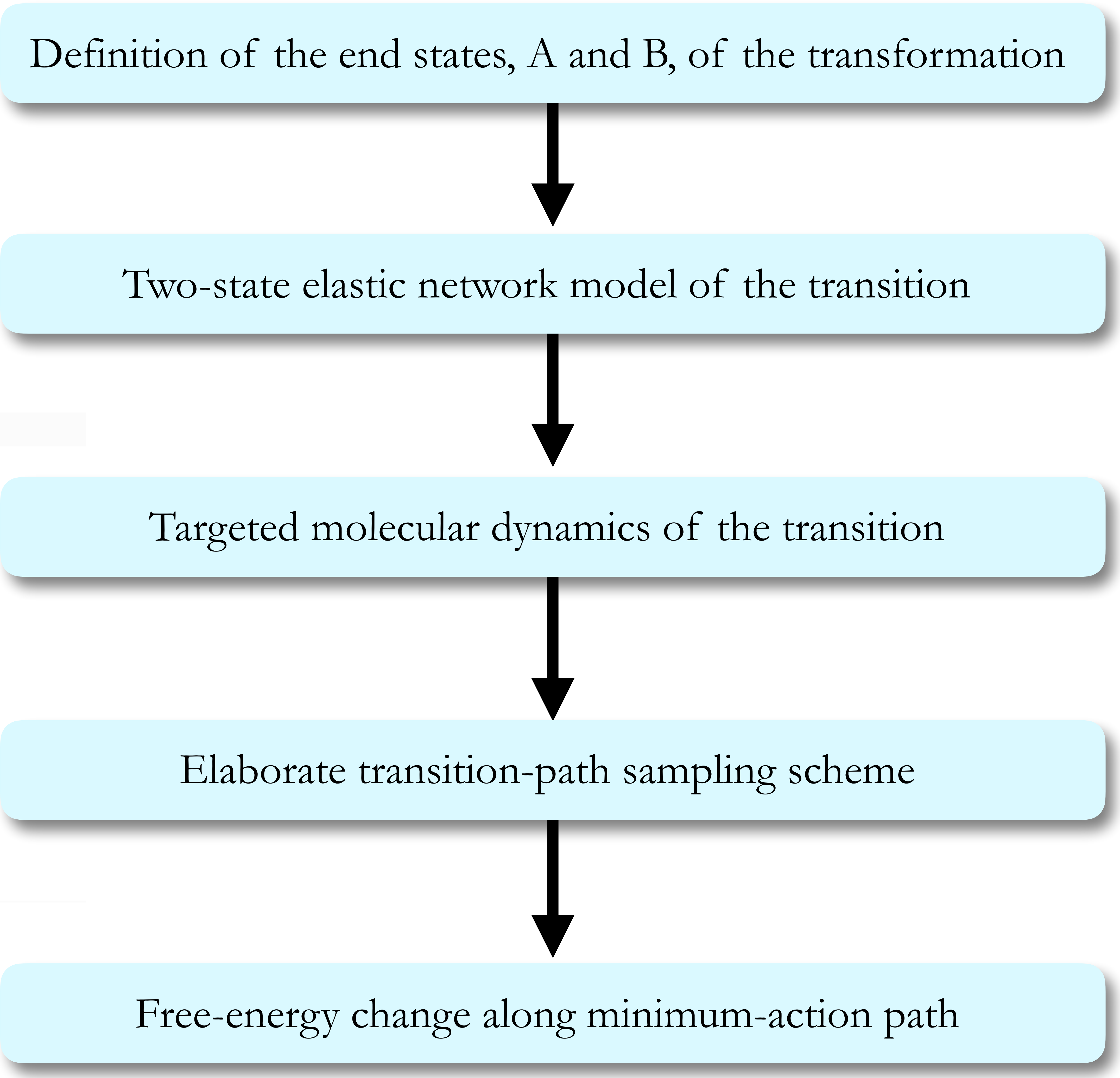


Deriving the one-dimensional free-energy profile



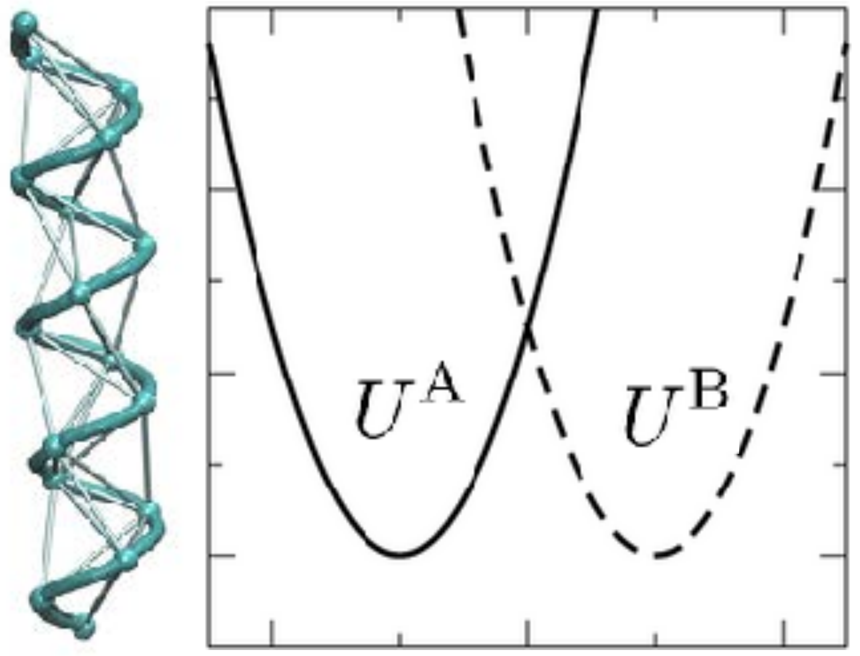
Definition of the end states, A and B, of the transformation

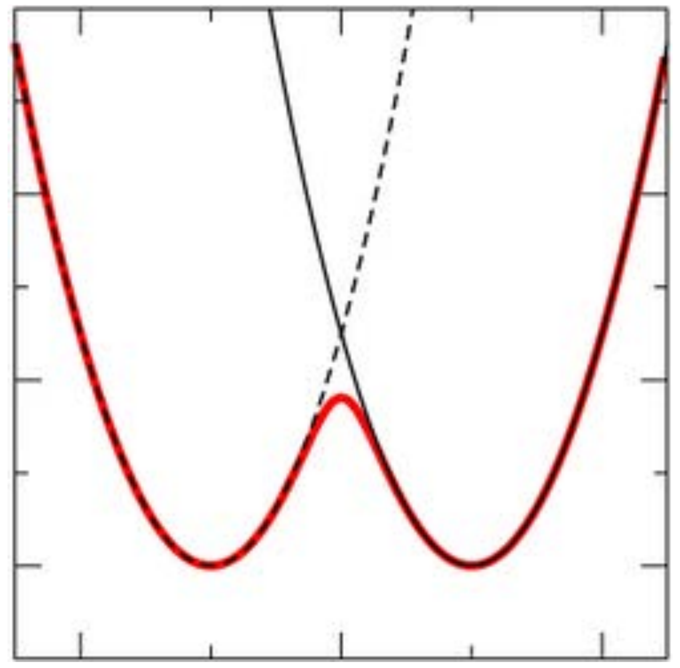
Two-state elastic network model of the transition

Targeted molecular dynamics of the transition

Elaborate transition-path sampling scheme

Free-energy change along minimum-action path





$$\exp(-\beta_{\mathrm{m}}U) = \exp(-\beta_{\mathrm{m}}U^{\mathrm{A}}) + \exp(-\beta_{\mathrm{m}}U^{\mathrm{B}})$$

Tirion, M. M. *Phys. Rev. Lett.* **1996**, *77*, 1905

Maragakis, P.; Karplus, M. *J. Mol. Biol.* **2005**, *352*, 807-822

Schlitter, J.; Engels, M.; Krüger, P. *J. Mol. Graph.* **1994**, *12*, 84-89

Singharoy, A.; Chipot, C. *J. Phys. Chem. B* **2017**, *121*, 3502–3514

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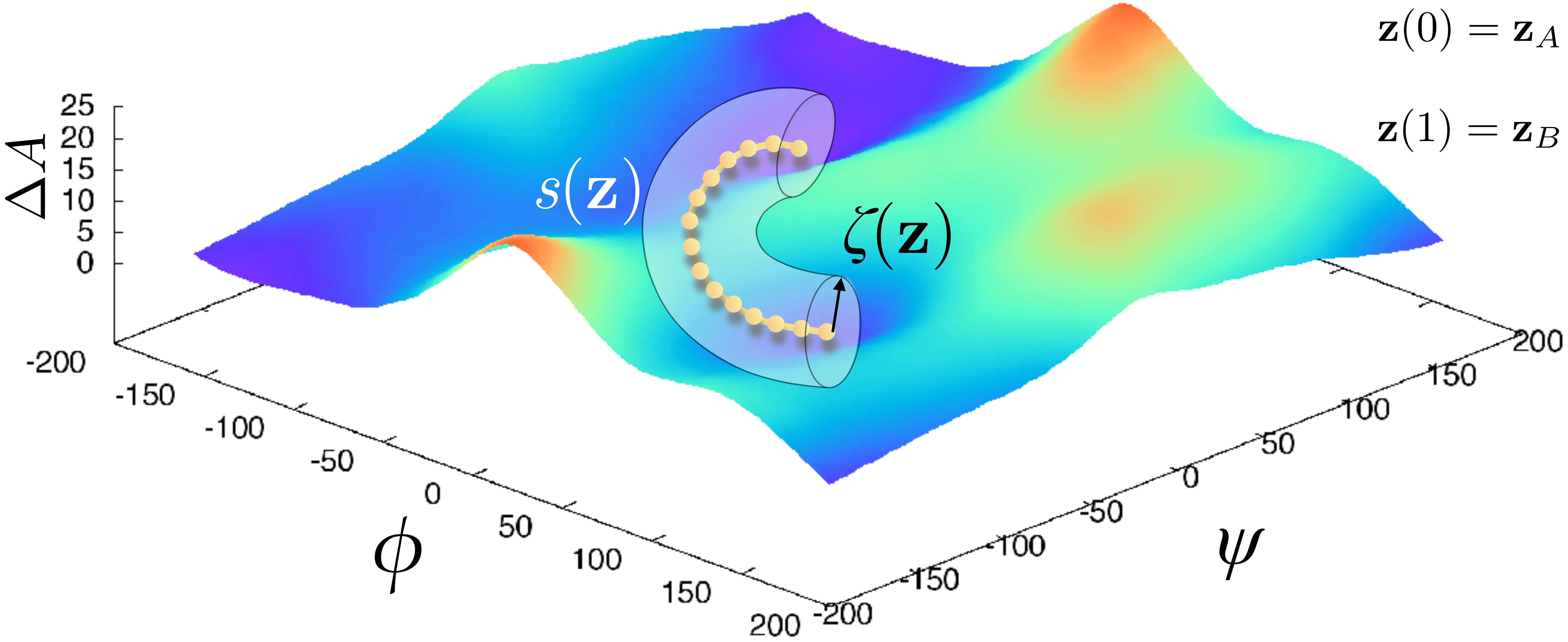
DERIVING THE ONE-DIMENSIONAL FREE-ENERGY PROFILE



$$\mathbf{z}(0) = \mathbf{z}_A$$

$$\mathbf{z}(1) = \mathbf{z}_B$$

Path collective variables:

$$s(\mathbf{z}) = \lim_{\lambda \to \infty} \frac{\displaystyle\int_0^1 \mathrm{d}t \; t \; \exp\{-\lambda[\mathbf{z} - \mathbf{z}(t)]^2\}}{\displaystyle\int_0^1 \mathrm{d}t \; \exp\{-\lambda[\mathbf{z} - \mathbf{z}(t)]^2\}}$$

$$\zeta(\mathbf{z}) = \lim_{\lambda \to \infty} -\frac{1}{\lambda} \int_0^1 \mathrm{d}t \; \exp\{-\lambda[\mathbf{z} - \mathbf{z}(t)]^2\}$$

Free-energy surface:

$$F(s, \zeta) = -\frac{1}{\beta} \ln \left\langle \delta\left[s - s(\mathbf{z})\right] \delta\left[\zeta - \zeta(\mathbf{z})\right] \right\rangle$$

Closest minimum free-energy path:

$$\mathscr{T}(\mathbf{z}) = \int_0^1 \mathrm{d}s \; F(s, \zeta)$$

Variational principle: $\dfrac{\delta \mathscr{T}(\mathbf{z})}{\delta \mathbf{z}} = 0$

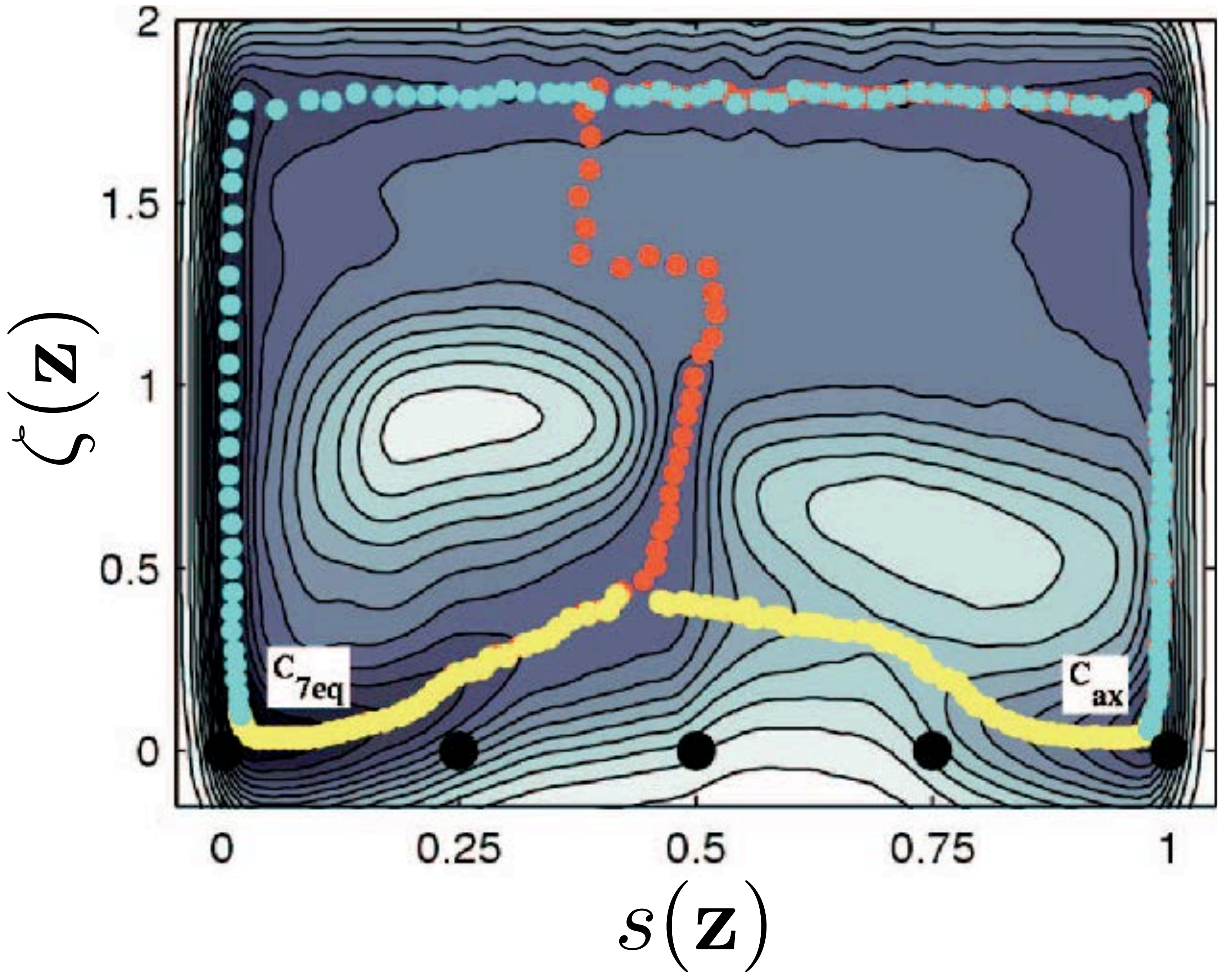
Branduardi, D.; Gervasio, F. L.; Parrinello, M. *J. Chem. Phys.* **2007**, *126*, 054103

DERIVING THE ONE-DIMENSIONAL FREE-ENERGY PROFILE

Discrete case: The putative reaction coordinate, $\mathbf{z}(t)$, is discretized in a collection of images.

$$s(\mathbf{z}) = \frac{1}{N-1} \frac{\sum_i (i-1) \exp\left\{ -\lambda\left[\mathbf{z}-\mathbf{z}(i)\right]^2\right\}}{\sum_i \exp\left\{ -\lambda\left[\mathbf{z}-\mathbf{z}(i)\right]^2\right\}}$$

$$\zeta(\mathbf{z}) = -\frac{1}{\lambda} \ln\left(\sum_i \exp\left\{ -\lambda\left[\mathbf{z}-\mathbf{z}(i)\right]^2\right\}\right)$$

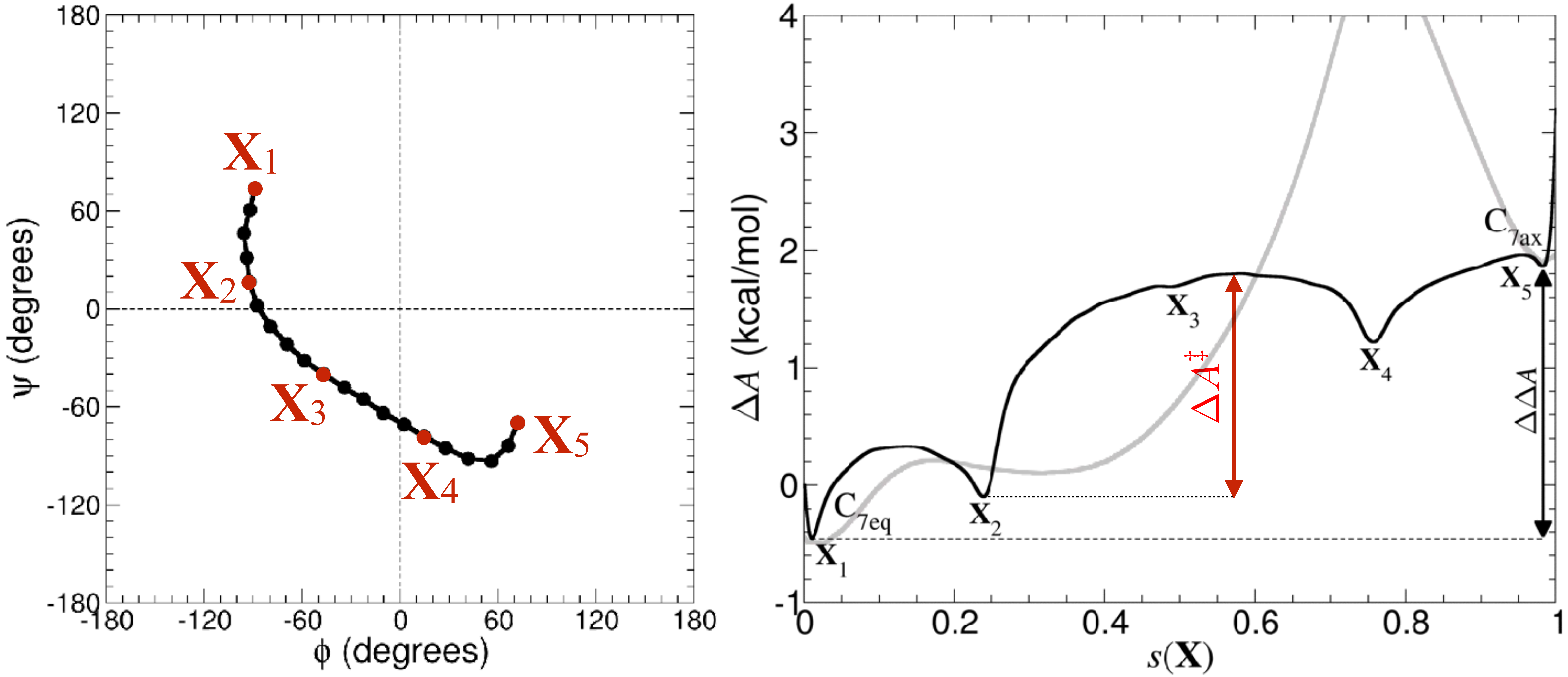


Closest minimum free-energy path:

$$\mathscr{T}(\mathbf{z}) = \frac{1}{N}\left\{ \frac{1}{2}\left[F\Big(s\big(\mathbf{z}(1)\big),0\Big) + F\Big(s\big(\mathbf{z}(N)\big),0\Big)\right] \sum_{i=-2}^{N-1} F\Big(s\big(\mathbf{z}(i)\big),0\Big)\right\}$$

Branduardi, D.; Gervasio, F. L.; Parrinello, M. *J. Chem. Phys.* **2007**, *126*, 054103

DERIVING THE ONE-DIMENSIONAL FREE-ENERGY PROFILE

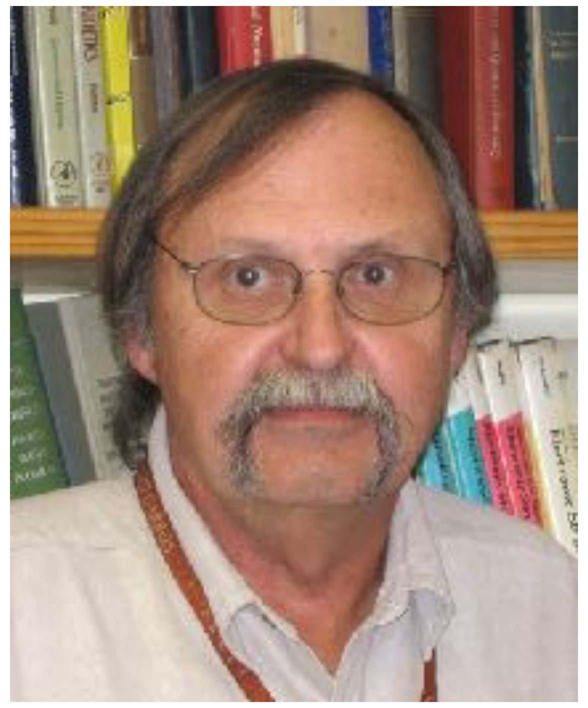


From the integration of C_{7eq} and C_{7ax} basins, $\Delta\Delta A = 2.5$ kcal/mol.

From the difference of RMSD's, $\Delta A^{\ddagger} = 5.6$ kcal/mol.

Hénin, J.; Fiorin, G.; Chipot, C.; Klein, M. L. *J. Chem. Theor. Comput.* **2010**, *6*, 35-47

DERIVING THE ONE-DIMENSIONAL FREE-ENERGY PROFILE



Free energy of the biased system, or perturbed free energy,

$$\mathrm{e}^{-\beta F(\boldsymbol{\eta})} = \int \mathrm{d}\boldsymbol{\zeta} \mathrm{e}^{-\beta\left(\mathrm{G}(\boldsymbol{\zeta})+\mathrm{U}_{\boldsymbol{\eta}}(\boldsymbol{\zeta})\right)}$$

$$\mathrm{e}^{-\beta G(\boldsymbol{\zeta})} \propto \mathrm{e}^{-\frac{1}{2\beta k}\boldsymbol{\nabla}_{\zeta}^2} \mathrm{e}^{-\beta F(\boldsymbol{\zeta})}$$

For large k, in the stiff-spring approximation, one may expand the PMF to extract the first two terms in $1/k$,

$$G(\boldsymbol{\zeta}) \approx F(\boldsymbol{\zeta}) + \frac{1}{2\beta k}\Big(\beta\boldsymbol{\nabla}_{\zeta}F(\boldsymbol{\zeta})\cdot\boldsymbol{\nabla}_{\zeta}F(\boldsymbol{\zeta}) - \boldsymbol{\nabla}_{\zeta}^2 F(\boldsymbol{\zeta})\Big)$$

Assuming that $\zeta(s)$ approximately represents the minimum free–energy path, and s is its arc-length,

$$G\Big(\boldsymbol{\zeta}(s)\Big) \approx F(s) + \frac{1}{2\beta k}\left\{\beta\left(\frac{\mathrm{d}}{\mathrm{d}s}F(s)\right)^2 - \frac{\mathrm{d}^2}{\mathrm{d}s^2}F(s)\right\}$$

The perturbed free energies, $F_i = F(\zeta(s_i))$, can be estimated by solving self-consistently,

$$\mathrm{e}^{-\beta F_i} = \sum_t \frac{\mathrm{e}^{-\beta U_i(\boldsymbol{\zeta}^t)}}{\sum_j T_j \mathrm{e}^{-\beta\left(U_j(\boldsymbol{\zeta}^t)-F_j\right)}} \qquad w^t = \left(\sum_i T_i \mathrm{e}^{-\beta\left(U_i(\boldsymbol{\zeta}^t)-F_i\right)}\right)^{-1}$$

Alternatively,
$$\begin{cases} w^t = \left(\sum_i T_i \mathrm{e}^{-\beta\left(U_i(\boldsymbol{\zeta}^t)-F_i\right)}\right)^{-1} \\ \mathrm{e}^{-\beta F_i} = \sum_t w^t \mathrm{e}^{-\beta U_i(\boldsymbol{\zeta}^t)} \end{cases}$$

$$G(\boldsymbol{\xi}) = -\beta^{-1}\ln\left\{\sum_t w^t\mathbf{K}\Big(\boldsymbol{\xi}(\mathbf{x}^t) - \boldsymbol{\xi}\Big)\right\}$$

Hummer, G.; Szabo, A. Proc. Natl. Acad. Sci. U. S. A. 2010, 107, 21441–21446
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INTRODUCTION

Why do we need reaction coordinates?

WHAT IS A GOOD REACTION-COORDINATE MODEL ?

- Reaction coordinate versus order parameter
- Committor distributions

THE STRING METHOD

- The basic string method
- The string method with swarms of trajectories

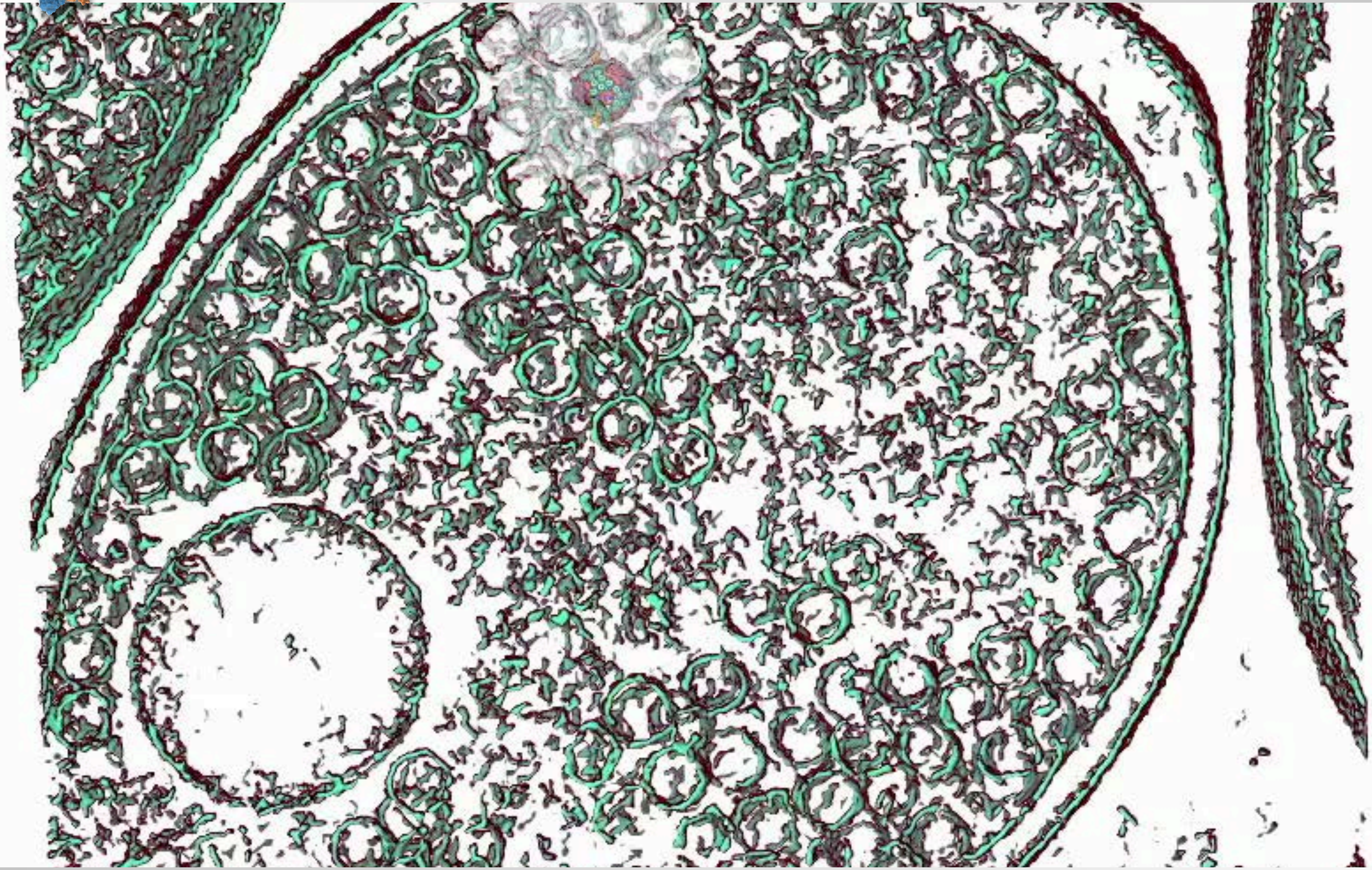
EXTRACTING THE FREE ENERGY FROM THE MINIMUM-ACTION PATH

- Path-collective variables
- Perturbative approach

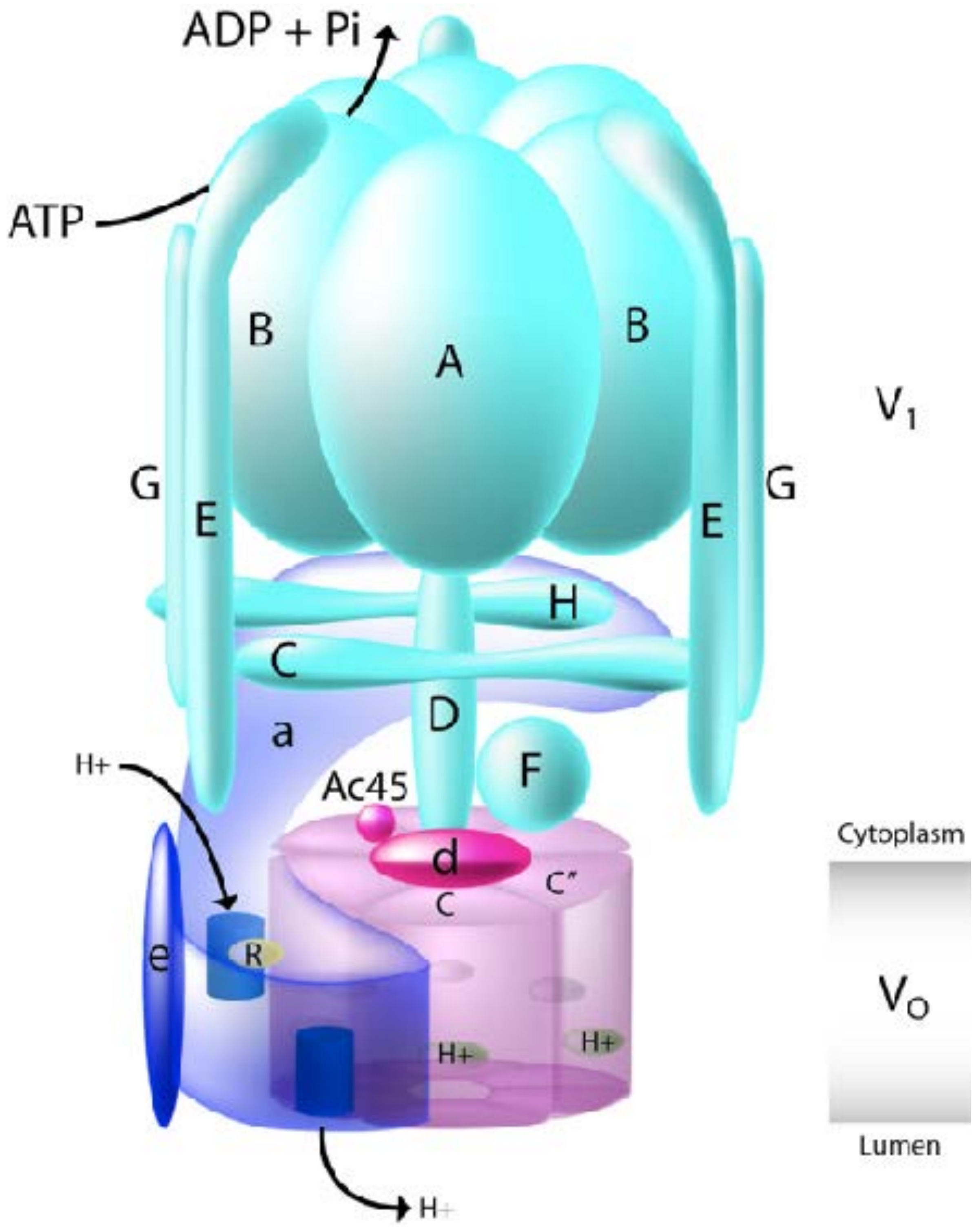
APPLICATIONS

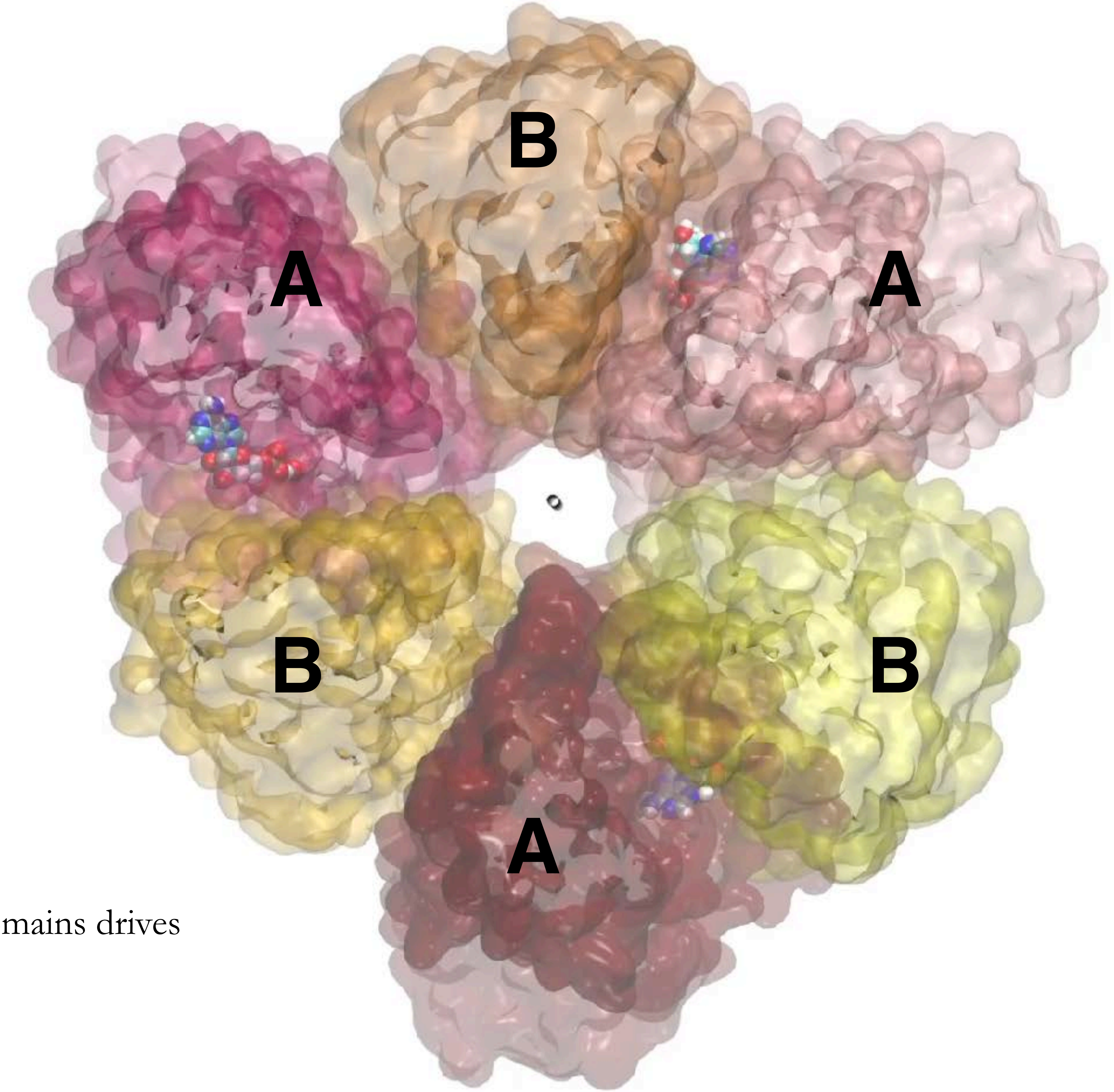
- Transition path of activation loop in c-Src kinase
- Chemomechanical coupling in V_1-ATPase

RECONCILING THERMODYNAMICS AND KINETICS



Chemomechanical coupling in V1-ATPase

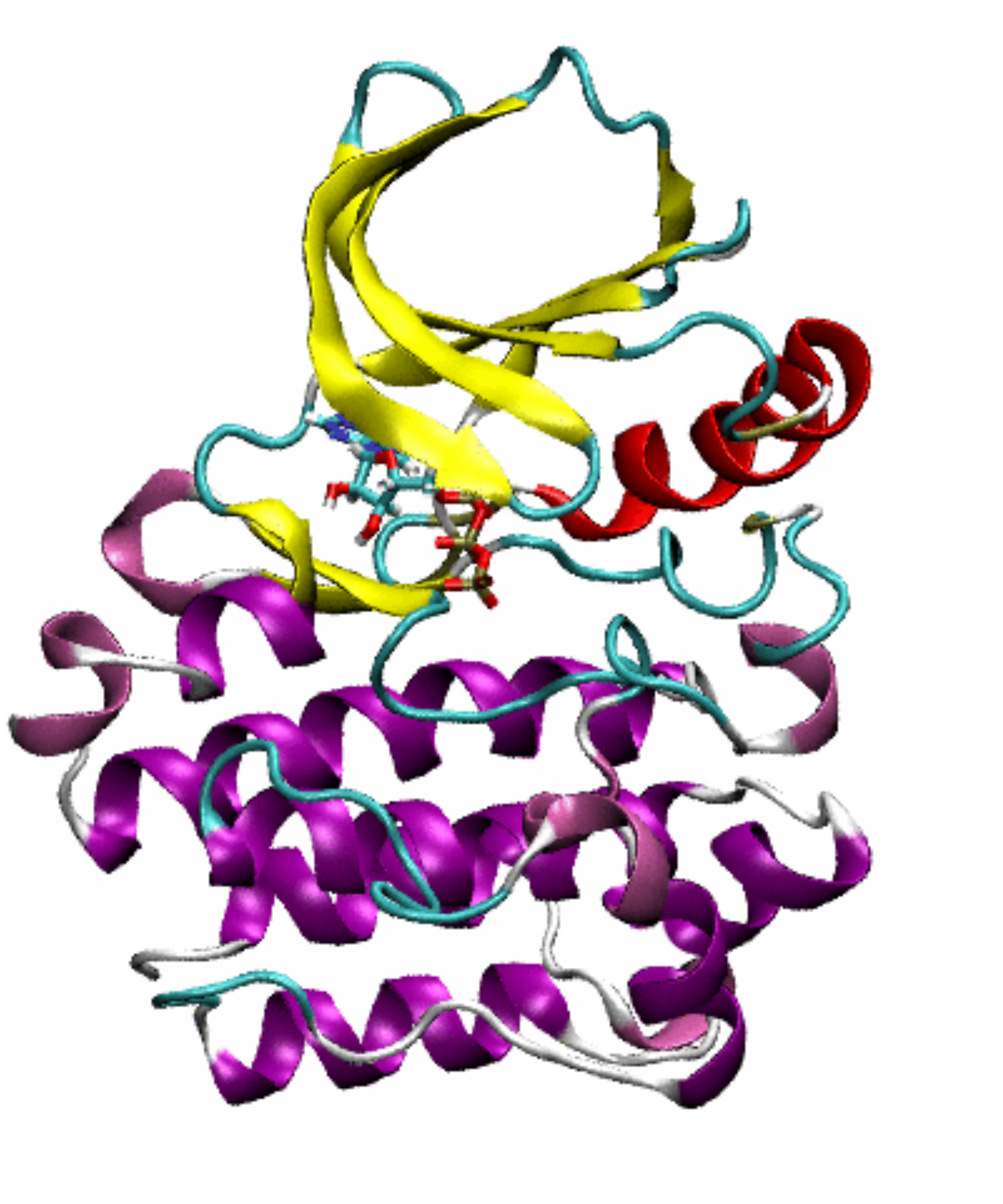


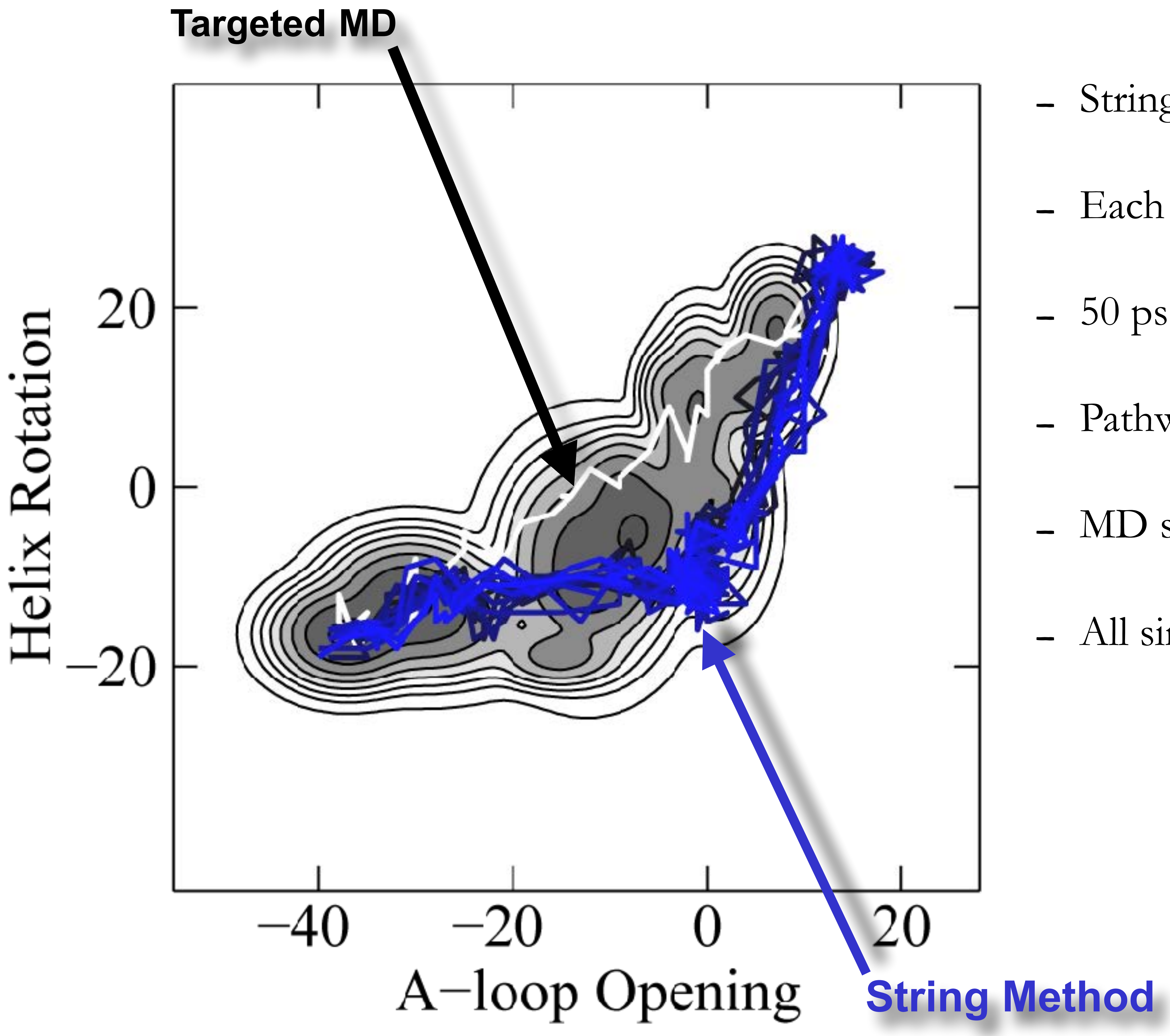


ATP hydrolysis-driven conformational transitions in the A_3B_3 domains drives rotation of the central stalk.

Singharoy, A.; Chipot, C.; Moradi, M.; Schulten, K. *J. Am. Chem. Soc.* **2017**, *139*, 293-310

Transition Path of Activation Loop in c-Src Kinase





- String has 51 images
- Each swarm contains 100 trajectories, 1 ps each
- 50 ps for constrained equilibration
- Pathways is evolved for 100 iterations
- MD simulations are done with NAMD
- All simulations with explicit solvent

Meng, Y.; Pond, M. P.; Roux, B. *Acc. Chem. Res.* **2017**, *50*, 1193-1201

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RECONCILING THERMODYNAMICS AND KINETICS

Beyond thermodynamics

$$\Delta Z = \beta D(Z_t) F(Z_t, t) \Delta t + \nabla D(Z_t) \Delta t + \sqrt{2D(Z_t)\Delta t}\ g_t$$

Let: $\begin{cases} \mu = \beta D(Z_t) F(Z_t, t) \Delta t + \nabla D(Z_t) \Delta t \\ \sigma^2 = 2D(Z_t)\Delta t \end{cases}$

Then: $\Delta Z = \mu + \sigma\ g_t$

$$P[\Delta Z | w(z), D(z)] = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(\Delta Z - \mu)^2}{2\sigma^2}\right)$$

Probability over the entire trajectory, given the parameters:

$$P[Z(t) | w(z), D(z)] = \prod_i \frac{1}{\sigma_i \sqrt{2\pi}} \exp\left(-\frac{(\Delta Z_i - \mu_i)^2}{2\sigma_i^2}\right)$$

(1) The molecular dynamics supplies the trajectory of the collective variable, $Z(t)$.

(2) The molecular dynamics supplies also, $f_{\text{bias}}(t)$.

(3) Pick trial parameters, $w(z)$ and $D(z)$.

(4) Assume a propagator, e.g., Brownian dynamics.

(5) Calculate the probability of the trajectory given the parameters.

(6) Bayes's theorem: Get the probability of the parameters given the trajectory.

(7) Optimize the parameters to yield the greatest probability.

Comer, J. R.; Chipot, C. J.; González-Nilo, F. D. *J. Chem. Theory Comput.* **2013**, *9*, 876-882

Hummer, G. *New J. Phys.* **2005**, *7*, 34

Ermak, D.; McCammon, J. *J. Chem. Phys.* **1978**, *69*, 1352-1360

Türkcan, S.; Alexandrou, A.; Masson, J. *Biophys. J.* **2012**, *102*, 2288-2298

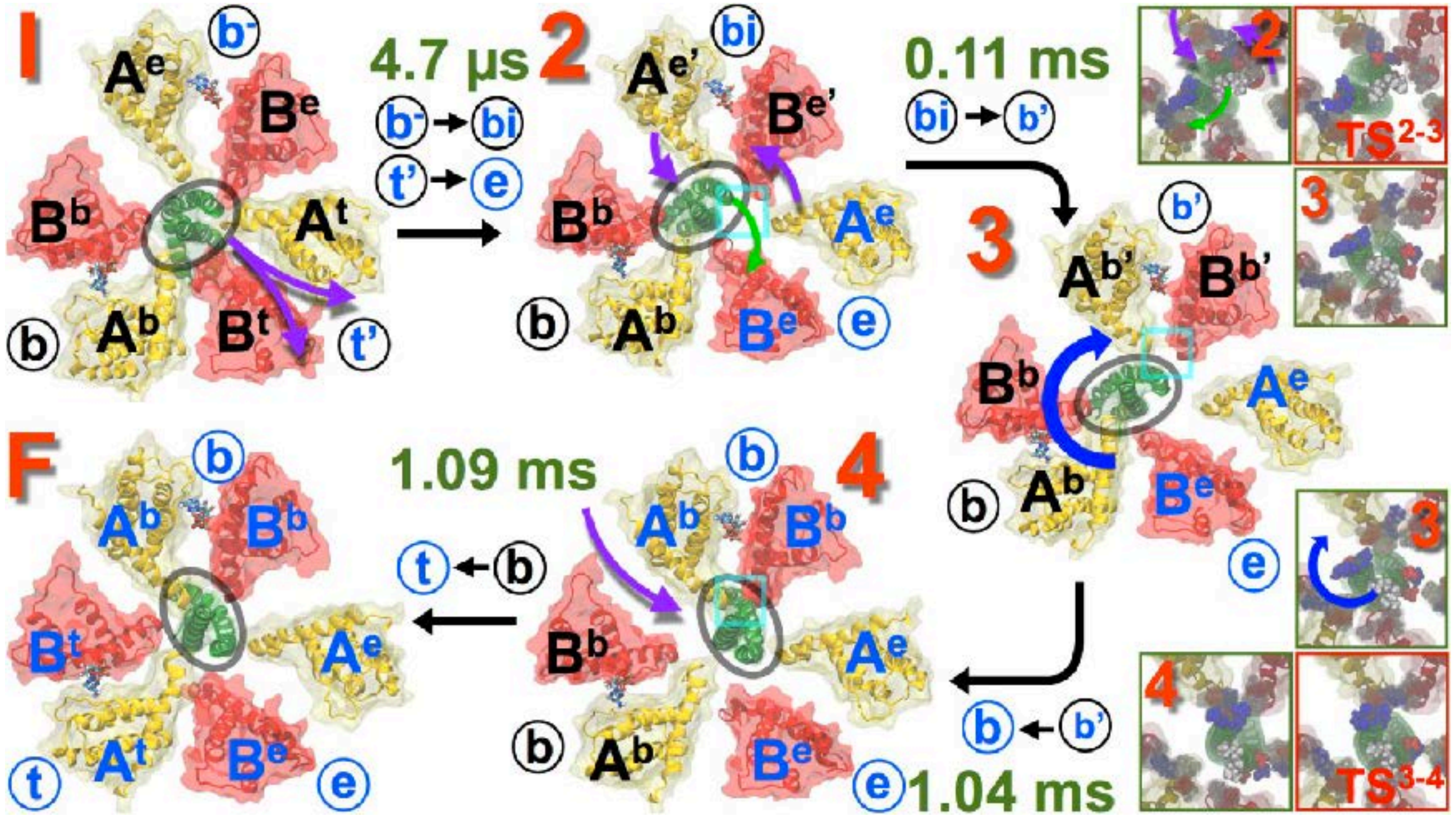
BEYOND THERMODYNAMICS

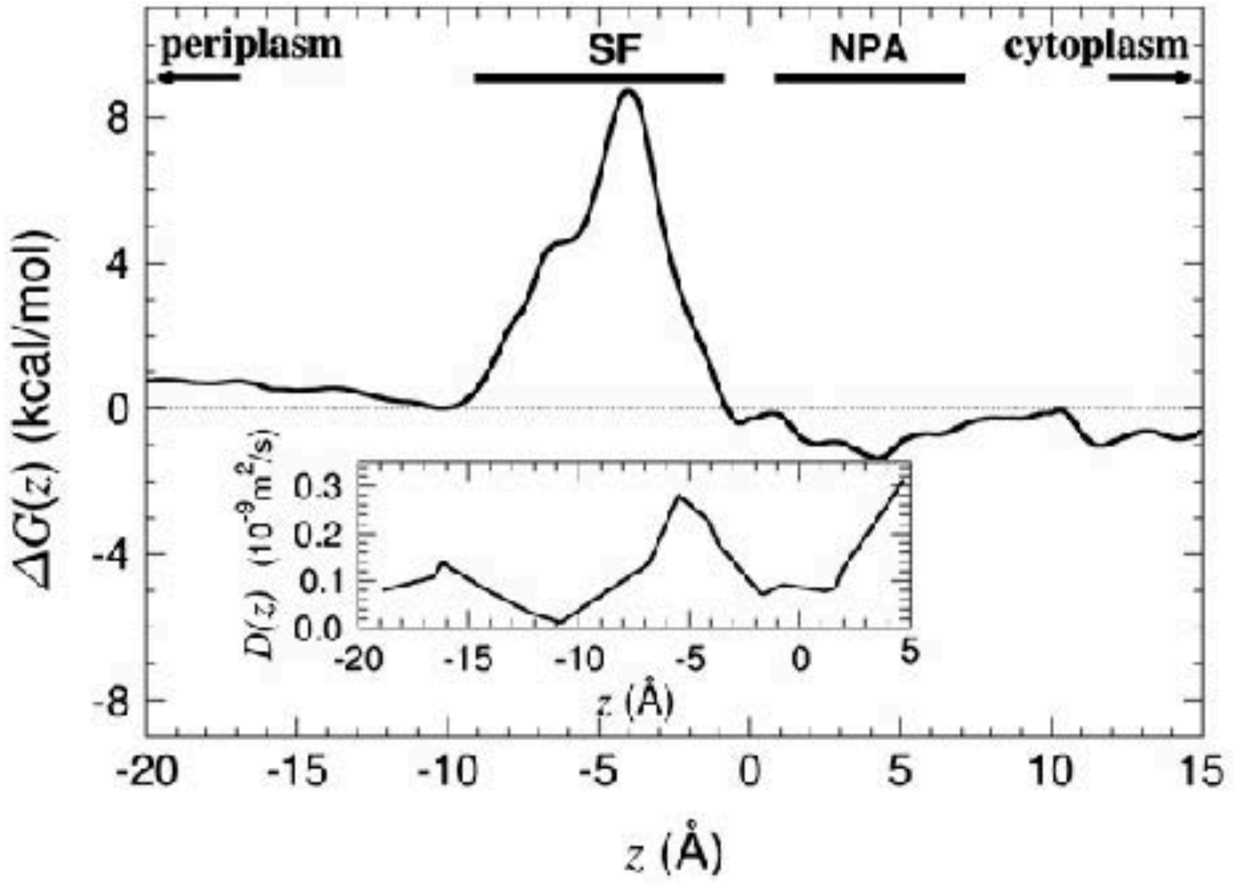
Mean first passage time:

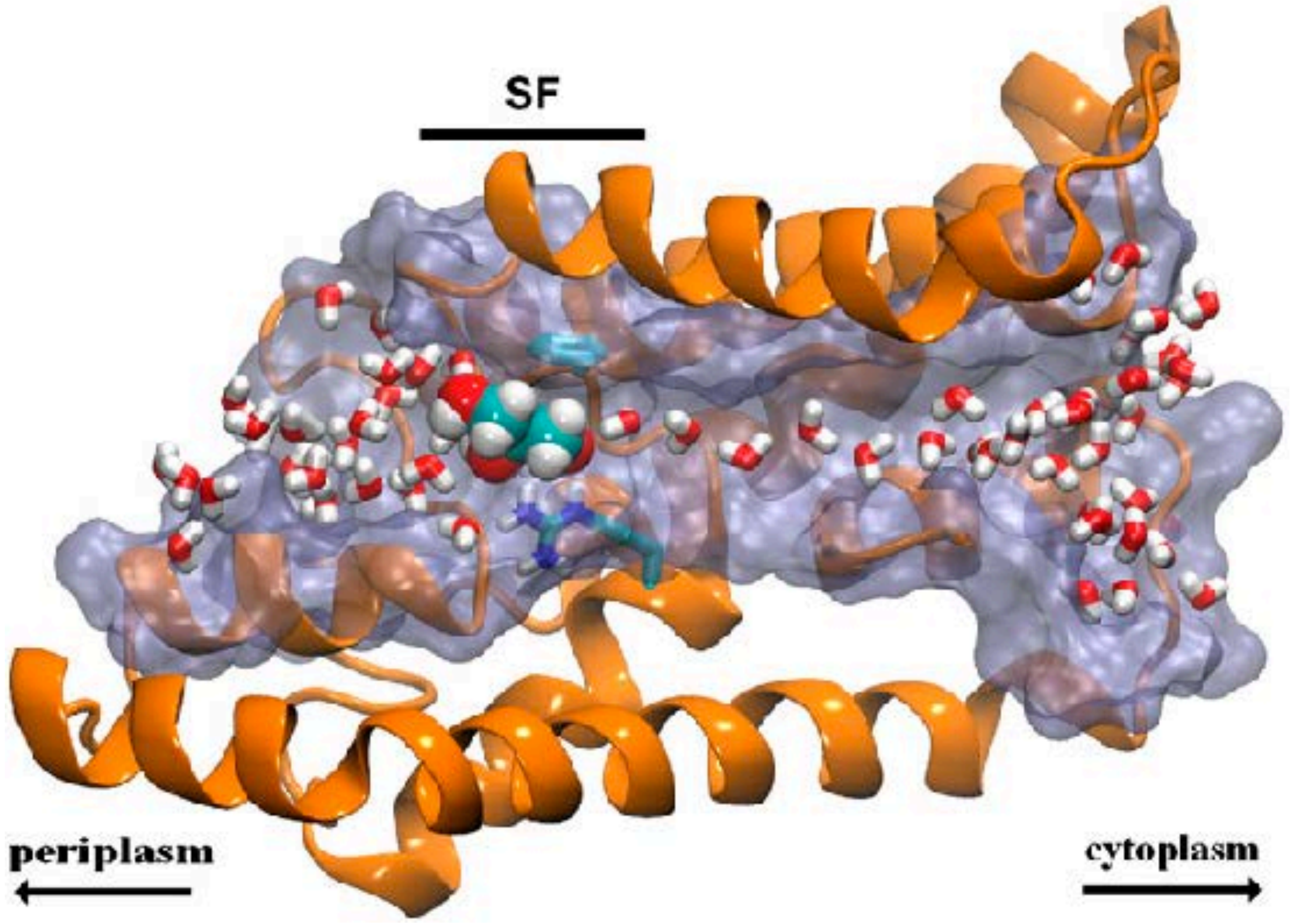
$$\tau = \int_a^b \mathrm{d}\xi \exp\big[\beta\Delta A(\xi)\big] D^{-1}(\xi) \int_a^{\xi} \mathrm{d}\xi' \exp\big[-\beta\Delta A(\xi')\big]$$

Rate constant:

$$k = 1/\tau$$







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Singharoy, A.; Chipot, C.; Moradi, M.; Schulten, K. *J. Am. Chem. Soc.* **2017**, *139*, 293-310

Hénin, J.; Tajkhorshid, E.; Schulten, K.; Chipot, C. *Biophys. J.* **2008**, *94*, 832-839

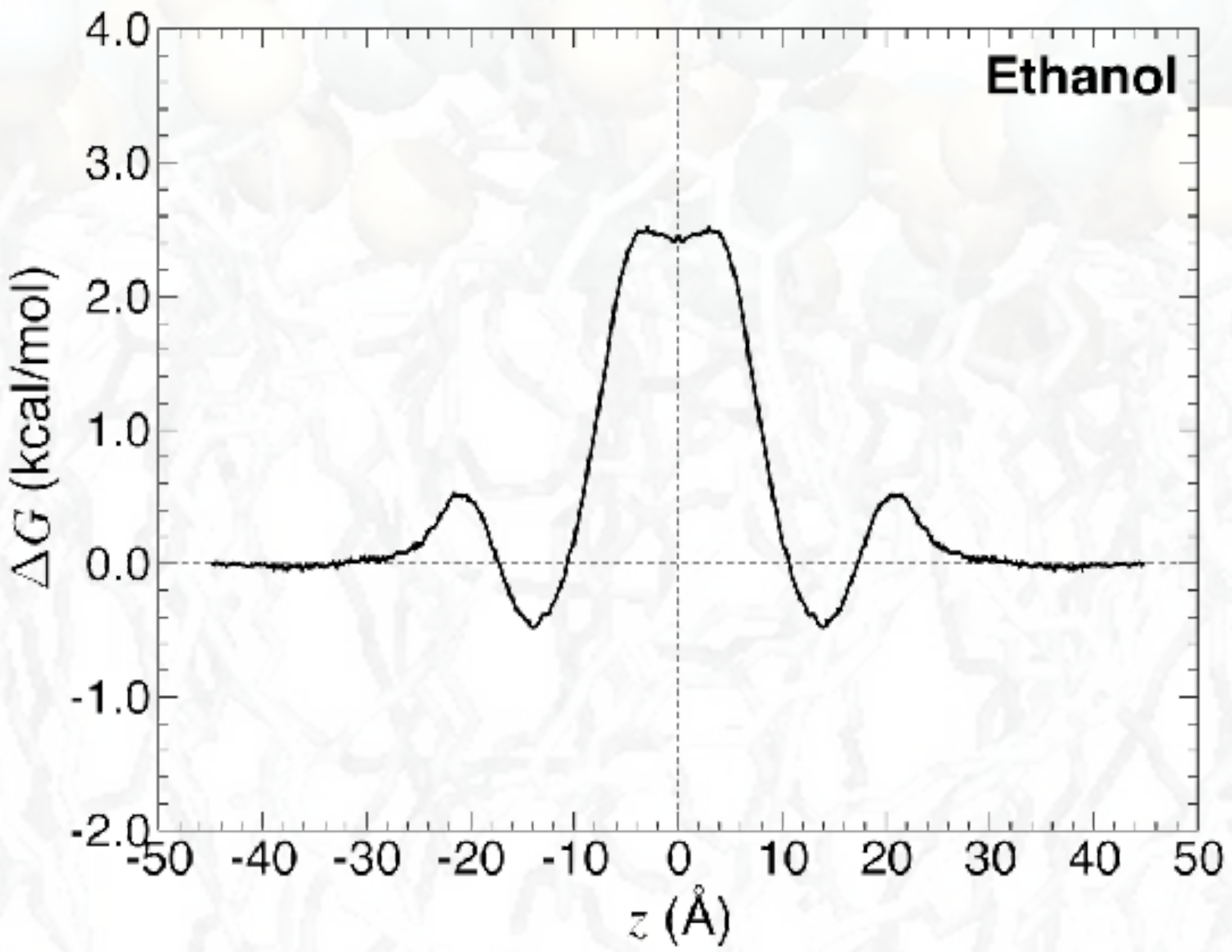
MEMBRANE PERMEABILITY TO SMALL ALCOHOLS

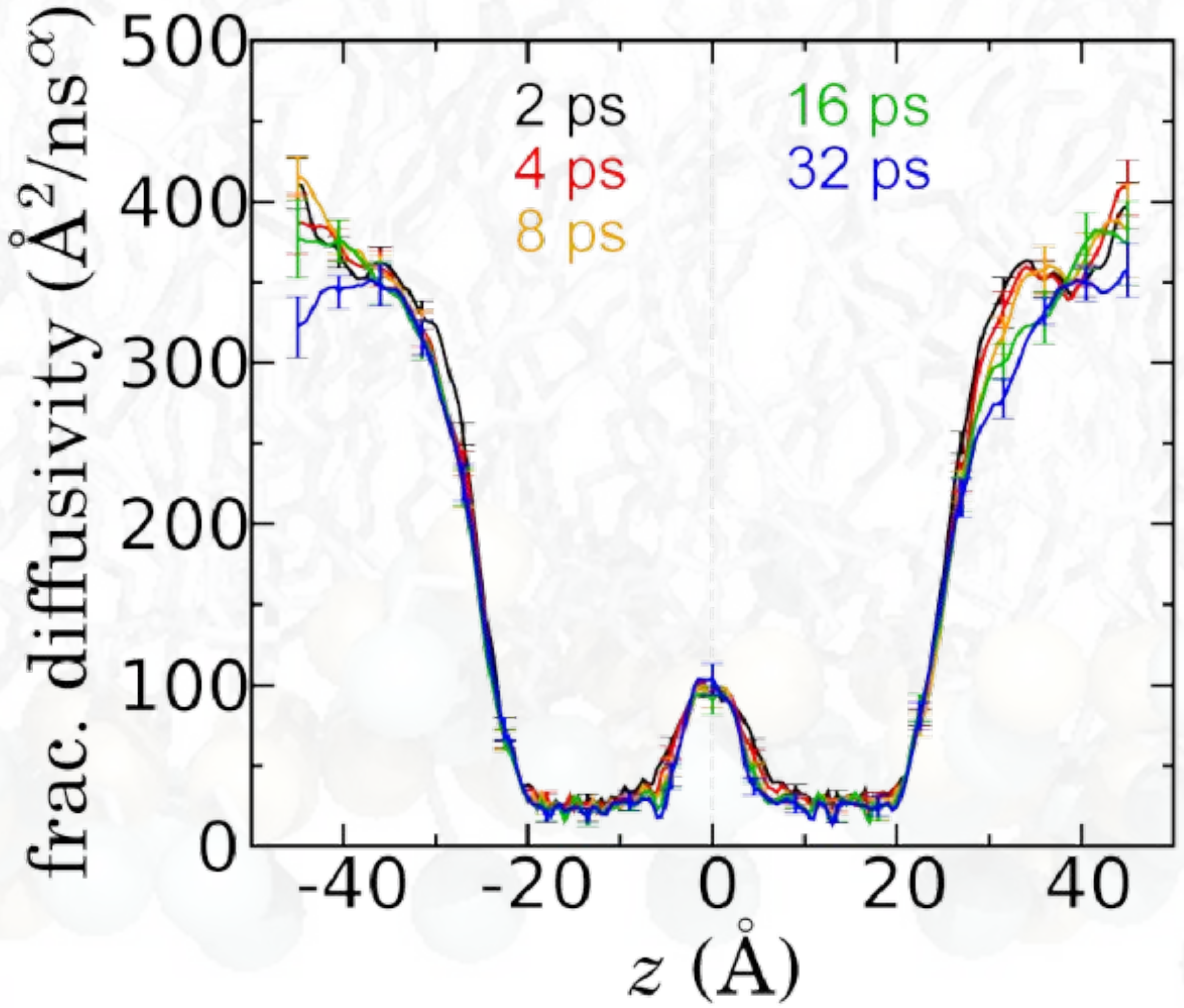
Naive model of the reaction coordinate: Euclidian distance separating the center of mass of the alcohol to that of the bilayer, projected onto z.

Permeation does not obey a random walk: $\langle z(t)^2 \rangle \sim K_\alpha t^\alpha$

Under these premises, one needs to turn to an alternate theoretical framework, based on fractional diffusion:

$$\partial_t^{\alpha(z)} c(z,t) = \partial_z \left[K_\alpha(z) \partial_z - \beta K_\alpha(z) F(z,t) \right] c(z,t)$$

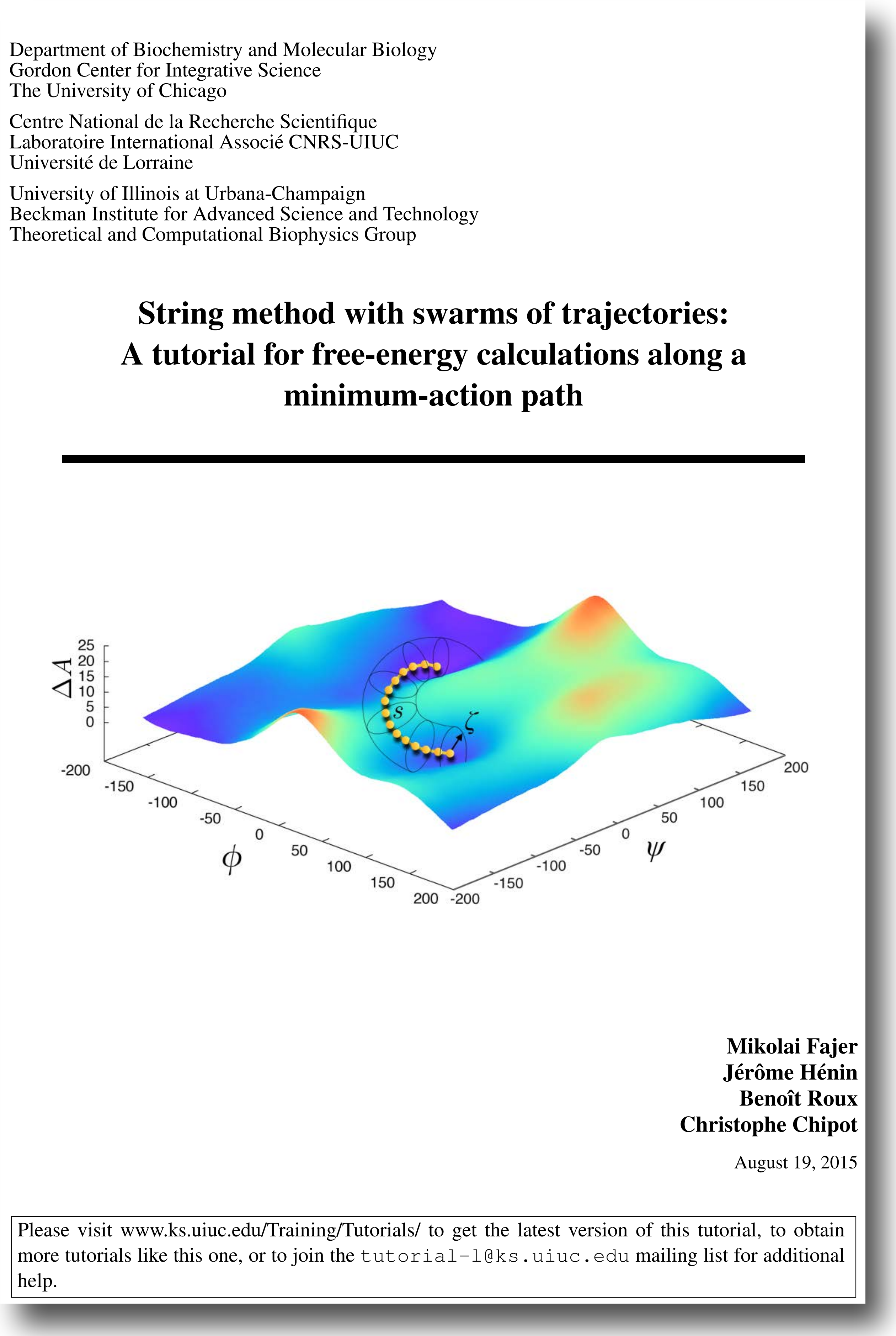




Comer, J.; Chipot, C.. *J. Chem. Theory Comput.* **2017**, *13*, 2523-2532 path sampling

string method with swarm of trajectories, free-energy calculations along a path-collective variable

advanced tutorial



Department of Biochemistry and Molecular Biology
Gordon Center for Integrative Science
The University of Chicago

Centre National de la Recherche Scientifique
Laboratoire International Associé CNRS-UIUC
Université de Lorraine

University of Illinois at Urbana-Champaign
Beckman Institute for Advanced Science and Technology
Theoretical and Computational Biophysics Group

String method with swarms of trajectories: A tutorial for free-energy calculations along a minimum-action path

Mikolai Fajer
Jérôme Hénin
Benoît Roux
Christophe Chipot

August 19, 2015

Please visit www.ks.uiuc.edu/Training/Tutorials/ to get the latest version of this tutorial, to obtain more tutorials like this one, or to join the `tutorial-l@ks.uiuc.edu` mailing list for additional help.

Contributors: Gumbart, J. C.; Hénin, J.; Fajer, M.; Roux, B.; Chipot, C.