Simulating dynamics of rare events using discretised relaxation path sampling

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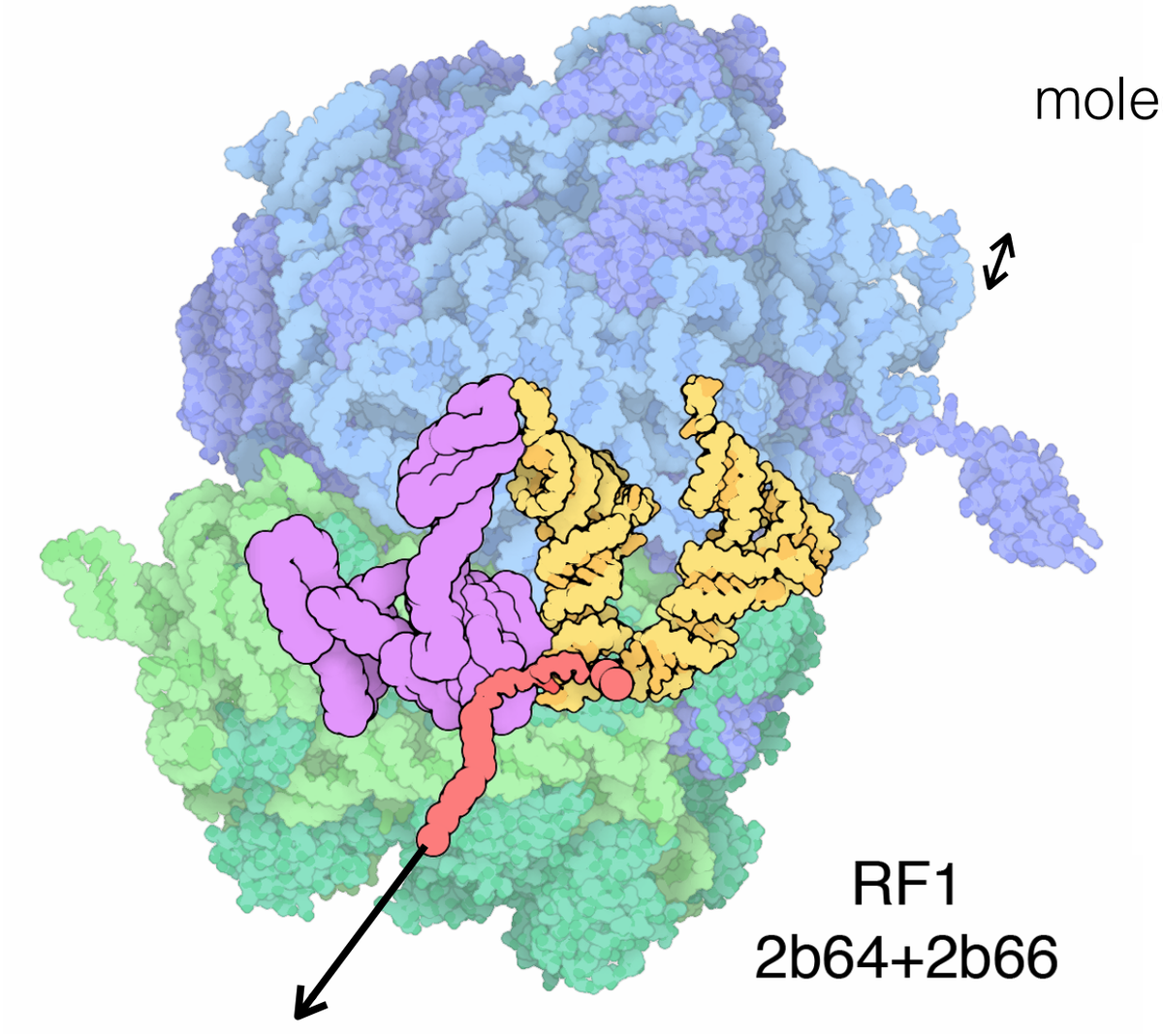
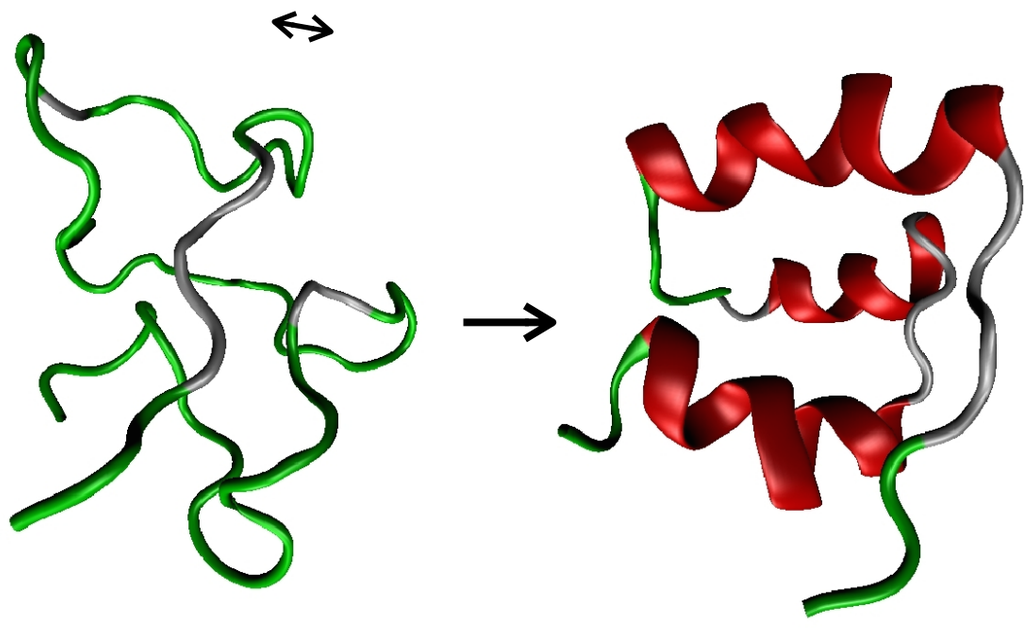
Rare events in nature

- ratio of the largest and lowest relevant timescales $\gg 1$



elongation of
protein chain (~40 ms)

molecular vibration
(~1 fs)

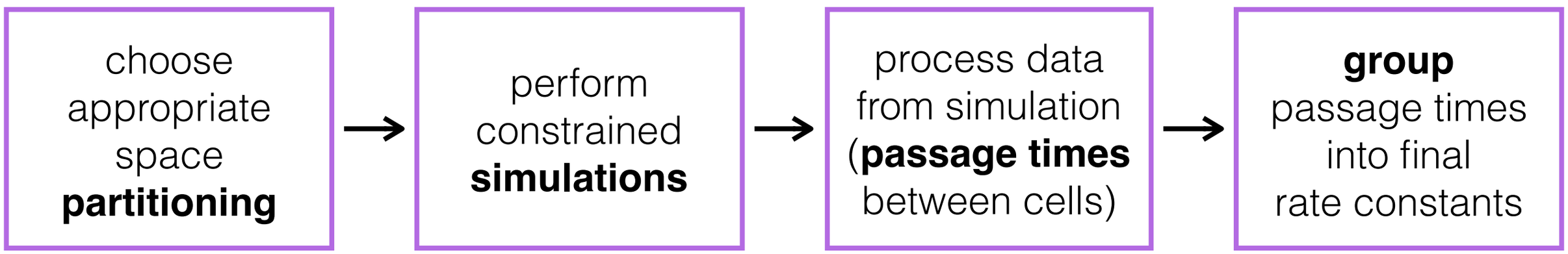


folding
(~1 ms)

(another definition: computer time > patience)

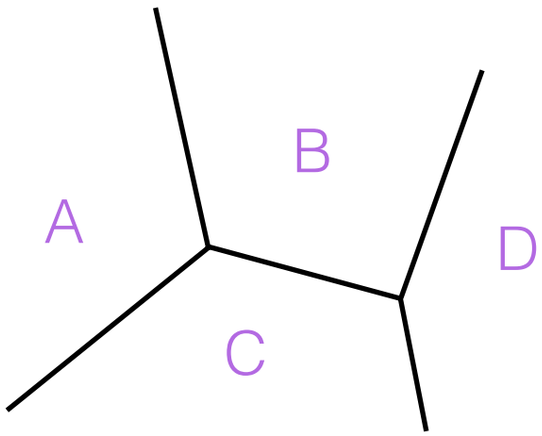
Towards dynamics of rare events

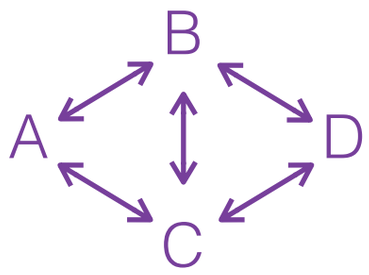
- coarse-graining / rigidification
- biasing the potential (metadynamics, …)
- efficient sampling in the trajectory space (TPS)
- space partitioning (milestoning, TIS, FFS, MSM,…)

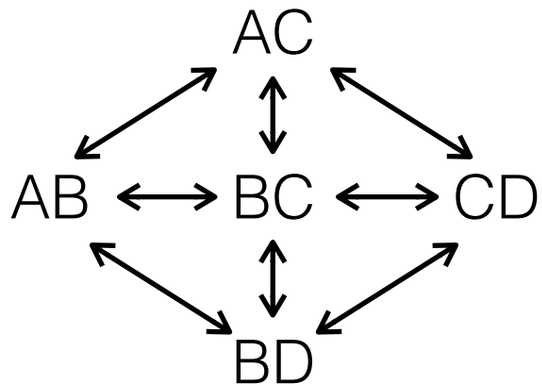


- discrete path sampling (DPS)

Cell-to-cell rate constant



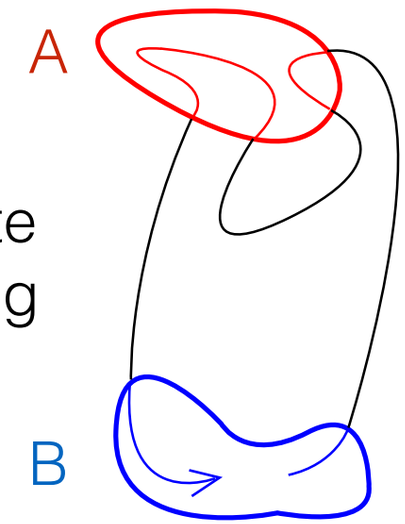




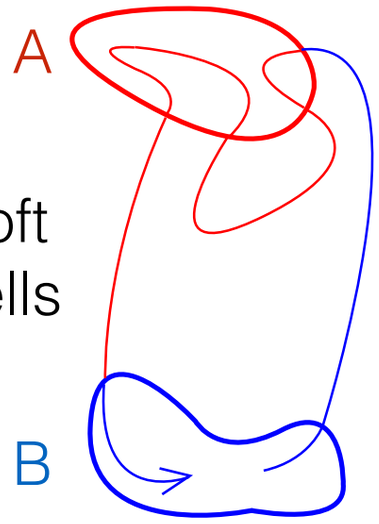
- soft cells were developed to allow complete space partitioning using surface-surface rate constants

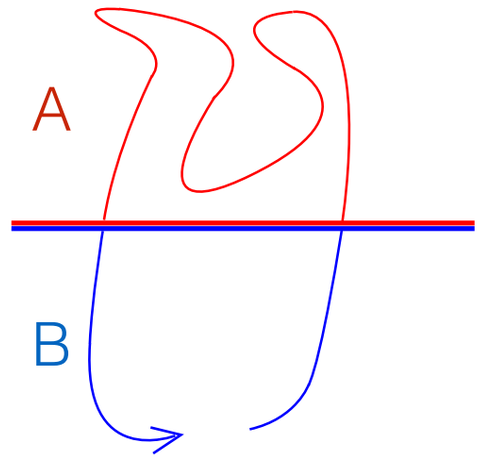
- inconvenient for observables, incompatible with DPS

incomplete partitioning



soft cells

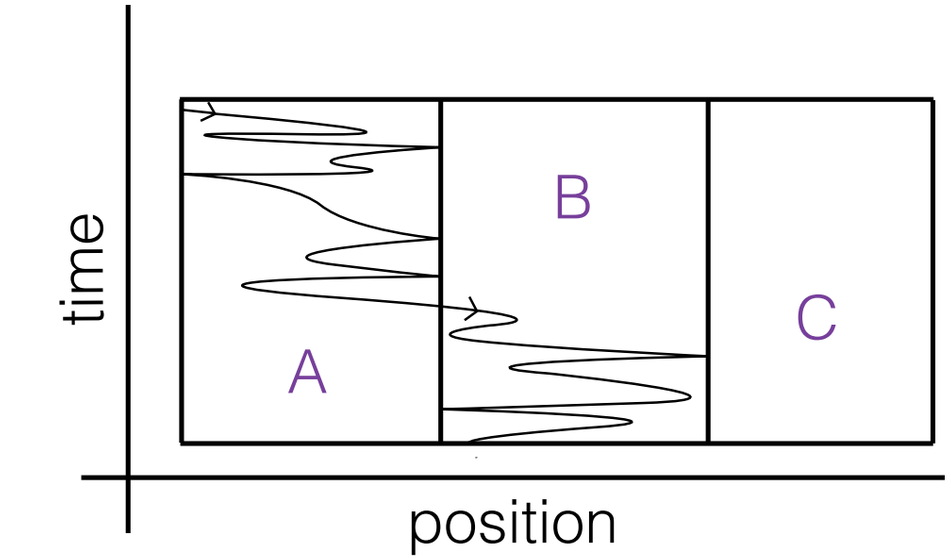


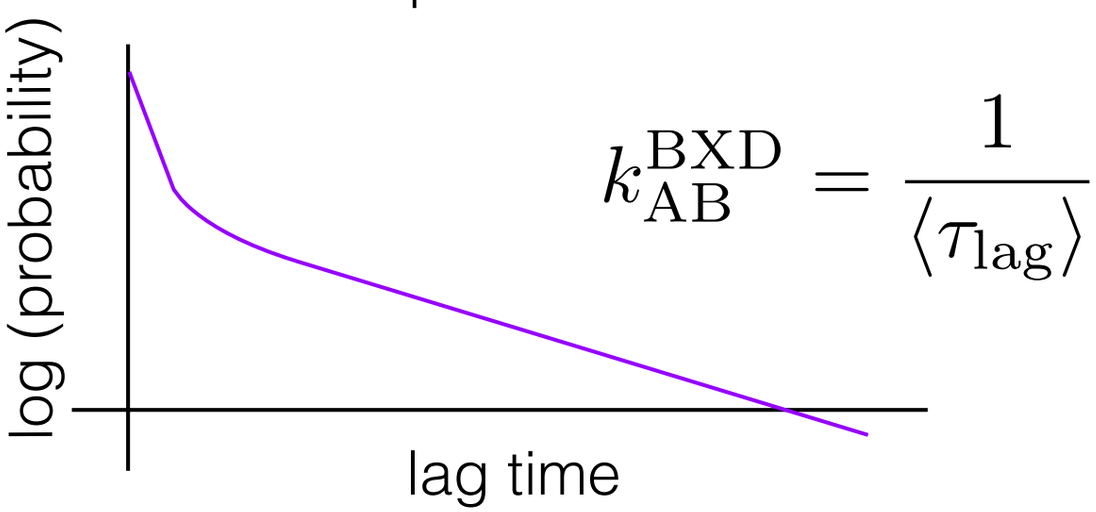


hard cells

Methods using hard cells

- boxed molecular dynamics (BXD) - sampling enhanced by space partitioning

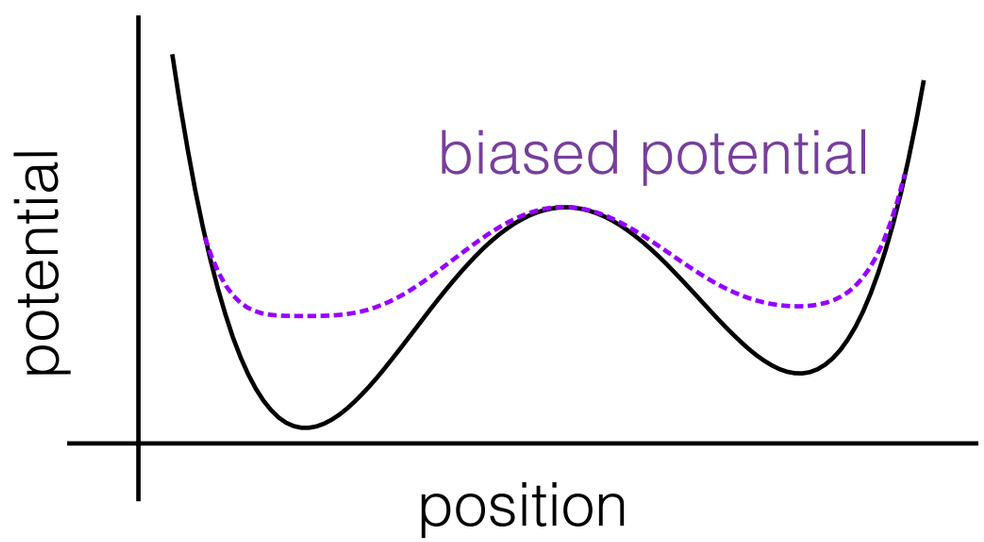




$$k_{\mathrm{AB}}^{\mathrm{BXD}} = \frac{1}{\langle \tau_{\mathrm{lag}} \rangle}$$

- hyperdynamics (hyperMD) - sampling enhanced by biasing the potential

- dividing surface defined by a certain plane involving the saddle point

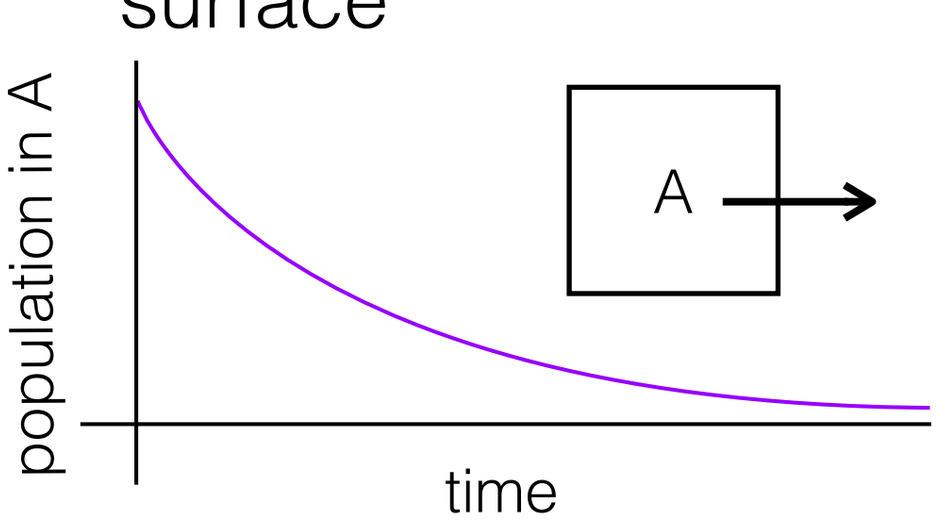


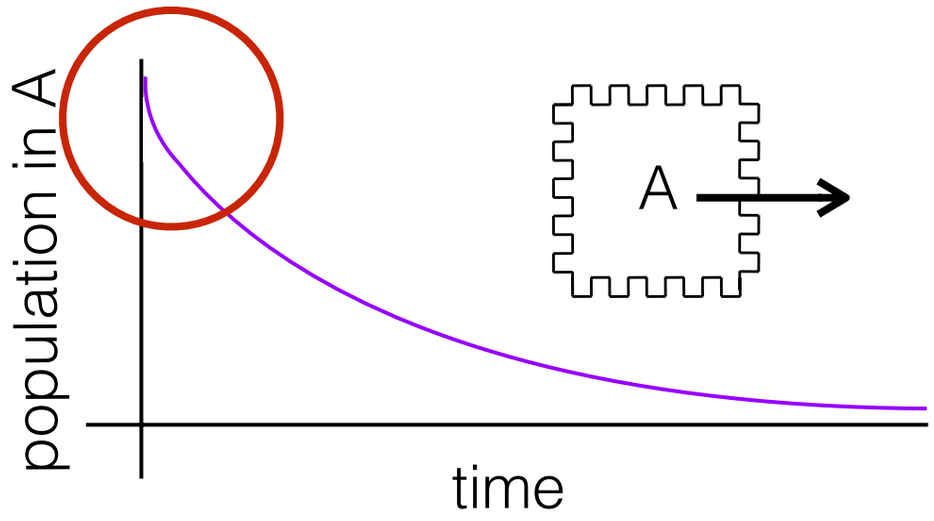
Limits of TST

- transition state theory - rate constant = equilibrium flux / equilibrium population

$$k_{\mathrm{AB}}^{\mathrm{TST}} = \frac{\text{flux}}{\text{population}} = \frac{\langle P(\mathbf{x})\,[\mathbf{n}(\mathbf{x})\cdot\mathbf{v}]\rangle_{\partial \mathrm{A}}}{\langle P(\mathbf{x})\rangle_{\mathrm{A}}} = \frac{\partial_t p_{\mathrm{A}}(0)}{p_{\mathrm{A}}(0)}$$

- the rate constant is very sensitive to definition of the dividing surface





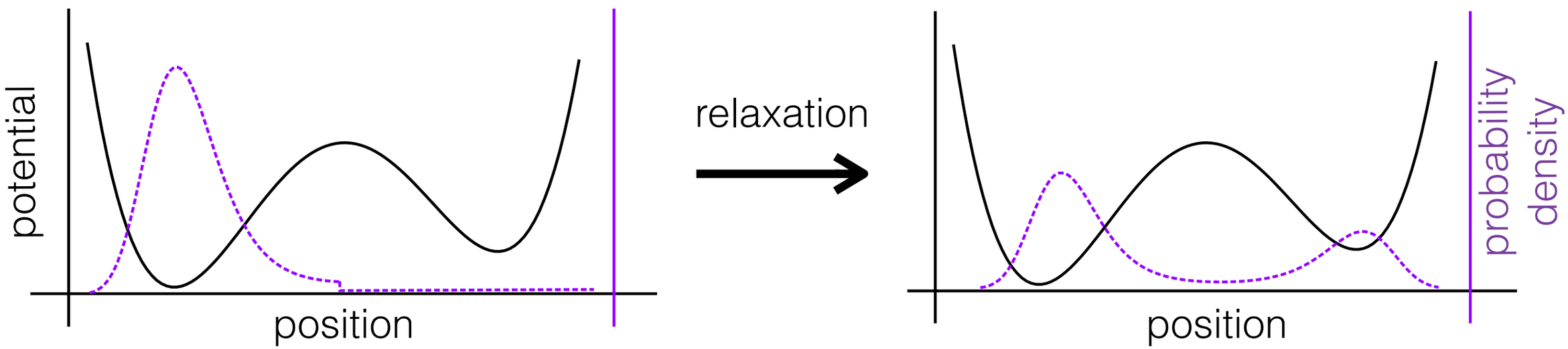
Rate constants from trajectories

- (if we have to simulate trajectories) CAN WE DO BETTER?

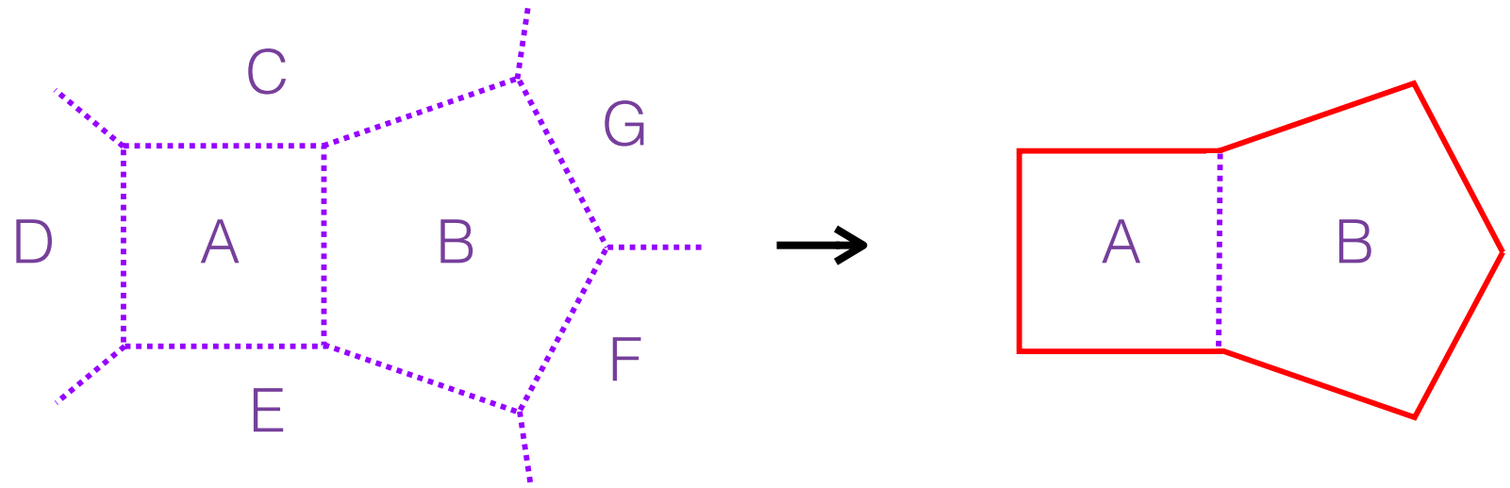
- for system of 2 states, over damped dynamics, rate constant from mean exit times (formula proven for 1D):

$$k_{\mathrm{AB}}^{\mathrm{ex}} = \frac{p_{\mathrm{B}}^{\mathrm{eq}}}{p_{\mathrm{A}}^{\mathrm{eq}}\tau_{\mathrm{B}}^{\mathrm{ex}} + p_{\mathrm{B}}^{\mathrm{eq}}\tau_{\mathrm{A}}^{\mathrm{ex}}}$$

- relaxation involves both exit and penetration - best approach

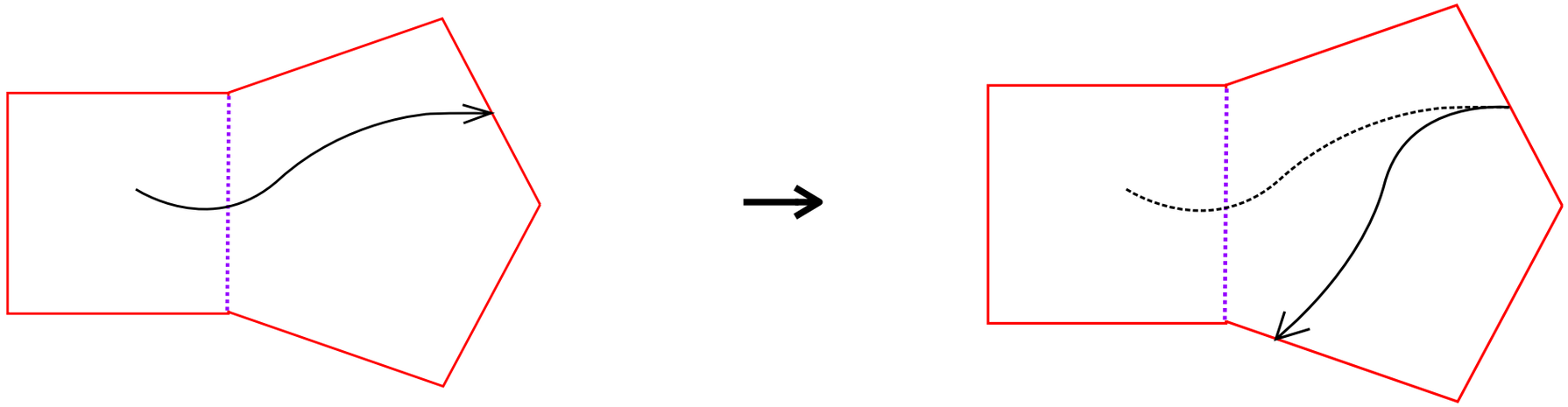


No-flux boundary conditions



- isolation of A and B from the rest by placing hard walls

- straightforward for overdamped dynamics

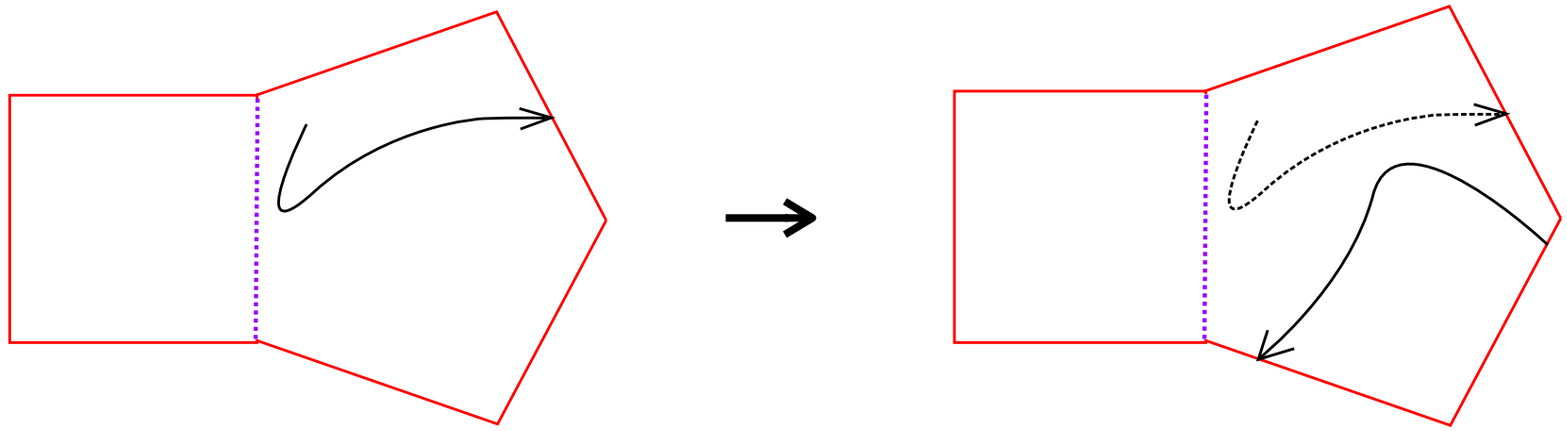


- impossible for Hamiltonian (deterministic) dynamics

Equilibrium boundary conditions

- placing an equilibrated neighbour at the boundary

- exiting particle is replaced by a particle from the equilibrium distribution



- the equilibrium distribution is not known *a priori*

- TRICK: independence of exiting and entering particles ➢ reduction of dynamics to propagation of response functions

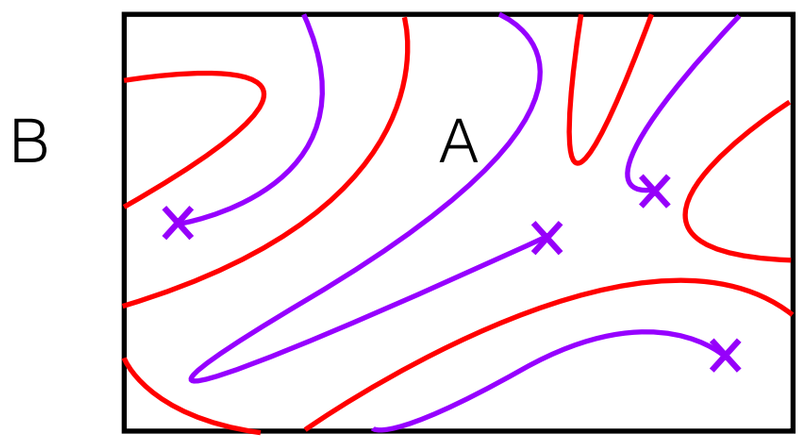
Insight into the response functions

- exit response function $F_{i|k}(t)$ is the distribution of first passage times

- response to supply at the boundary $L_{ij|k}(t)$ is the trajectory lengths

- analytical solution for 1 trajectory averaged over trajectories

- RIGHT: response function for a system with 2 cells (A and B)



trajectories from equilibrium distribution

trajectories from the boundaries

$$F_{\mathrm{B}|\mathrm{A}}(t) = \partial_t p_{\mathrm{A}}(t) \ ,$$

$$L_{\mathrm{BB}|\mathrm{A}}(t) = \frac{\partial_t F_{\mathrm{B}|\mathrm{A}}(t)}{F_{\mathrm{B}|\mathrm{A}}(0)}$$

Optimised simulation protocol

- different for over damped dynamics and inertial dynamics with large friction

1. partitioning of space into cells

2. constrained Monte Carlo sampling

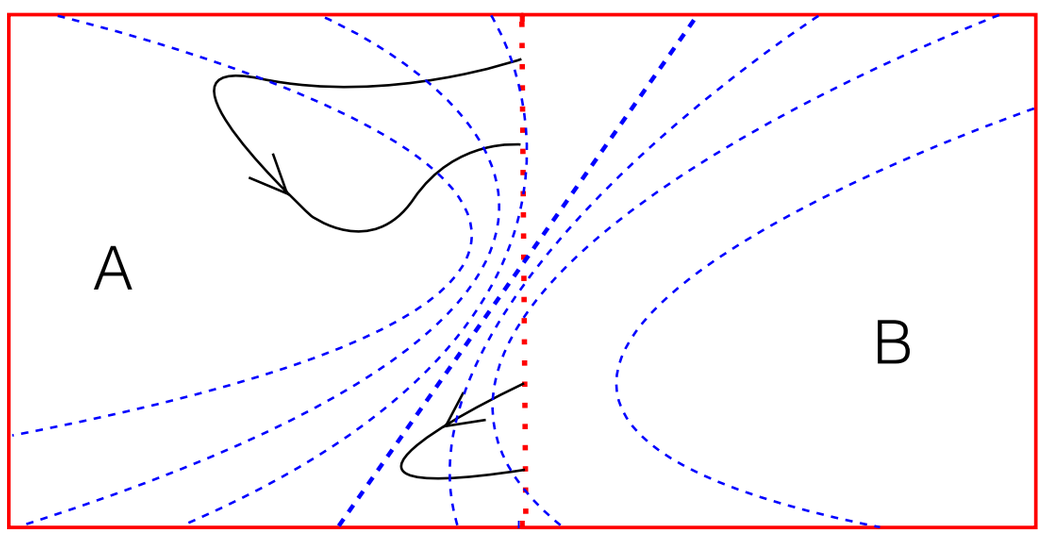
3. molecular dynamics from random initial points terminated at cell boundaries

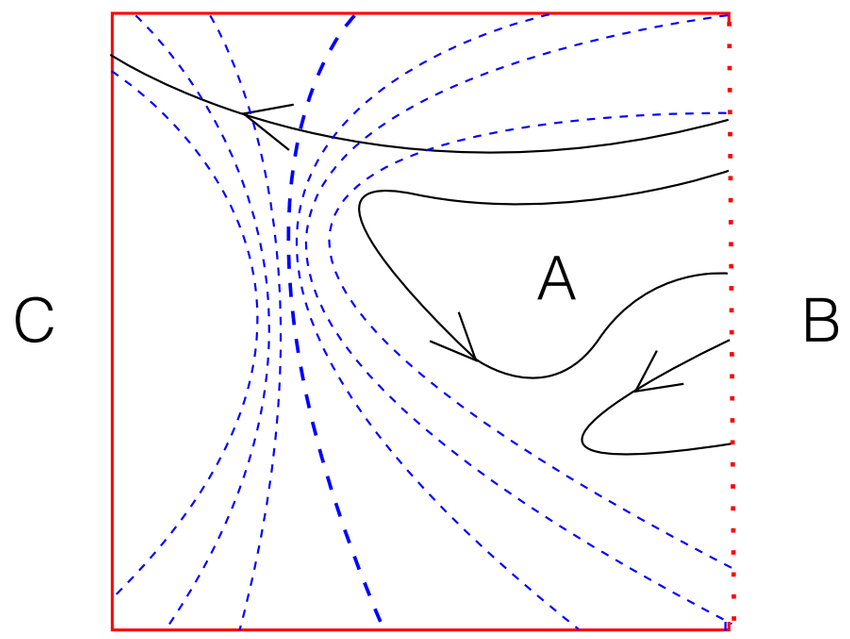
4. propagation of the response functions - fit of the relaxation

5. graph transformation / lumping

Limits of the method

- decorrelation of exiting and entering trajectories at the boundaries is assumed
- internal barriers invalidate Markovian assumption
- some types of breakdowns can be identified from the simulation



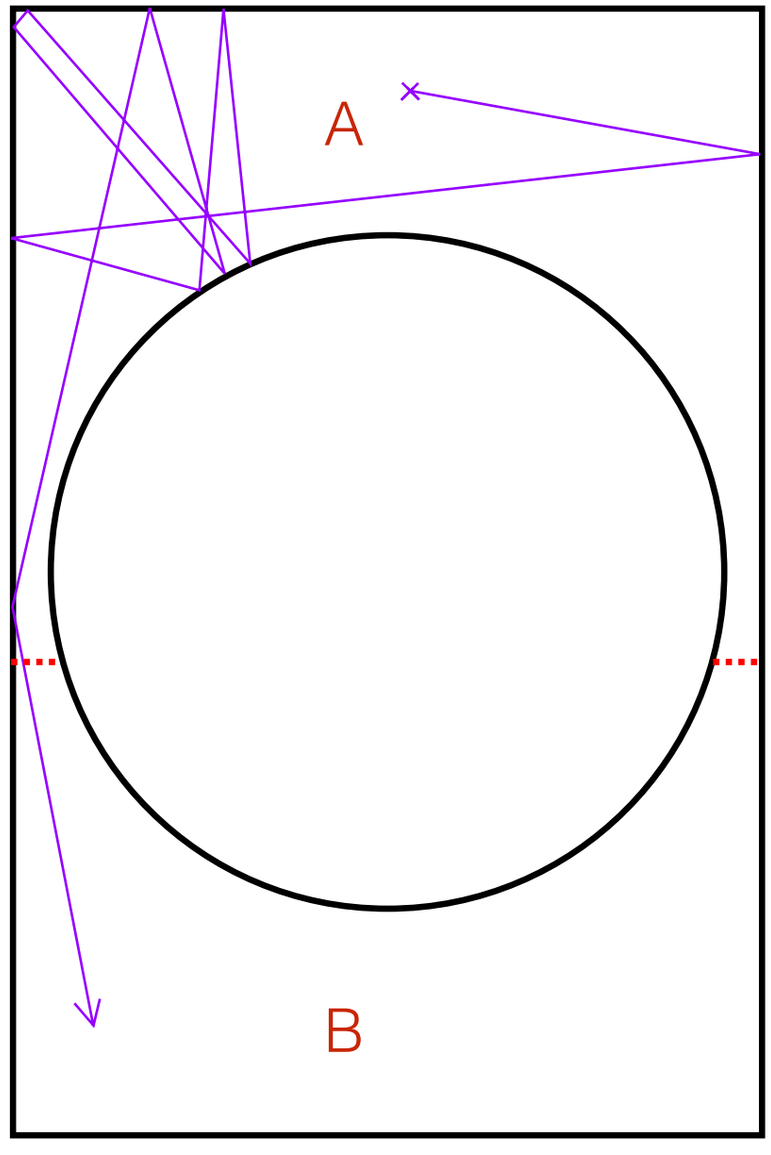


Application of estimator: Sinai billiards

- non-interacting particles with equal velocities elastically reflect from walls of the billiard and the circle inside

- circle forms a bottleneck - transition through the dividing surface is a rare event

- small change in definition of the dividing surface should not cause large change in the rate constants



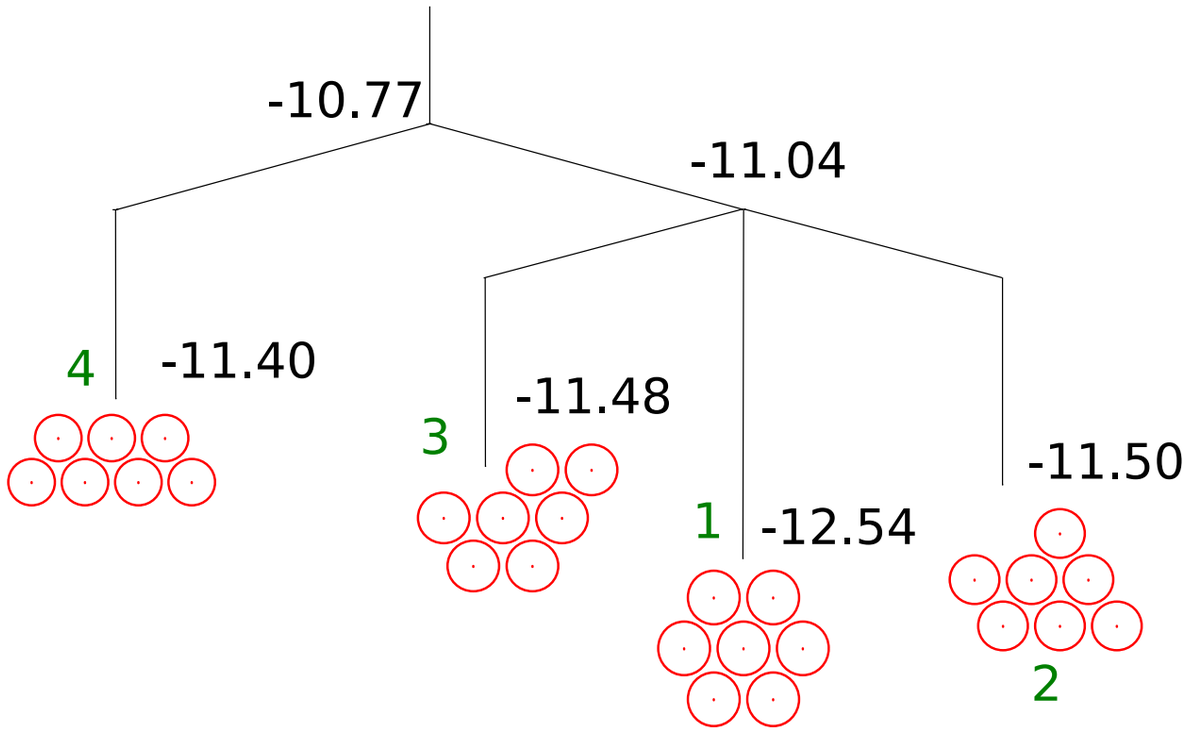
Application of estimator: Sinai billiards

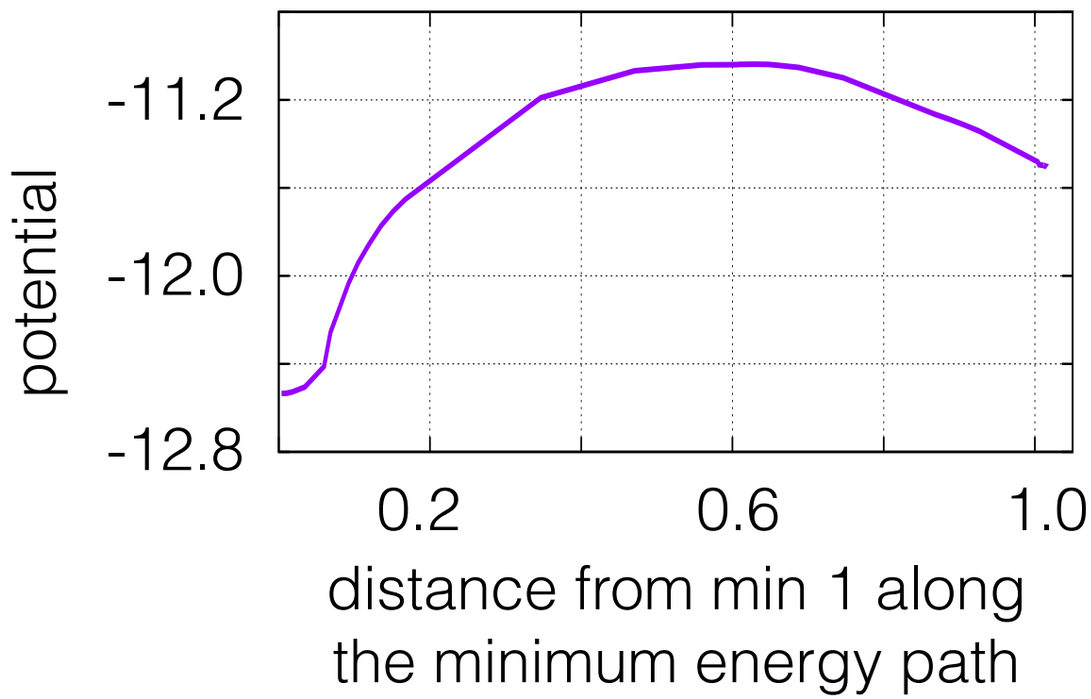
- RXN - “true” rate constant - from relaxation
- TST rate constant - analytical
- BXD constant from simulated equilibrium flux
- exit rate constant from mean exit times
- DRPS - our estimator
- results for 2 dividing surfaces

	position of the dividing surface	
	good	poor
$k_{\mathrm{AB}}^{\mathrm{RXN}}$	11.1	10.8
$k_{\mathrm{AB}}^{\mathrm{TST}}$	12.11	31.58
$k_{\mathrm{AB}}^{\mathrm{BXD}}$	12.11	31.6
$k_{\mathrm{AB}}^{\mathrm{ex}}$	5.64	7.96
$k_{\mathrm{AB}}^{\mathrm{DRPS}}$	10.62	10.56

rate constants
(in arbitrary units)

Application of DRPS: Cluster of Lennard-Jones disks

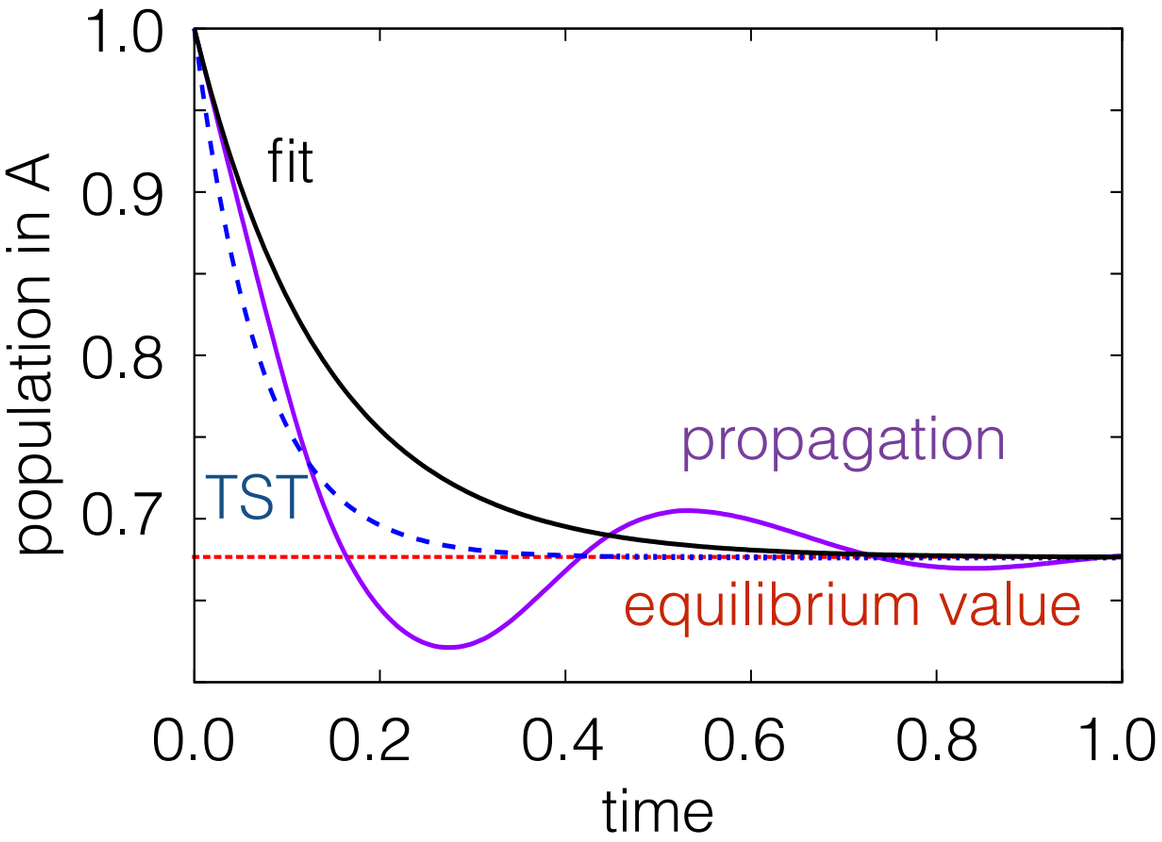


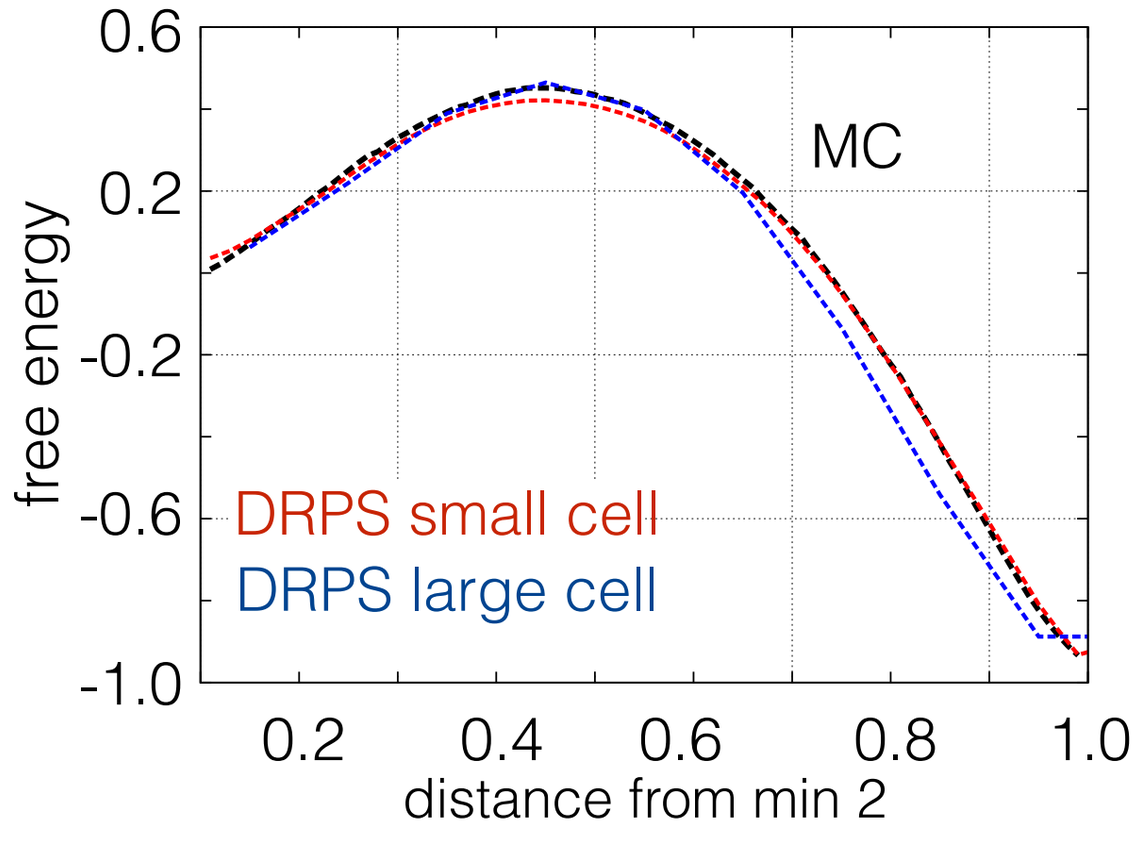


- search for rotation-permutation isomers
- 10-50 cells placed along the collective coordinate - root mean square distance from minimum 2

Application of DRPS: Cluster of Lennard-Jones disks

	box 2	box 5	box 10	TPS	DPS
$\ln(k_{12}/\tau_0)$	-28.9 $\pm$ 0.3	-29.6 $\pm$ 0.5	-30.5 $\pm$ 1.0	-28.7	-26.9
$\ln(k_{21}/\tau_0)$	-9.3 $\pm$ 0.2	-9.4 $\pm$ 0.3	-9.7 $\pm$ 0.7	-7.2	-9.2



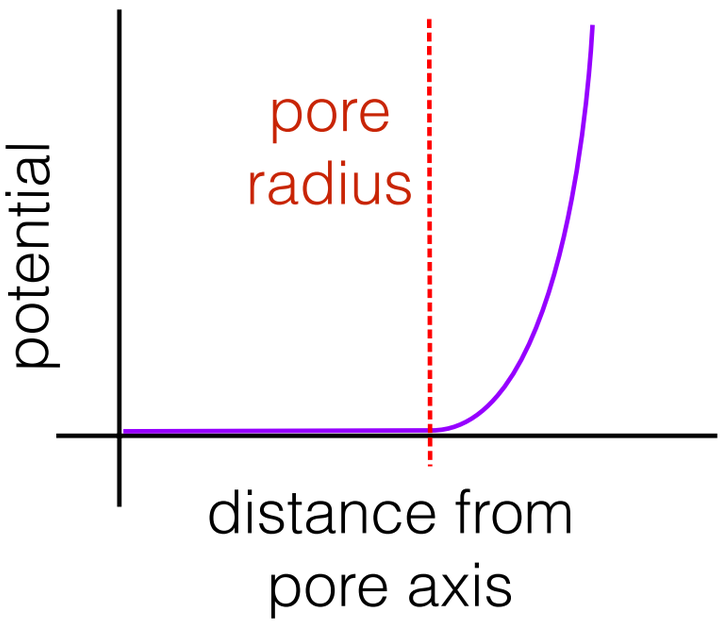


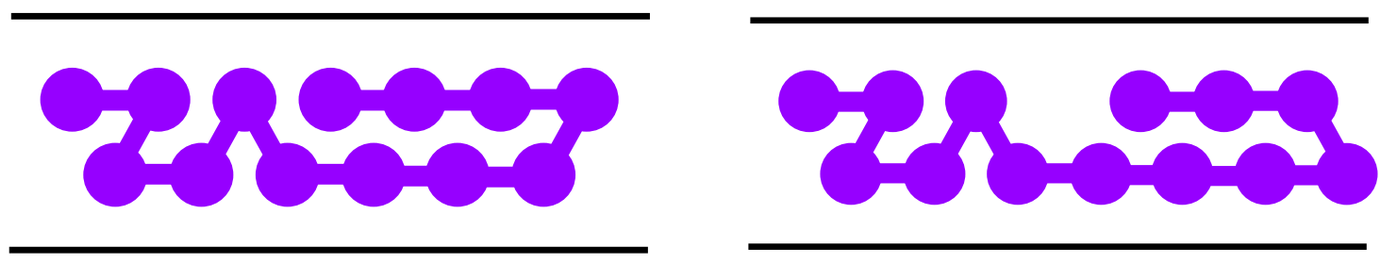
New application:
Polymer reversal in a narrow pore

- polymer confined in a pore is a simple model of DNA or peptide in a synthetic or a biological pore

- dynamics of an LJ polymer can be directly studied by DPS

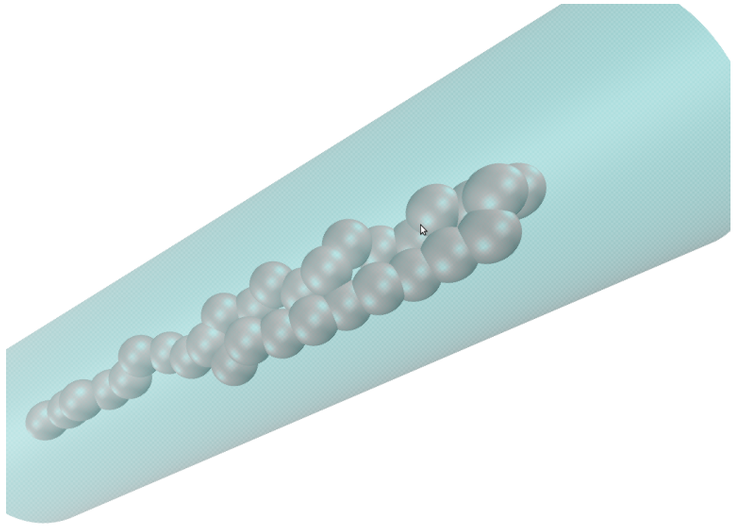
- at higher temperatures / truncated potentials ➢ DRPS



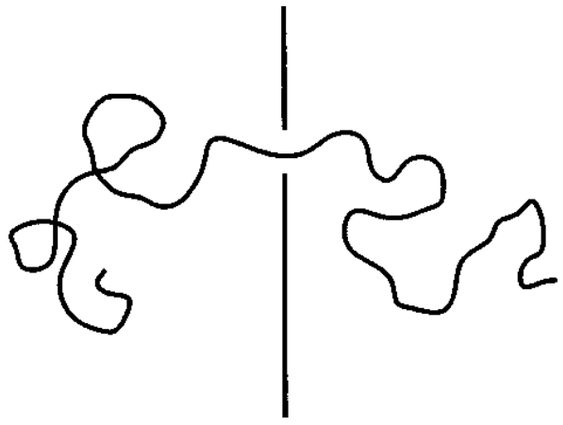


for polyLJ$_{13}^{2D}$ all minima can be easily found

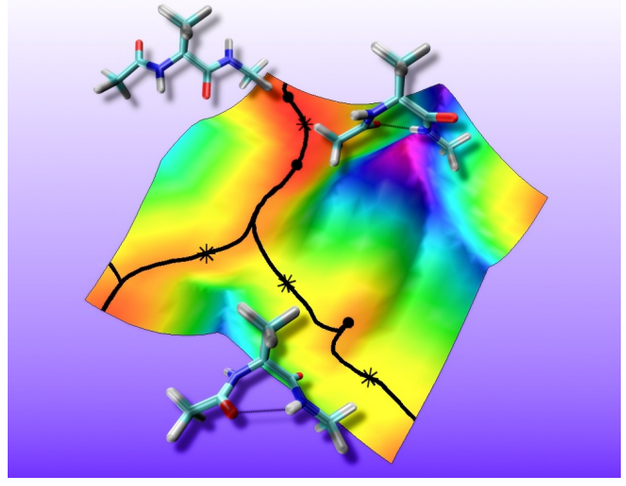
Future applications



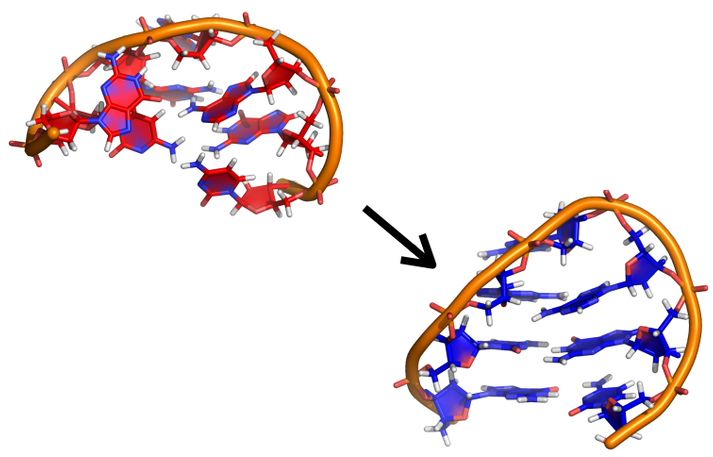
polymer reversal



polymer translocation



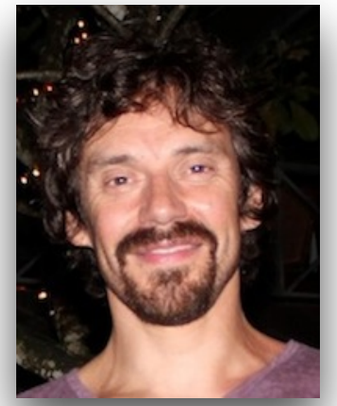
peptide dynamics



biomolecular folding

- surface reactions
- (with rigidification) conformational transitions of large proteins
- collaboration? 😊

Acknowledgements



Nadace
Zdeňka Bakaly

Rate constants from response functions

- simulating relaxation from cell *i* to *j* with neighbours *k*:

$$\partial_t F_{j|i}(s,t) = \partial_s F_{j|i}(s,t) + F_{k|i}(0,t)L_{kj|i}(s) + F_{i|j}(0,t)L_{jj|i}(s) \ ,$$
$$\partial_t F_{k|i}(s,t) = \partial_s F_{k|i}(s,t) + F_{k|i}(0,t)L_{kk|i}(s) + F_{i|j}(0,t)L_{jk|i}(s) \ ,$$
$$\partial_t F_{i|j}(s,t) = \partial_s F_{i|j}(s,t) + F_{k|j}(0,t)L_{ki|j}(s) + F_{j|i}(0,t)L_{ii|j}(s) \ ,$$
$$\partial_t F_{k|j}(s,t) = \partial_s F_{k|j}(s,t) + F_{k|j}(0,t)L_{kk|j}(s) + F_{j|i}(0,t)L_{ik|j}(s)$$

- with initial conditions:

$$F_{j|i}(s,0) = F_{j|i}(s) \ ,$$
$$F_{k|i}(s,0) = F_{j|i}(s),$$
$$F_{i|j}(s,0) = 0 \ ,$$
$$F_{i|j}(s,0) = 0 \ .$$

$$p_i(t) = \int_0^\infty F_{j|i}(s) + F_{k|i}(s)\mathrm{d}s$$