The rebinding effect and reduced models for ligand binding processes

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Mathematics for key technologies

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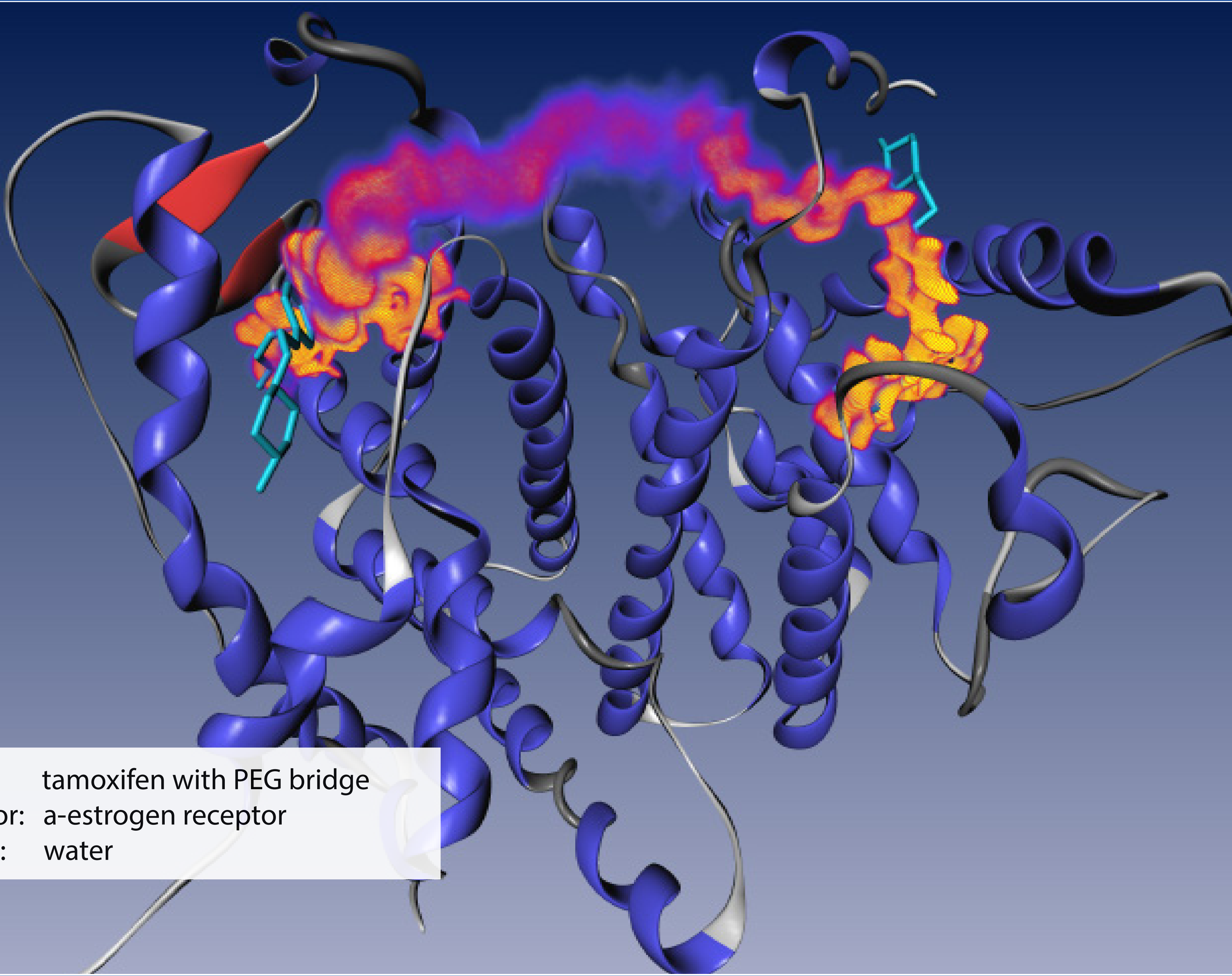
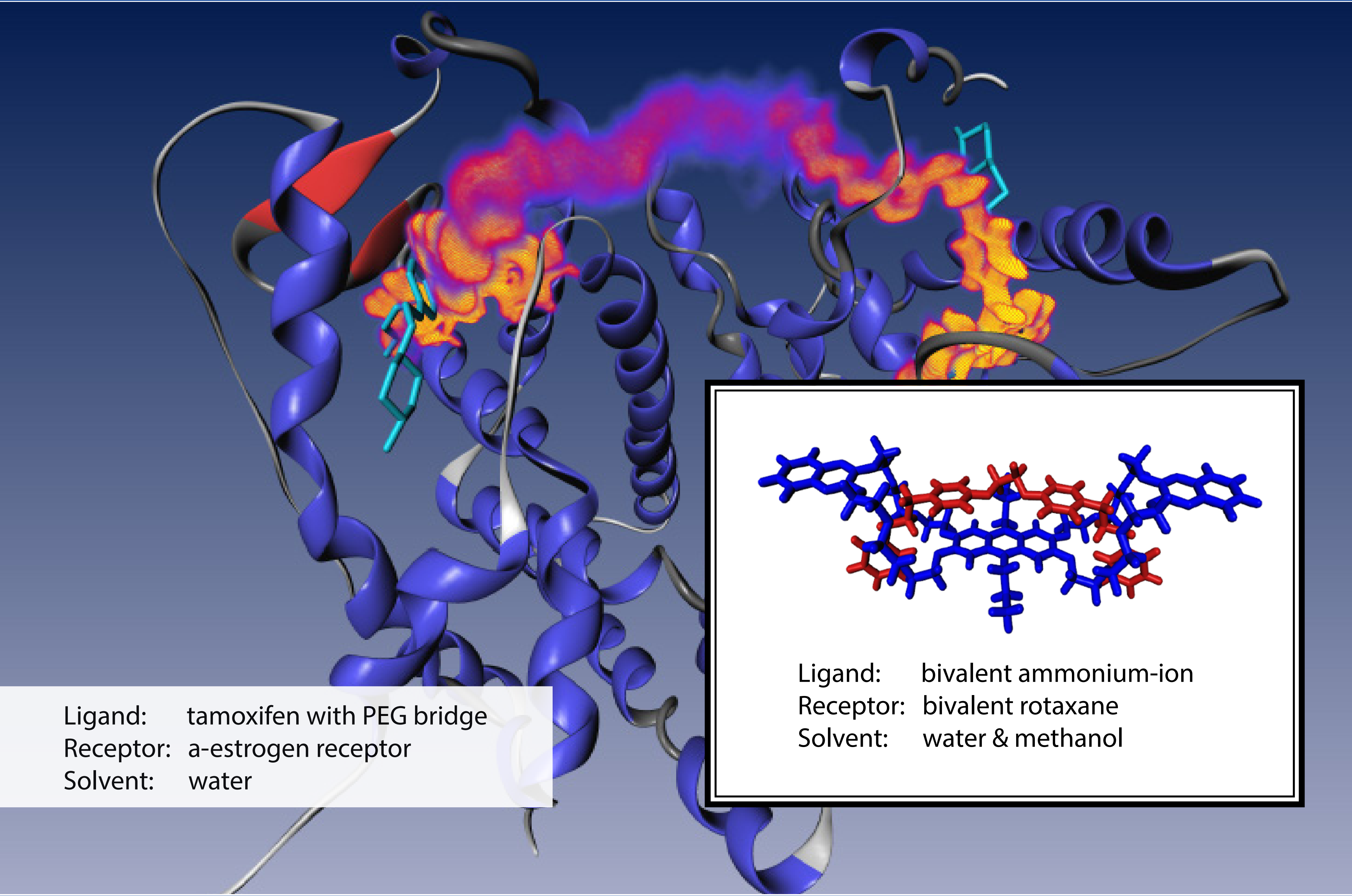
Bivalent docking examples



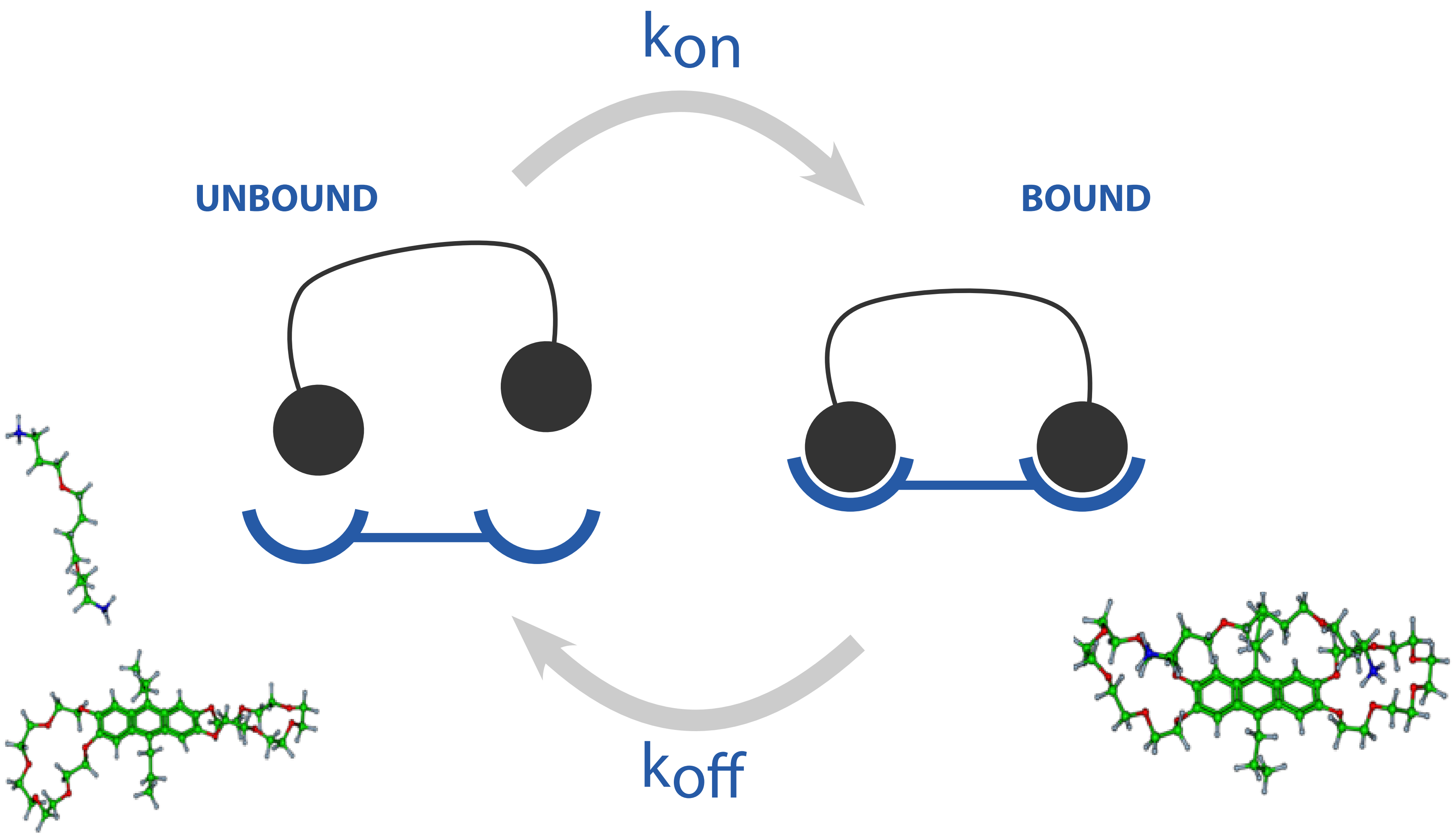
Ligand: tamoxifen with PEG bridge
Receptor: a-estrogen receptor
Solvent: water

Bivalent docking examples



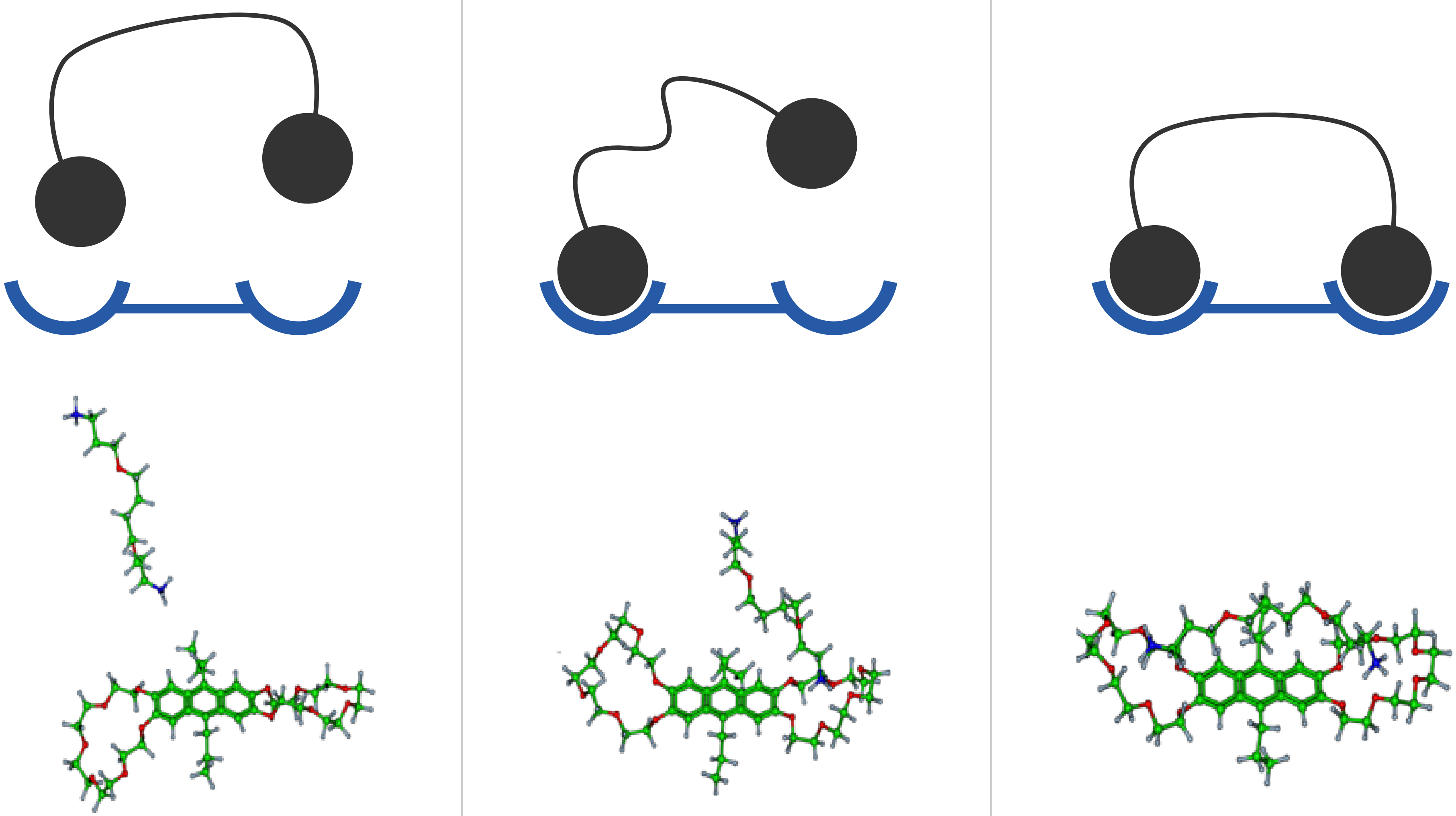
Ligand: tamoxifen with PEG bridge
Receptor: a-estrogen receptor
Solvent: water

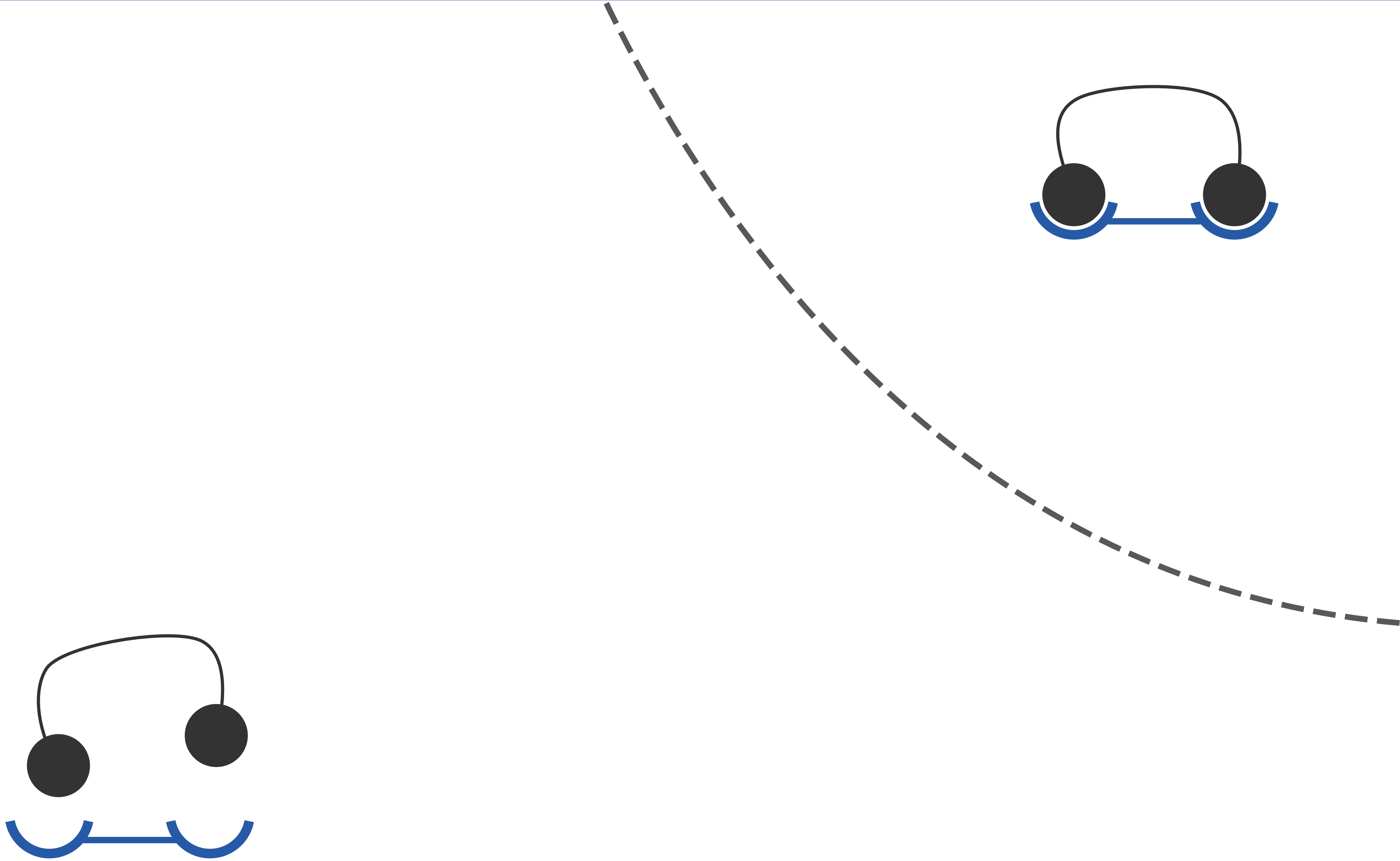
Ligand: bivalent ammonium-ion
Receptor: bivalent rotaxane
Solvent: water & methanol


kon
UNBOUND
BOUND
koff

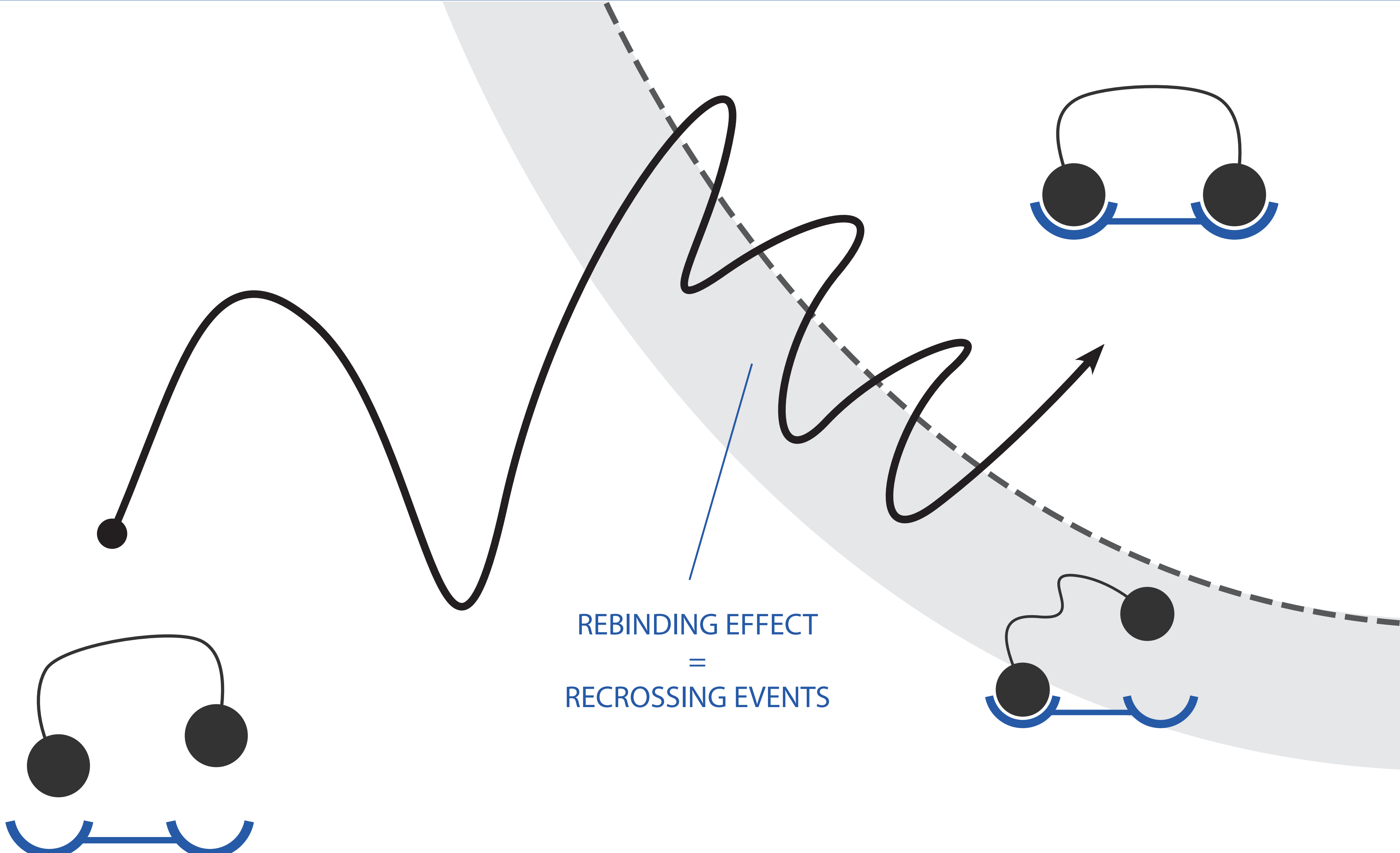
Intermediate states lead to problems

UNBOUND	SINGLY BOUND	DOUBLY BOUND





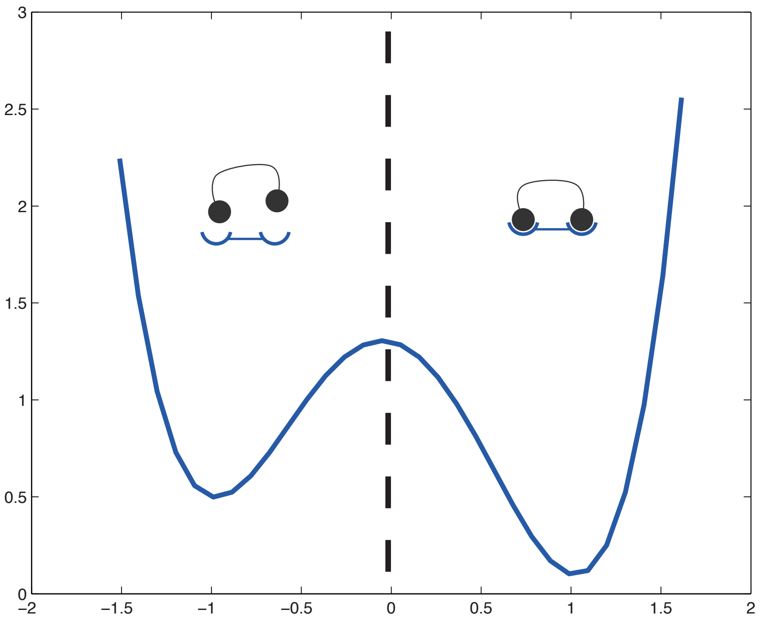
Rebinding effect as recrossing problem



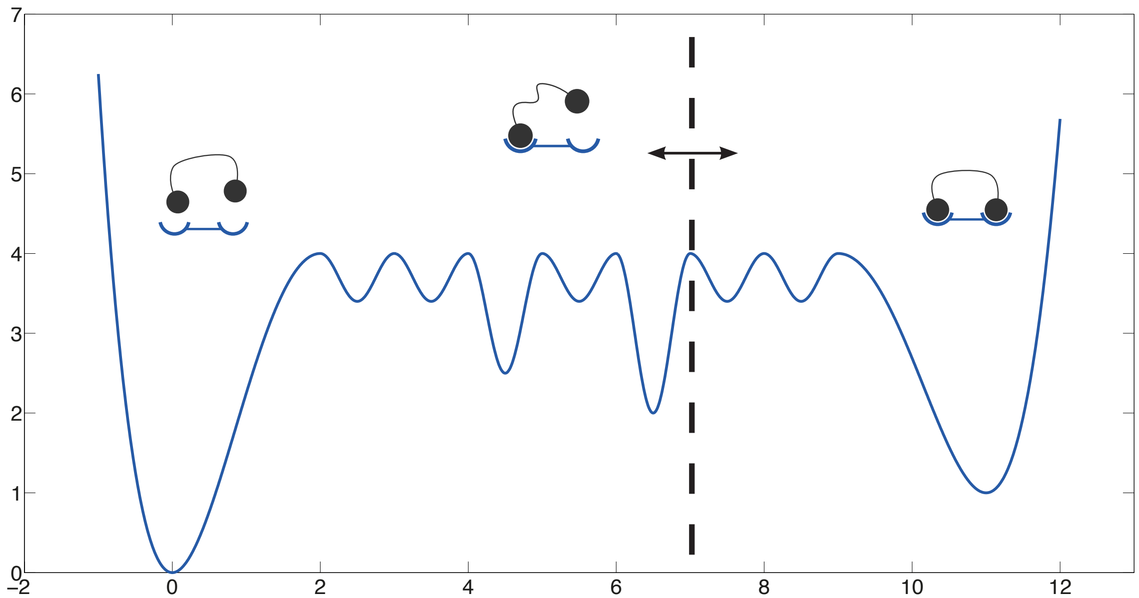
Weber, Fackeldey, 2013.

Potential energy landscapes

$$dX_t = -\nabla V(X_t)dt + \sigma dB_t$$



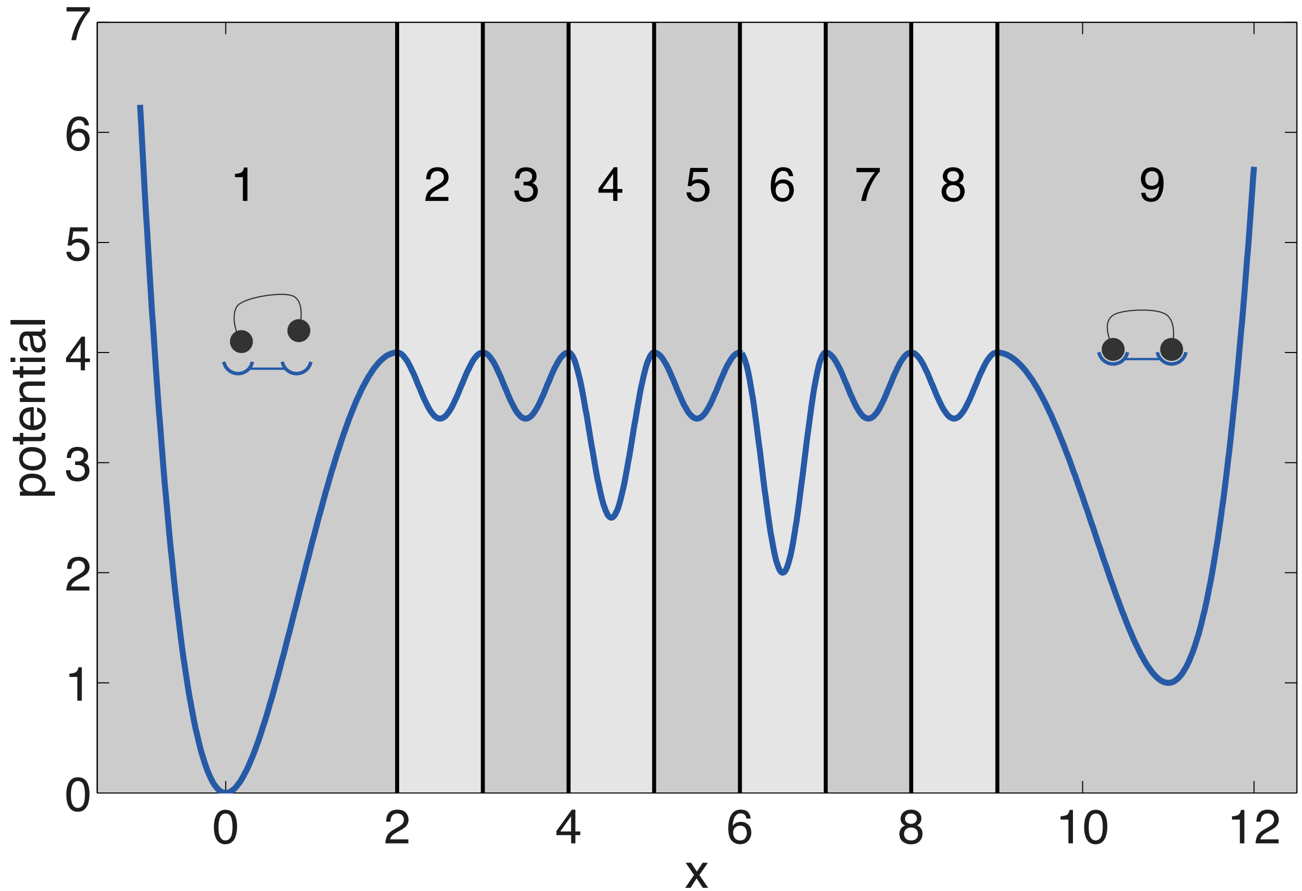
Less pronounced rebinding effect



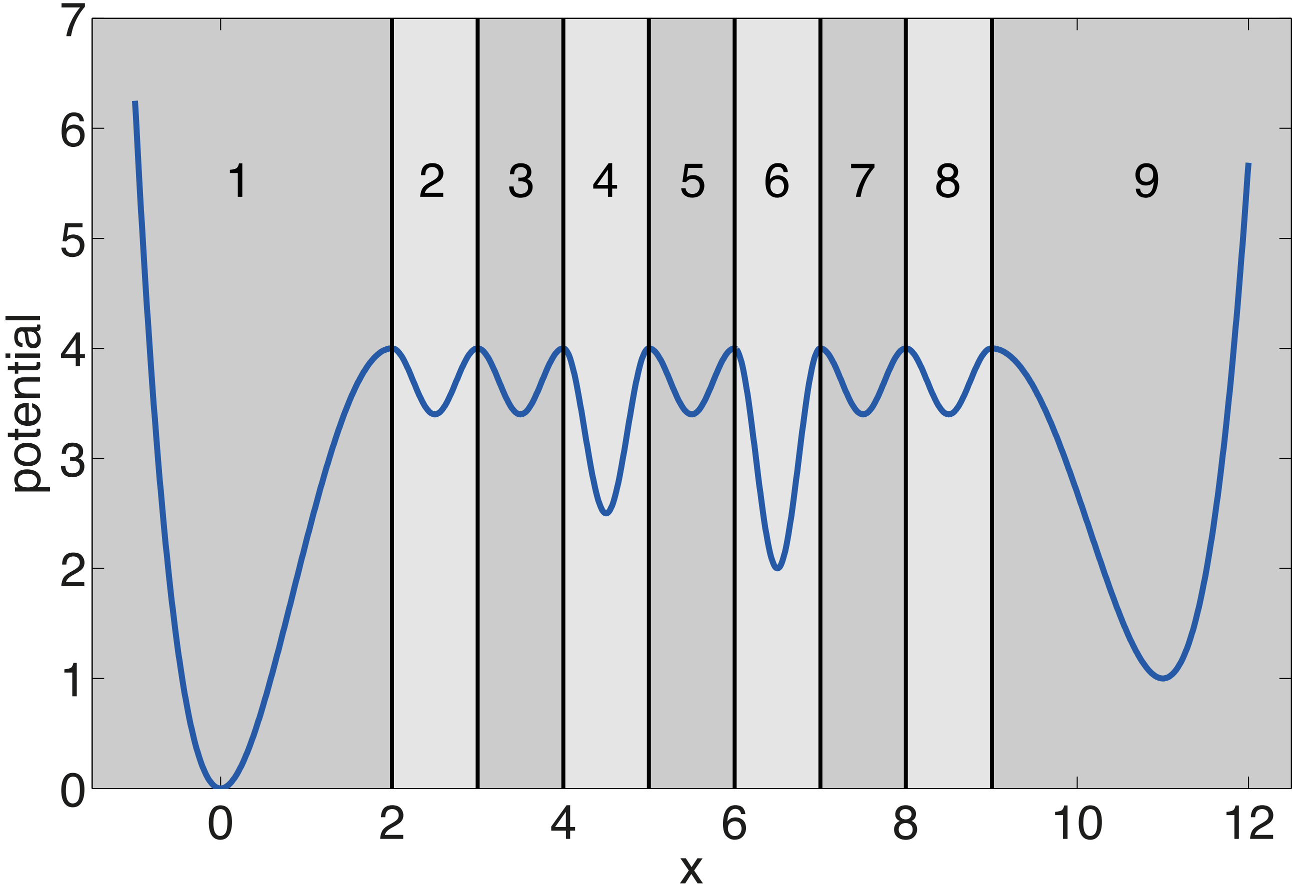
Strong rebinding effect for all possible boundaries

Introduce intermediate macro states

Does this solve the problem?



How well does the Markov chain $P_{ij} = \mathbb{P}[X_{t+\tau} \in A_j | X_t \in A_i]$ approximate the dynamics?



Transfer operator:

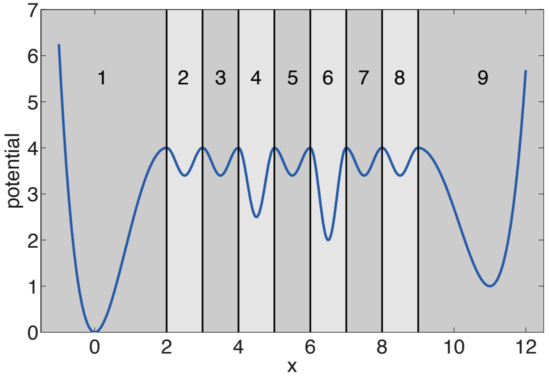
$$T := T_\tau = e^{L\tau}, \qquad (Lv)(x) = \frac{1}{2}\sigma^2 \Delta v(x) - \nabla V(x) \cdot \nabla v(x).$$

Implied timescales

$$\eta_i = -\frac{\tau}{\log \lambda_i}$$

λ_i - largest eigenvalues of transfer operator and its approximation.

	η_1	η_2	η_3	η_4
original	17.5267	3.1701	0.9804	0.4524
full partition	16.5478	2.9073	0.8941	0.4006



$D = span\{\mathbb{1}_{A_1}, ..., \mathbb{1}_{A_n}\}$

Q - orthogonal projection onto D

P can be considered as projection of the original transfer operator of the system

$$QT : D \to D,$$

T : self-adjoint transfer operator (reversible dynamics)

λ : some eigenvalue

u : a corresponding normalized eigenvector

λ_1 : largest non-trivial eigenvalue of $T (\lambda_1 < 1)$

Q : orthogonal projection onto some subspace D

$\delta = \|Qu - u\|$ projection error of eigenvector

Then

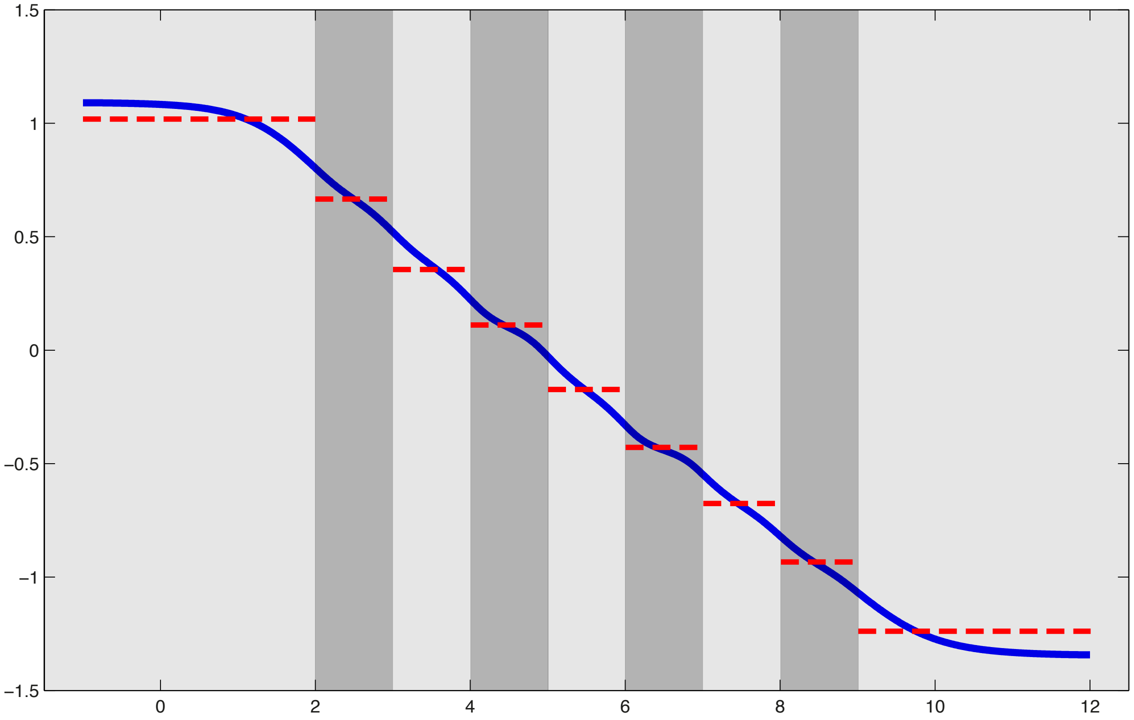
QT has an eigenvalue $\hat{\lambda}$ with

$$|\lambda - \hat{\lambda}| \leq 2\lambda_1\delta.$$

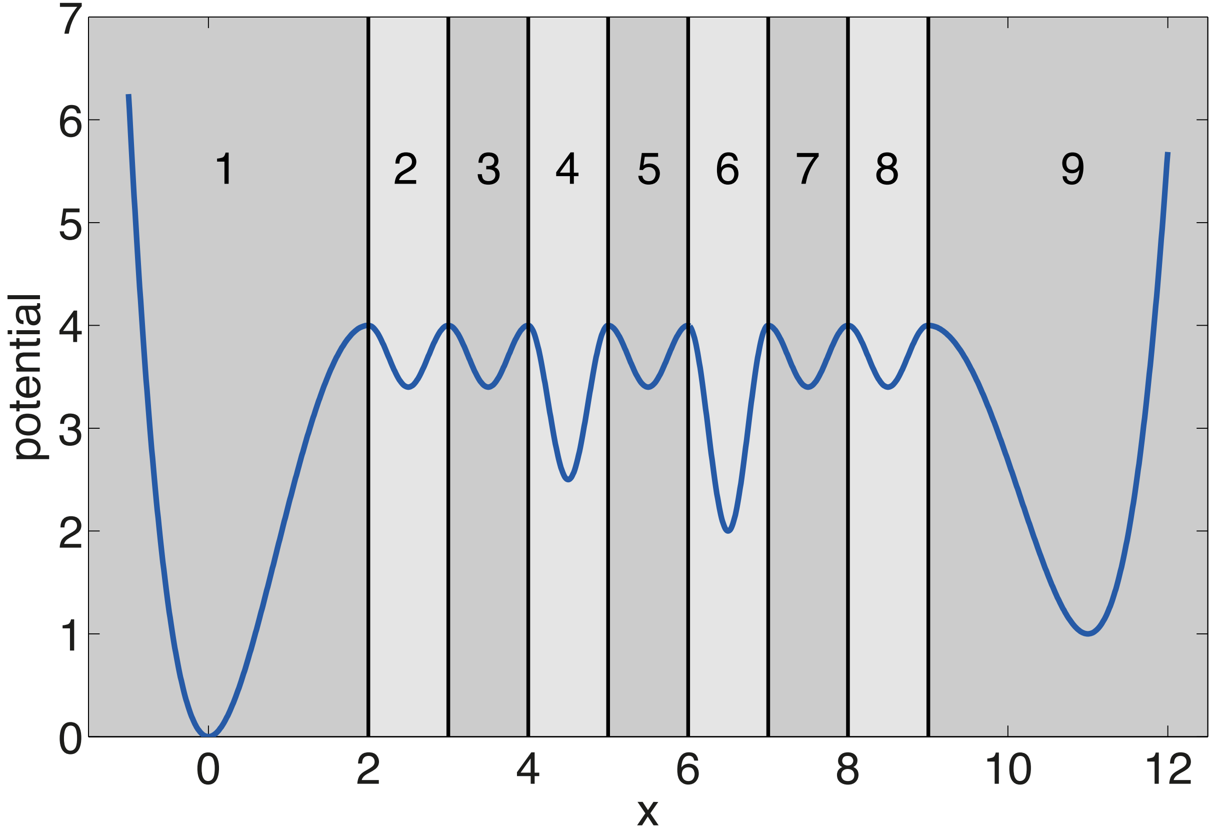
Sarich, Schütte. Comm. Math. Sci., 2012.

Projection error for the example

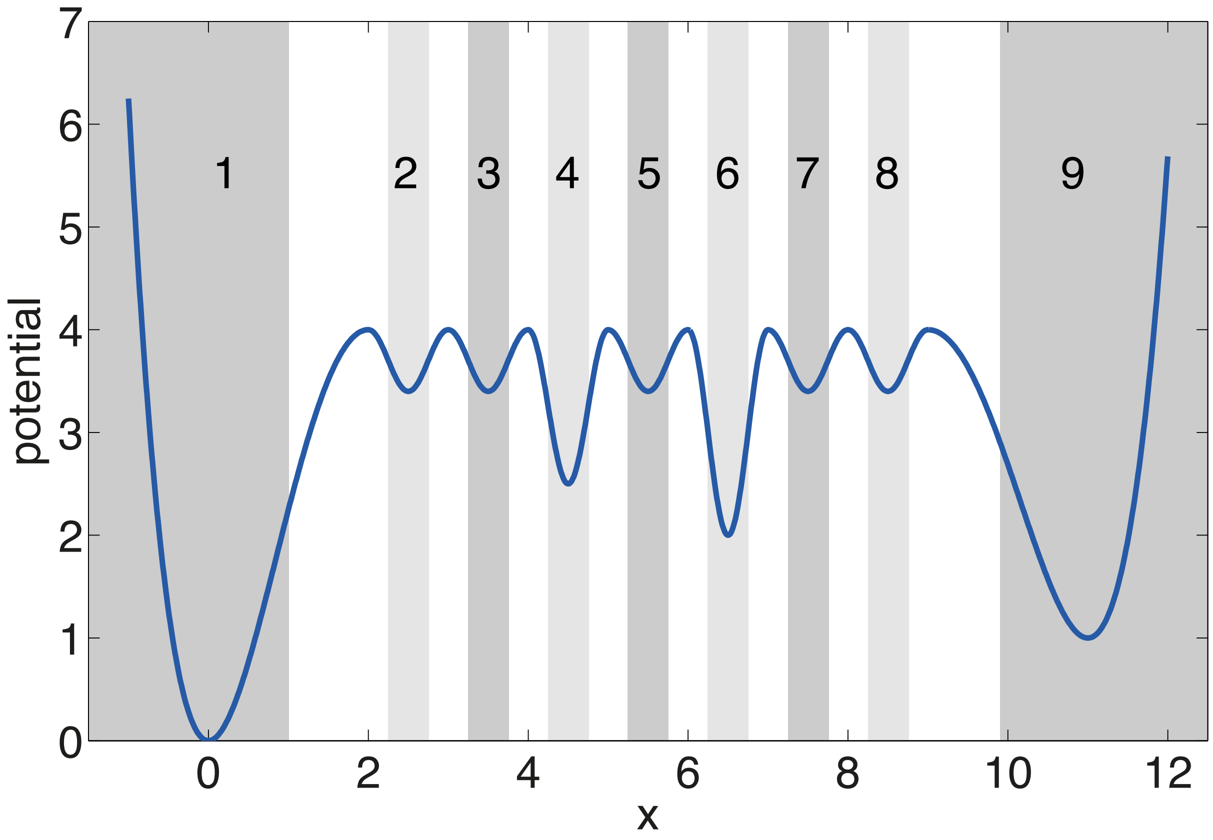
	η_1	η_2	η_3	η_4
original	17.5267	3.1701	0.9804	0.4524
full partition	16.5478	2.9073	0.8941	0.4006

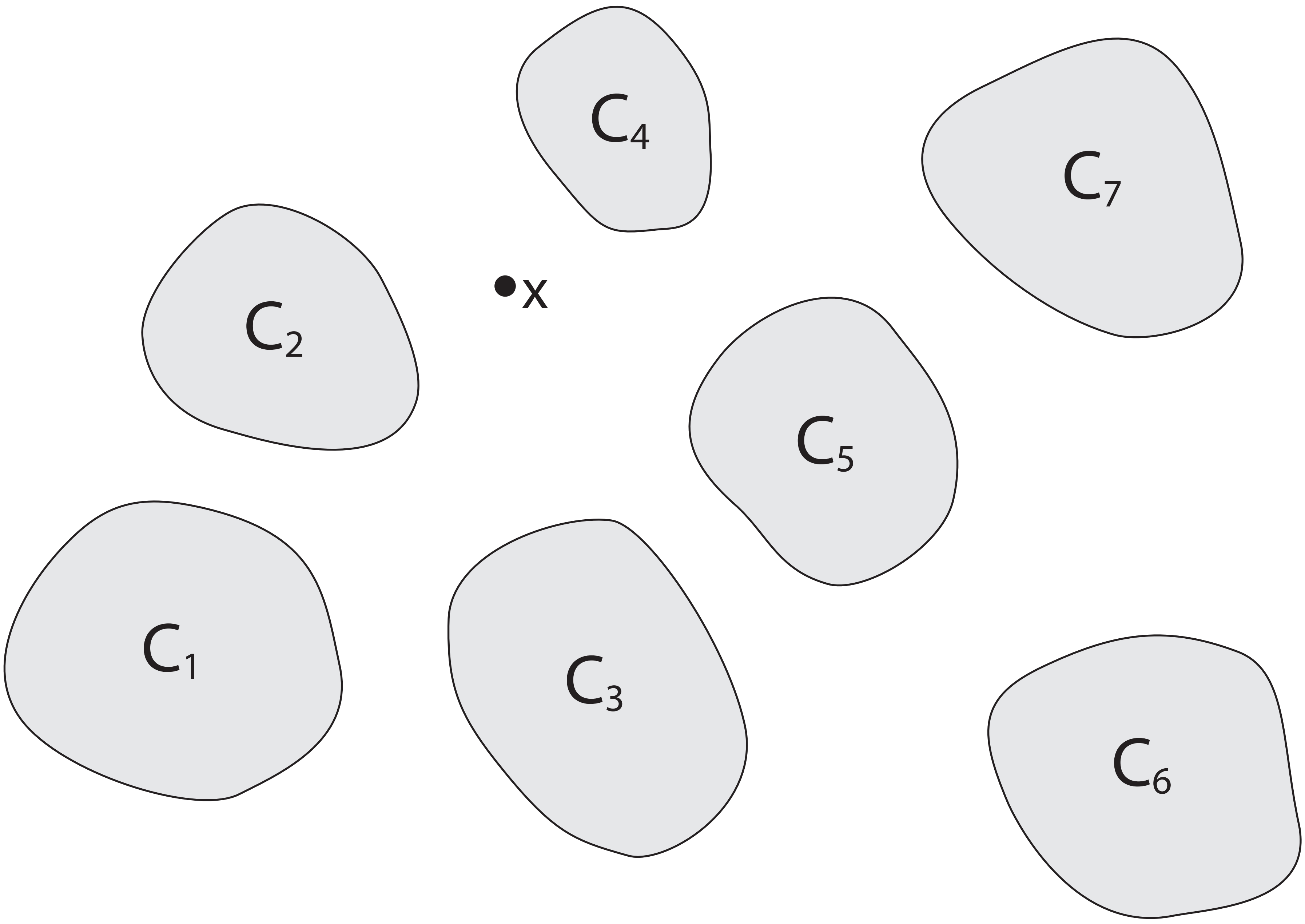


Use instead of a full partition....

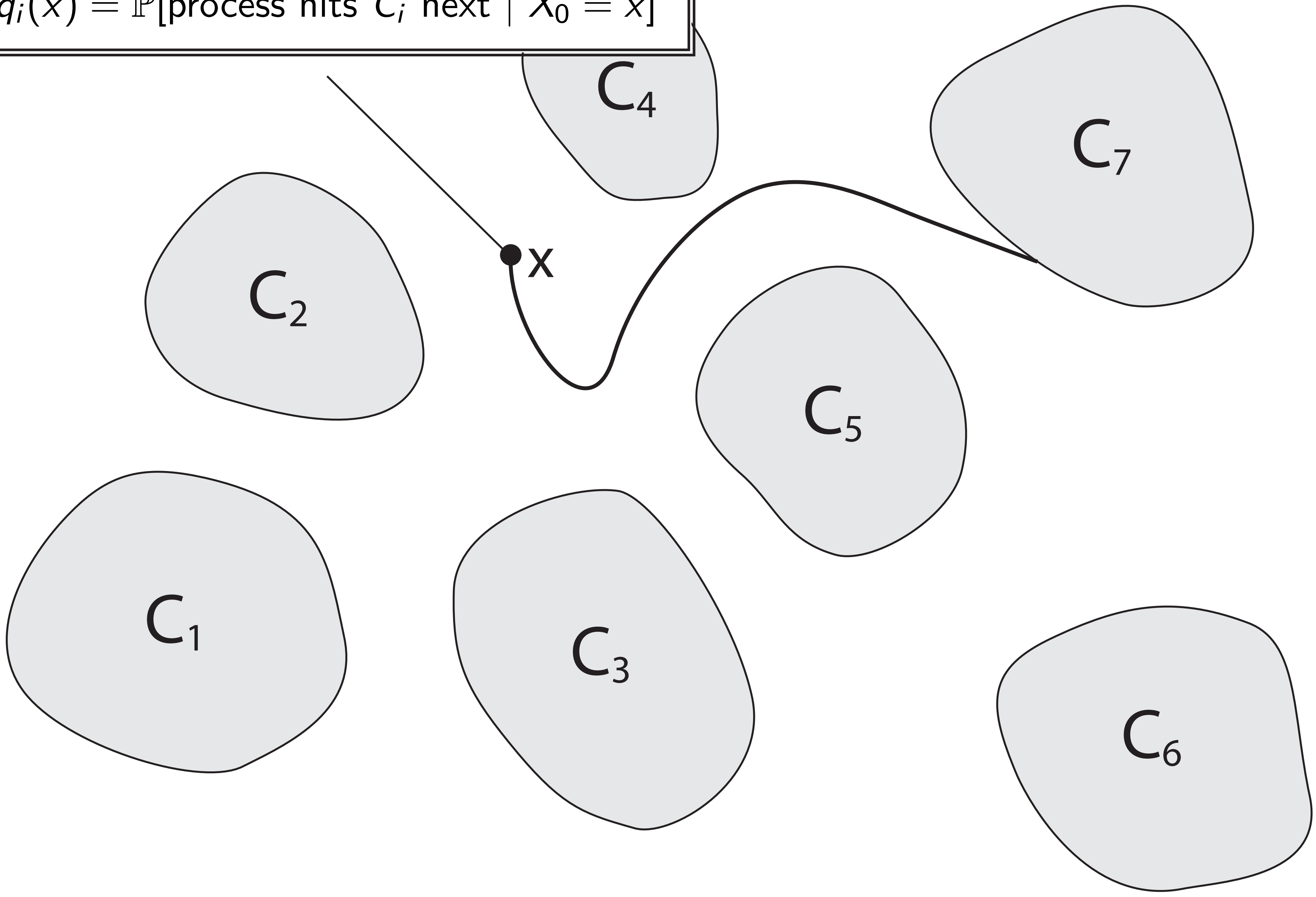


...so called **core sets** by cutting out a transition region.




C4
C7
C2
x
C5
C1
C3
C6

$$q_i(x) = \mathbb{P}[\text{process hits } C_i \text{ next} \mid X_0 = x]$$

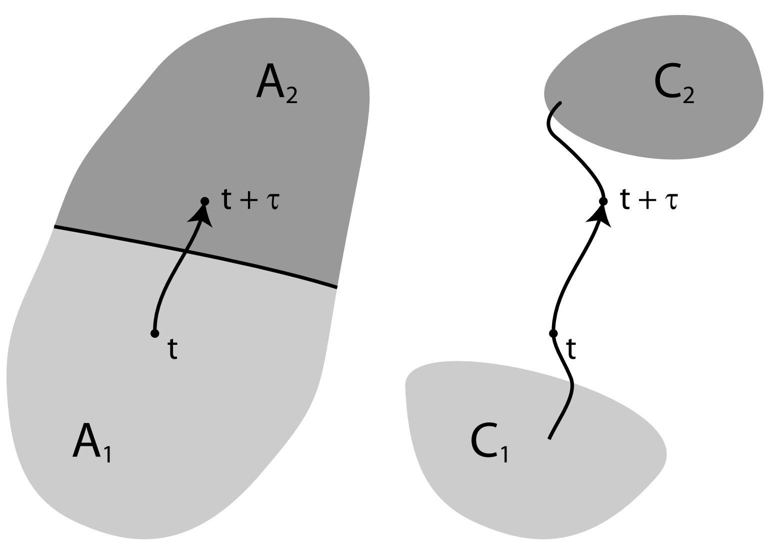


Projection of transfer operator QT onto $D = span\{q_1, ...q_n\}$ leads to matrix $P = \hat{T}M^{-1}$ with

$$M_{ij} = \mathbb{P}[\text{after time } t \text{ process will hit next } C_j \mid \text{at time } t \text{ process came last from } C_i]$$

and

$$\hat{T}_{ij} = \mathbb{P}[\text{after time } t+\tau \text{ process will hit next } C_j \mid \text{at time } t \text{ process came last from } C_i].$$



...and it can be proven to be more accurate!

$$\|u - Q_{cores}u\| \leq \|u - Q_{full}u\| - \|(u - Q_{full}u)\big|_C\| + \frac{\rho}{\eta},$$

- $\rho \leq \max_{x \in C} \mathbb{E}_x[\tau(C^c)|]$
- η implied timescale belonging to u
- C region that is cut out

Sarich, Schütte. Comm. Math. Sci., 2012.

The benefit of core sets

removing the error that comes from approximation by a stepfunction in the region that is cut out

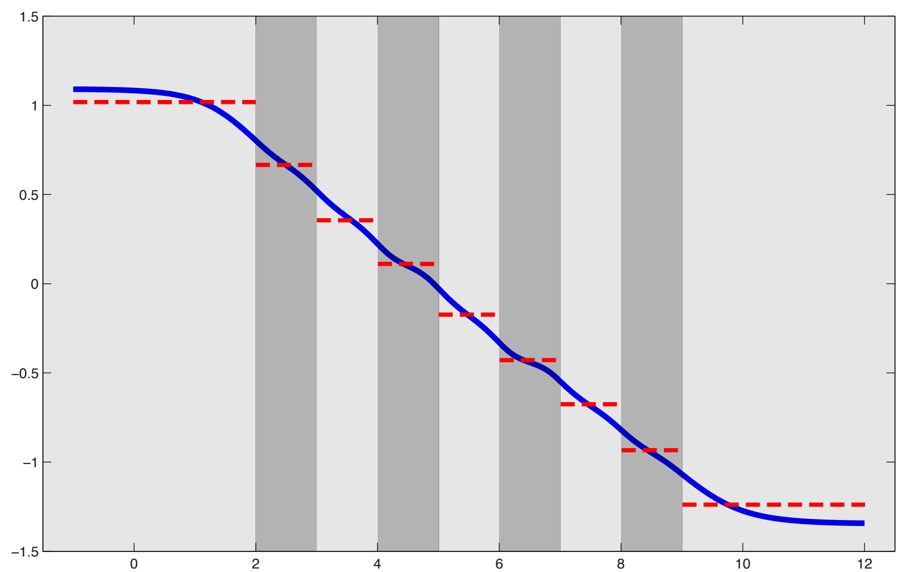
$$\|u - Q_{cores}u\| \leq \|u - Q_{full}u\| - \|(u - Q_{full}u)\big|_C\| + \frac{\rho}{\eta},$$

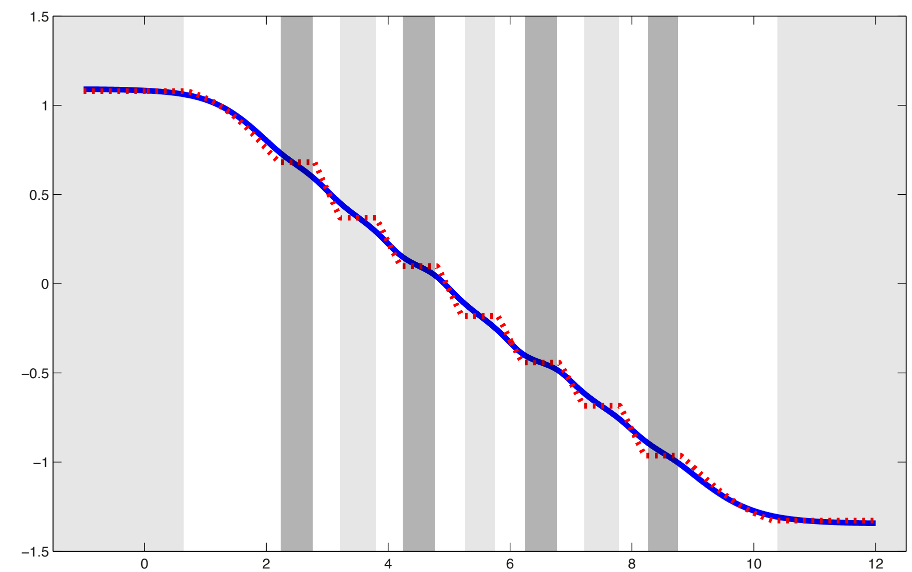
- $\rho \leq \max_{x \in C} \mathbb{E}_x[\tau(C^c)|]$
- η implied timescale belonging to u
- C region that is cut out

ratio is small if the region that is cut out is left on a much faster timescale than the timescale of interest

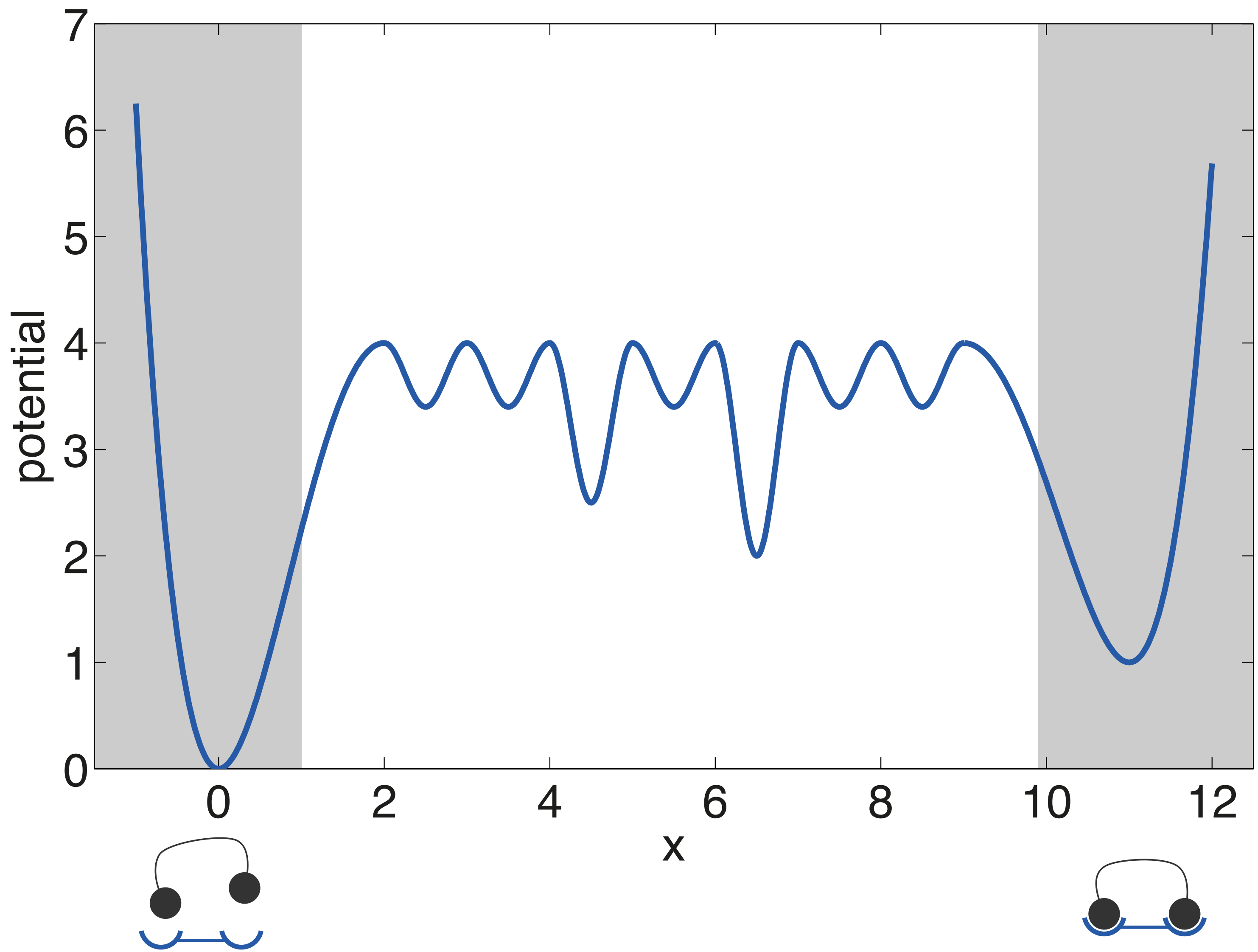
Example

	η_1	η_2	η_3	η_4
original	17.5267	3.1701	0.9804	0.4524
core sets	17.3298	3.1332	0.9690	0.4430
full partition	16.5478	2.9073	0.8941	0.4006

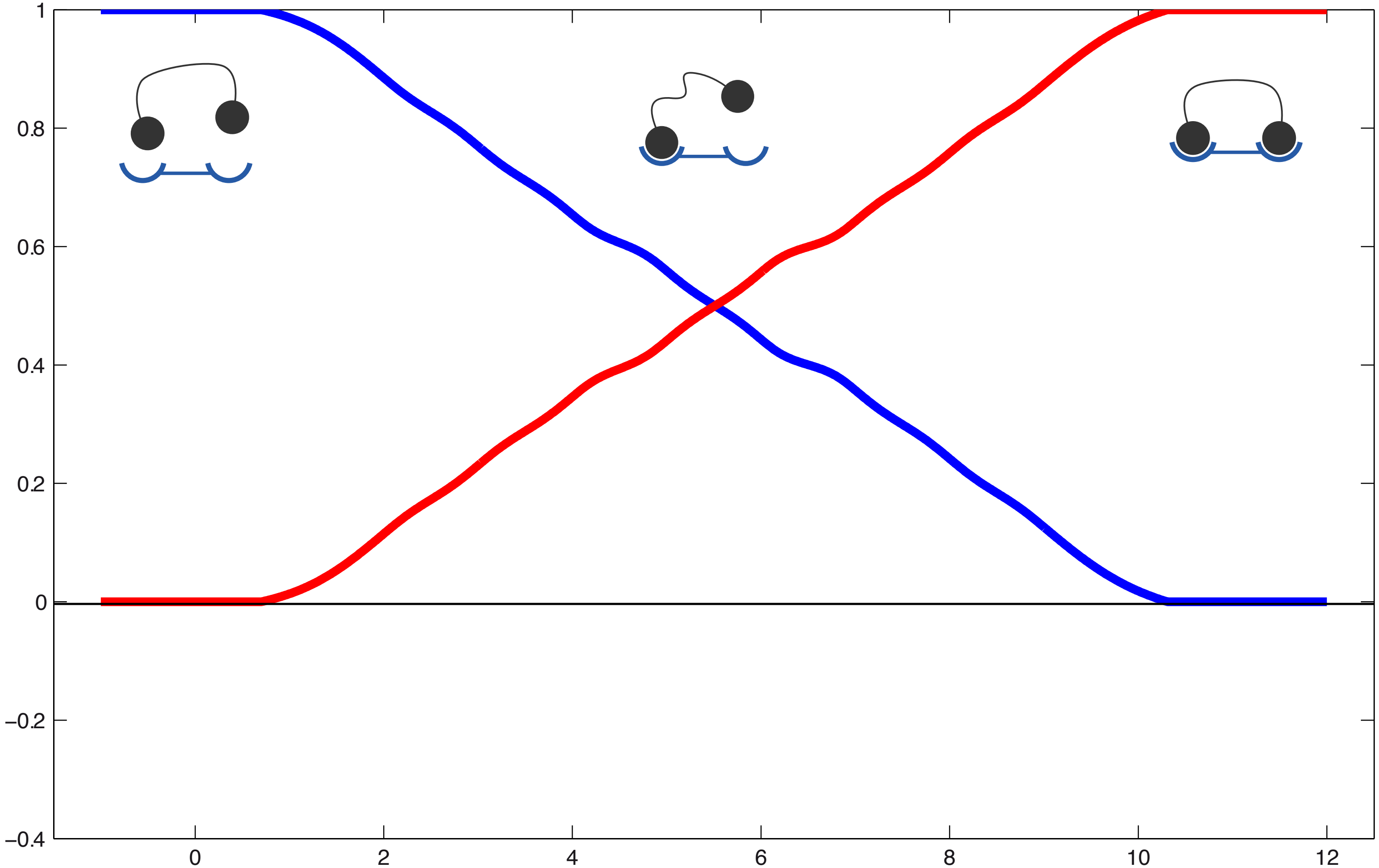




What if we use no intermediate states?

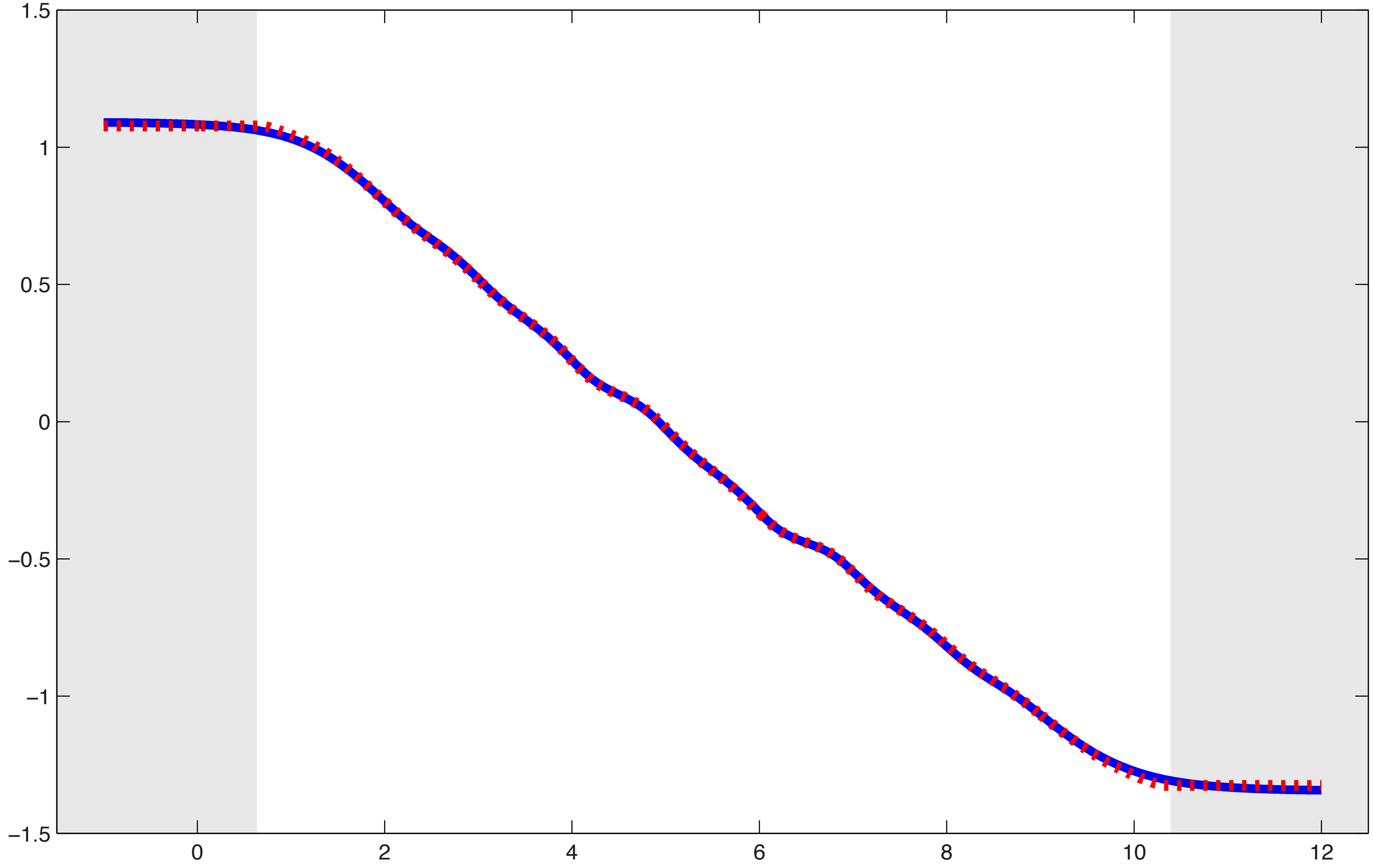


A „soft“ partitioning into bound and unbound state



The two committor functions define affiliations to the bound and unbound state.

Very accurate approximation = no rebinding effect



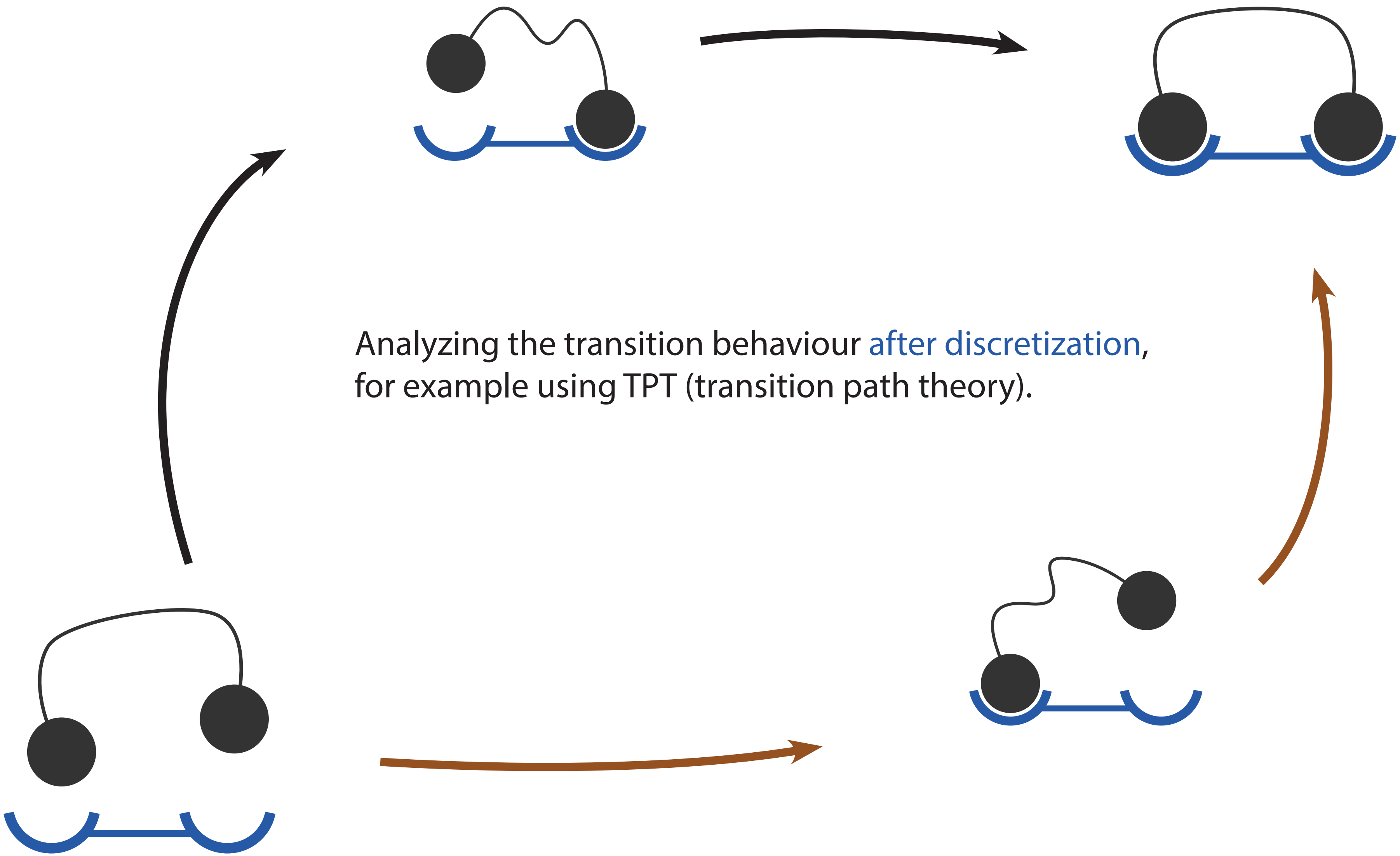
Approximation of the eigenvector by the committors with respect to two macro states.

Very accurate approximation = no rebinding effect

Example

	T_1	T_2	T_3	T_4
original	17.5267	3.1701	0.9804	0.4524
2 core sets	17.5043	-	-	-
9 core sets	17.3298	3.1332	0.9690	0.4430
full partition	16.5478	2.9073	0.8941	0.4006

Building a finer model

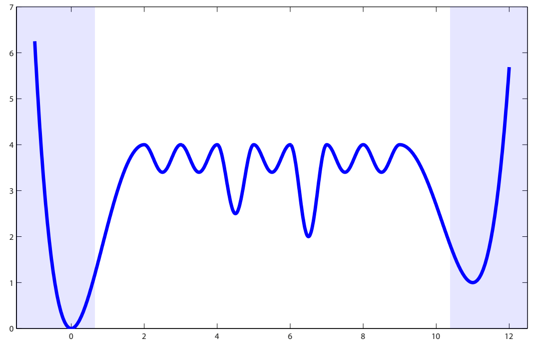


Analyzing the transition behaviour after discretization, for example using TPT (transition path theory).

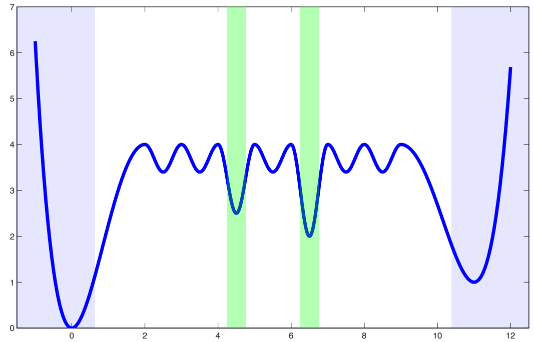
Using a multigrid

Let $\mathcal{C}_j = \{C_1^j, \ldots, C_{n_j}^j\}$ be an increasing sequence of core set discretizations, i.e.

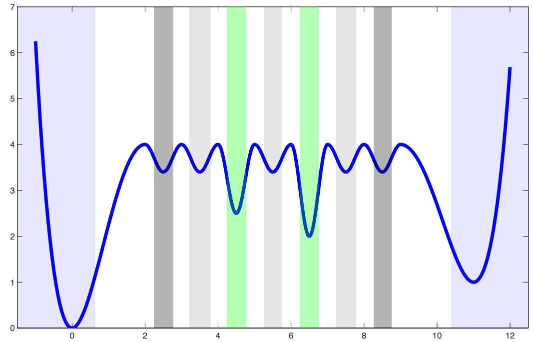
$$\mathcal{C}_i \subset \mathcal{C}_j \text{ for all } j \geq i.$$



Level 1



Level 2



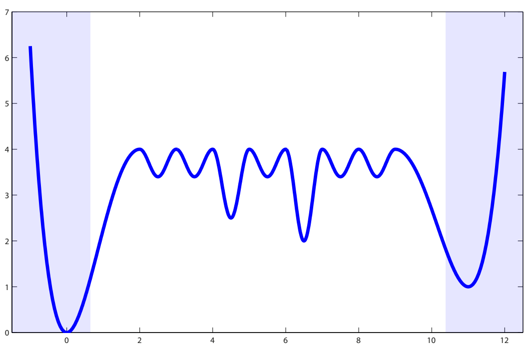
Level 3

A multilevel/multigrid approach

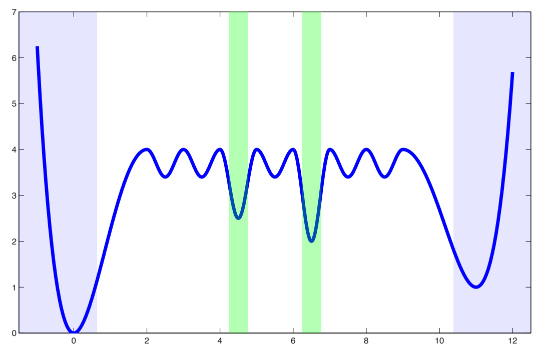
Using a multigrid

Let $\mathcal{C}_j = \{C_1^j, \dots, C_{n_j}^j\}$ be an increasing sequence of core set discretizations, i.e.

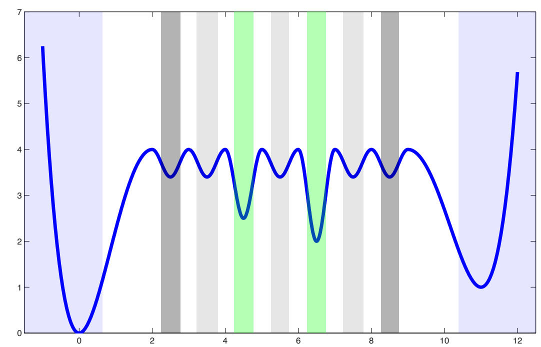
$$\mathcal{C}_i \subset \mathcal{C}_j \text{ for all } j \geq i.$$



Level 1



Level 2



Level 3

Iterative Space Construction

Level 1: $D_1 = span\{q_1, \dots, q_n\}$, q_i usual committors.

Level $k+1$: $D_{k+1} = \hat{D}_{k+1} \cap D_k^{\perp}$, where $\hat{D}_{k+1}$ is the usual committor space for the cores on level $k+1$.

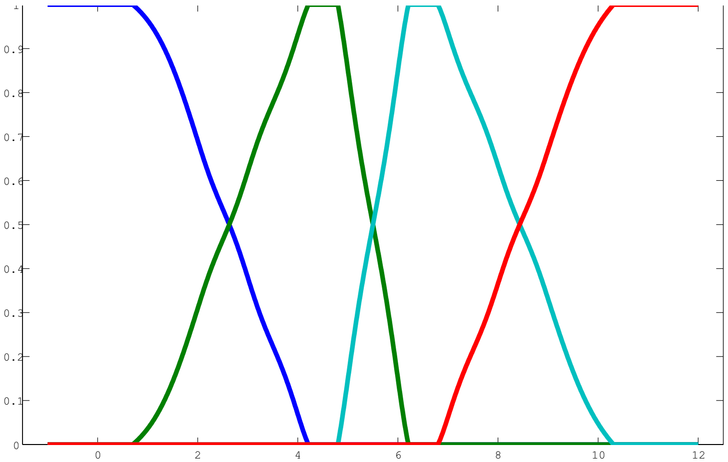
Total space for projection with m levels: $D = D_1 + \dots + D_m$

Computing the model

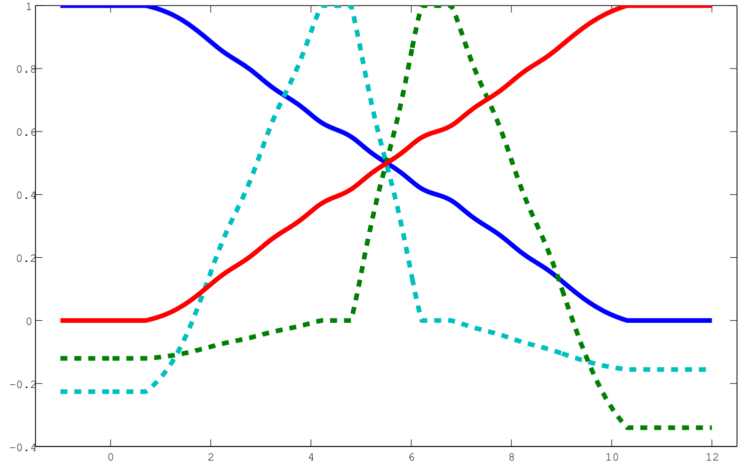
A matrix representation $P = \hat{T}M^{-1}$ can again be computed from stochastic quantities.

Assume C_i was first introduced on level k and C_j was first introduced on level l, then

$$M_{ij} = \mathbb{P}[\text{hit } C_j \text{ next on level } l \mid \text{came from } C_i \text{ on level } k].$$



Usual committors for 4 sets.



Mutilevel committors for 4 sets and 2 levels.

Example

	T_1	T_2	T_3	T_4
original	17.5267	3.1701	0.9804	0.4524
9 cores multigrid	17.5043	3.1579	0.9703	0.4441
9 core sets	17.3298	3.1332	0.9690	0.4430
full partition	16.5478	2.9073	0.8941	0.4006
2 core sets	17.5043	-	-	-

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M. Weber, K. Fackeldey. Computing the Minimal Rebinding Effect Included in a Given Kinetics. Submitted to MMS, 2013.

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M. Sarich, F. Noe, and Ch. Schütte. On the approximation quality of markov state models. Multiscale Modeling and Simulation, 8(4): 1154–1177, 2010.