Variational Coarse-graining and Mean First Passage Times in Markov State Models

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Warwick Centre for Predictive Modelling, 11 May 2020

Outline

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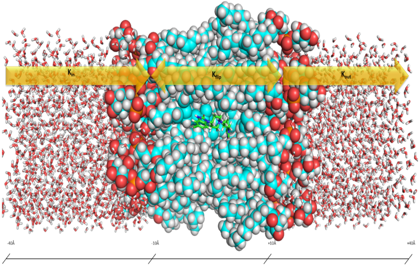

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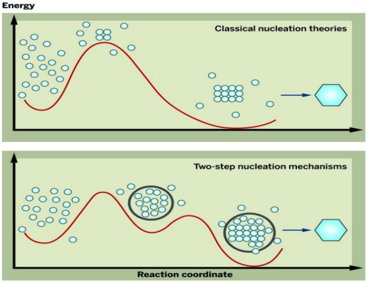
J. Kemsley, *Chem. Eng. News*, **93**(2):28-29 (2015)



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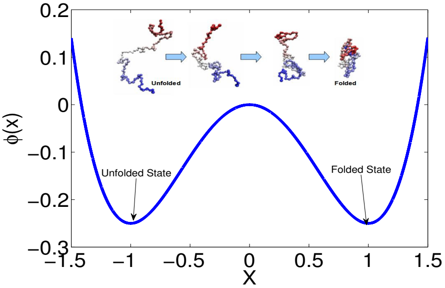

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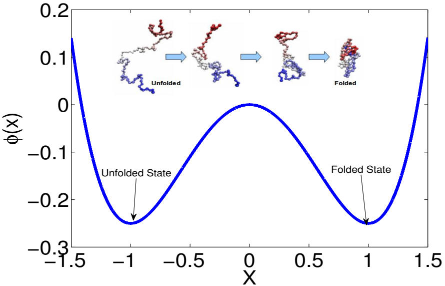

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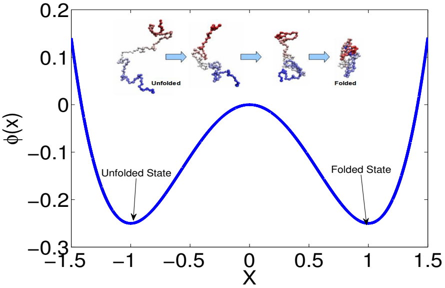

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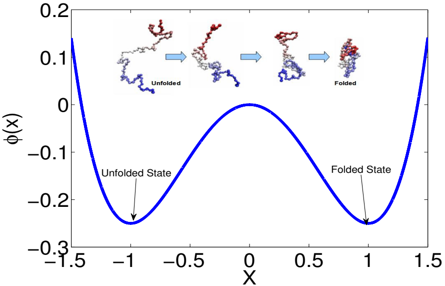

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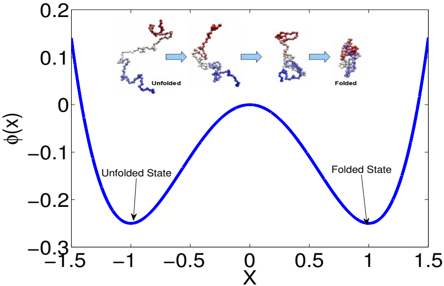

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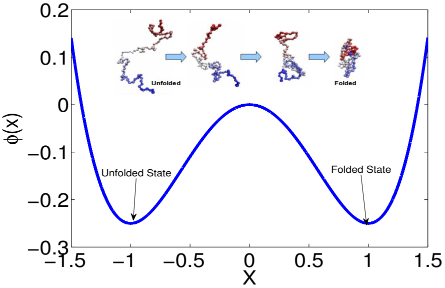

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  Markov State Models

  [Kube & Weber (2007), Noe, Schutte & Smith (2007), Chodera *et al.* (2007), Bicout & Szabo (2000) Buchete & Hummer (2008), Voelz, Bowmanm, Beauchamp, Pande (2010)]

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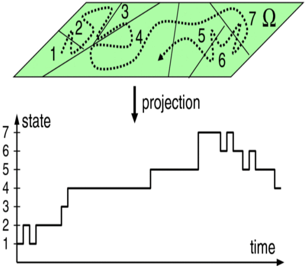

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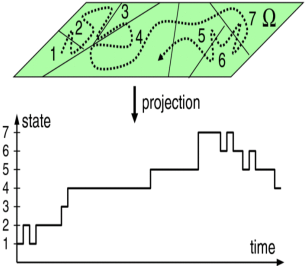

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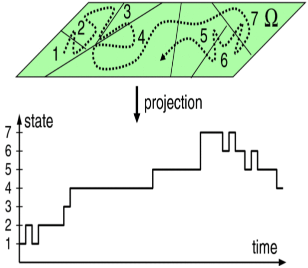

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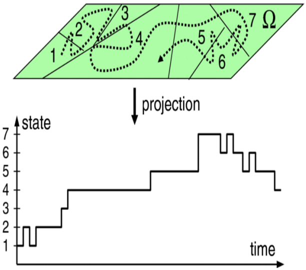

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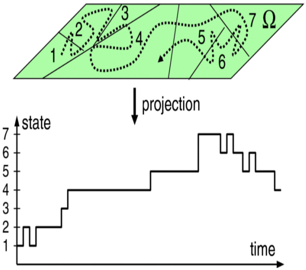

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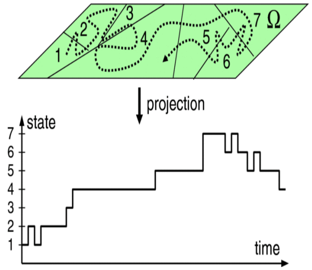

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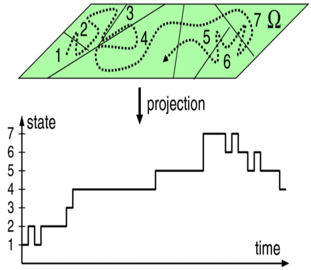

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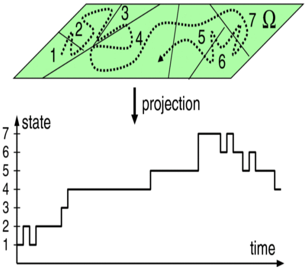

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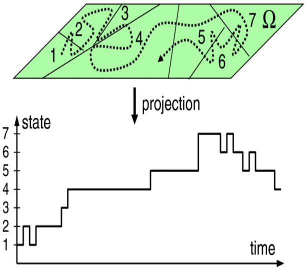

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- need **kinetically relevant RC**

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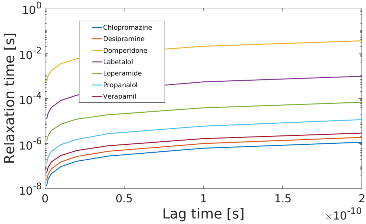

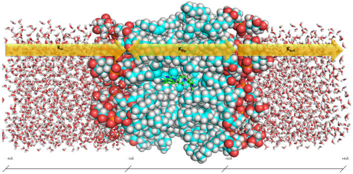

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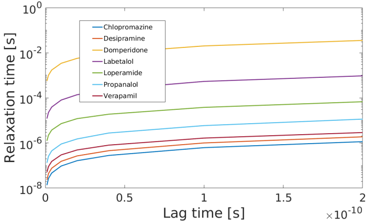

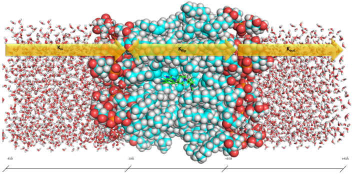

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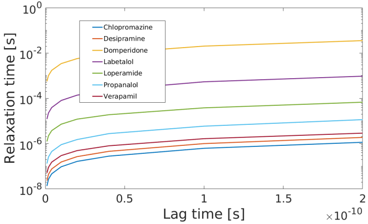

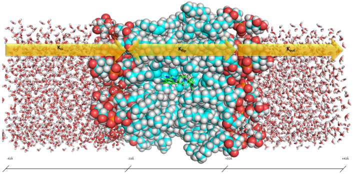

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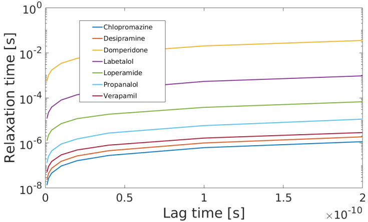

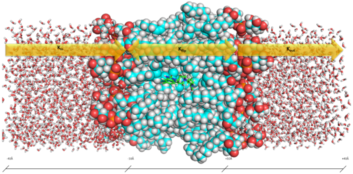

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- if timescale never level-off: likely poor discretization or poor choice of RC

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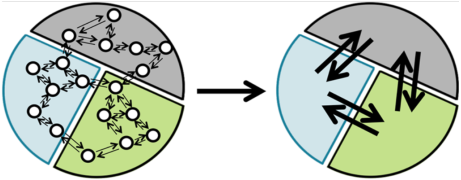

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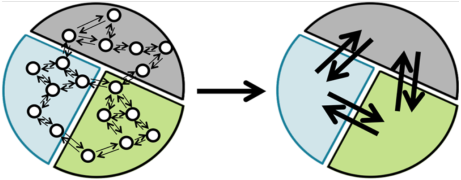

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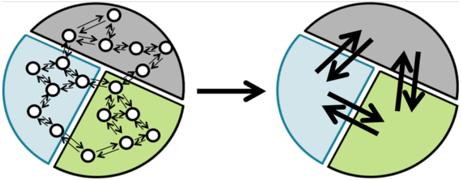

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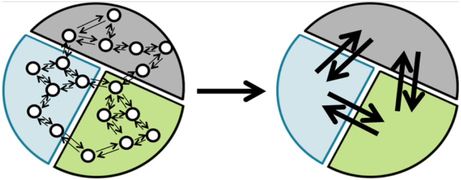

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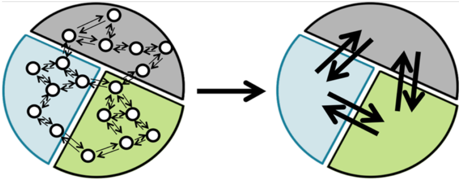

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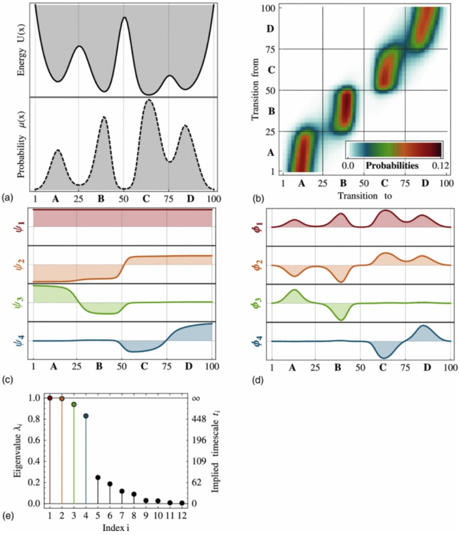

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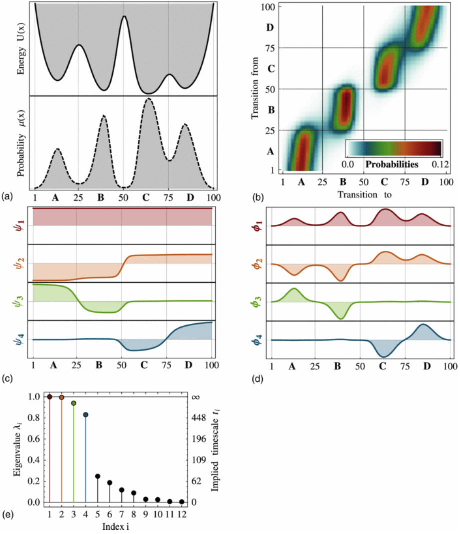

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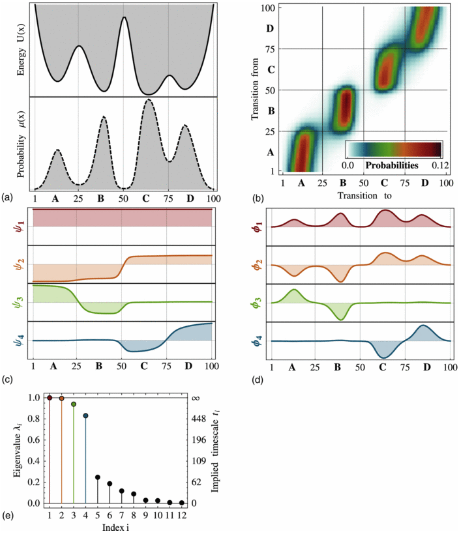

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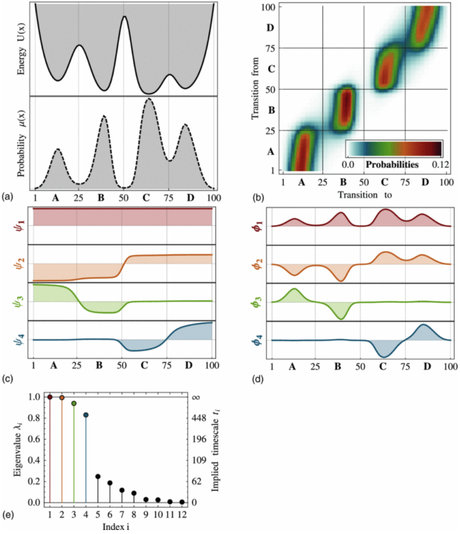

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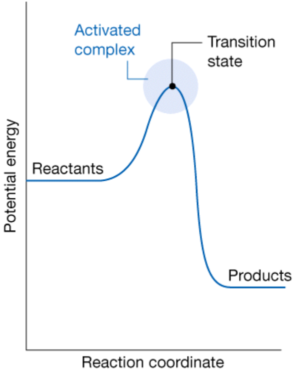

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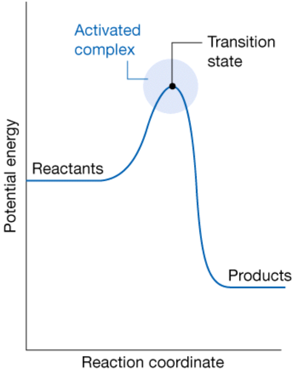

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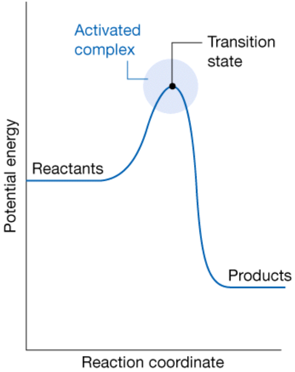

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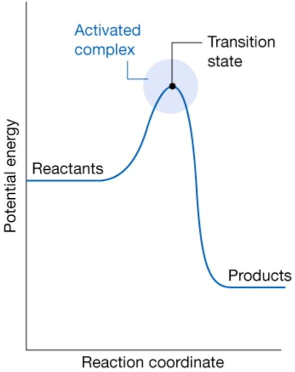

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- **Algorithms** to automatically and reliably detect TSs?

Outline

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exact correlations at **chosen** lag-time

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Hummer, Szabo, J Phys Chem B. 119(29):9029-37 (2015)

Outline

Projection method

Projection on to some sub-space via operator $\mathcal{P}$ ($\mathcal{Q}=\mathbf{I}_n-\mathcal{P}$):

$$\frac{d\mathbf{p}}{dt} = \mathbf{K}\boldsymbol{p} \qquad \mathbf{u}=\mathcal{P}\mathbf{p}, \qquad \mathbf{v}=\mathbf{p}-\mathbf{u} = \mathcal{Q}\mathbf{p}$$

$$\frac{d\mathbf{u}}{dt} = \mathcal{P}\mathbf{K}\mathbf{u} + \mathcal{P}\mathbf{K}\mathbf{v}$$

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with **memory kernel**

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or $\quad \hat{\mathbf{M}}(s)=s\mathcal{P}\mathbf{K}(s\mathbf{I}-\mathbf{K}+\mathcal{P}\mathbf{K})^{-1}$

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- Projection corresponding to clustering protocol $\mathbf{A}$?

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Retrieve **local equilibrium**

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Outline

Variational principle

- In fact, can build Markovian approximations that preserve other *properties of correlation functions*:

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[Kells, Mihálka, Annibale, Rosta, *J. Chem. Phys.* (2019)]

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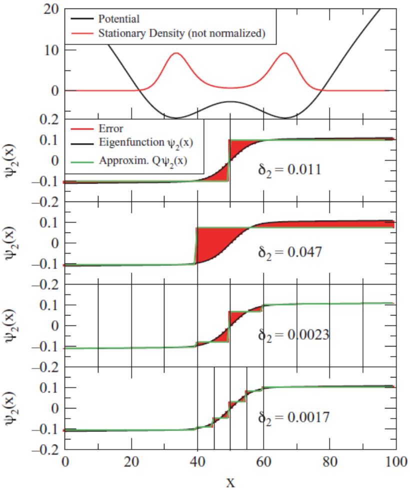

[Prinz et al, JCP (2011); Sarich, Noe, Schutte MMS (2010), Djurdjevac, Sarich, Schütte (2012), Noe & Nüske, MMS (2013)]

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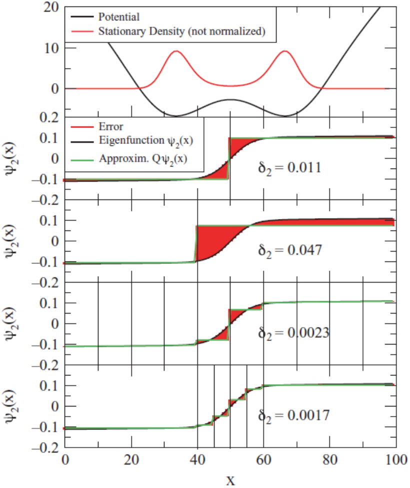

"In contrast to previous practice, it becomes clear that the best MSM is not obtained by the most metastable discretization, but the MSM can be much improved if non-metastable states are introduced near the transition states"

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Variational coarse-graining

- Idea: **choose $\mathbf{A}$** that **minimizes $|\mu_2|$**

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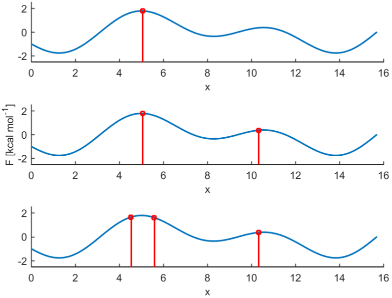

[Martini *et al.*, PRX 7, 031060 (2017)]

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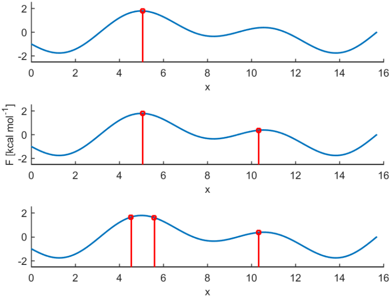

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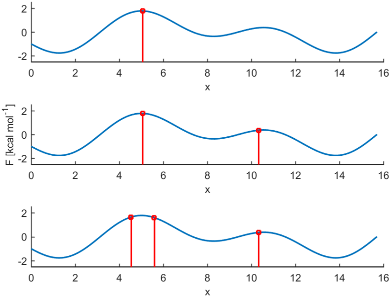

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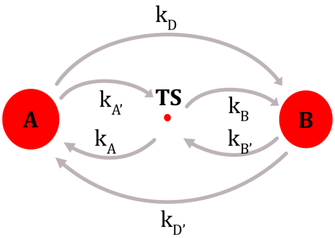

- Minimization of $|\mu_2|$ correctly identifies **key** metastable states & **transition states**, as one increases the number of clusters
- Aim: define **minimal variationally optimal** transition network consisting of key mestastable & transition states

Outline

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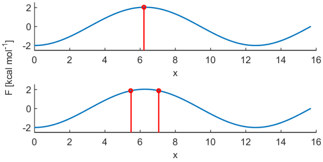

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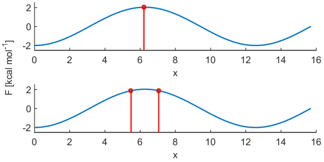

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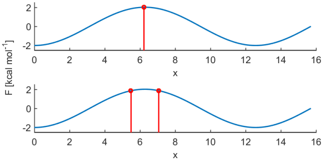

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  $\Rightarrow$ 2-state clustering:

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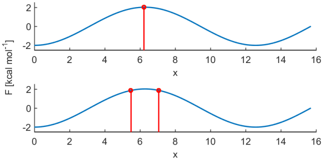

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- Can expand integral of correlation in terms of potential

$$\int_0^\infty \langle \delta\theta_i(0)\delta\theta_i(t)\rangle dt = \int_{-\infty}^\infty \frac{dx}{De^{-\beta v(x)}} \frac{[\int_x^\infty \delta\theta_i(y) e^{-\beta v(y)} dy]^2}{\int_{-\infty}^\infty e^{-\beta v(x)} dx}$$

[Szabo, Shulten and Shulten, JCP (1980), Bicout & Szabo, JCP (1997)]

- **mean first passage time** to reach barrier at a starting in 2

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[Kells, Mihálka, Annibale, Rosta, *J. Chem. Phys.* (2019)]

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- for 3-state clustering, symmetric potential (boundaries $\pm a$)

$$\boxed{P_1^{\text{eq}} t_{-aa} = t_{-a1}}$$

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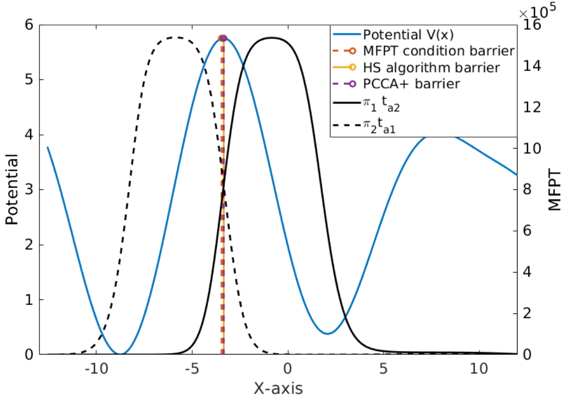


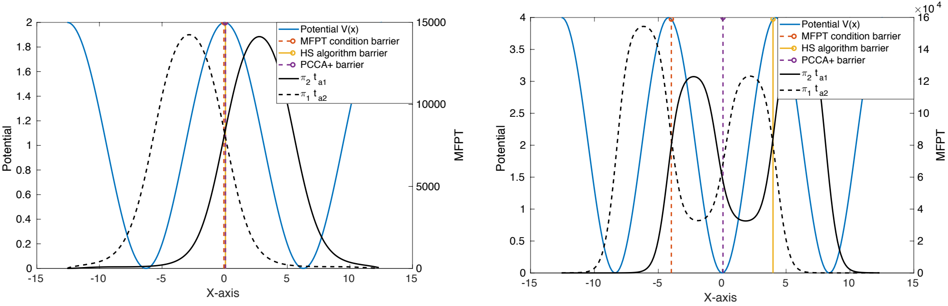
MFPT computed via Meyer method

$$t_{ji} = \tau Q_{ji}(\tau) + \sum_{k(\neq j)} Q_{ki}(\tau)(t_{jk} + \tau)$$

Test on symmetric potentials

Two-state clustering

[Kells, Mihálka, Annibale, Rosta, *J. Chem. Phys.* (2019)]



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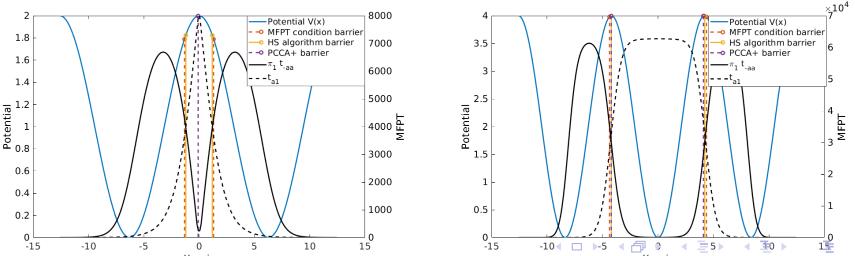
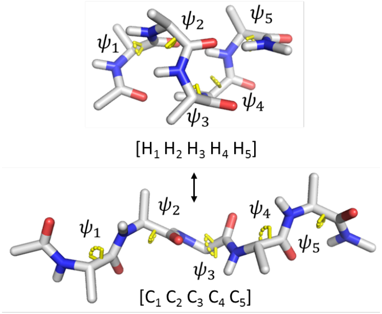
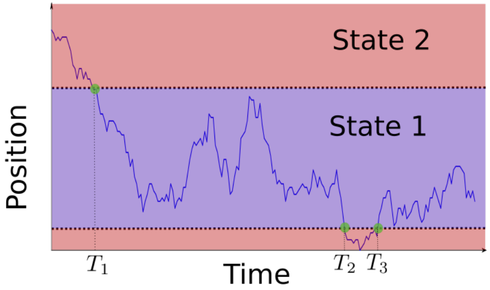


Simulations of Alanine Pentapeptide (Ala_5)





[Martini, *et al.*, PRX (2017)]

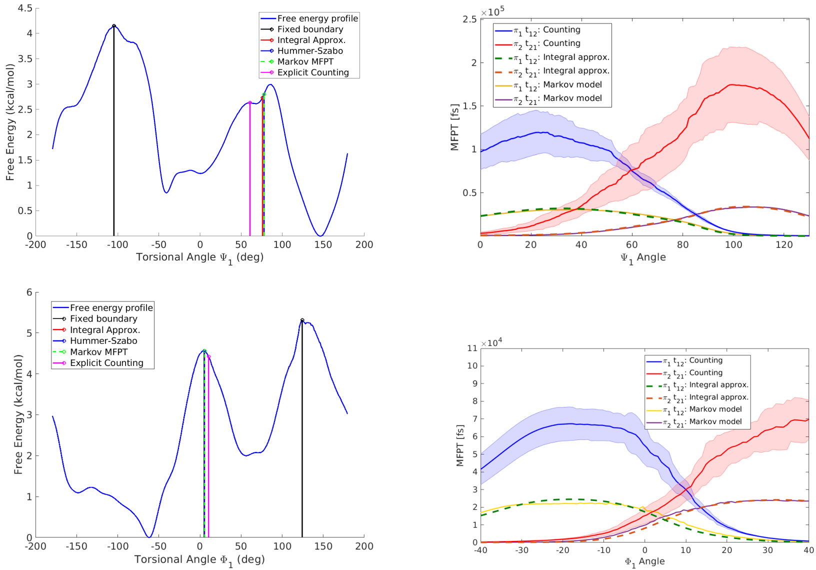
[Kells, Mihálka, Annibale, Rosta, *J. Chem. Phys.* (2019)]

Estimating MFPT: $T_1, \ldots, T_k$ crossing times

$$\boxed{\frac{\sum_i^{k/2} \sum_{j=1}^{N_i} j}{\sum_i^{k/2} N_i} = \frac{\sum_i^{k/2} (N_i+1)N_i/2}{\sum_i^{k/2} N_i}}$$

k crossing events
$N_i = (T_{i+1} - T_i)/\tau$

Simulations of Ala5



Error bars are obtained from 4 equal segments of the MD simulation trajectory. [Kells *et al.*, JCP (2019)]

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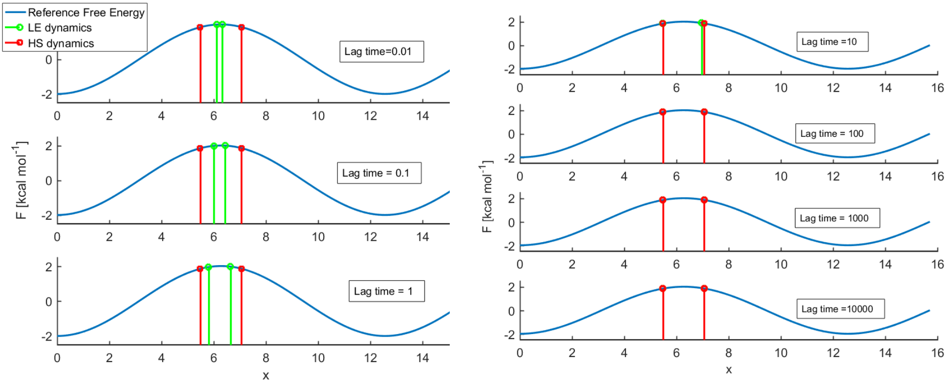

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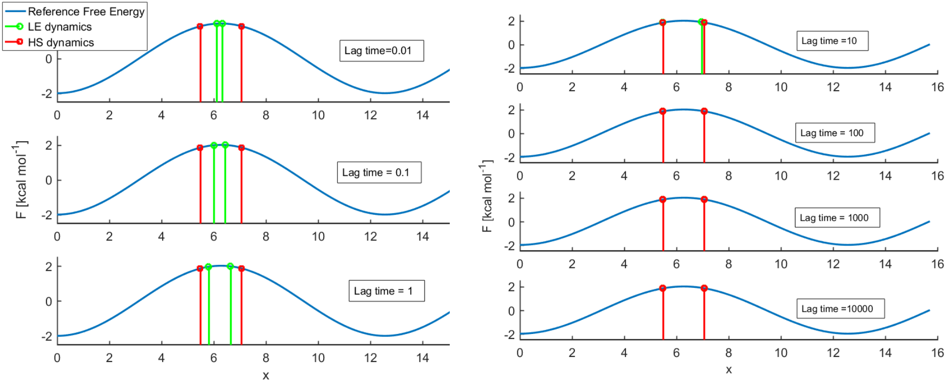

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Can we use functional dependence of eigenvalue on the lag-time, to infer the true relaxation time?

Outline

Limiting relaxation time

$$\boldsymbol{Q}\boldsymbol{\phi}^{(i)} = \lambda_i \boldsymbol{\phi}^{(i)} \qquad \boldsymbol{\psi}^{(i)}\boldsymbol{Q} = \lambda_i \boldsymbol{\psi}^{(i)} \qquad \phi_n^{(i)} = p_n^{\mathrm{eq}} \psi_n^{(i)}$$

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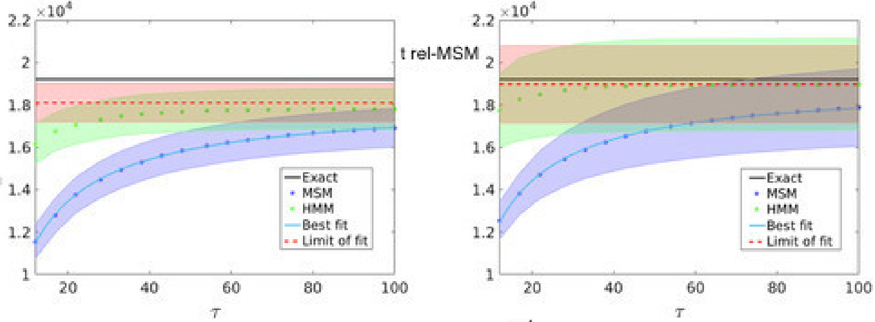
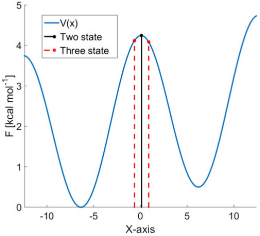
- ϵ useful indicator of how Markovian selected variable is!

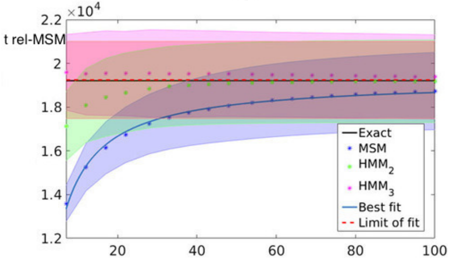
Test on analytical potential [Kells, Annibale, Rosta, JCP (2018)]

2-state MSM: 100 traject. length αt_{relax}; left $\alpha = 0.5$, right $\alpha = 2$



3-state MSM





Simulation of Ala5

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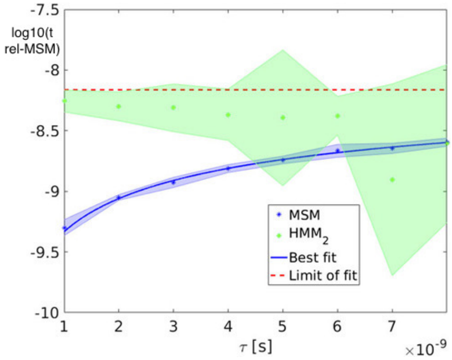
Data: four 250ns simulations, started at different initial conditions, $\Delta = 1$ps

Results for ϕ_3



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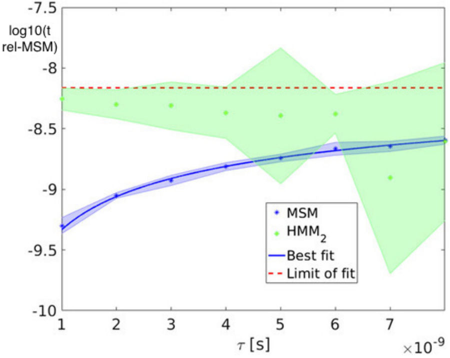

COORDINATE	LT=1	LT=1000	EPSILON	LIMITING RT
1 (Φ1)	6.5	516.1	1.81	6976.3
2 (Ψ1)	952.2	2700.7	0.23	4711.3
3 (Φ2)	25.5	567.7	1.75	6042.0
4 (Ψ2)	687.2	3353.6	0.17	6571.1
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6 (Ψ3)	653.2	2813.0	0.22	5101.8
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8 (Ψ4)	490.0	1929.3	0.47	5325.4
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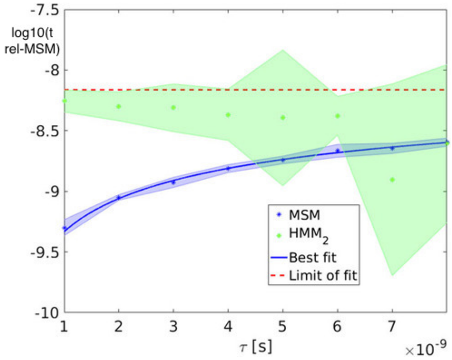

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- For 1D diffusion in potential, transparent interpretation in terms of MFPTs

Conclusion

- Suggested Markovian Approximations of Coarse-grained descriptions based on projections
- Proved a variational principle for second largest eigenvalue
- Identification of the minimum required number of metastable states and TSs for an optimally coarse grained network
- For 1D diffusion in potential, transparent interpretation in terms of MFPTs
- Proposed a method to infer true relaxation time from (optimal) MSMs

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