Finding the Rate-Limiting Permeation Step: Committor and Rate Constant Analysis

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CUP 2023

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Outline

A dead person quote

Introduction to permeability and our goals

Gaining more insight into permeability: Committor analysis

Gaining more insight into permeability: Rate constant analysis

Conclusions and outlook

A dead person quote

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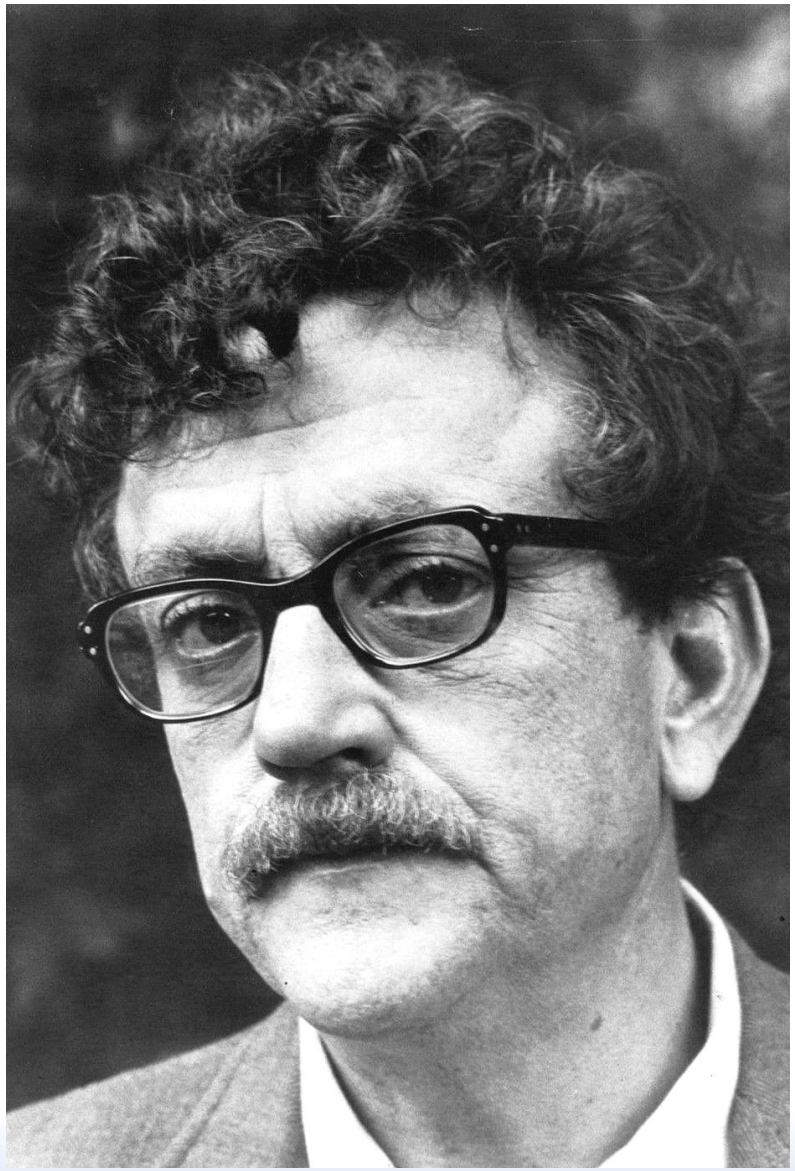
Conclusions and outlook

Kurt Vonnegut: He shared the OpenEye mentality

***Cat's Cradle*, 1963**

"… any scientist who couldn't explain to an eight-year-old what he was doing was a charlatan."



Credit: wikipedia

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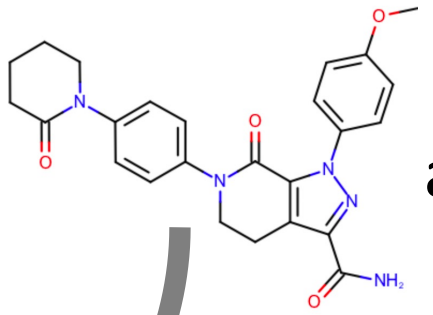
Drug Discovery Realms

Permeability Modeling

Introduction to permeability

outside the cell



apixaban

Fick's model of diffusion

$$J_m = P_m(C_{in} - C_{out})$$

Permeability coefficient

inside the cell

We still have some questions about permeability…

Previously, we developed a method to predict permeability from the kinetic rate constant of membrane crossing:

$$P_m = k_{out \rightarrow in} l_{out}$$

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Mechanistic Insights into Passive Membrane Permeability of Drug-like Molecules from a Weighted Ensemble of Trajectories

She Zhang, Jeff P. Thompson, Junchao Xia, Anthony T. Bogetti, Forrest York, A. Geoffrey Skillman, Lillian T. Chong*, and David N. LeBard*

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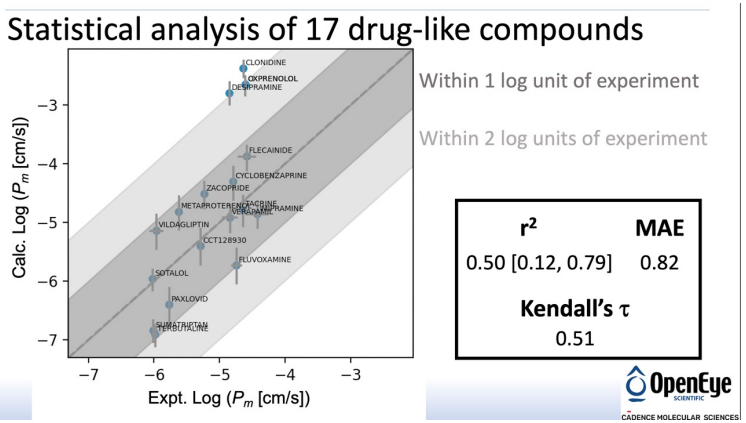
SUBJECTS: Computational chemistry, Interface engineering, Membranes, Molecules,

Journal of Chemical Information and Modeling

We even demonstrated at miniCUPs/JCUP last year that this method can predict permeability for a wide range of drug-like compounds:



1) What regions within the membrane cause the permeant molecule to progress or regress?
2) Can we identify a rate-limiting step in the membrane traversal process?

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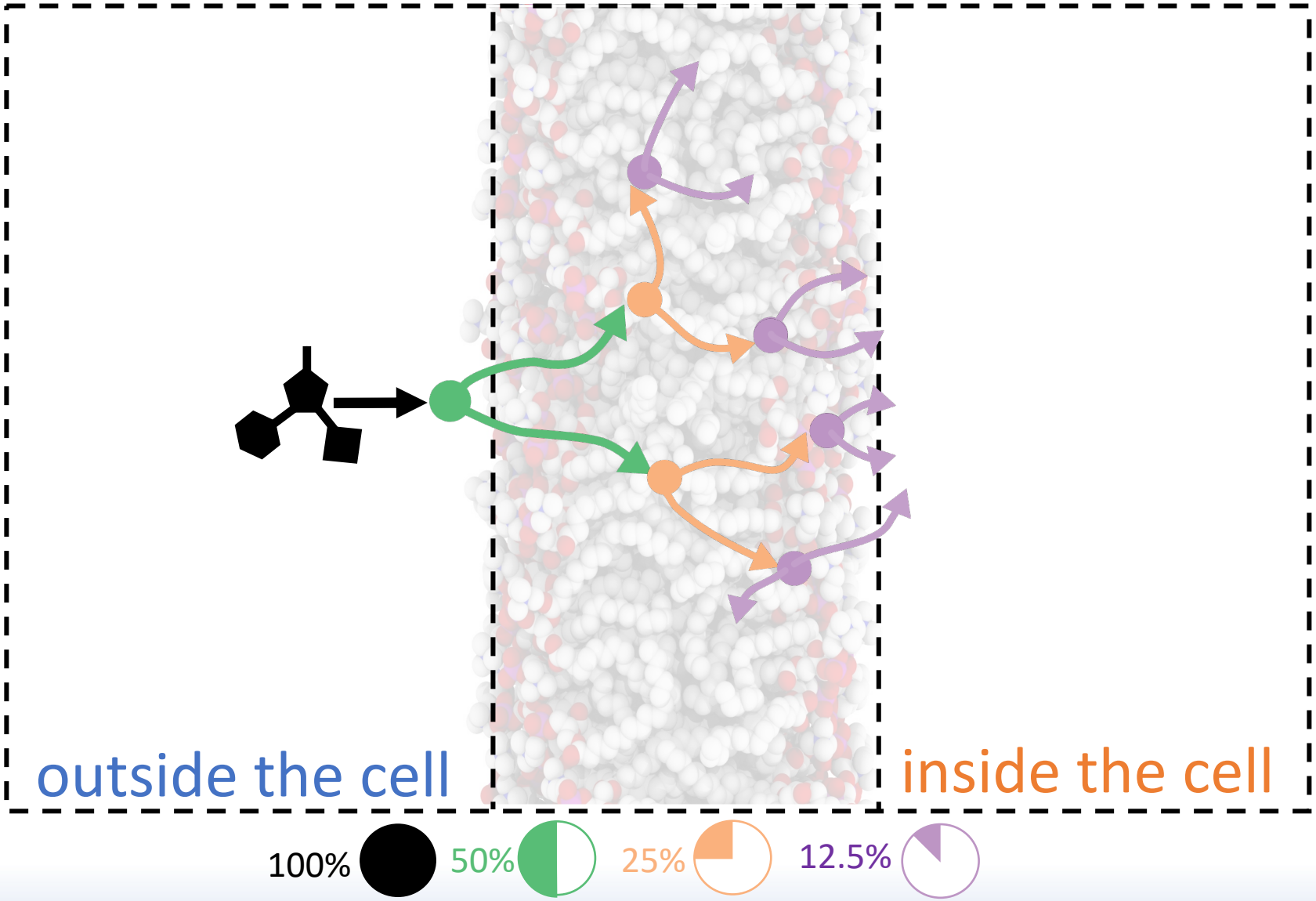
Our Weighted Ensemble algorithm for permeability



JCIM 2022: Zhang S., Thompson J., Xia J., Bogetti A., York F., Skillman A. G., Chong L. T., LeBard D. N.

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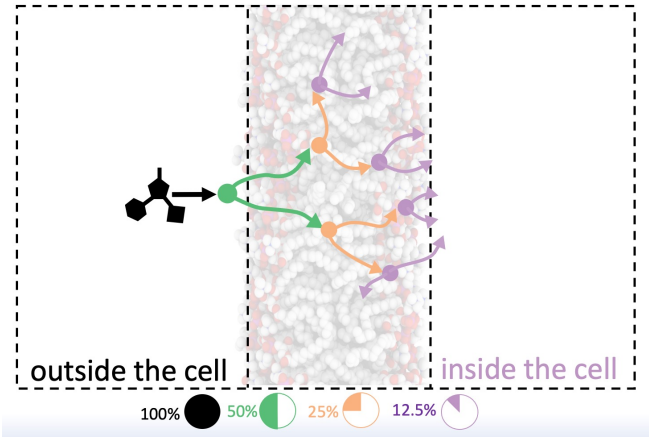
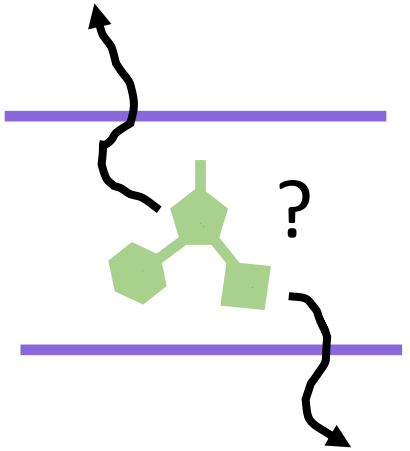
How to gain more insight into a permeation process?

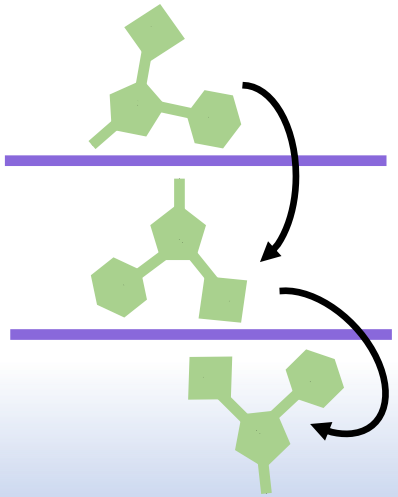
1. Run our weighted ensemble protocol



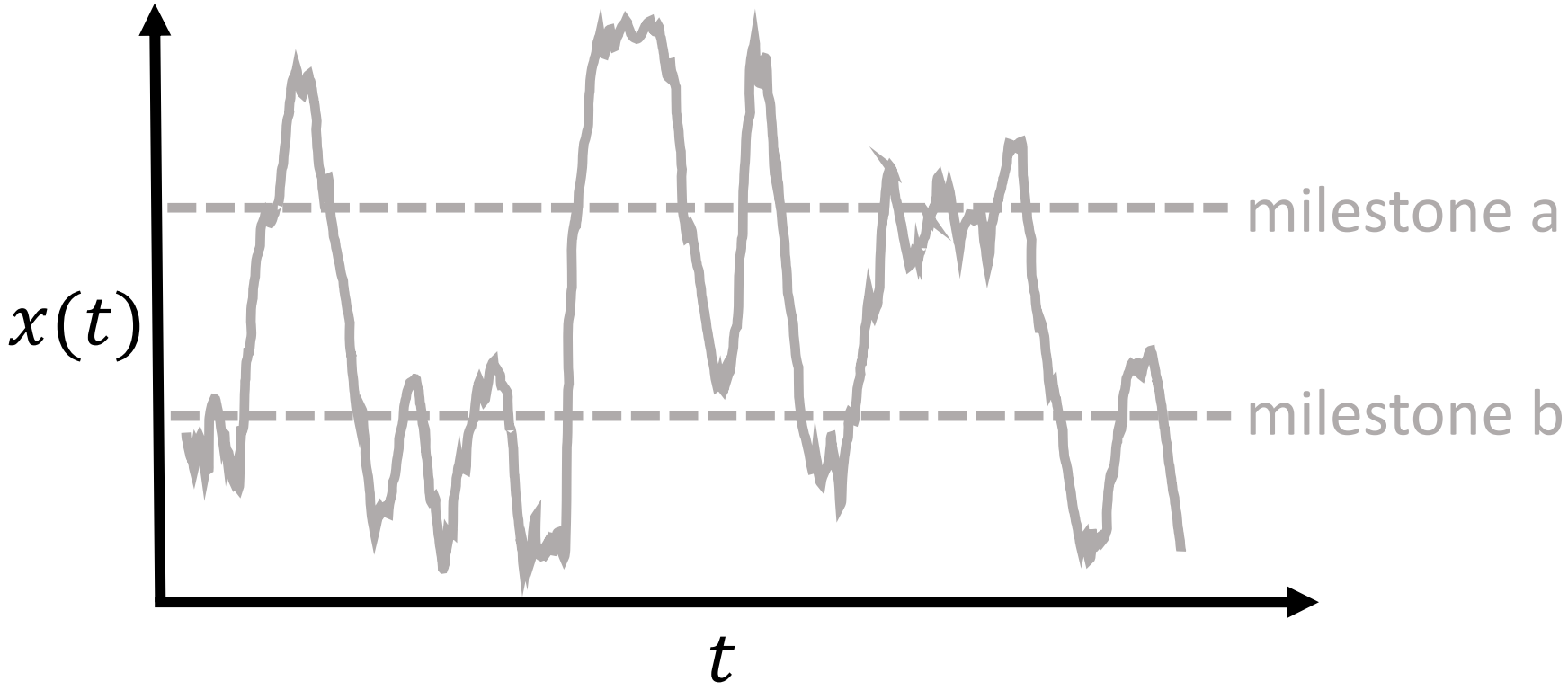
2. Understand when a molecule will likely progress or regress (committor analysis)



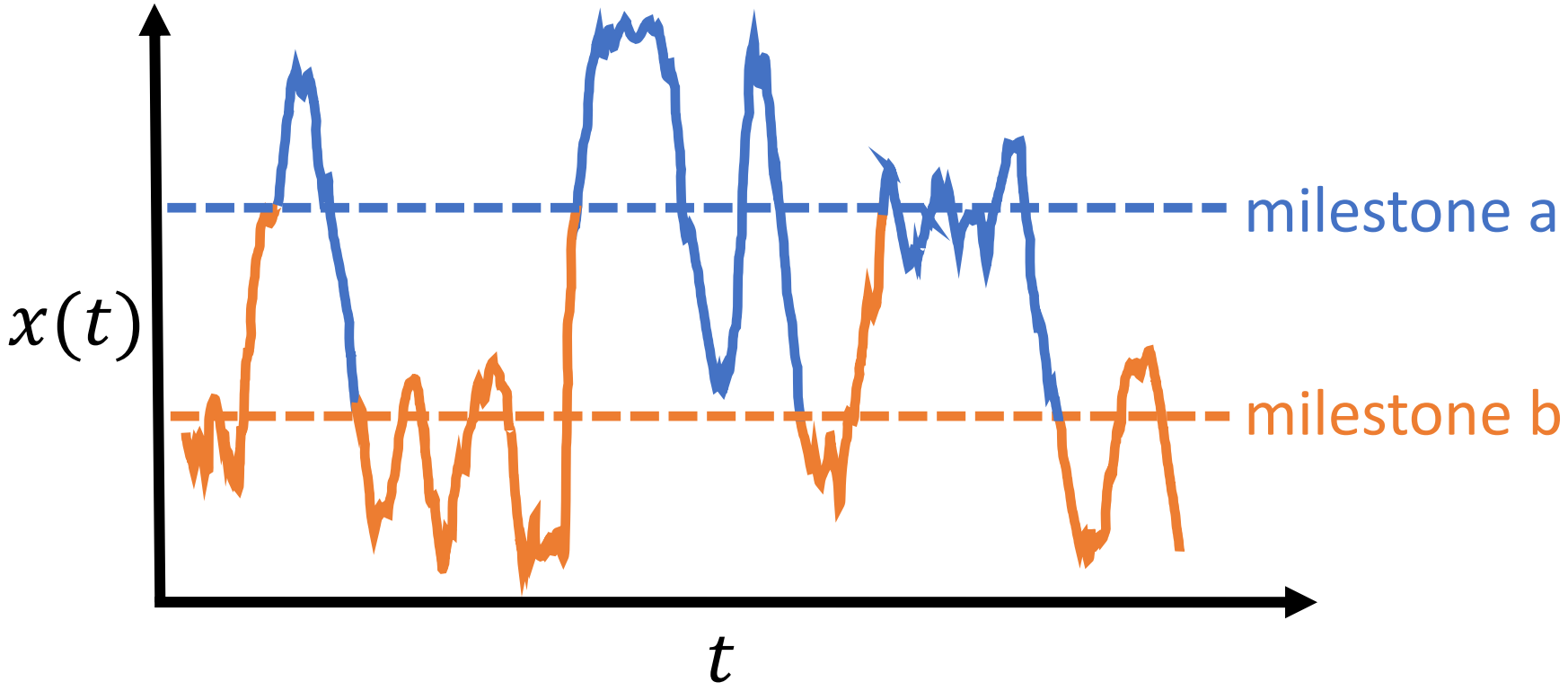
3. Analyze the underlying sub rate constants



Understanding the committor though trajectories

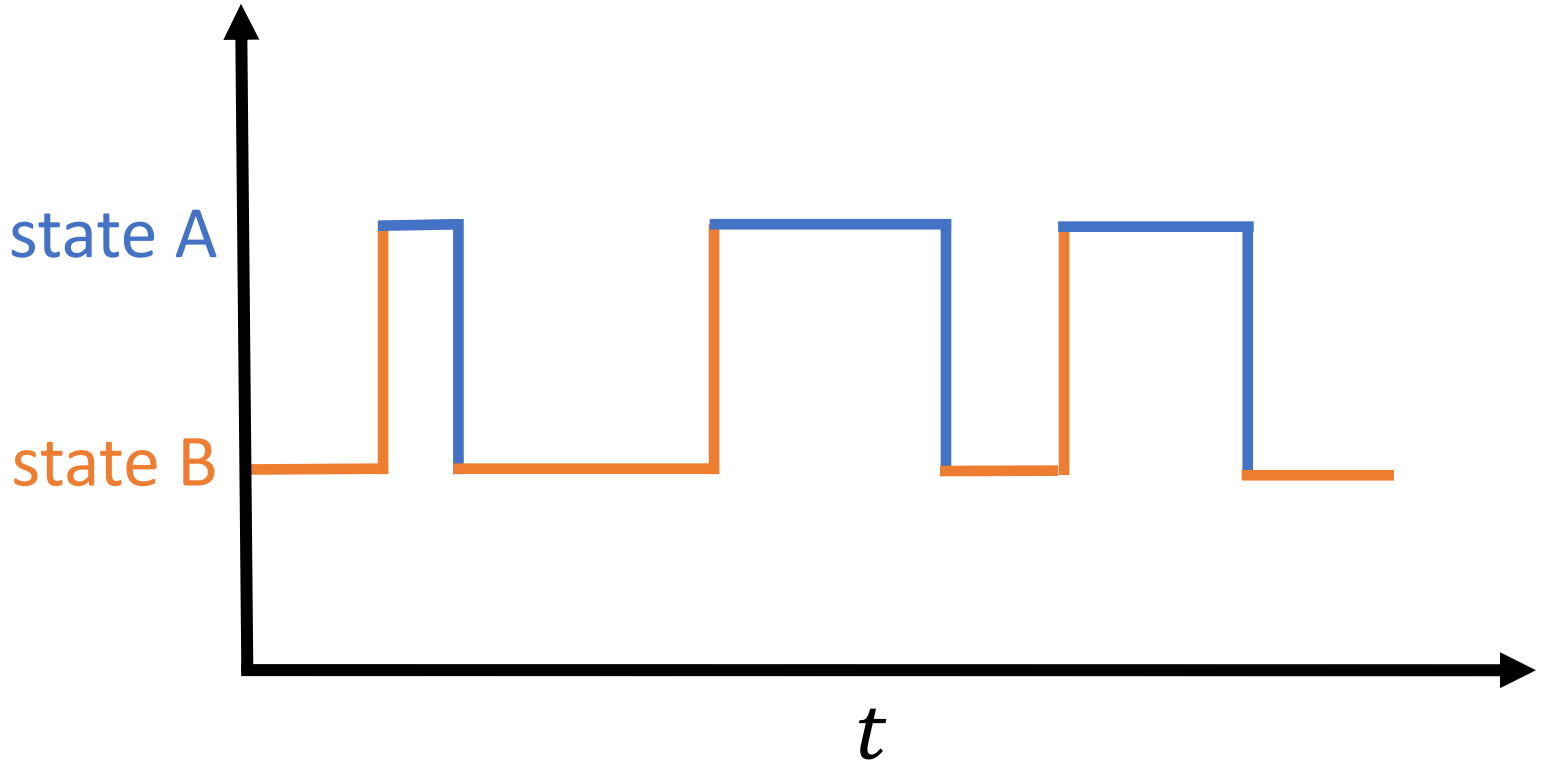


Understanding the committor: Coloring trajectories



A trajectory $x(t)$ is in state A if it last passed through milestone a, and it's in state B if it last passed through milestone b.

From colored trajectories to discretized states

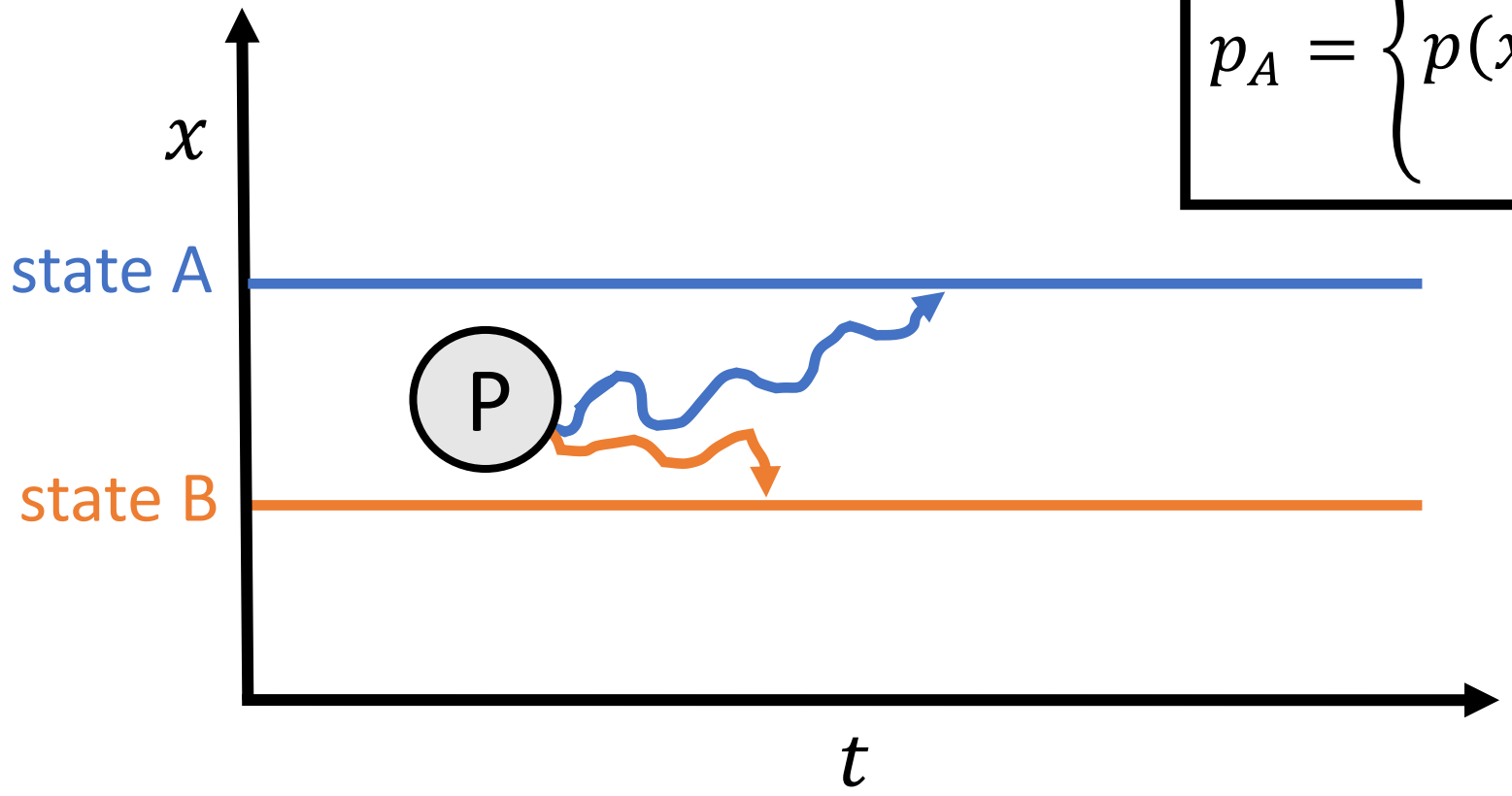


Now, we can use the information about the time spent in state A and the time spent in state B to make a transition matrix (MSM).

How to predict if a particle P will visit A before B?

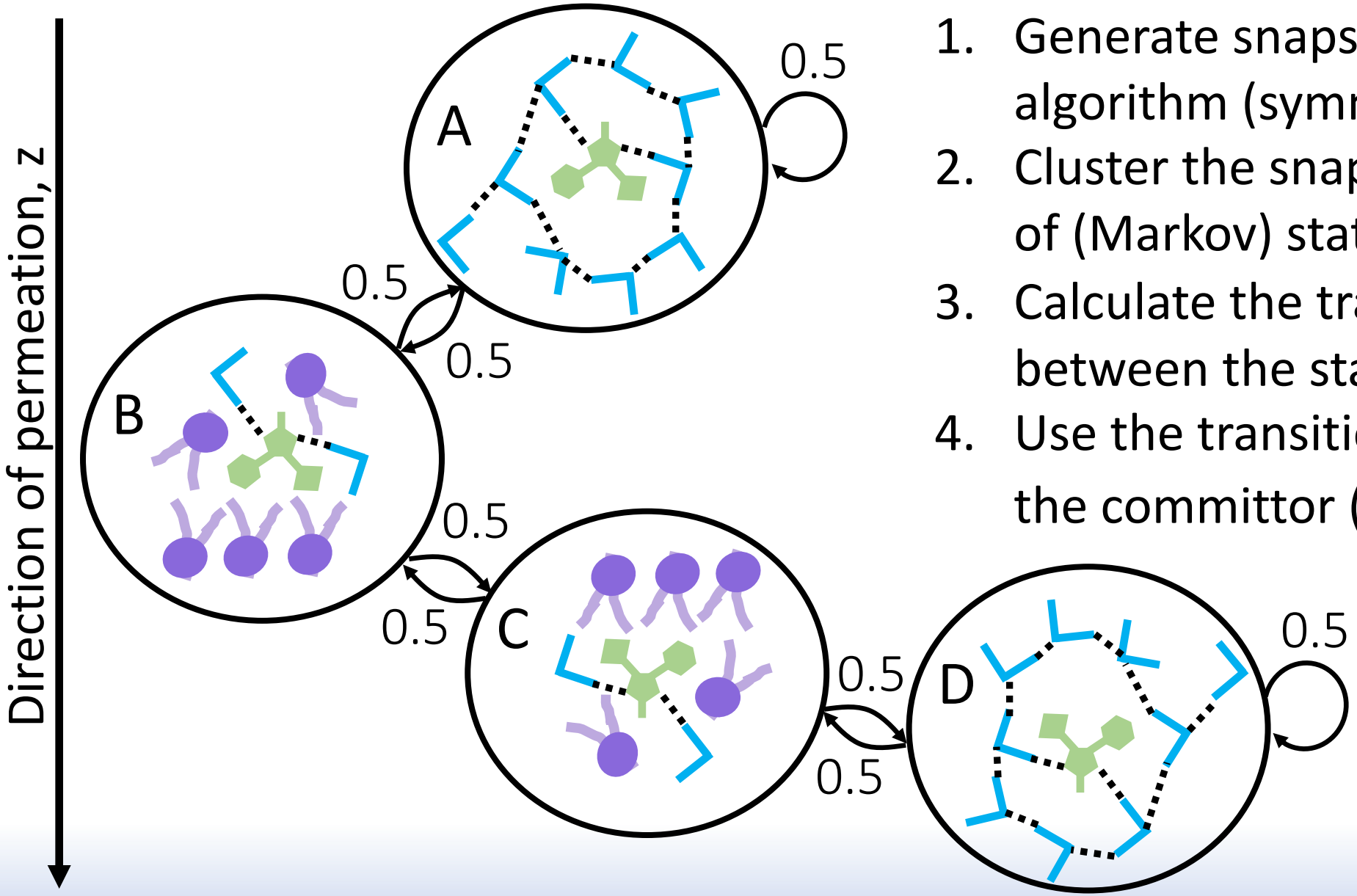
$$p_A = \begin{cases} 1, & x \geq a \\ p(x \to a), & b \leq x \leq a \\ 0, & x \leq b \end{cases}$$

$$p_A = 1 - p_B$$



The committor probability, p_A is the probability that a pathway initiated at a point (P) will end in state A before state B.

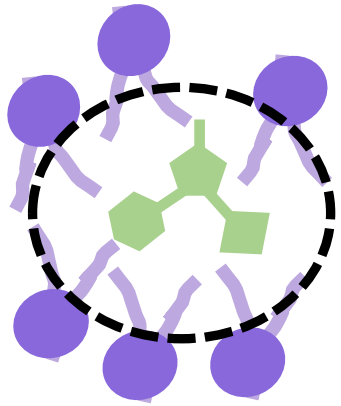
How do we perform committor analysis?



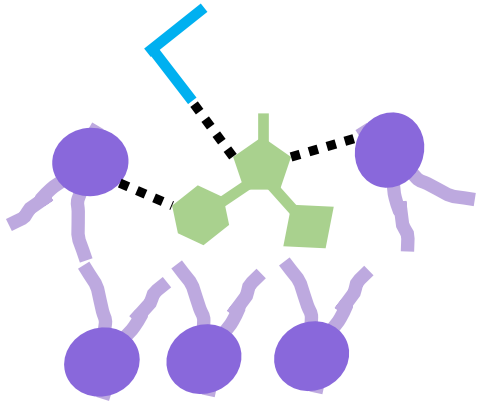
1. Generate snapshots using the WE algorithm (symmetrize!)
2. Cluster the snapshots to define a set of (Markov) states
3. Calculate the transition matrix ($\boldsymbol{K}^{(C)}$) between the states
4. Use the transition matrix to calculate the committor ($\boldsymbol{C}$): $\left(\boldsymbol{I} - \boldsymbol{K}^{(C)}\right)\boldsymbol{C} = \boldsymbol{0}$

Elber, R., et al. (2017). Calculating iso-committor surfaces as optimal reaction coordinates with milestoning. Entropy, 19(5), 219.

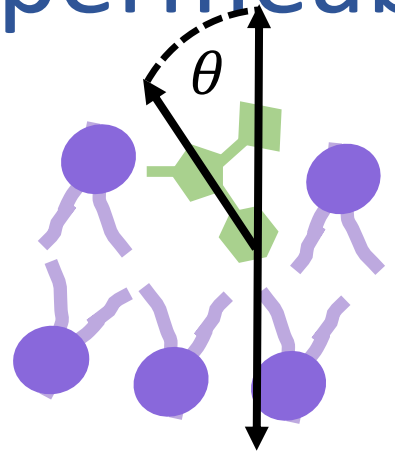
Features used to build the permeability committor



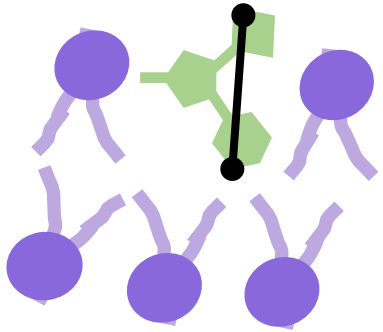
No. hydrophobic contacts



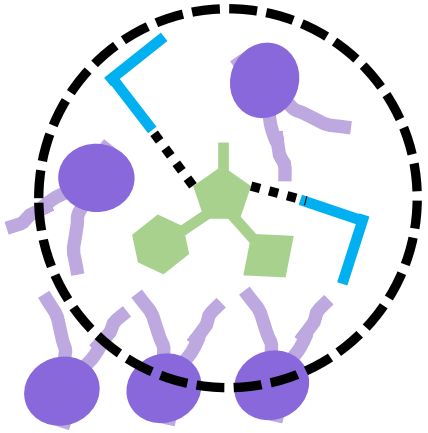
No. hydrogen bonds (d/a + w/m)



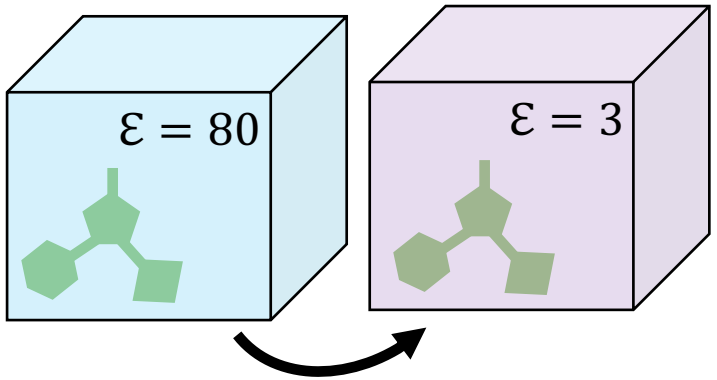
Cosine of angle relative to $\hat{z}$



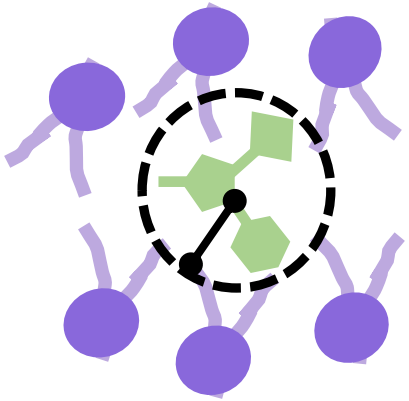
End-to-end distance



No. waters in first solvation shell



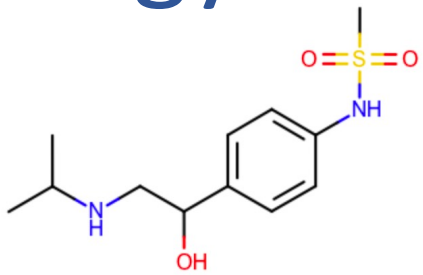
Desolvation penalty

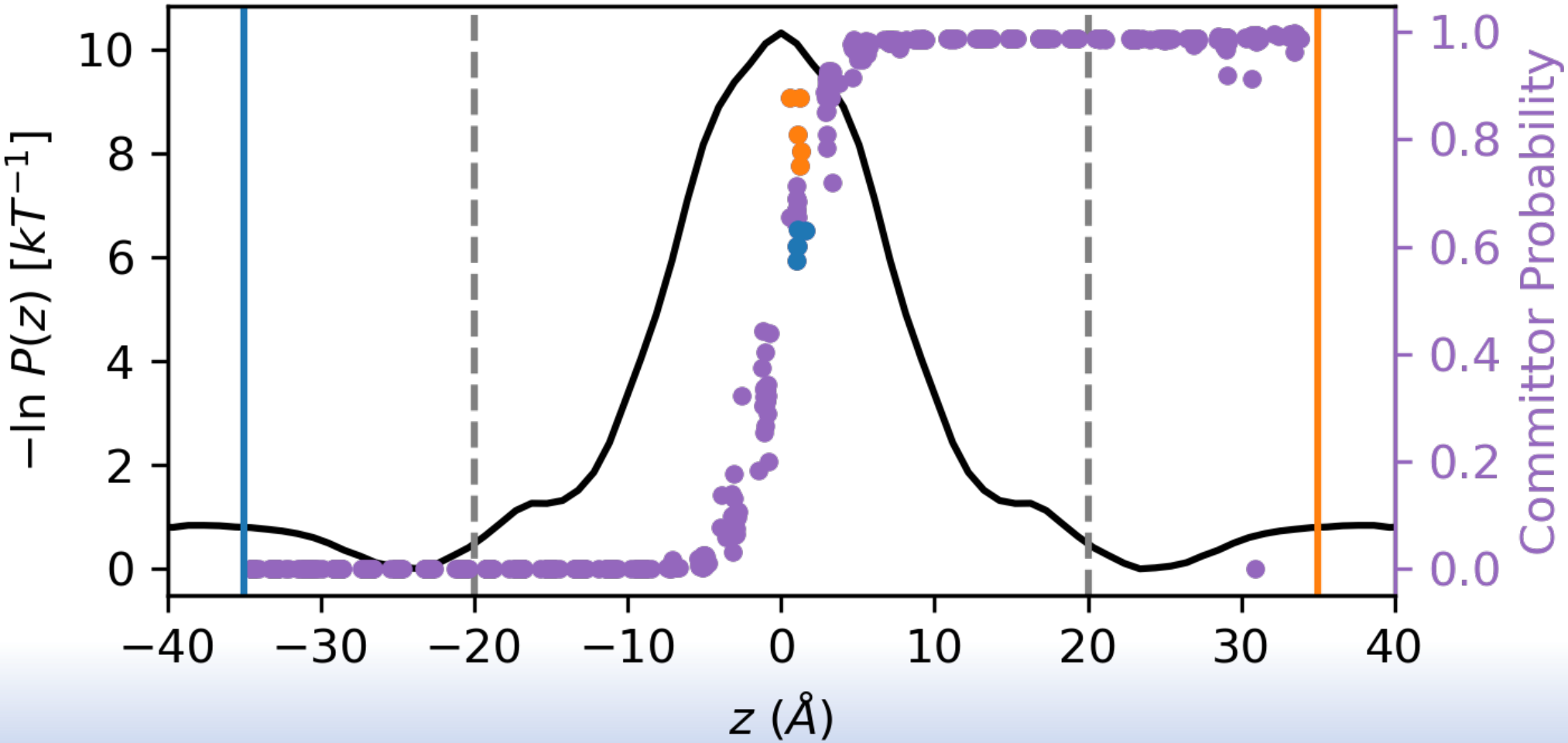


Radius of gyration

Committor and free energy analysis of sotalol

Sotalol:





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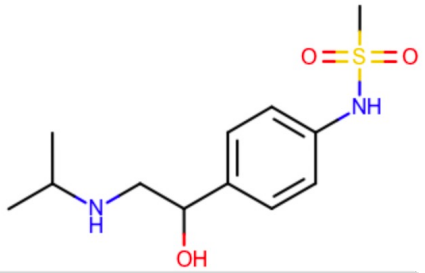
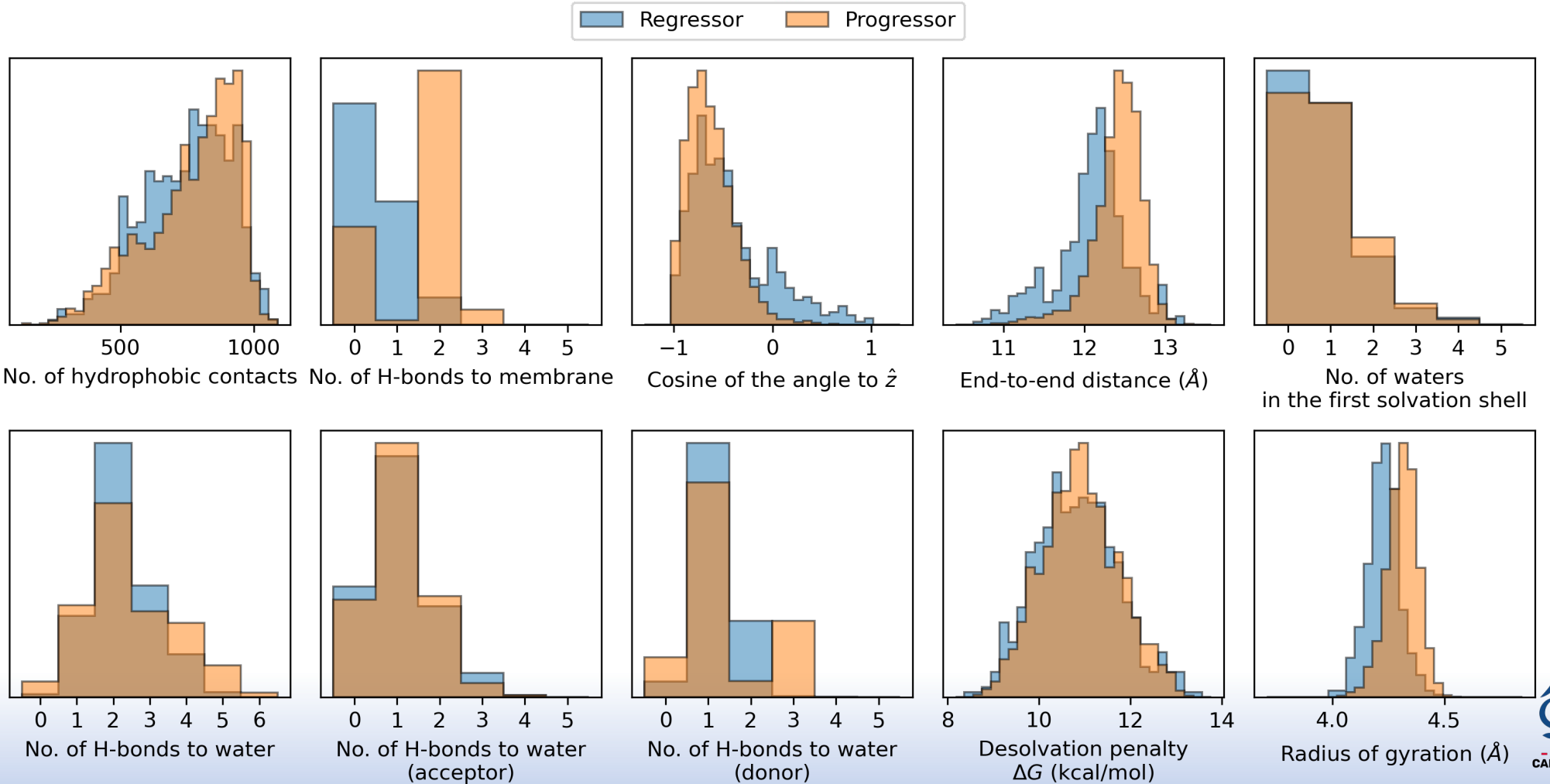
MD Feature data for sotalol inside the membrane

Sotalol:





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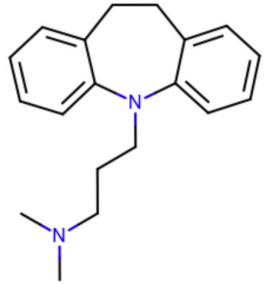
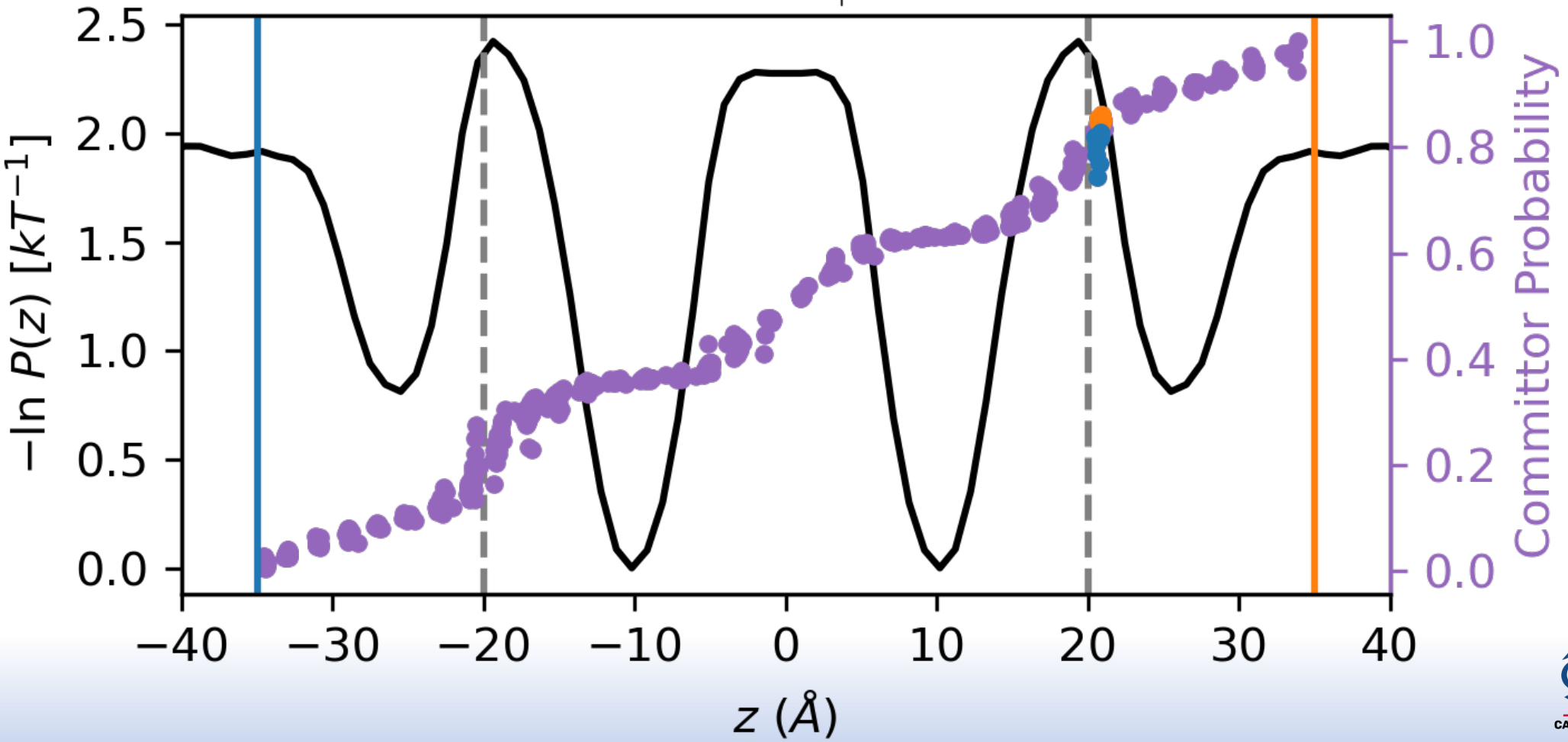
Committor and free energy analysis of imipramine

Imipramine:





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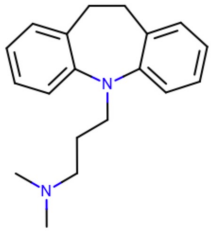
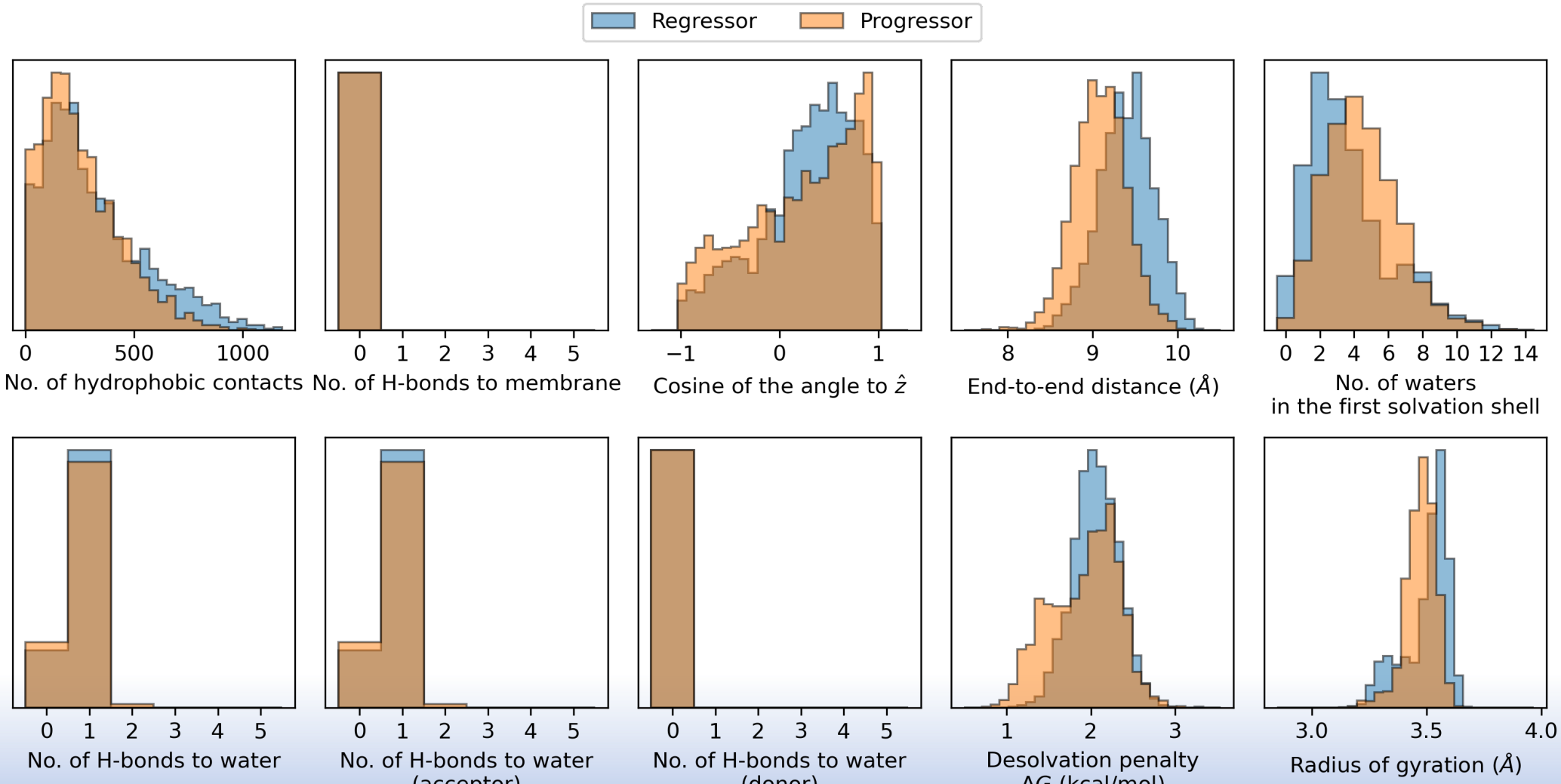
MD Features for imipramine on the other leaflet

Imipramine:





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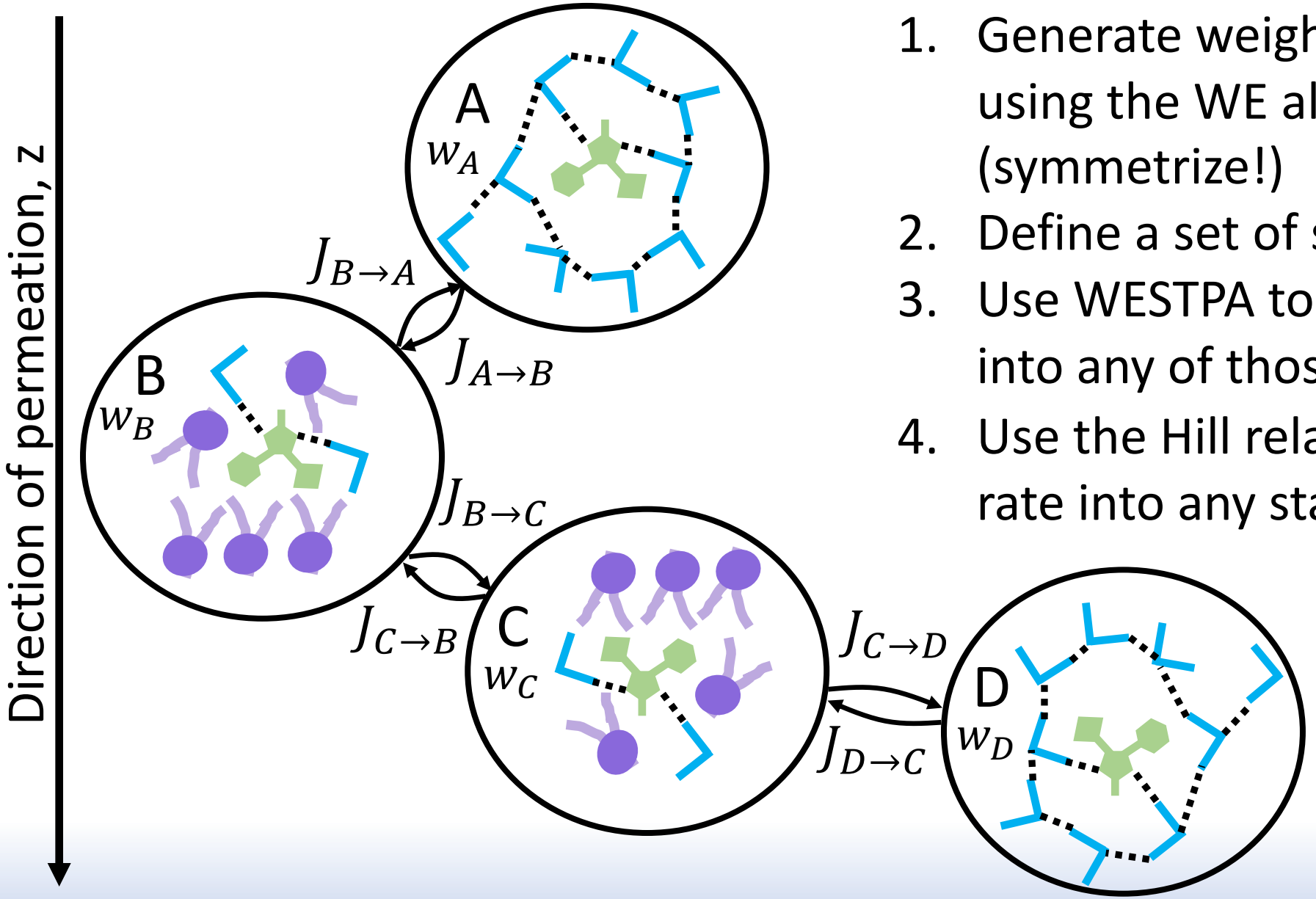
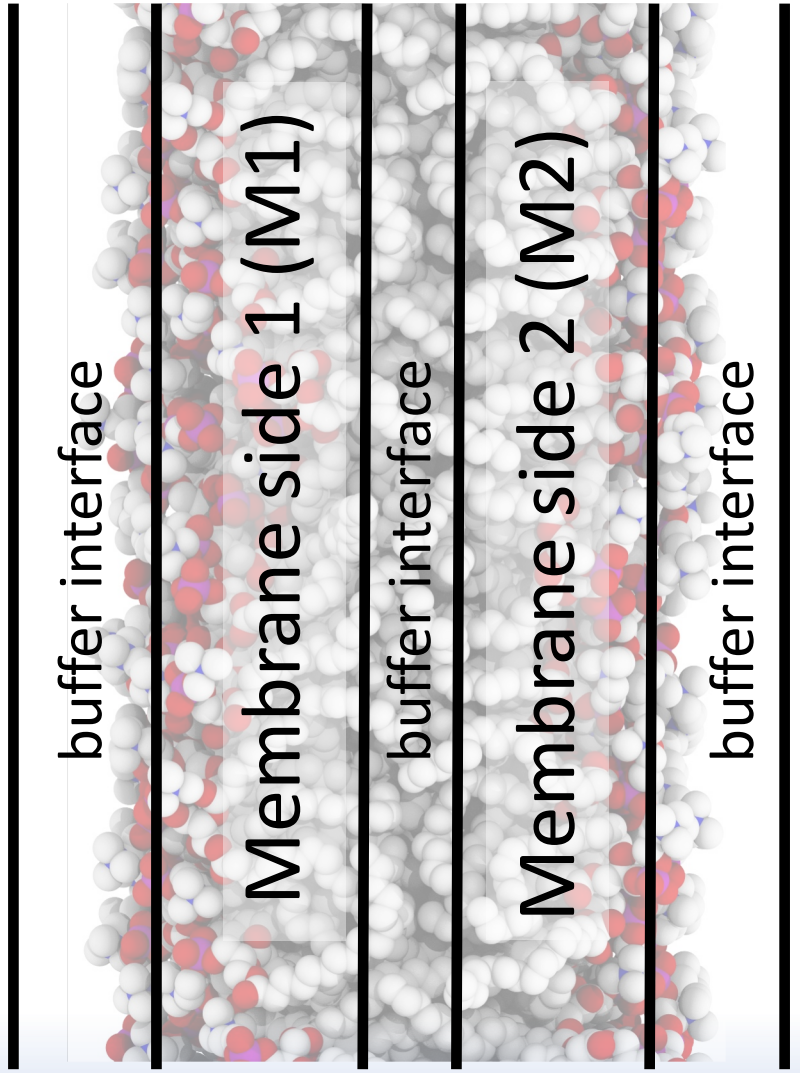
How do we perform rate analysis?



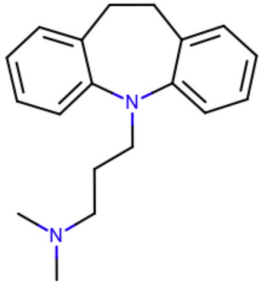
1. Generate weighted (w_i) snapshots using the WE algorithm (symmetrize!)
2. Define a set of states of interest
3. Use WESTPA to analyze the fluxes into any of those states state ($J_{i\to j}$)
4. Use the Hill relation to calculate the rate into any state: $k_{i\to j} = J_{i\to j}/w_i$

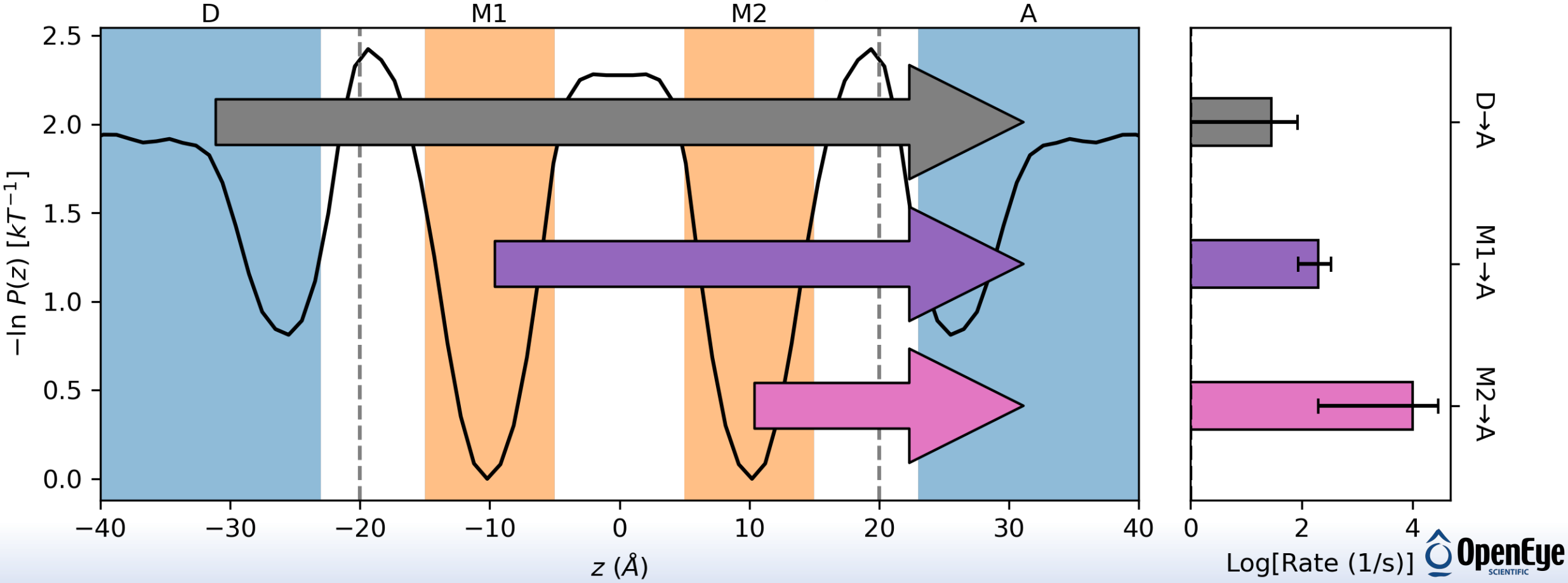
Four state definitions for rate constant analysis



Permeability rate constants for imipramine

Imipramine:





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Conclusions

Previously, we developed a kinetic model for permeability, and we demonstrated it has predictive utility on several compounds.

Now, we are interested in gaining more insight into permeability from our trajectory data. We are performing committor analysis and rate constant analysis to understand the rate limiting step(s), and the physical features affecting permeation for a given compound.

Future work is focused on using data generated here to build a classifier model to help a medicinal chemist understand when to expect a molecule to cross various energetic barriers within a model membrane.

Acknowledgements

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Orion Frontend developers

WESTPA developers


Thank You
The End
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