Identification of states and rates for higher level(lower resolution) simulations

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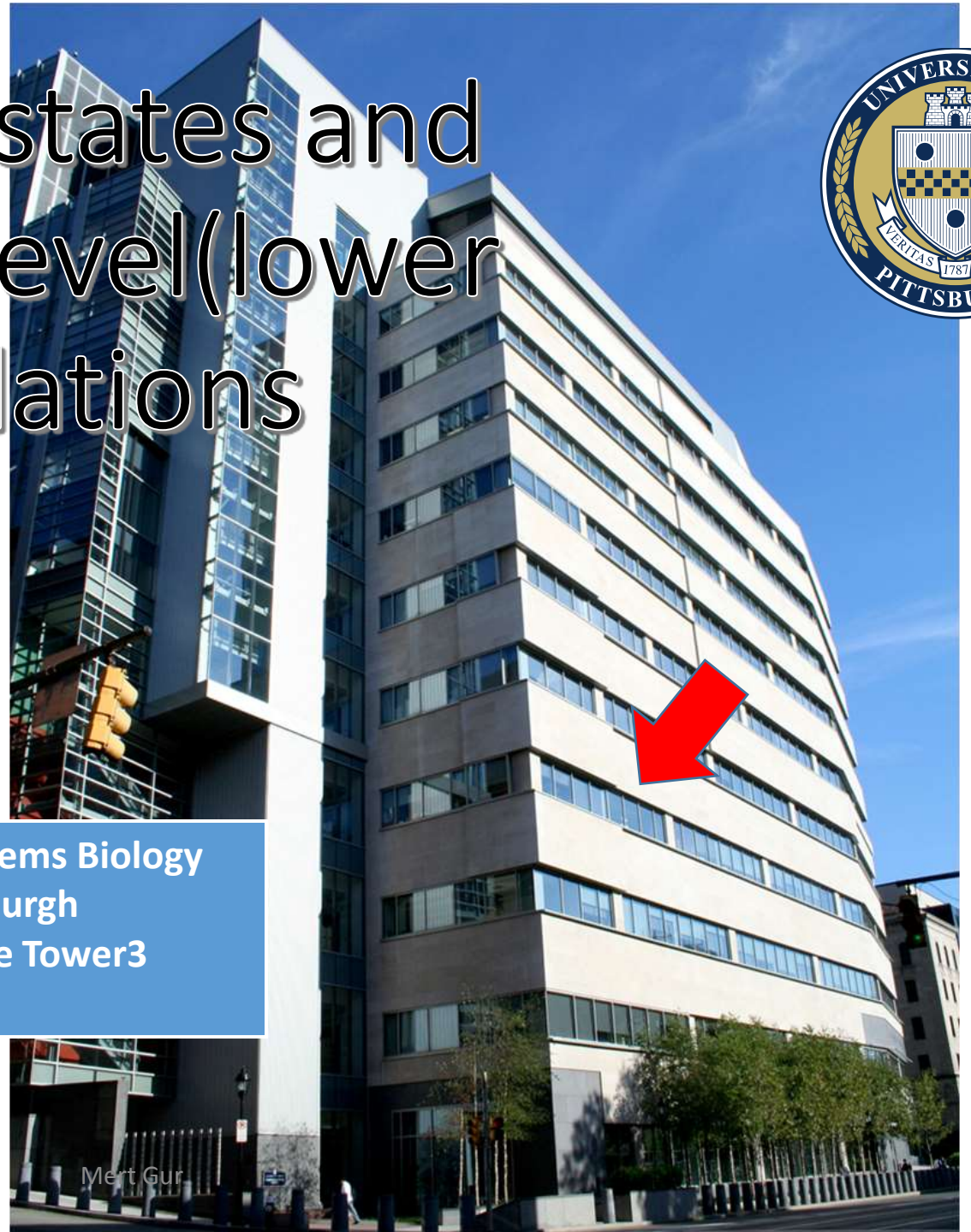


Introduction

- Neurotransmitter:sodium symporters (NSSs) are involved in many neurological disorders including epilepsy, depression , anxiety and Parkinson disease, and are targets of both clinical and illicit drugs, including stimulants such as cocaine and amphetamine and antidepressants such as fluoxetine.

- NSSs carry out their role by coupling the energetically unfavorable translocation of their substrate across the cell membrane to that of other ions, namely sodium.

- The sodium:leucine transporter from *Aquifex aeolicus* (LeuT), a bacterial NSS, has served as a model for NSSs due to its high-resolution crystal structures resolved in various functional states; It is widely used to predict/investigate the functional dynamics of the dopamine transporter

Identification of States

Sampled States and subStates in the Molecular Dynamics Simulations can be identified

Based on the conformations (via PCA)

Free Energy Surface

Based on Binding States

Part 1: Identification of States based on Conformations

MD simulations of the LeuT

We have performed 20μs of conventional Molecular Dynamics simulations of the LeuT as a dimer and 1 μs as a monomer.

run	conformer	LeuT	bound substrate/ions	duration (μs)
1	OF open	dimer	2 Na^+	1.075
2			Ala, 2 Na^+	0.55
3a-c			Leu, 2 Na^+	(a) 1.94, (b) 1.51, (c)1.075
4	OF occluded		none	1.05
5			Ala, 2 Na^+	2.63
6a-c			Leu, 2 Na^+	(a) 3.365, (b) 3.03, (c)1.585
7a-b	IF open		none	(a) 1.07, (b) 1.065

Anton simulations

Zomot, E., M. Gur, and I. Bahar. 2014. Microseconds simulations reveal a new sodium-binding site and the mechanism of sodium-coupled substrate uptake by LeuT. *Journal of Biological Chemistry* (Under revision).

Identifying Principal Motions in the MD trajectories

A covariance matrix **C** was constructed for the LeuT protomer using all conformers from MD simulations of the LeuT dimer and monomer as follows

$$\mathbf{C} = \left\langle \left(\mathbf{R} - \langle \mathbf{R} \rangle\right)\left(\mathbf{R} - \langle \mathbf{R} \rangle\right)^{\mathrm{T}} \right\rangle$$

Here **R** is the 3*N*-dimensional configuration vector composed of the instantaneous C^{α}-atom coordinates of the *N* residues of the protein.

Principal Components **(PC**s) are obtained by eigenvalue decomposition

$$\mathbf{C} = \sum_{i=1}^{3N} \sigma_i \mathbf{p}_i \mathbf{p}_i^{T}$$

Here $\mathbf{p}_i$ is the i^{th} PC (*i*th eigenvector) and s_i is the corresponding variance (eigenvalue), ordered in descending order with respect to s_i.

Free energy

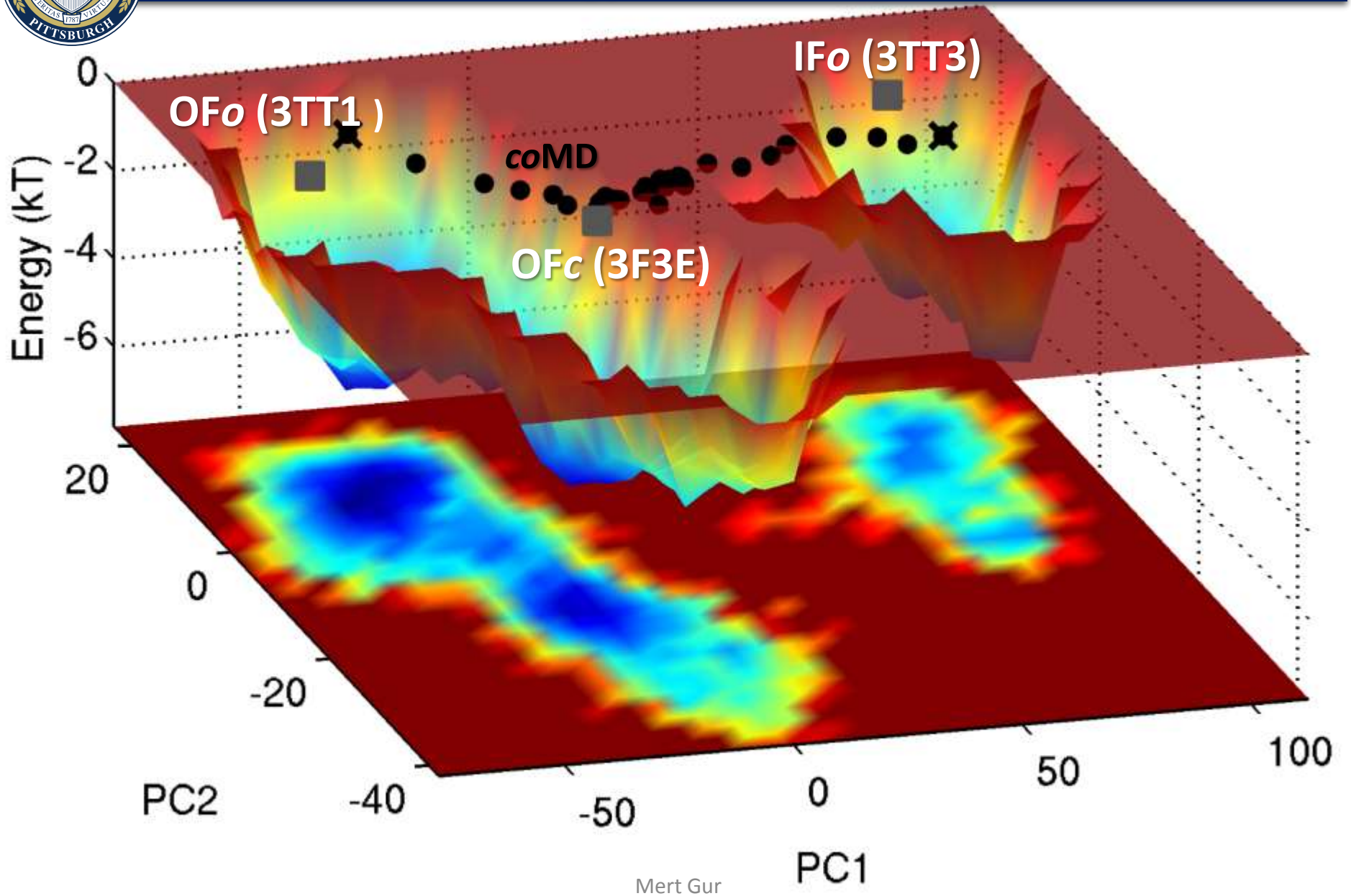
The conformational space sampled by MD is divided into grids, which are suitably grouped into subspaces. $N(\Phi_s)$ designates the number of conformers in each of these subspaces. The probability distribution function becomes;

$$f(\mathbf{R}) = N(\Phi_s) / \sum_s N(\Phi_s)$$

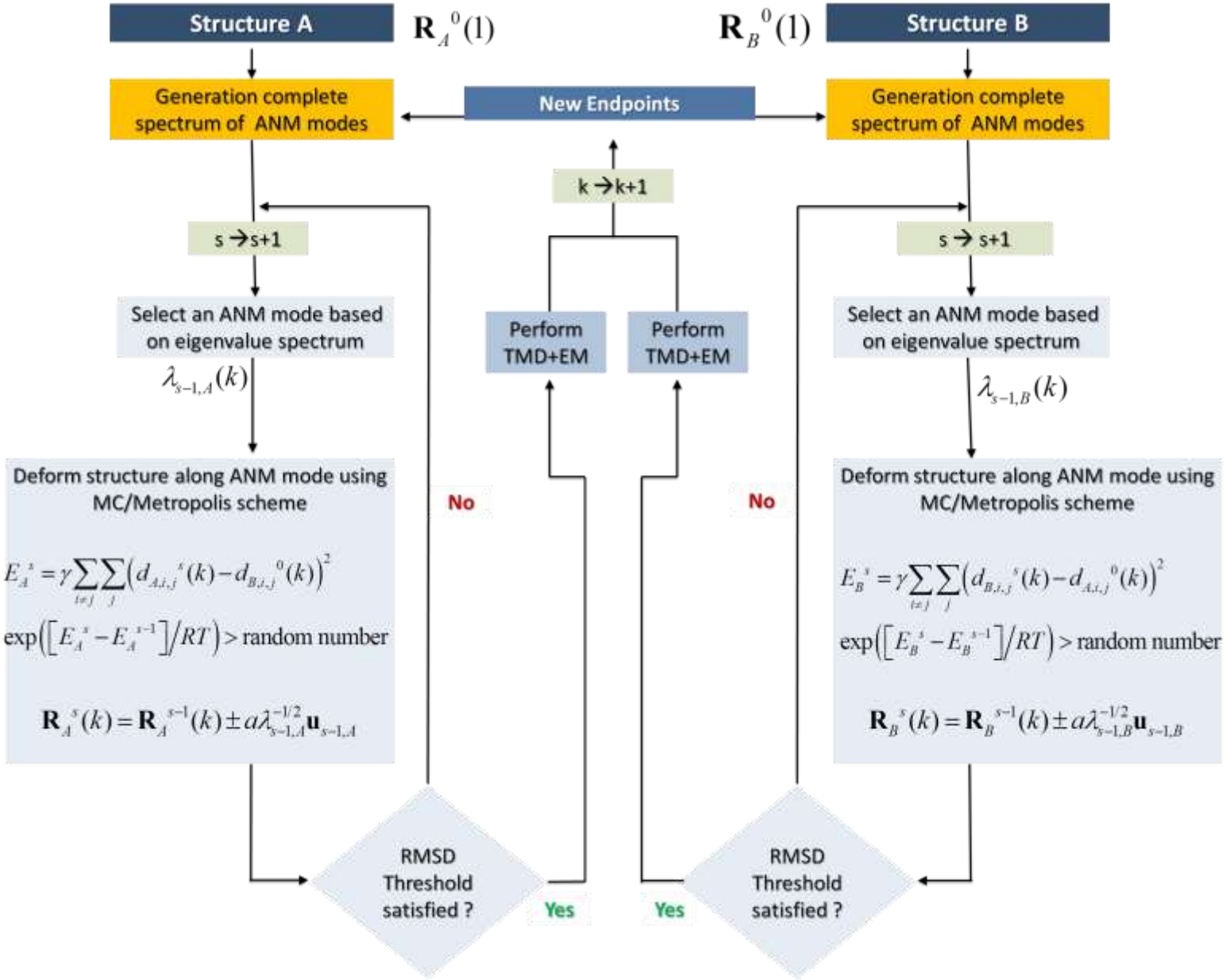
The **free energy surface** is evaluated using this probability distribution function as

$$A(\mathbf{R}) = -kT \ln\left\{ f\left(\mathbf{R}\right)\right\} + \text{ct}$$

Free energy surface along PCs

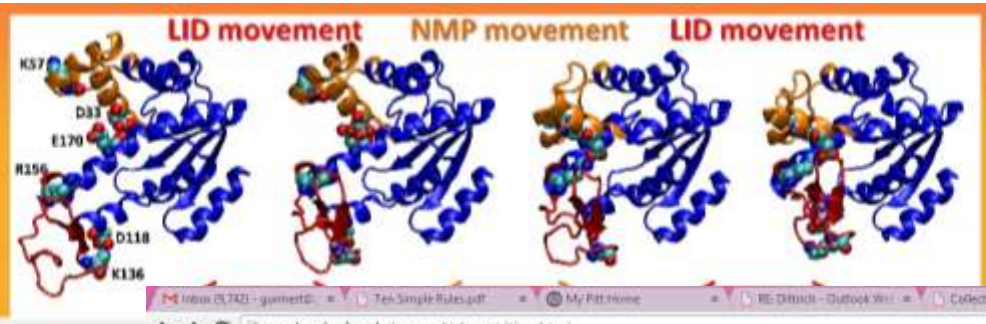


coMD



M. Gur, J. Madura and I. Bahar. 2013. Global Transitions of Proteins Explored by a Multiscale Hybrid Methodology: Application to Adenylate Kinase . *Bophysical Journal,* 105: 1643-1652.

Incorporating coMD into Prody



coMD »

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Learn how to use coMD for genera

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  - Running coMD simulatic
  - Postprocessing
- Credits

prody.csb.pitt.edu/manual/about/citing.html

ProDy

Protein Dynamics & Sequence Analysis

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Citing

When using *ProDy* or *MWWin* published work, please cite:

Bakan A, Meireles LM, Bahar I.
ProDy: Protein Dynamics Inferred from Theory and Experiments.
Bioinformatics **2011** 27(11):1575-1577.

When using *pairwise2* or *KDTree* modules in published work, please cite:

Cock PJ, Antao T, Chang JT, Chapman BA, Cox CJ, Dalke A, Friedberg I, Hamelryck T, Kauff F, Wilczynski B, de Hoon MJ.
Biopython: freely available Python tools for computational molecular biology and bioinformatics.
Bioinformatics **2009** 25(11):1422-3.

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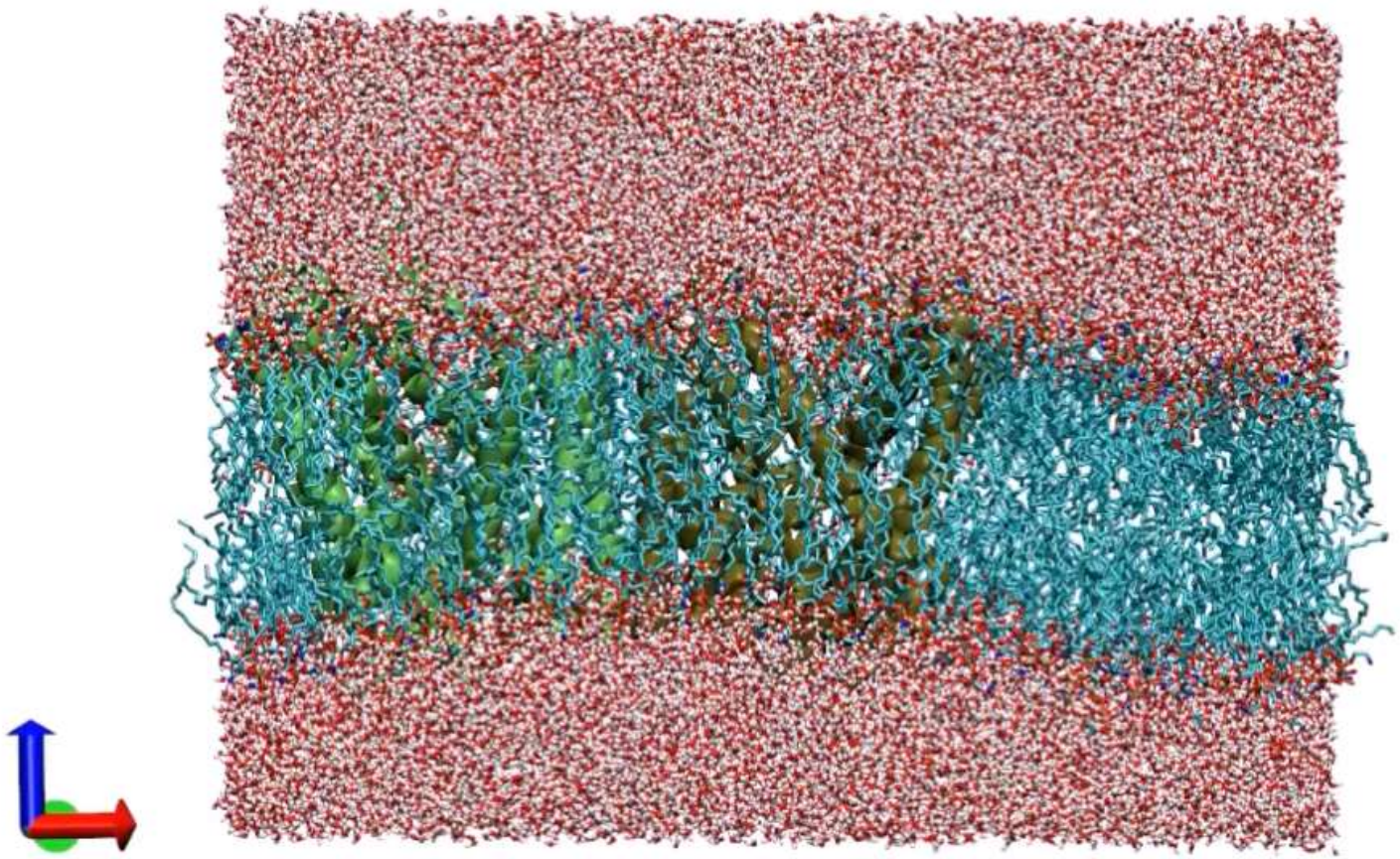
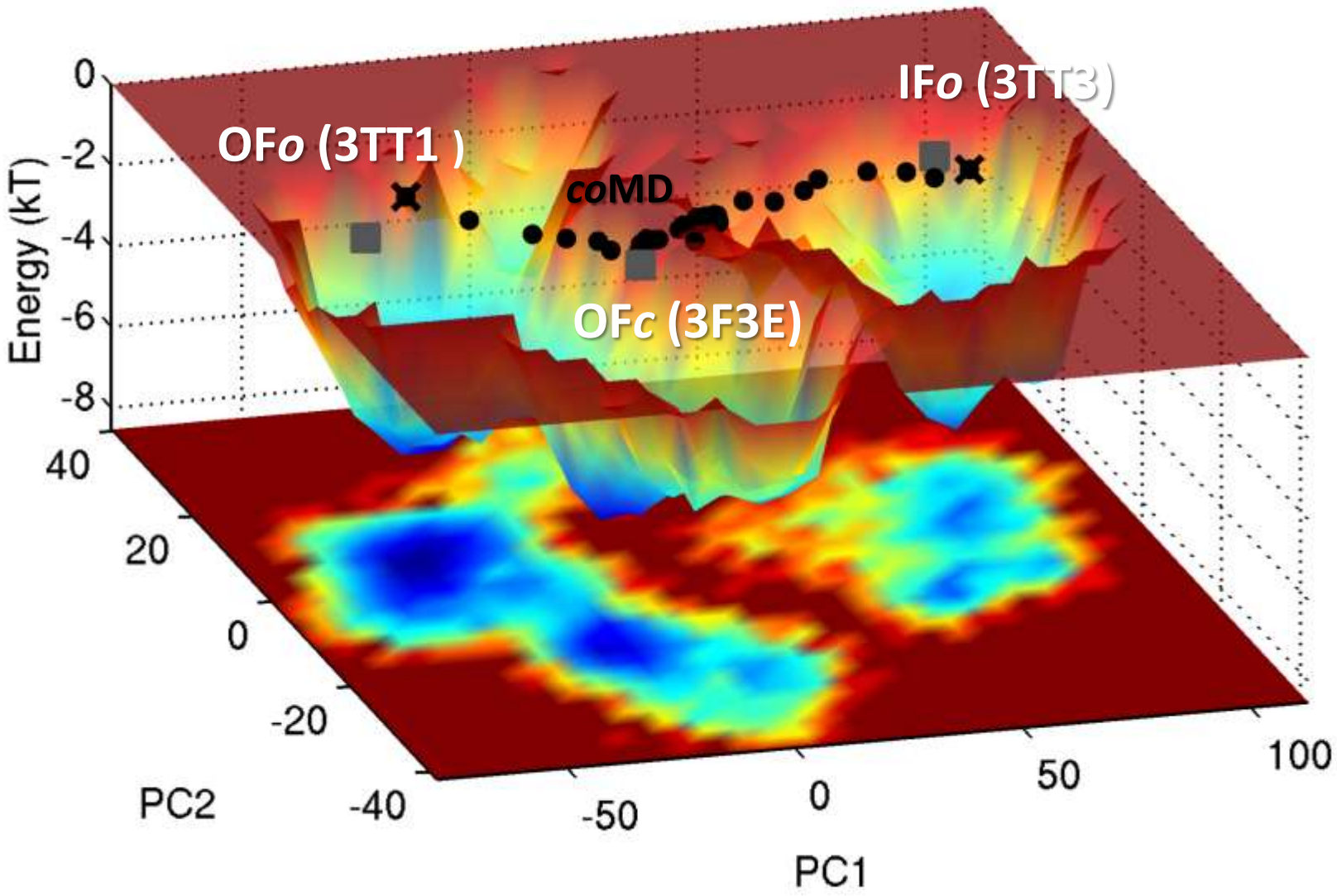
http://www.csb.pitt.edu/comd/

Bakan A,* Dutta A,* Mao W, Liu Y, Chennubhotla C, Lezon TR, Bahar I (2014) Evol and ProDy for Bridging Protein Sequence Evolution and Structural Dynamics

Transition mechanism of the LeuT from coMD



Free energy surface along PCs



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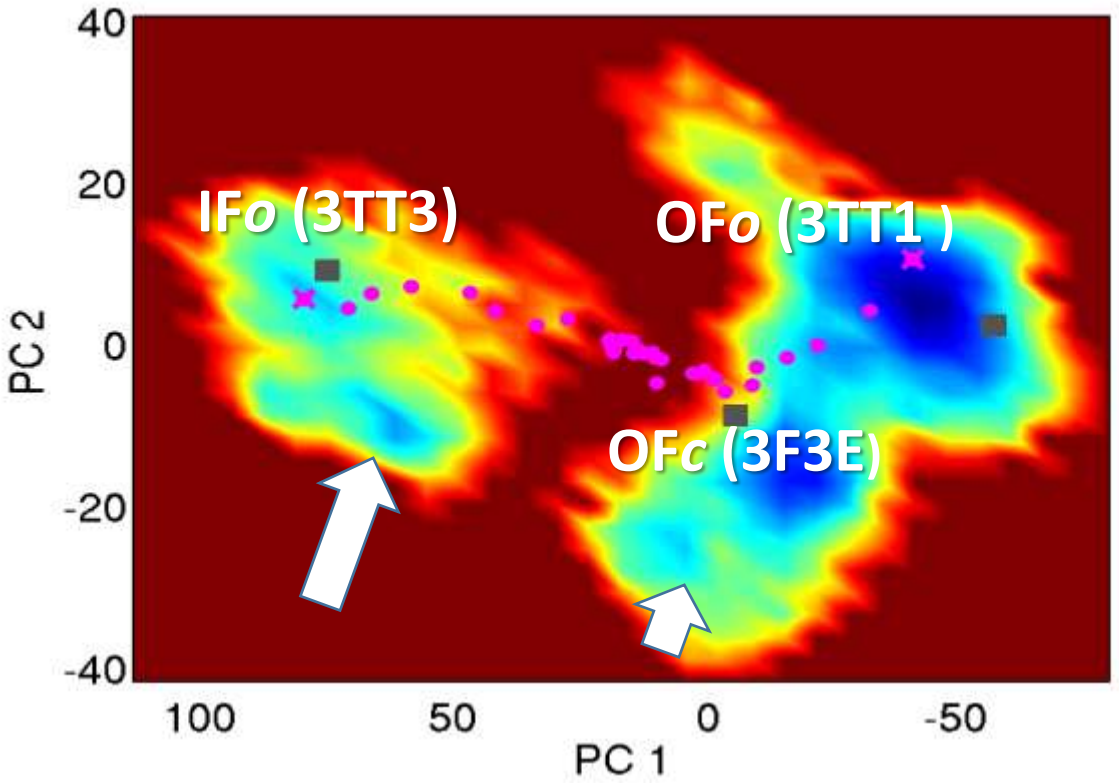
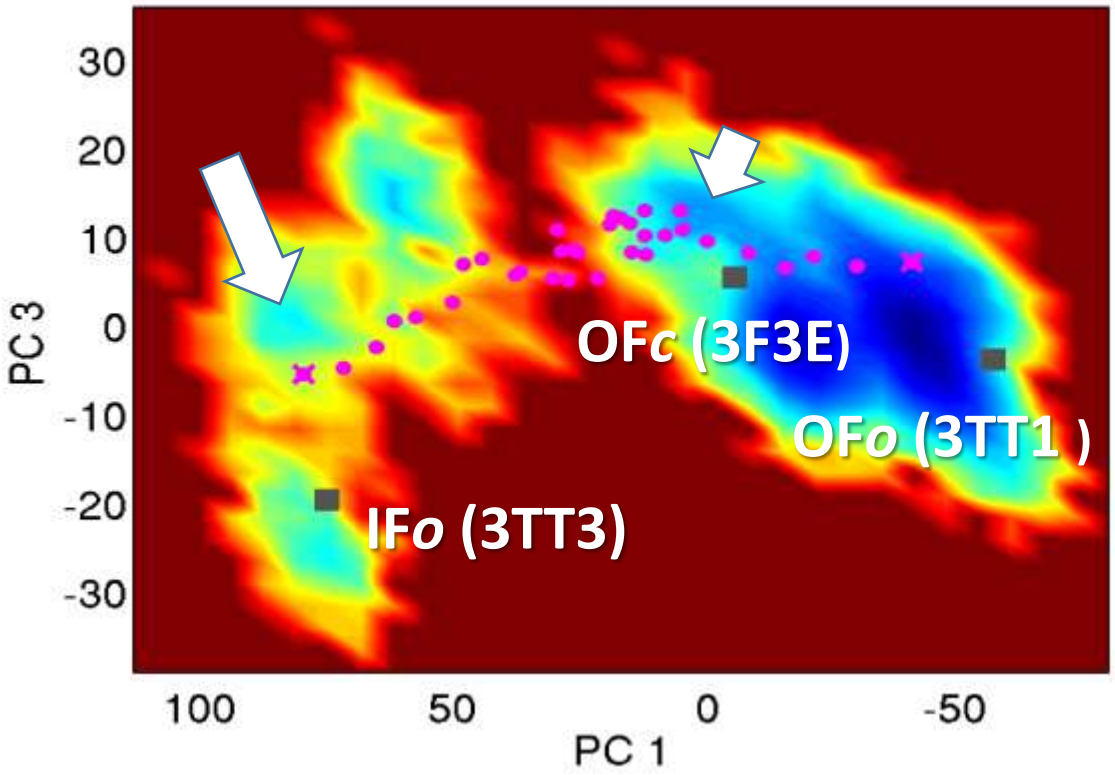
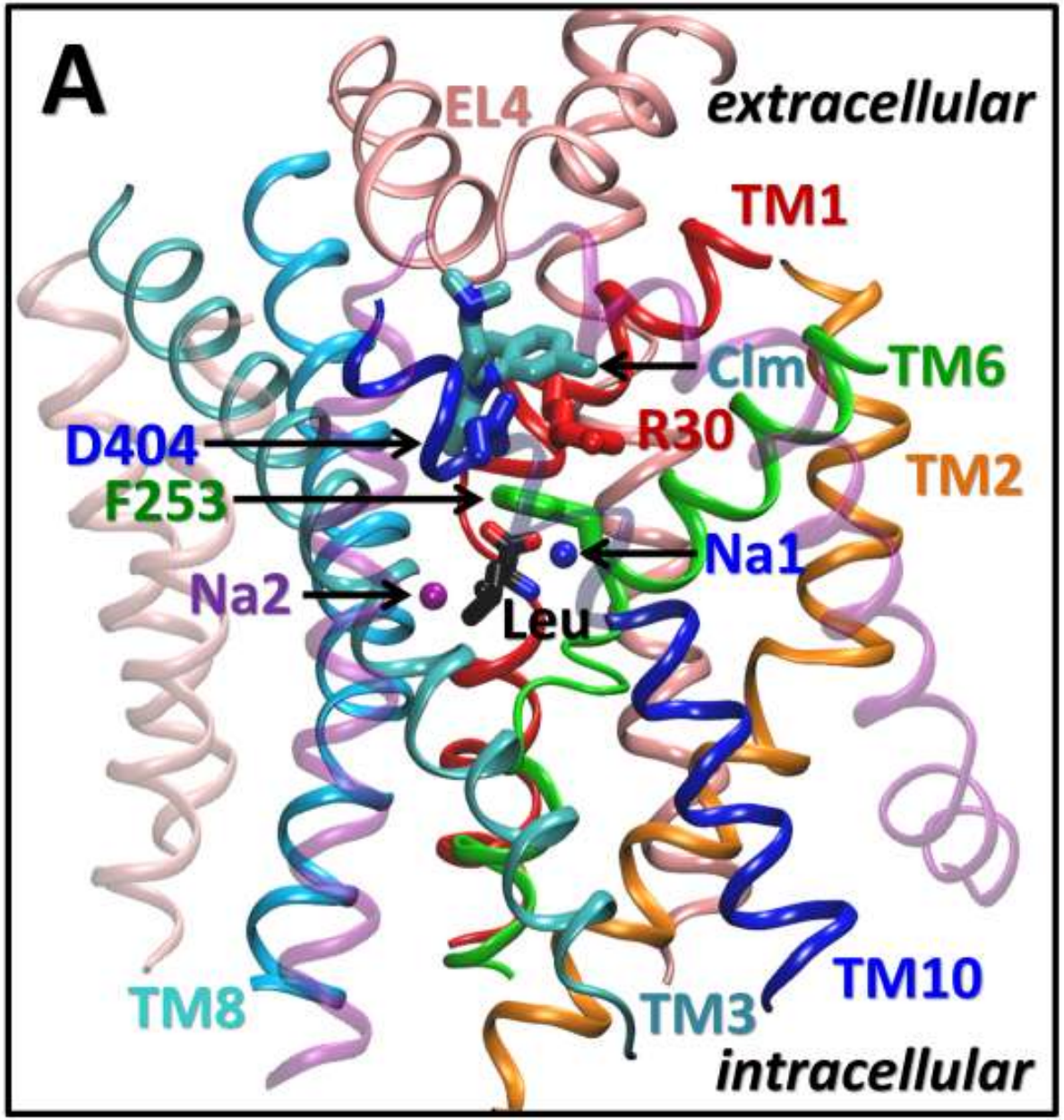




Part 2: Identification of States based on Binding States

Binding Sites



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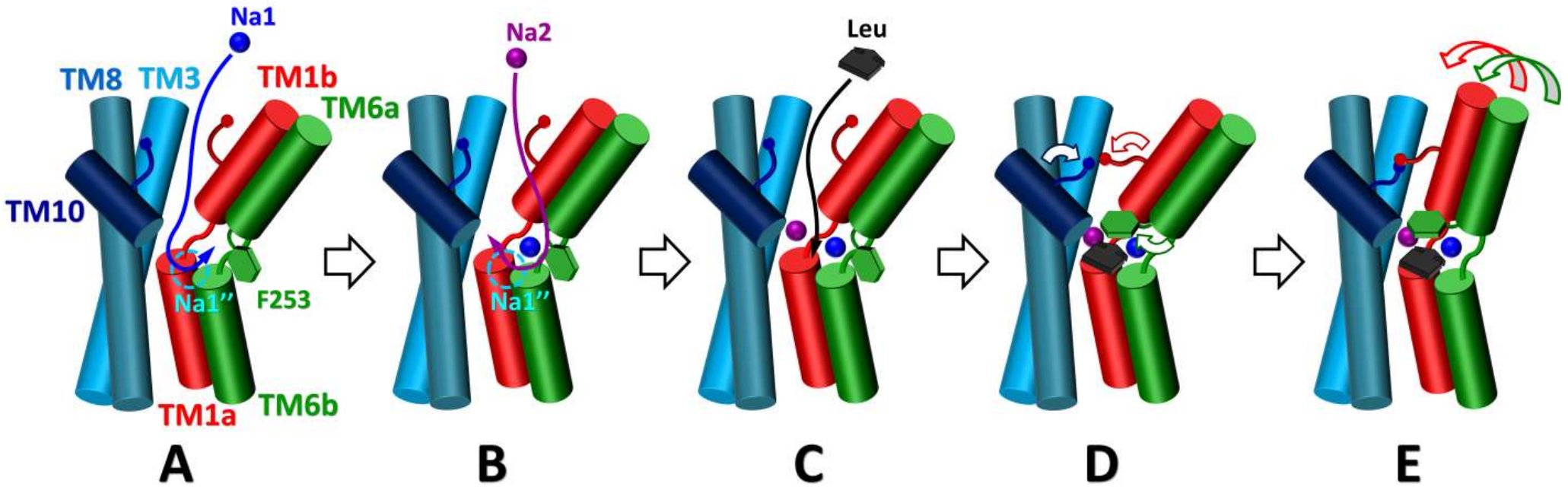
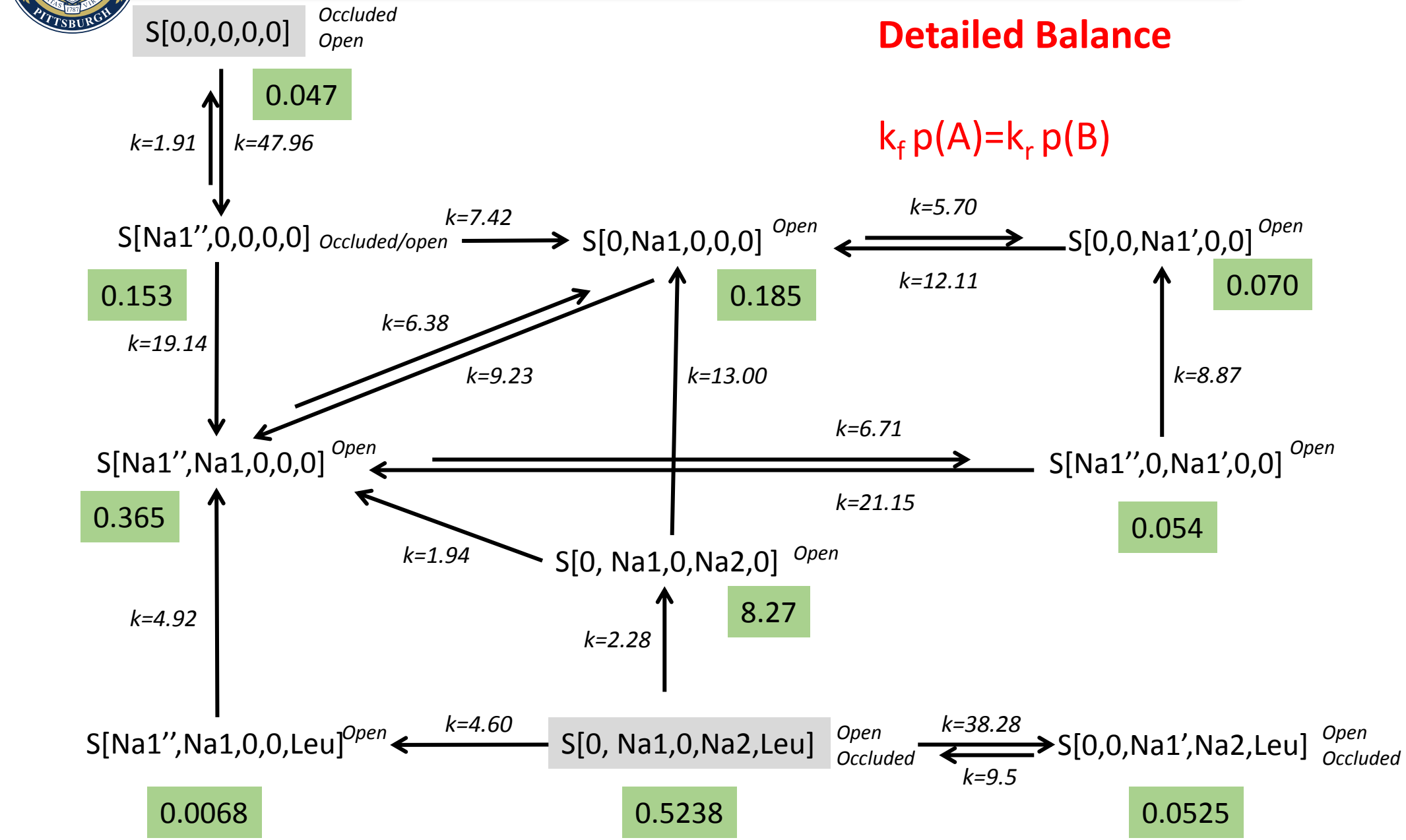
Binding Sites



S[0,0,0,0,0]	S[0,Na1,0,0,0]	S[0, Na1,0,Na2,0]	S[0, Na1,0,Na2,Leu]	S[0, Na1,0,Na2,Leu]

Summary of all Transitions

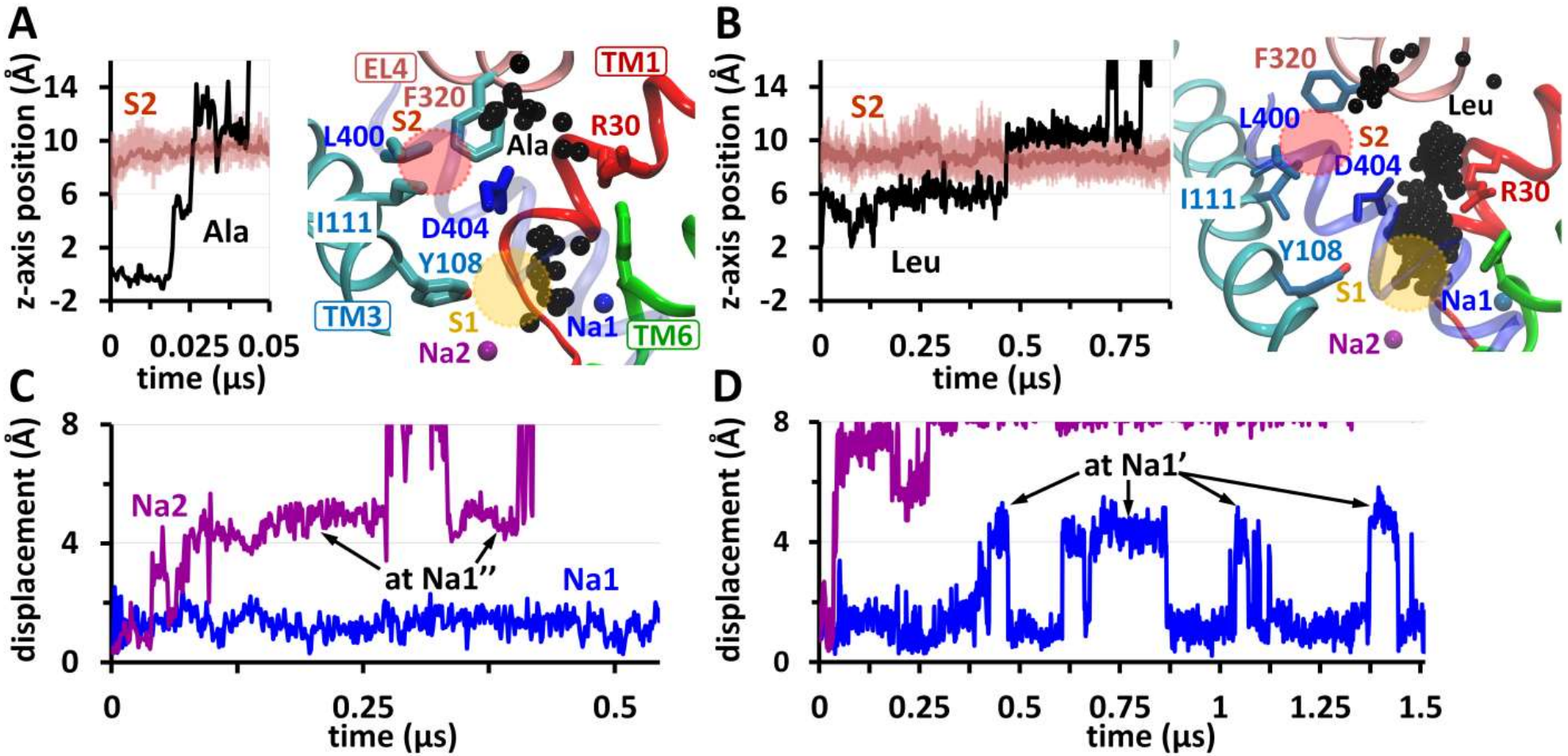


Detailed Balance

$k_f\, p(A) = k_r\, p(B)$

Summary of all Transitions

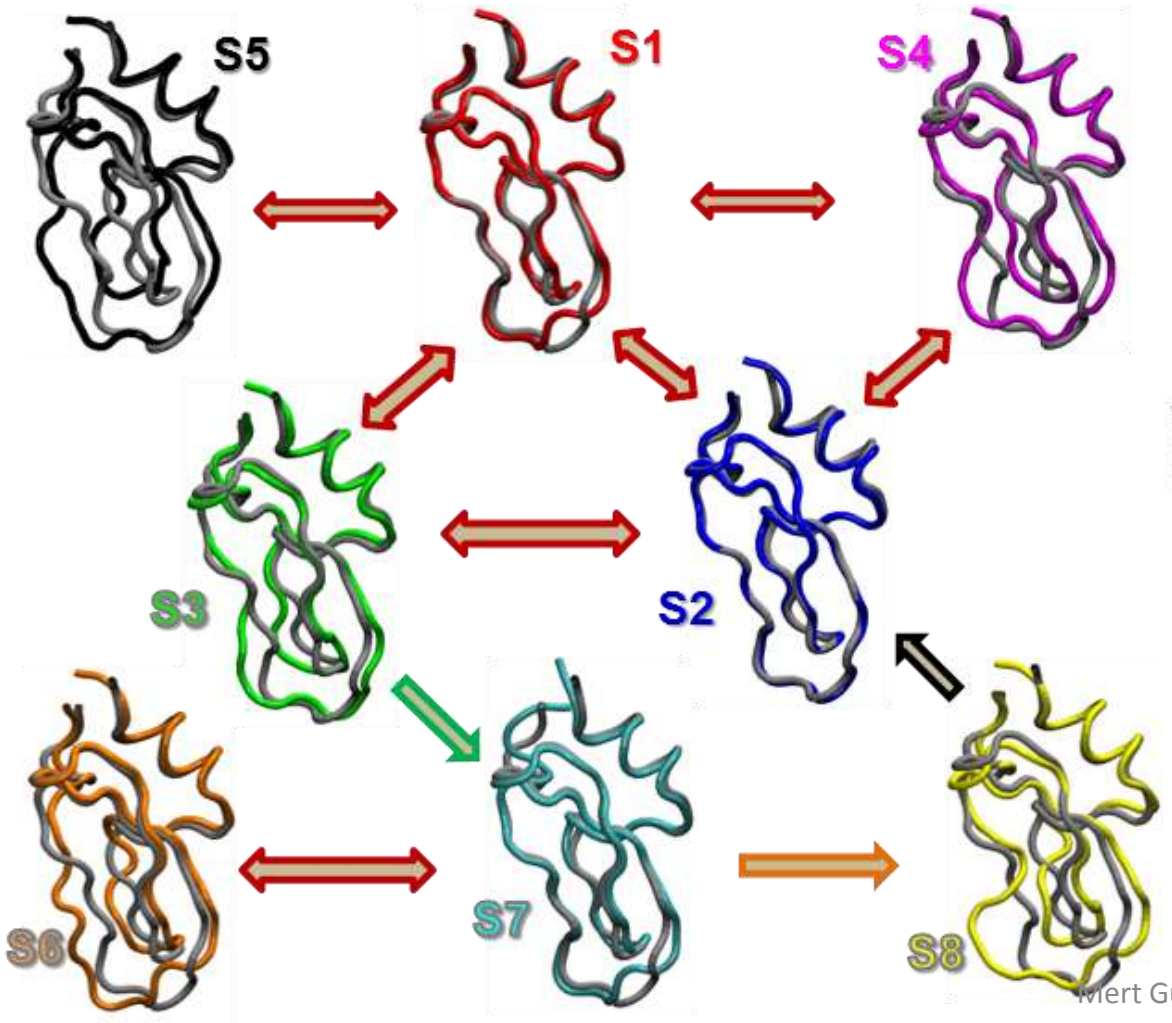
Longer simulations are needed for such a detailed mapping but only a few binding-states of Na+ may be statistically/reliably quantified.

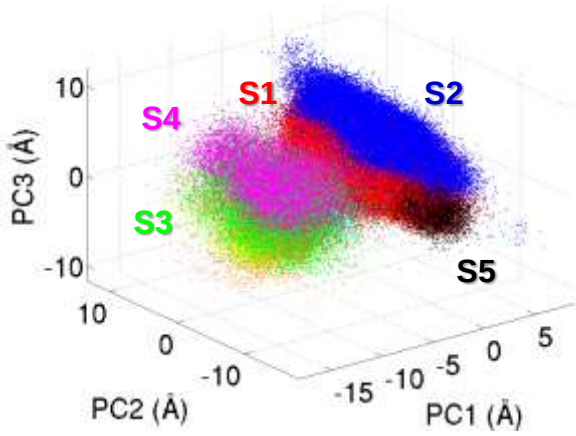


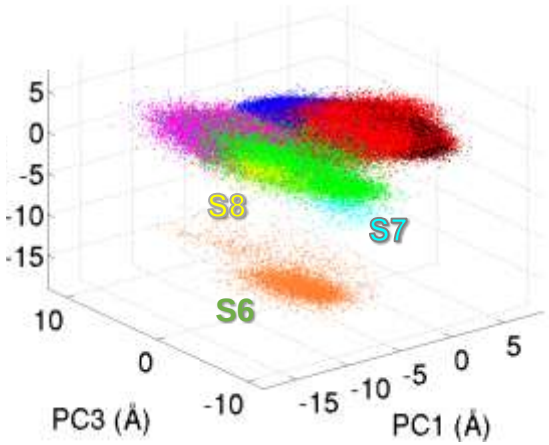
Zomot, E., M. Gur, and I. Bahar. 2014. Microseconds simulations reveal a new sodium-binding site and the mechanism of sodium-coupled substrate uptake by LeuT. *Journal of Biological Chemistry* (Under revision).

Smaller Protein: BPTI

1.013 millisecond on the native state dynamics of bovine pancreatic trypsin inhibitor (BPTI).

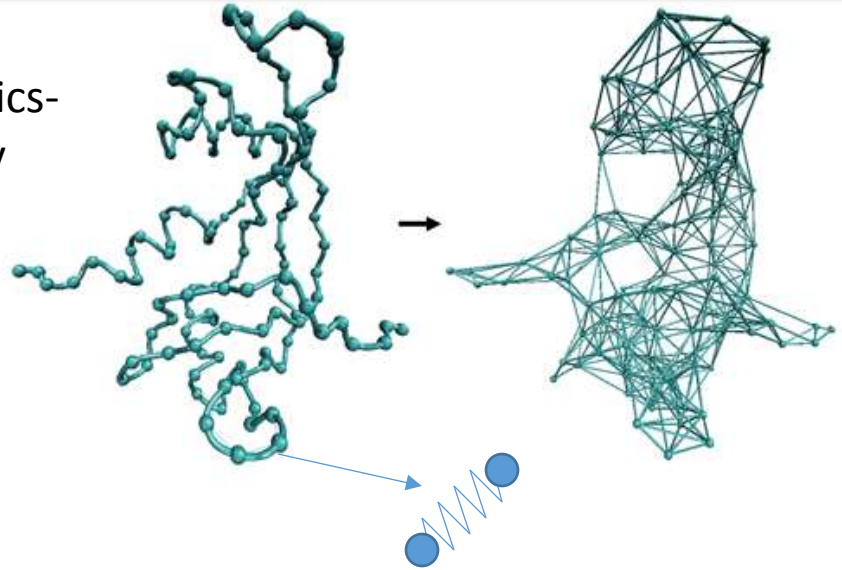






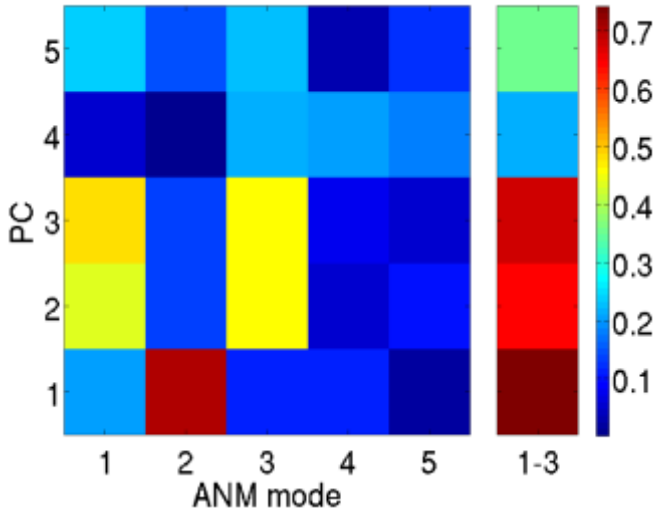
Comparison with a simple physics based model

Anisotropic Network Model (ANM) is a simple physics-based model of beads and springs, which exclusively depends on inter-residue contact topology;

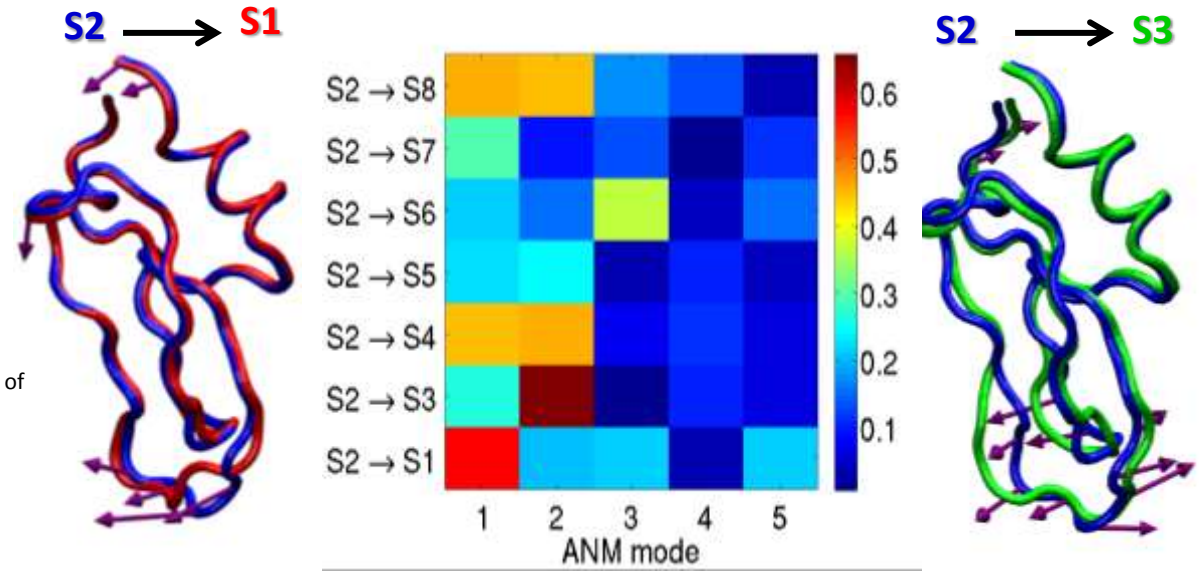


http://mmb.pcb.ub.es/FlexServ/help/NMA.php

Global Motions from MD and ANM are similar



ANM modes predict transitions between substates

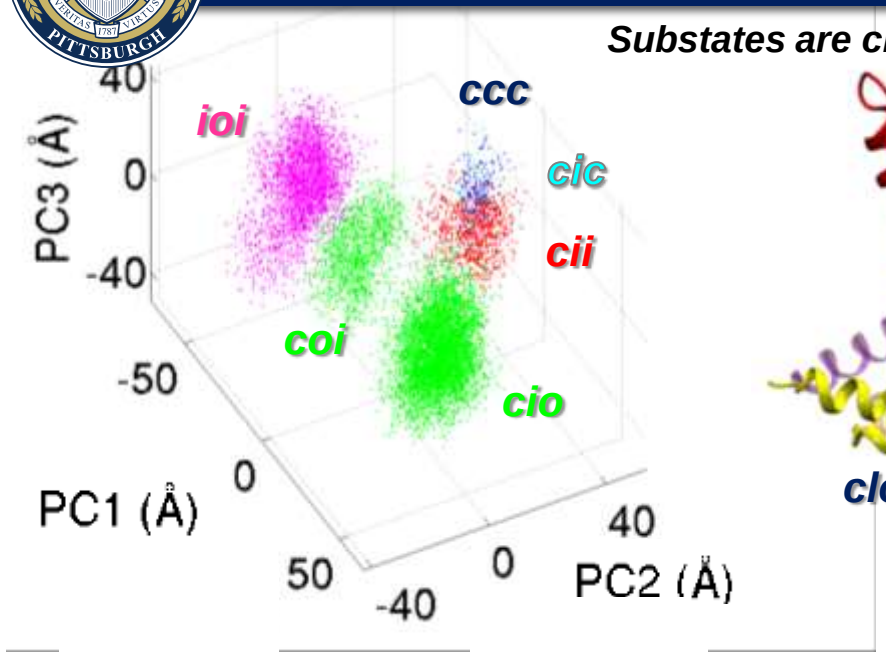


Atilgan, A. R., S. R. Durell, R. L. Jernigan, M. C. Demirel, O. Keskin, and I. Bahar. 2001. Anisotropy of fluctuation dynamics of proteins with an elastic network model. Biophys. J 80: 505-515.

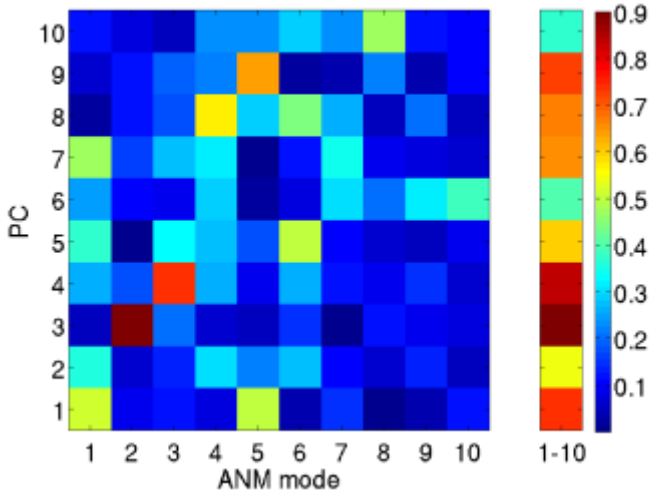
M. Gur, E. Zomot and I. Bahar. 2013. Global Motions Exhibited by Proteins in Micro- to Milliseconds Simulations Concur with Anisotropic Network Model Predictions . *J. Chem.Phys.* 139:121912

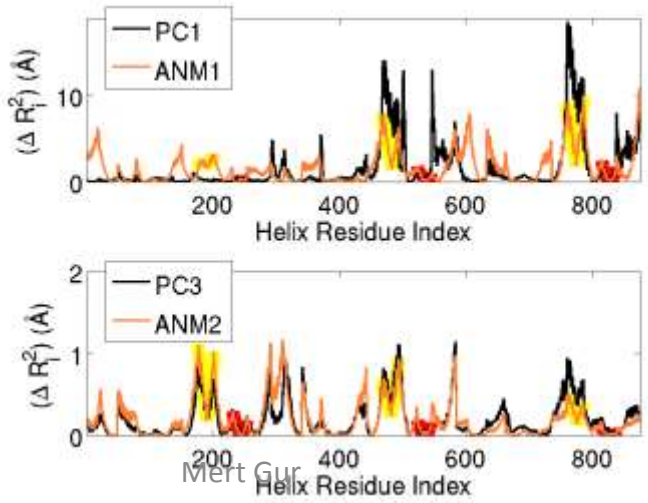
Gating mechanism of GltPh can be mapped by a few ANM modes

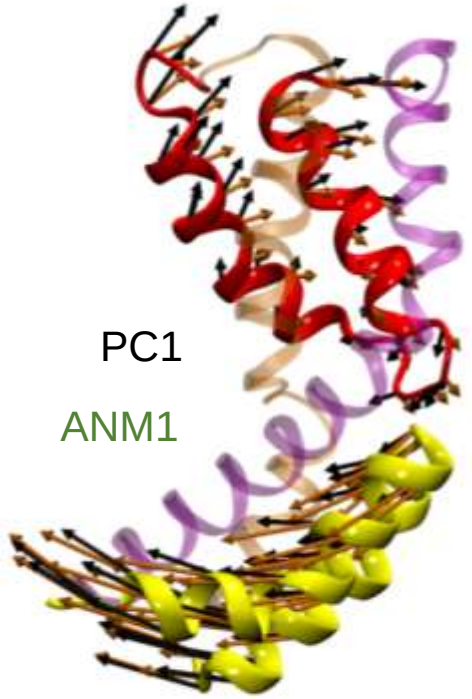
Substates are characterized by the degree of opening of the binding site



Global Motions from MD and ANM exhibit strong overlaps







Conclusion

- Molecular Dynamic simulations cannot provide unambiguous information on the complete conformational space and its energetics unless the simulations are performed for long time scales (e.g. milliseconds or longer), and even then, we obtain information on relatively localized events, not cooperative ones that involve entire multimeric structures.

- Results from simulations provide 'estimates' on accessible states and relative rates, along with insights into mechanisms, e.g. order of binding and unbinding events, relative rates of some of the steps along the transport cycle. Those binding or transport characteristics can be encoded into higher level simulations.

- There is a need to use hybrid methods (e.g. coMD that combine MD and ENM, WE, accelerated MD, ENMs) for accurate sampling of conformational space. The major challenge is then to recalibrate the results to extract quantitative information on transition rates and populations of substates