

Multiscale Investigation of Biomolecular Systems Dynamics

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Introduction

- Proteins undergo continual conformational changes under physiological conditions while maintaining their overall fold.
- Local changes, typically over timescales of up to tens of nanoseconds, can be efficiently modeled by all-atom simulations; whereas global transitions, which usually occur on the time scale of microseconds or more, are beyond the capacity of most computing systems.
- To simulate global transitions we developed a new methodology, called **collective molecular dynamics (coMD)**, which takes advantage of the global normal modes, while evaluating the interactions and energetics via a full-atomic molecular dynamics simulation protocol.



Can MD be guided by Normal/ANM modes?

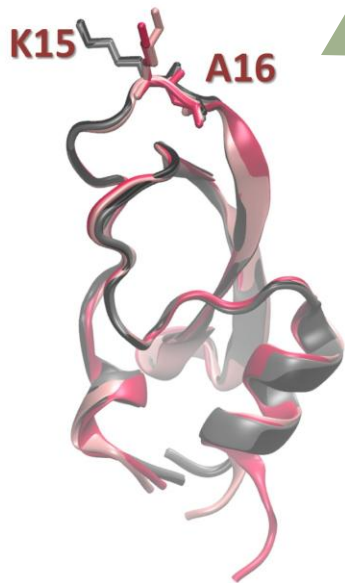
- Normal Modes are evaluated using the **Anisotropic Network Model (ANM)**.
- ANM is a simple physics-based model of beads and springs that exclusively depends on inter-residue contact topology.
- These slowest modes often relate to functional changes in structure, such as the fluctuations between the unbound (open) and bound (closed) conformers of a given enzyme, or the passage between the different substates of allosteric proteins (which are all experimentally resolved structures).
- A direct comparison of ANM-predicted dynamics with that observed in all-atom micro-to-milliseconds molecular dynamics is missing in the literature.



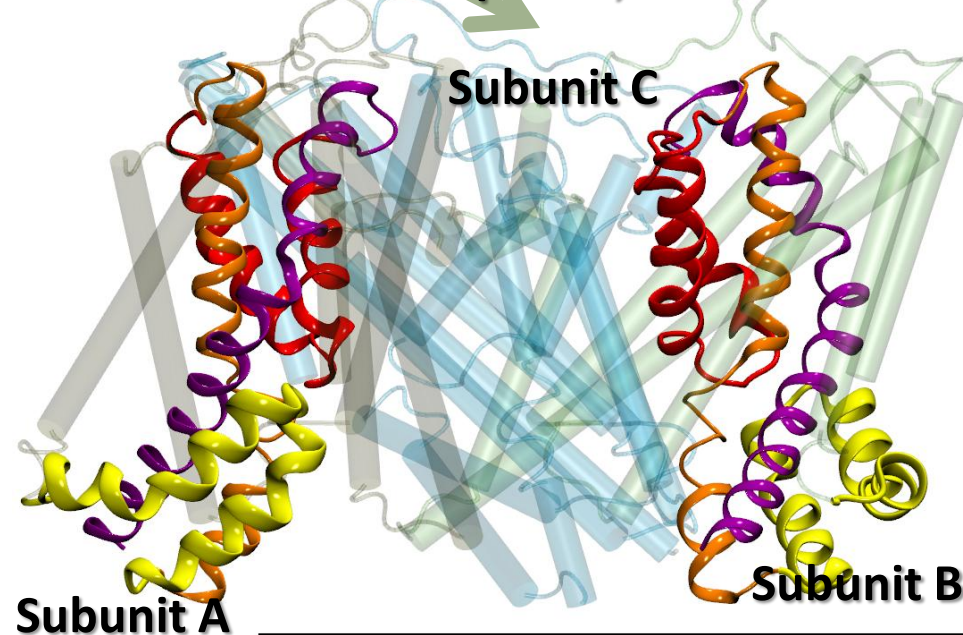
Introduction

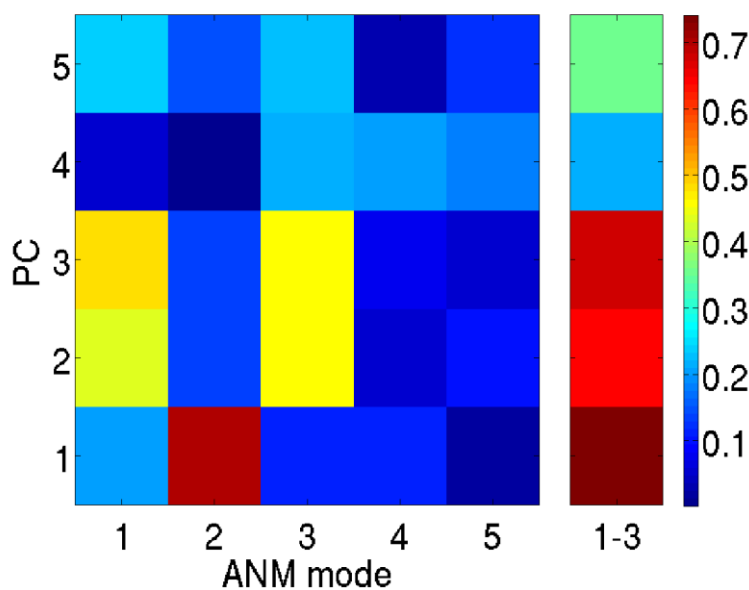
We analyze two Anton-generated trajectories

1.013 millisecond on the equilibrium dynamics of bovine pancreatic trypsin inhibitor (BPTI)

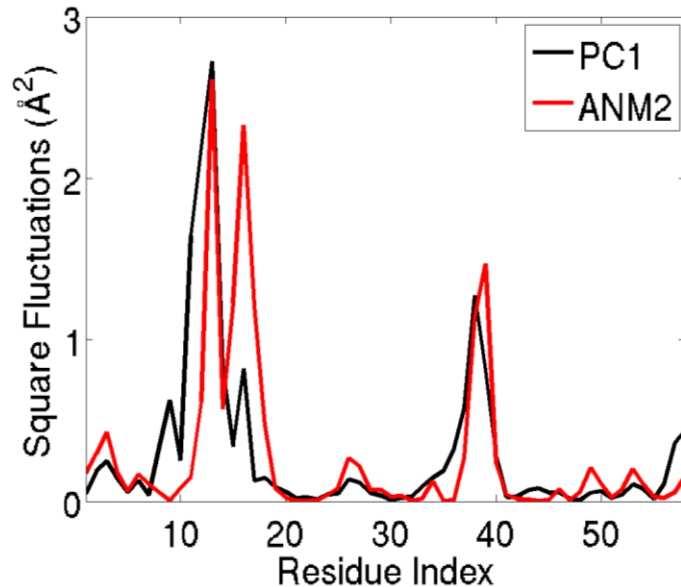


12 microseconds on the gating mechanism of archaeal aspartate transporter, GltPh

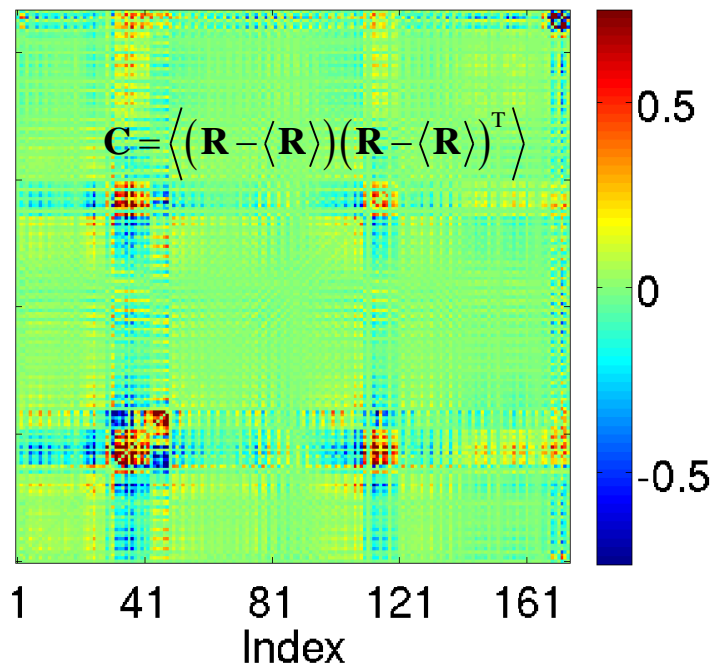
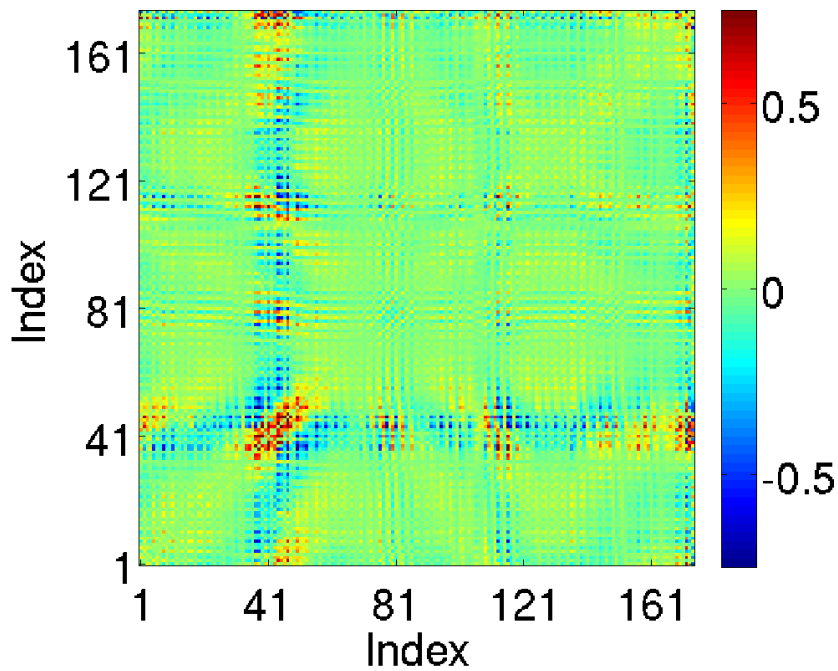




Covariance (ANM) first 3 modes



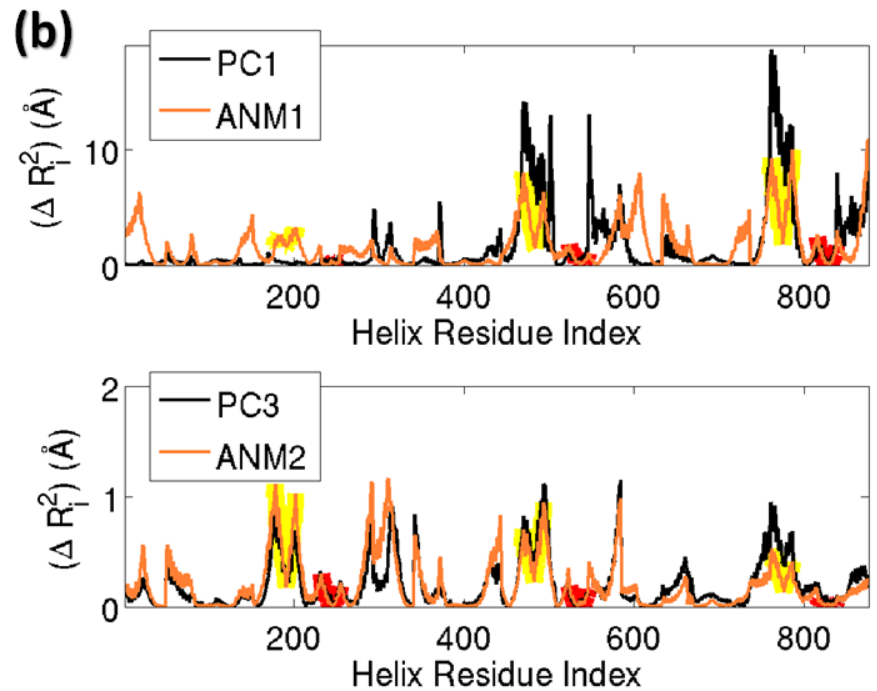
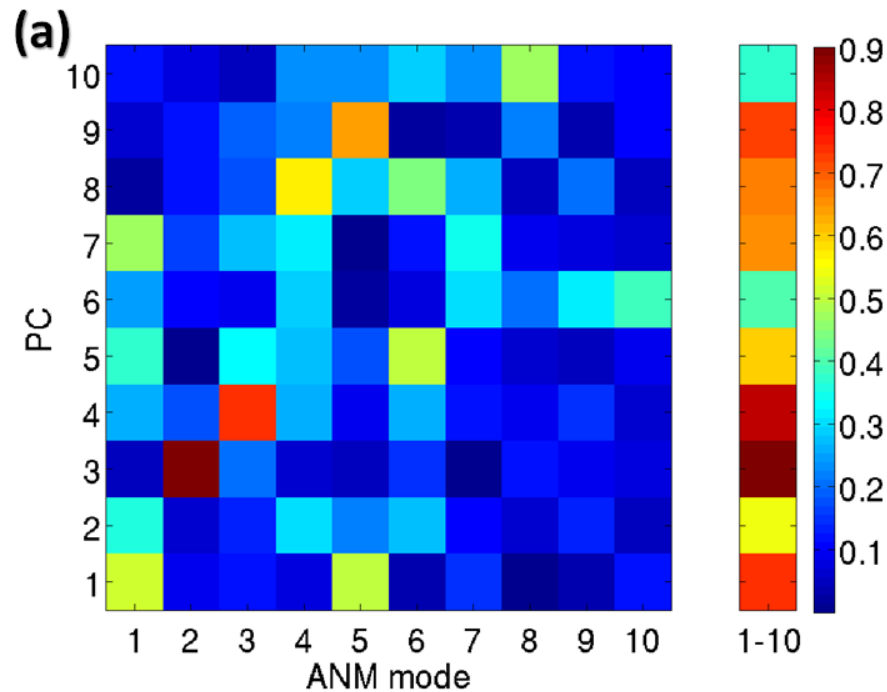
Covariance (MD) first 3 PCs



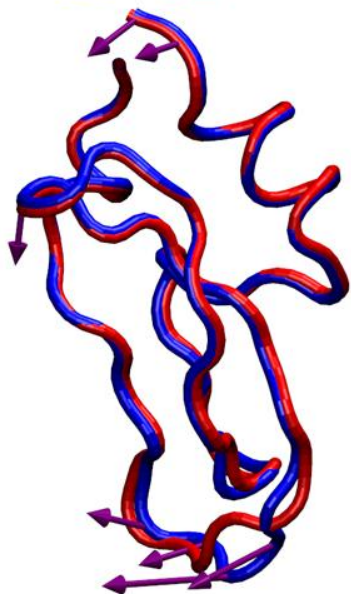
Bovine Pancreatic Trypsin Inhibitor

BPTI trajectory was generated by D. E. Shaw, P. Maragakis, K. Lindorff-Larsen, S. Piana, R. O. Dror, M. P. Eastwood, J. A. Bank, J. M. Jumper, J. K. Salmon, Y. B. Shan and W. Wriggers, Science **330**, 341 (2010)

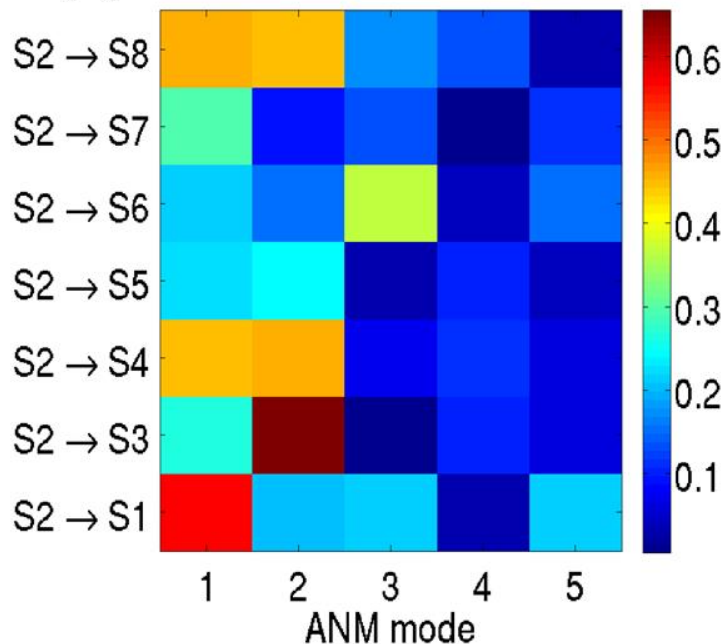
Archaeal Aspartate Transporter



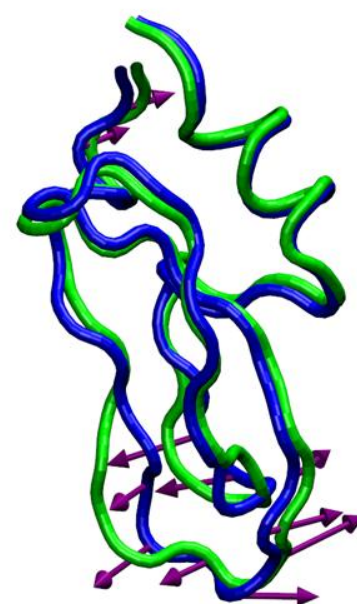
(a) S2 → S1



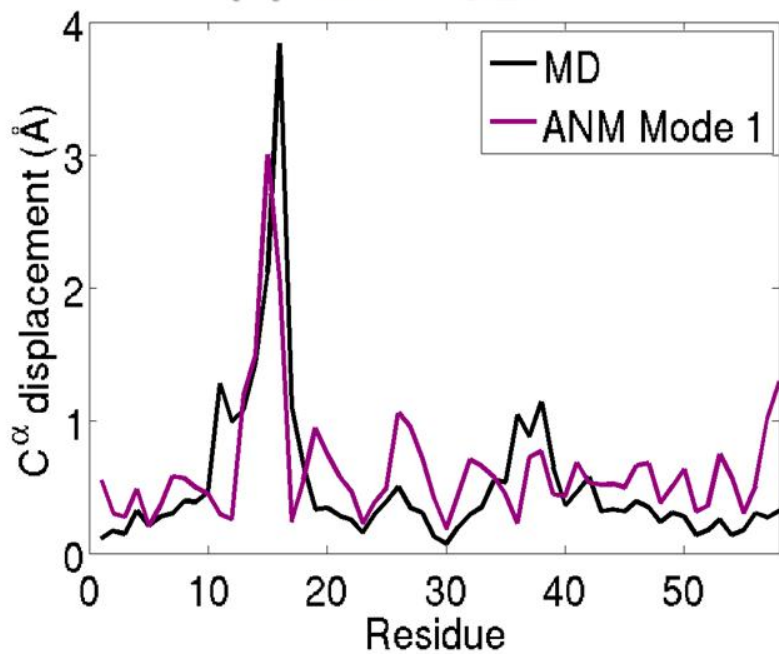
(b)



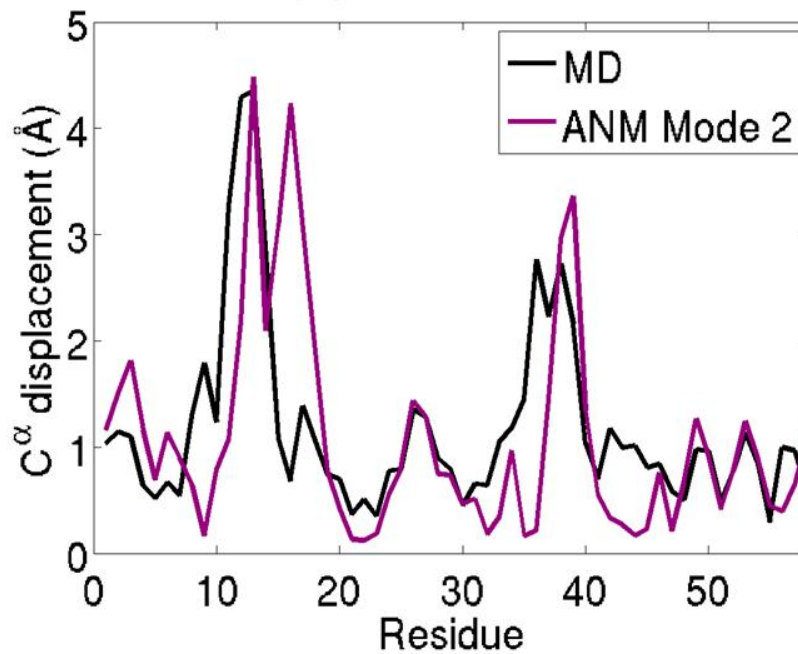
(c) S2 → S3



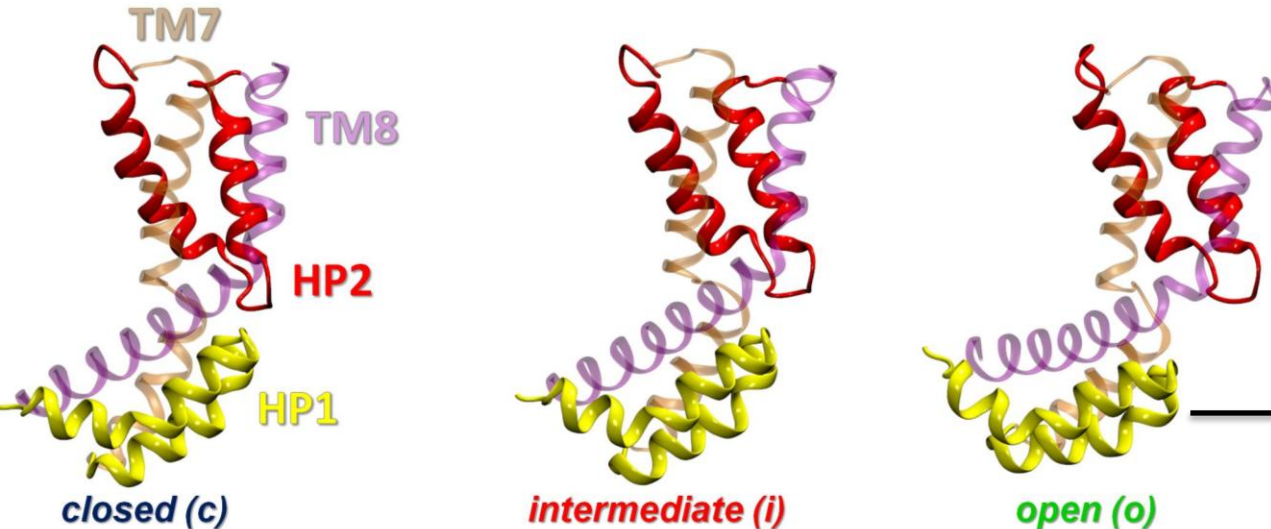
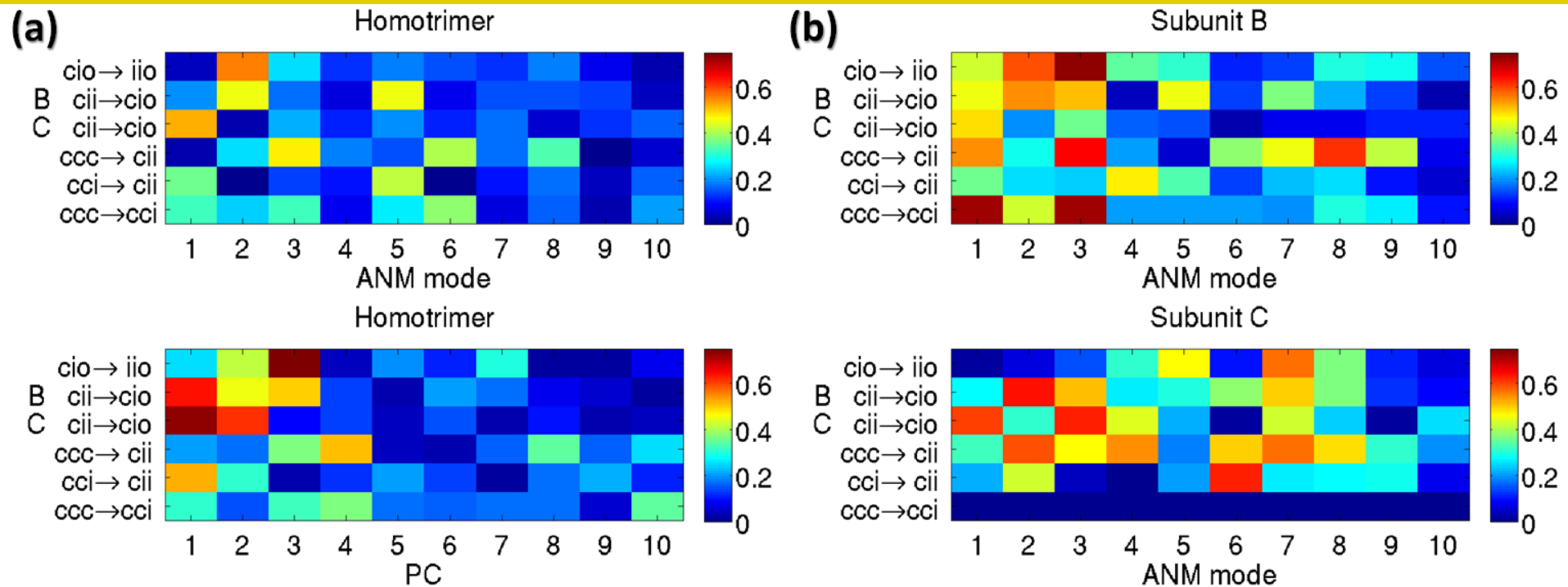
(d) S2 → S1



(e) S2 → S3

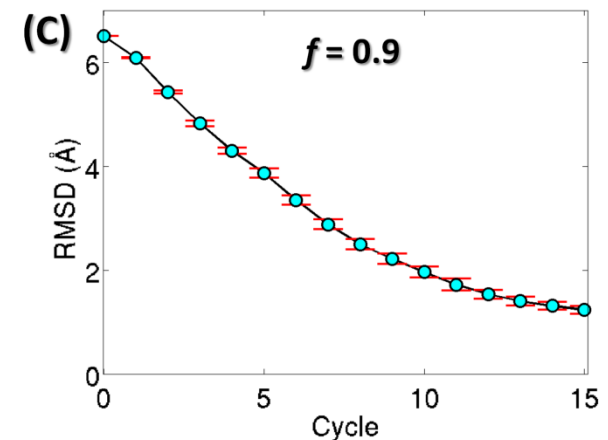
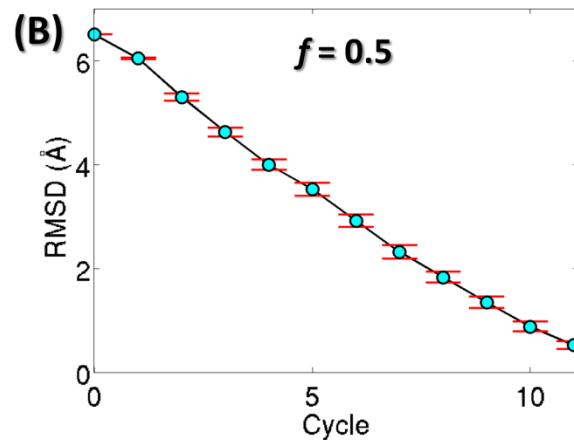
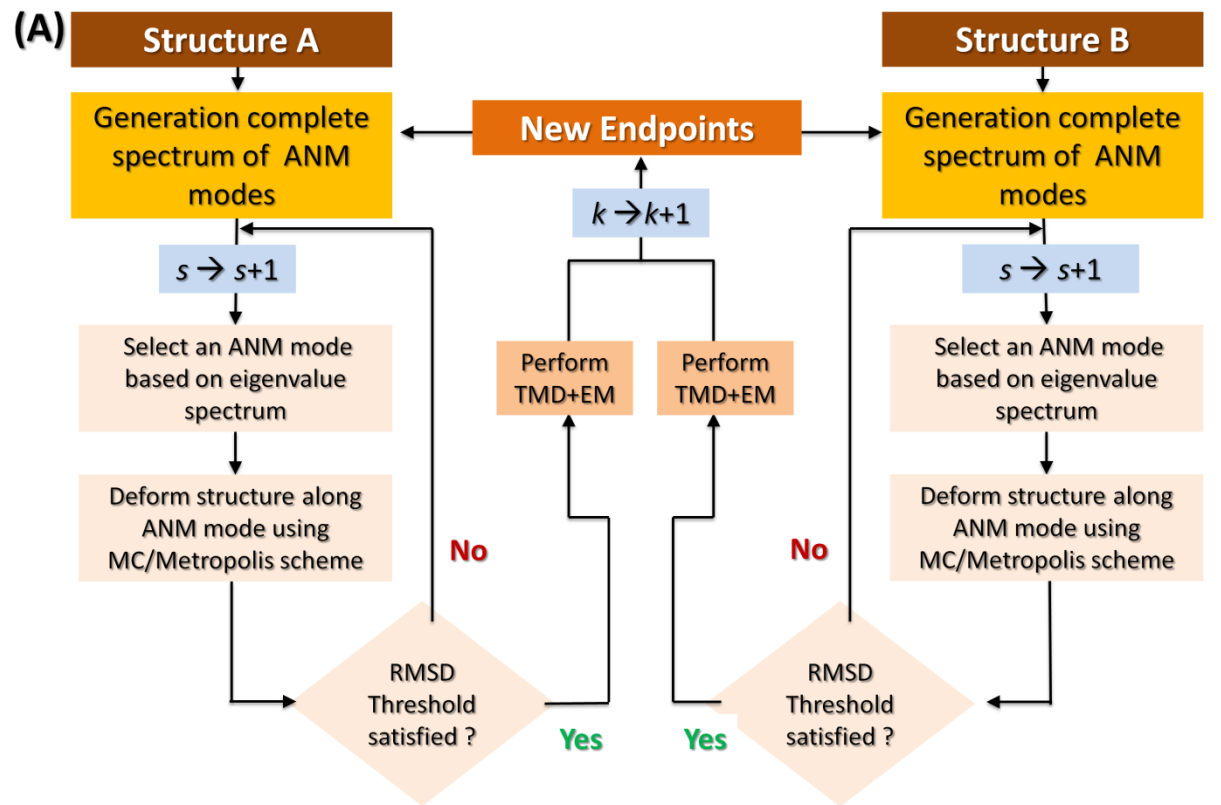


Archaeal Aspartate Transporter



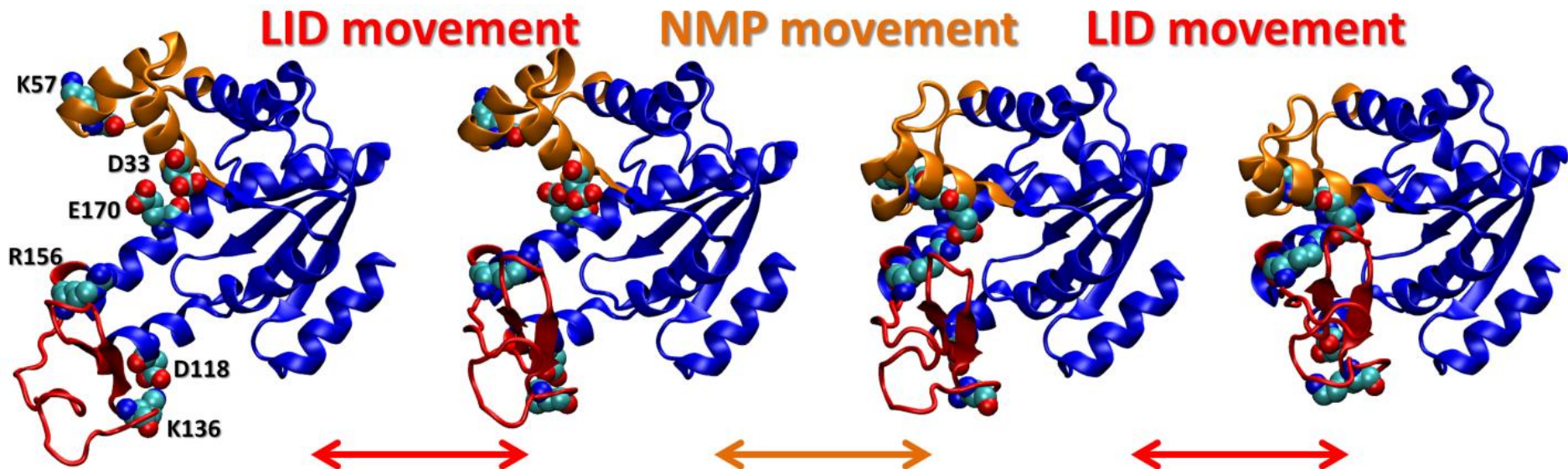
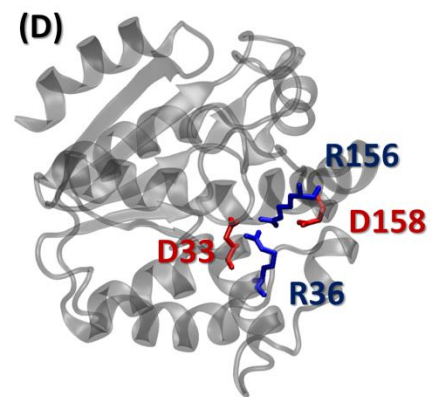
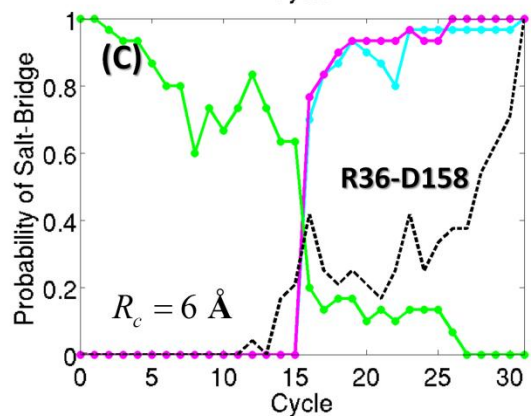
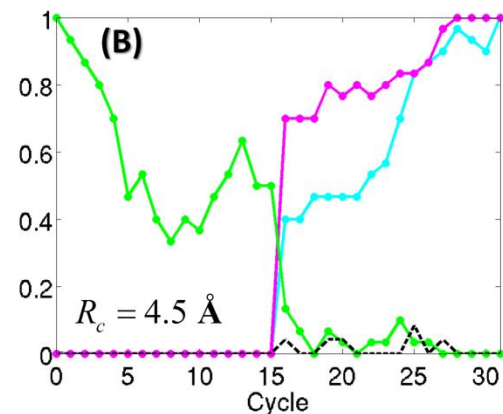
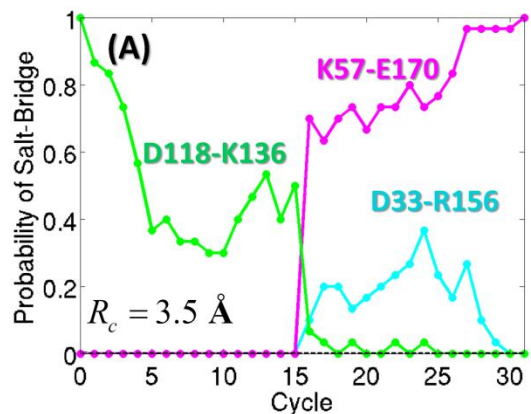
coMD

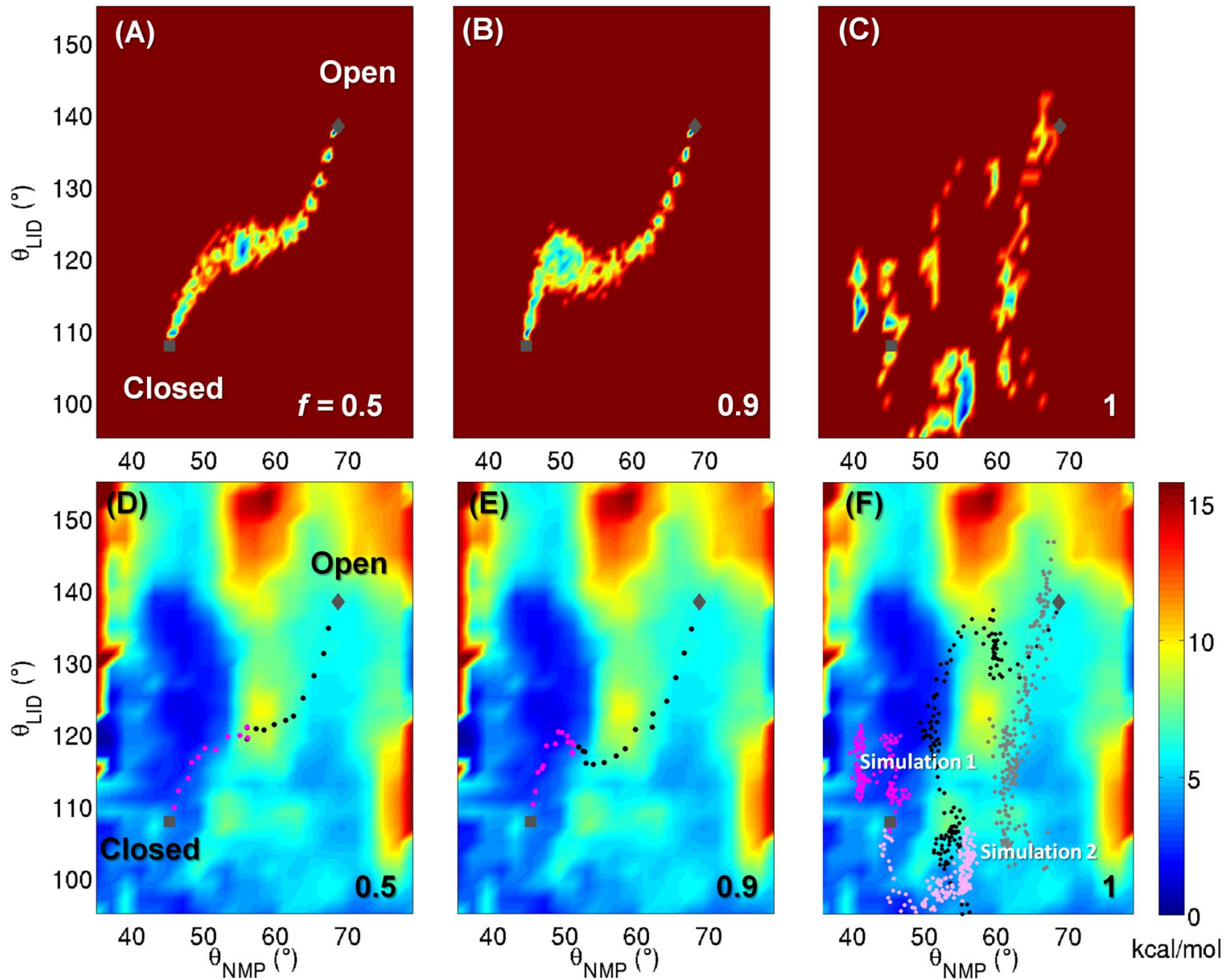
- The basic approach is to deform the structure collectively along the modes predicted by the anisotropic network model, upon selecting them via a Monte Carlo/Metropolis algorithm from amongst the complete pool of all accessible modes.



coMD

An energy-barrier crossing occurs during the NMP movements. The energy barrier originates from a switch between the salt bridges K136-D118 at LID-CORE interface and K57-E170 and D33-R156 at CORE-NMP and LID-NMP interfaces, respectively.

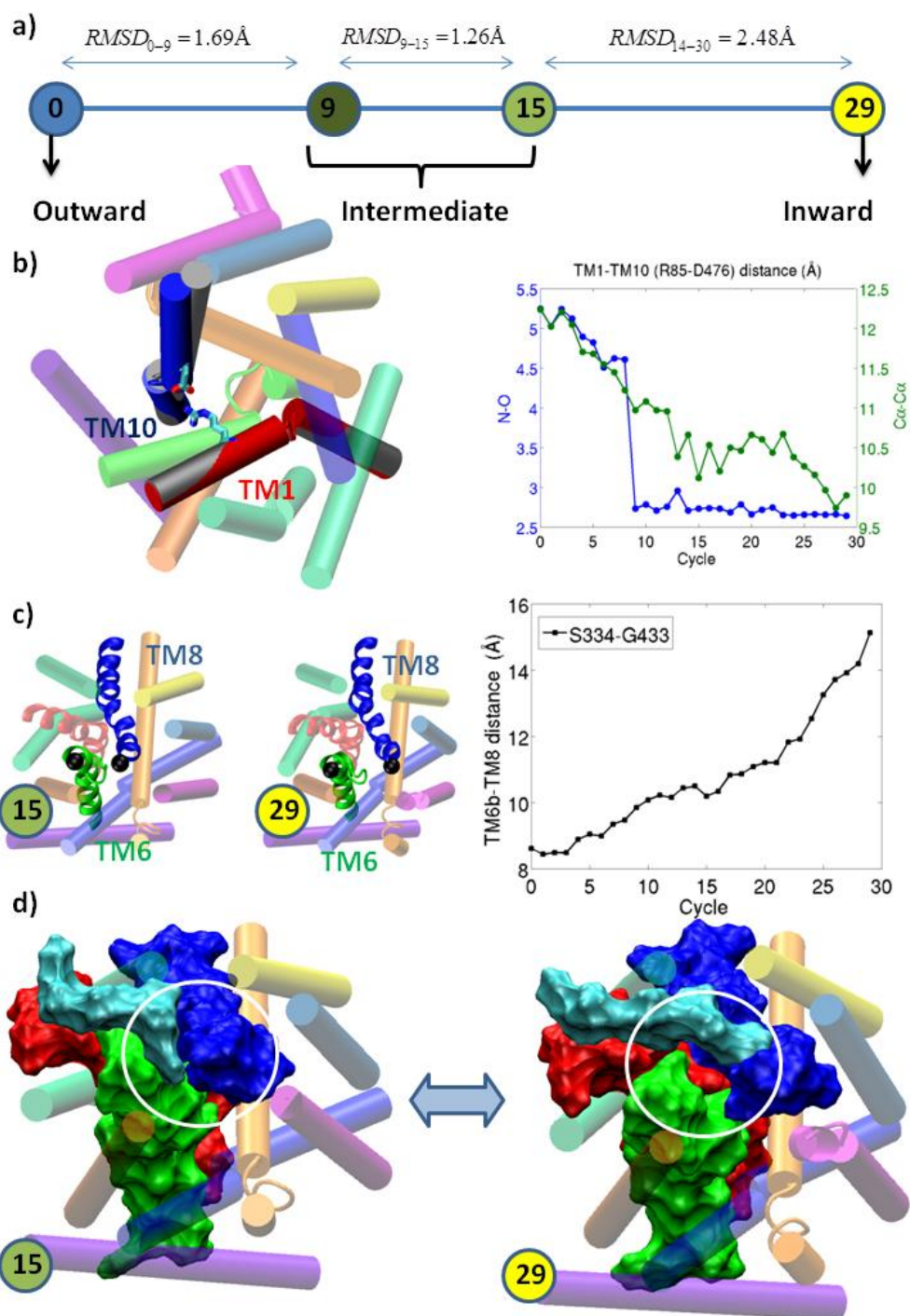




Potential of Mean Force surface was generated by Beckstein, O., E. J. Denning, J. R. Perilla, and T. B. Woolf. J. Mol. Biol. 394: 160-176. (2009)

coMD on performed on Dopamine Transporter

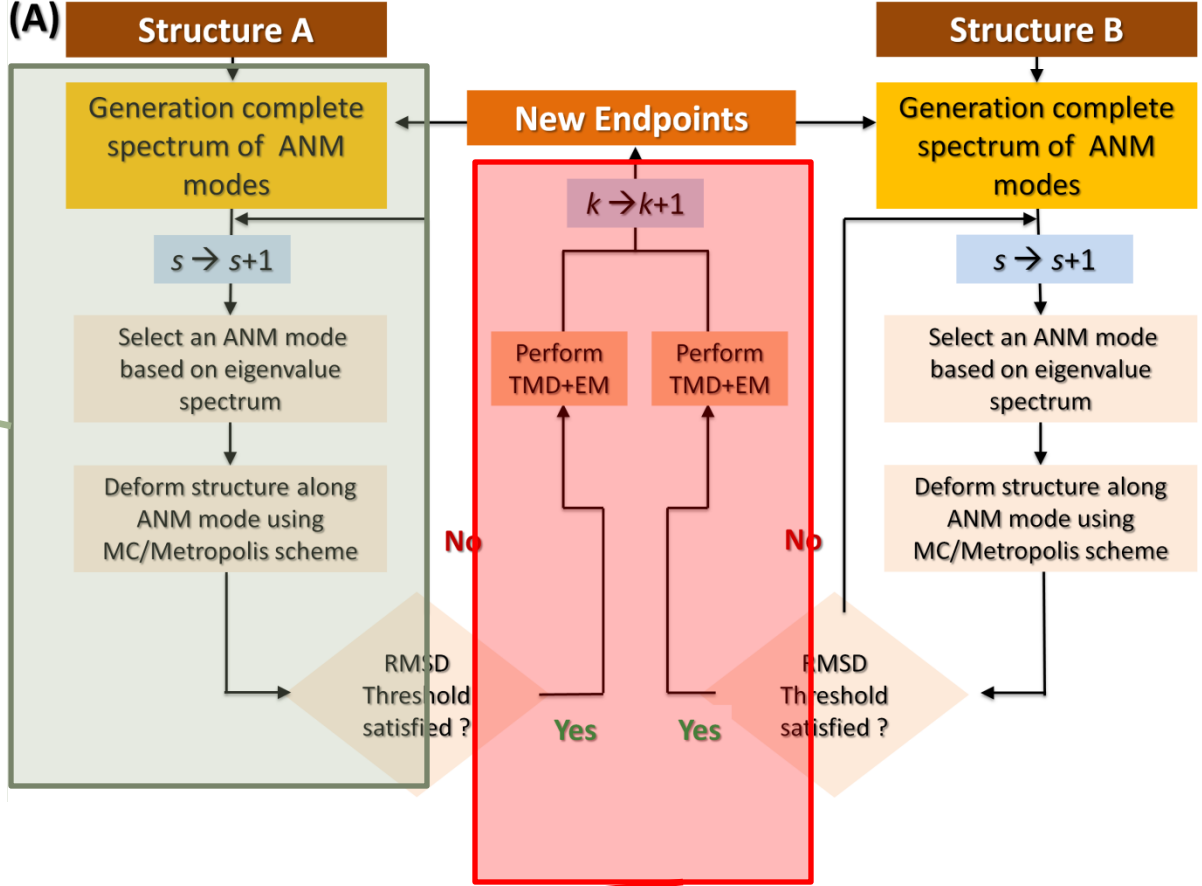
- The transition mechanism of dopamine transporter (DAT) between its inward- and outward-facing states were explored. An intermediate state occluded to both the extra- and intracellular regions is identified



coMD

MATLAB

Takes ~15 min for small system like AK and ~45 min for membrane transporter (LeuT,DAT)



NAMD

The longer the better!

Aiming to accelerate coMD simulations with GPUs!



Thank you!

Acknowledgment

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- Jeffry Madura
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