Multiscale Investigation of Biomolecular Systems Dynamics

Mert Gur and Ivet Bahar
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 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.
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

Archaeal Aspartate Transporter

(a) [Heatmap showing PC vs. ANM mode]

(b) [Graph showing R2(Δ) in black and ANM in red]

Mert Gur and Ivet Bahar

Department of Computational and Systems Biology
Archaeal Aspartate Transporter

(a) Homotrimer

(b) Subunit B

(c) Subunit C

TM7
TM8
HP2
HP1

closed (c)
intermediate (i)
open (o)

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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.
Application to adenylate kinase (AK), an allosteric enzyme composed of three domains, CORE, LID and NMP, shows that both open-to-closed and closed-to-open transitions of AK are readily sampled, being dominated by large-scale motions of the LID.
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.
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.
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!

Mert Gur and Ivet Bahar
Thank you!

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