The Secrets in their Landscapes: Elucidating Activation Mechanism of Proteins for Selective Drug Design

Diwakar Shukla
Assistant Professor, Chemical & Biomolecular Engineering
Blue Water Symposium 2015
illinois.edu
Cellular Signaling and human diseases
Cellular Signaling and diseases

- GPCRs 30%
- Kinases 47%
- Transporters 4%
- Other Receptors 8%
- Ion channels 7%
- Others 4%

Zanoni et. al., FEBS letters, 583, 11, 2009
Challenge: Long time scale associated with conformational change
Markov State Models (MSM)

The most basic ingredients of Markov State Models are the states and rate constants connecting them.

- States and rates are familiar in the context of chemical equilibria
- Complex networks of states and transitions are possible

\[
\frac{dP_i}{dt} = \sum_{j \neq i} k_{ji} P_j - \sum_{j \neq i} k_{ij} P_i
\]

\[i, j = A, B, C, D\]
Long timescale phenomena as series of Markov jump processes

\[ \frac{dP_i}{dt} = \sum_{j \neq i} k_{ji} P_j - \sum_{j \neq i} k_{ij} P_i \]

\( i, j = [0, 3000] \)

How do we get rates?

\( k_{AB} \) nanoseconds

\( k_{AC} \) 100’s of microseconds
Adaptive sampling of the conformational landscape

1. Select starting conformation
2. Conformational sampling
3. Build Markov State Model
4. Select new starting conformations
Adaptive sampling of the conformational landscape

MSM Adaptive Sampling

Single MD Trajectory
G-Protein Coupled Receptors

2012 Nobel Prize in Chemistry

Kinetics of GPCR molecular switches

**Activating ligand bound**
- Connector rmsd from active
- Helix 5 bulge rmsd from active
- NPxxY rmsd from active
- Helix 3-Helix6 Distance

**Receptor without ligand**
- Connector rmsd from active
- Helix 5 bulge rmsd from active
- NPxxY rmsd from active
- Helix 3-Helix6 Distance

Graphs showing the dynamics of various parameters over time.
Intermediate states select for novel drug molecules

Agonist Chemotype Enrichment

nature chemistry
Conformational changes in Calmodulin

Conformational changes in Calmodulin

 apo-CaM

 holo-CaM

Intermediate states along the highest flux pathway

Hydrophobic repacking of the core determines the substrate selectivity

red: Phe, orange: hydrophobic, grey: other

Shukla et al., Nat. Commun., In review, 2015
Prediction of chemically and sterically distinct binding interfaces

1: canonical apo topology (58%)

2: Phe-lined groove (7%)

3: canonical holo topology (19%)

1: canonical holo topology (55%)

2: Met-lined depressions (38%)

red: Phe; orange: hydrophobic; cyan: Met; grey: other
Prediction of chemically and sterically distinct binding interfaces

White dots represent the available CaM crystal structures in PDB. Simulations were started from only two structures of CaM.

colorbar units: kcal/mol
Molecular Design of Drought resistant plants

FUTURE DROUGHTS
The risk of a decade-long drought within the next century is highest in Texas and the Southwest.

Lamont Doherty Earth Observatory of Columbia University; U.S. Drought Monitor; Cornell University
Doyle Rice, Frank Pompa and Julie Snider, USA TODAY
Motivation: Climate Change, Population Growth, Improved Agrochemicals, Links to Human Health
Steroid signaling and plant development

1. Steroid binds to receptor on surface of membrane.
3. Steroid acts as glue.
Simulation and experiments for obtaining mechanistic insights in growth signaling
Computational Plant Engineering on Blue Waters

Model Types
MM – Molecular Modeling
ODE – Ordinary Diff. Eq.
ABM – Agent Based Modeling
FE – Finite Element
PDE – Partial Diff. Eq.

O’Dwyer: Ecosystem
Long: System
Marshall-Colon: Cell/Gene
Shukla: Molecule

Long et al., Cell, 2015
Acknowledgements

Blue Waters Supercomputer
Alexander S. Moffett
Zahra Shamsi
Prof. Vijay S. Pande, Stanford University