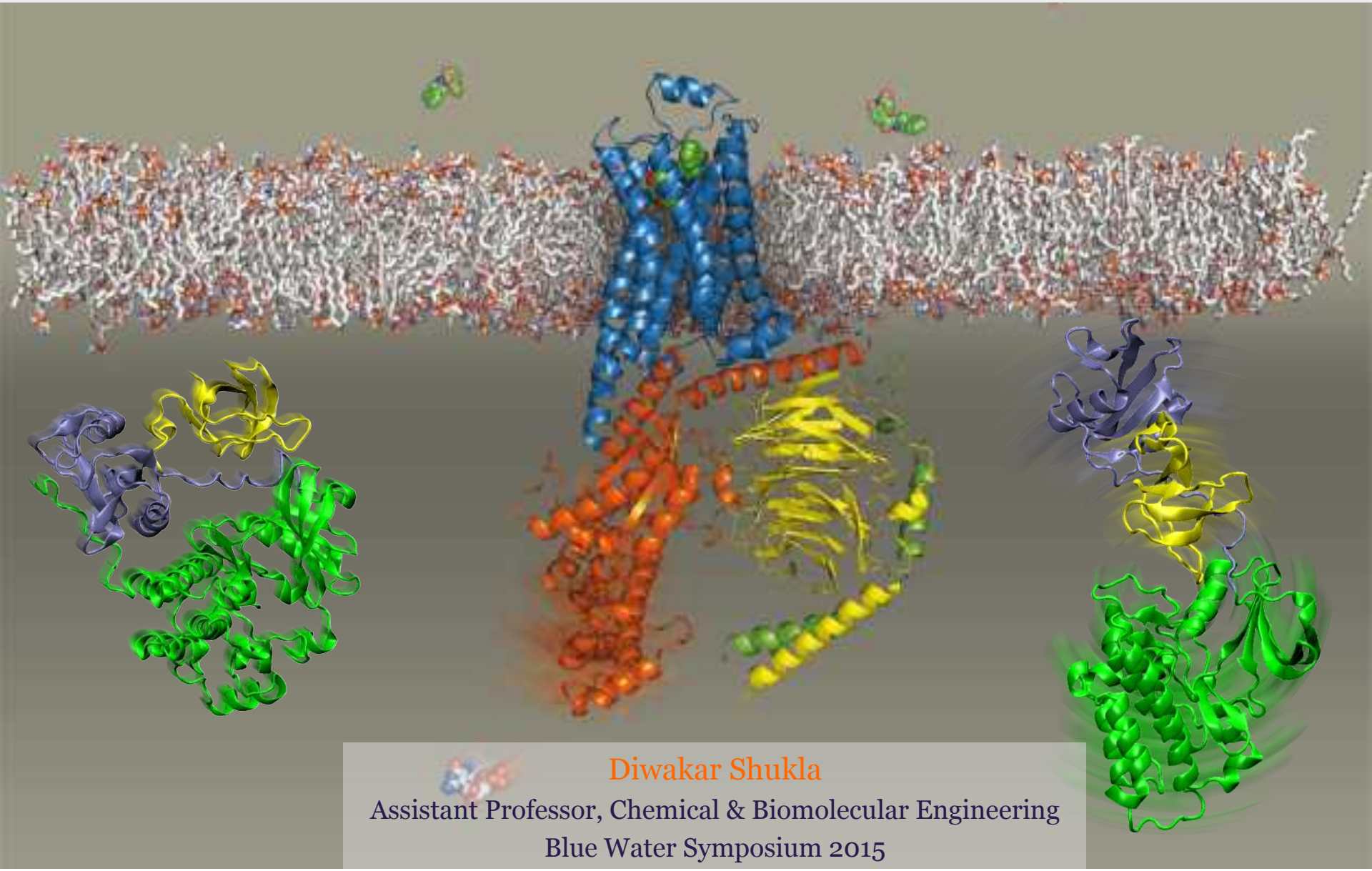
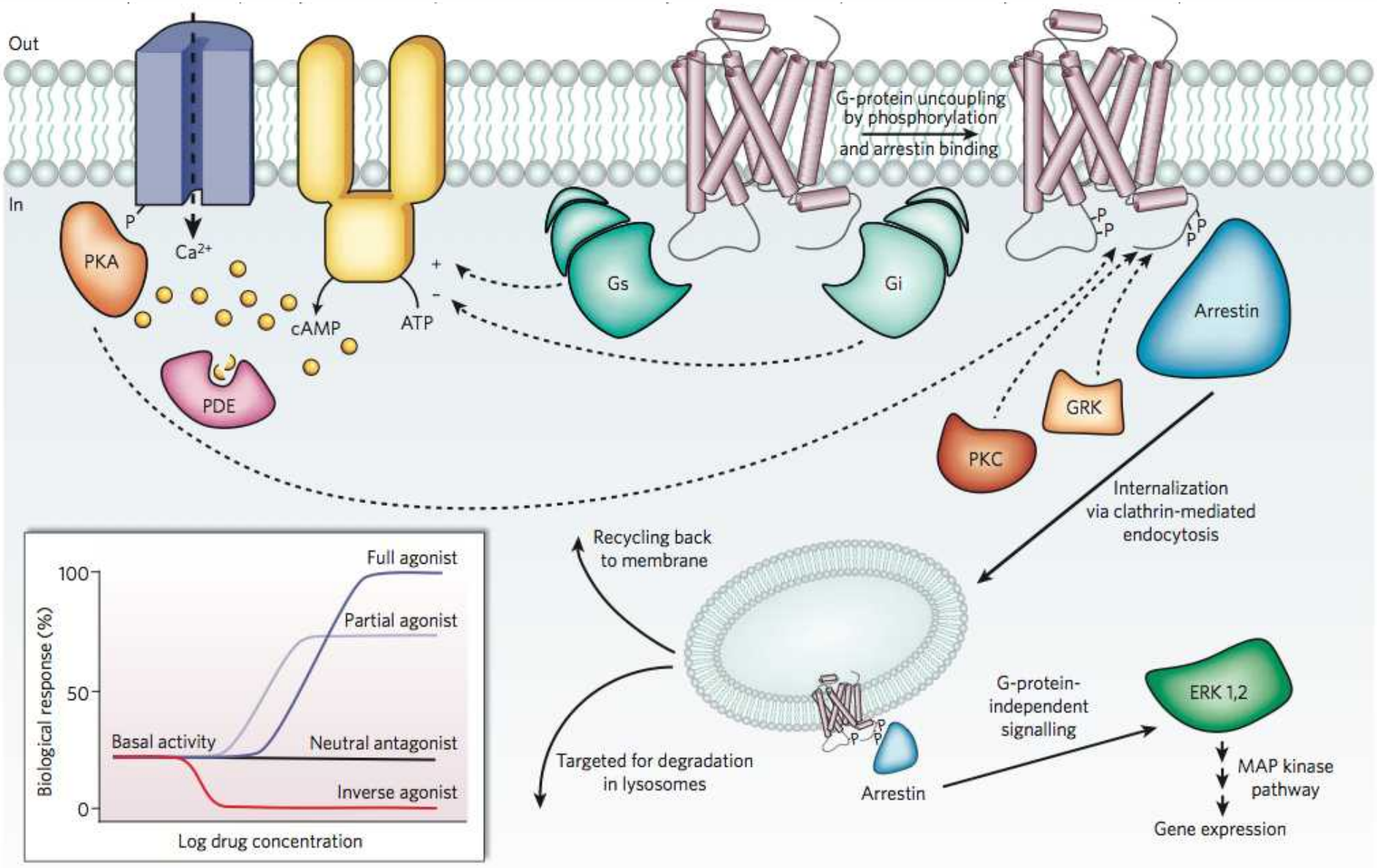
The Secrets in their Landscapes: Elucidating Activation Mechanism of Proteins for Selective Drug Design



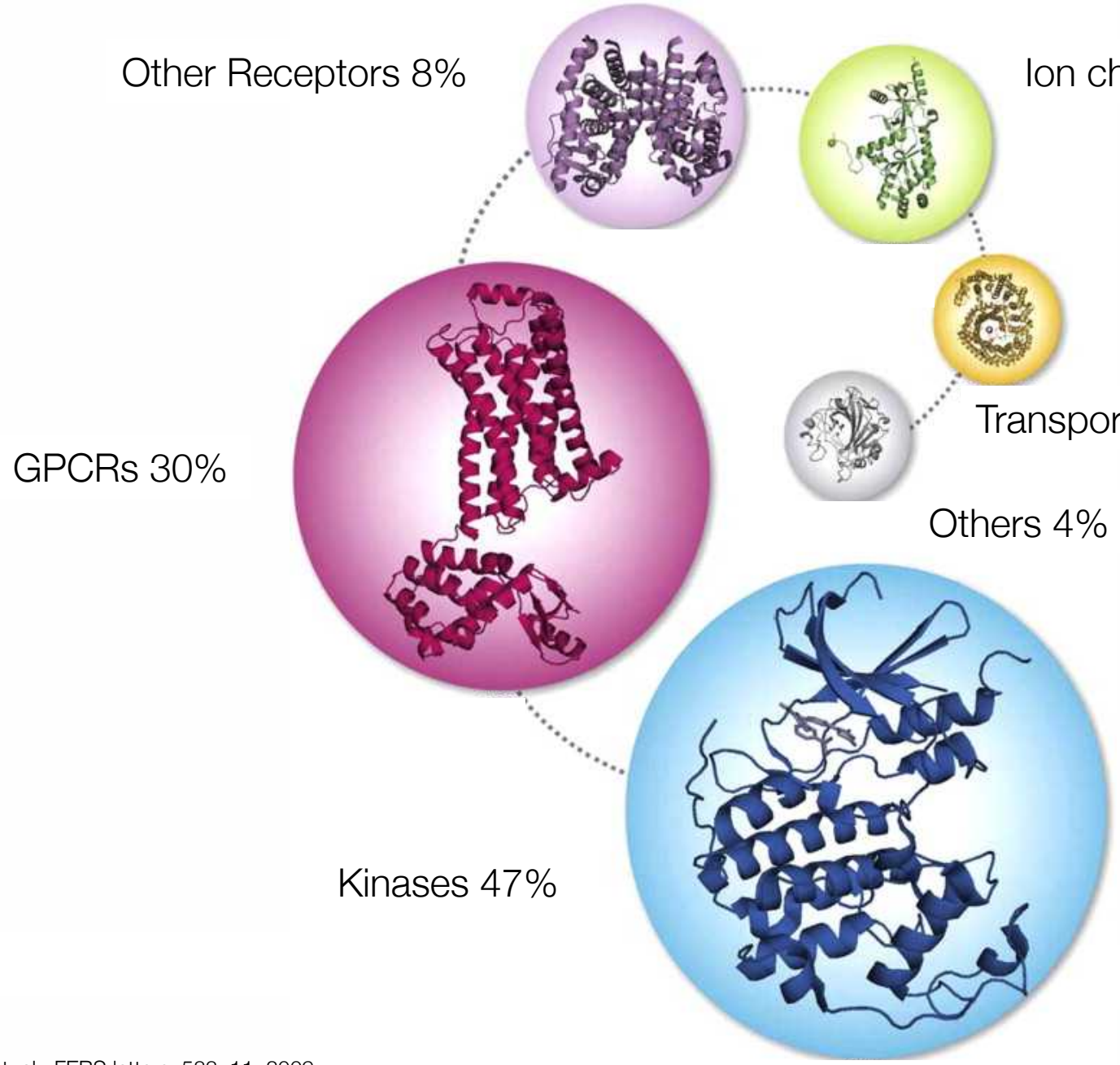
Diwakar Shukla
Assistant Professor, Chemical & Biomolecular Engineering
Blue Water Symposium 2015

Cellular Signaling and human diseases



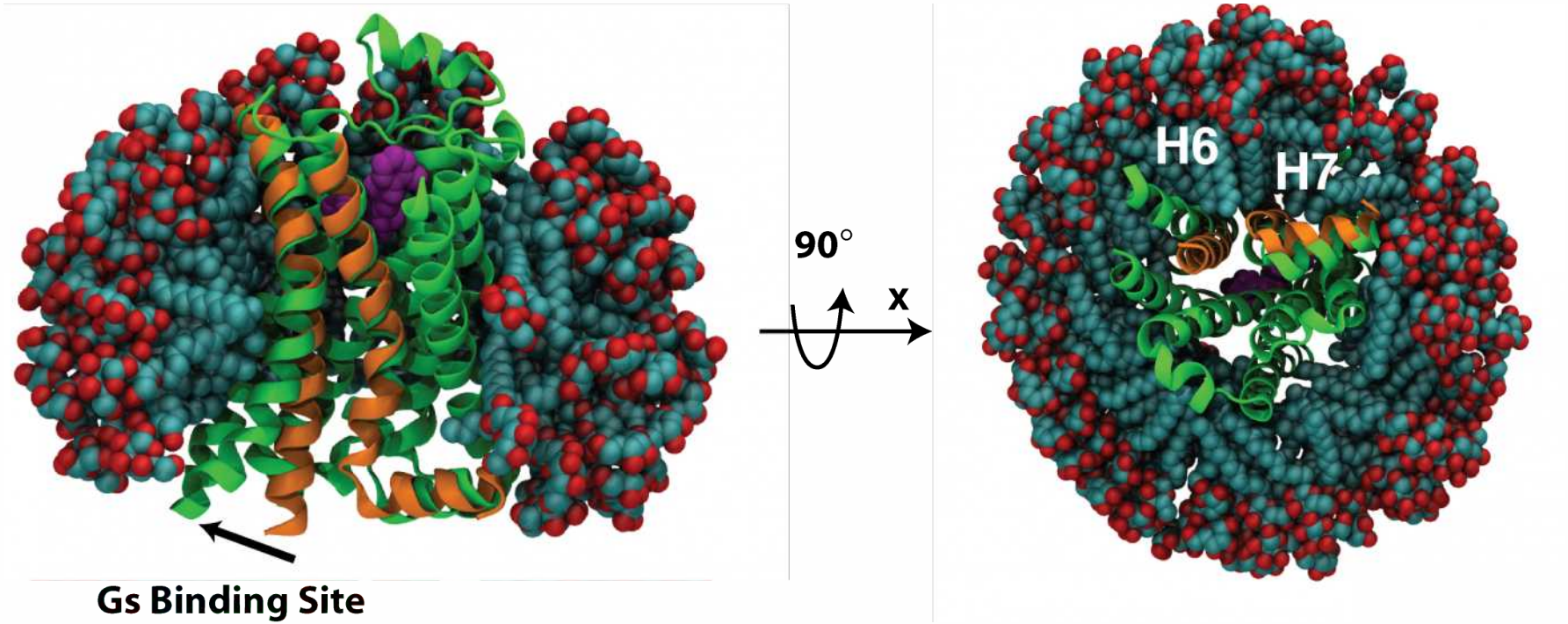
Rosenbaum et. al., Nature, 2009.

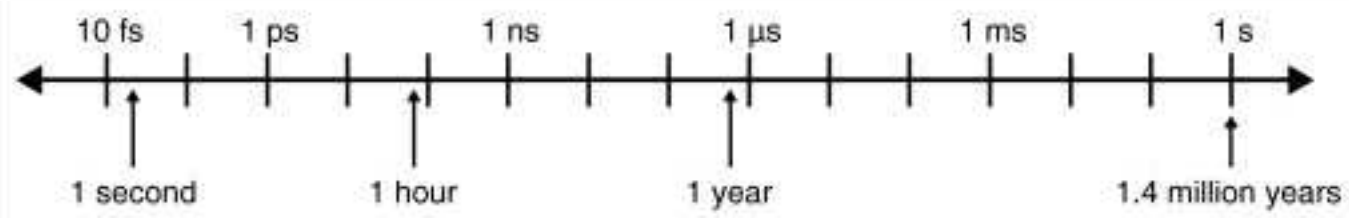
Cellular Signaling and diseases



Zanoni et. al., FEBS letters, 583, 11, 2009

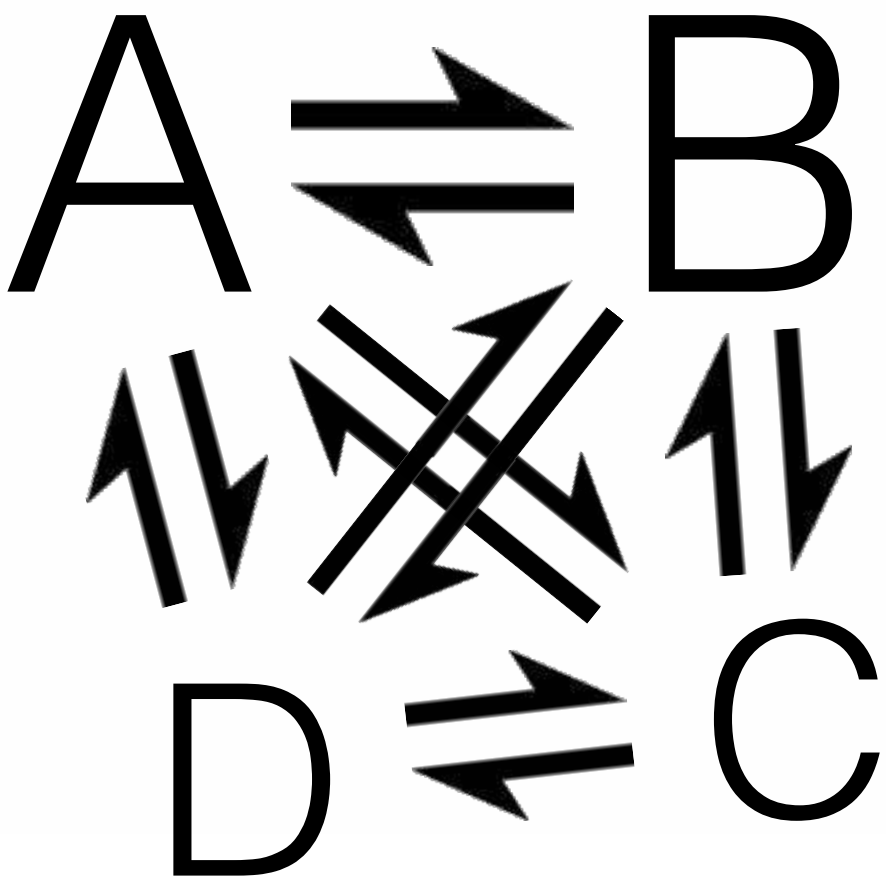
Challenge: Long time scale associated with conformational change





Markov State Models (MSM)

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

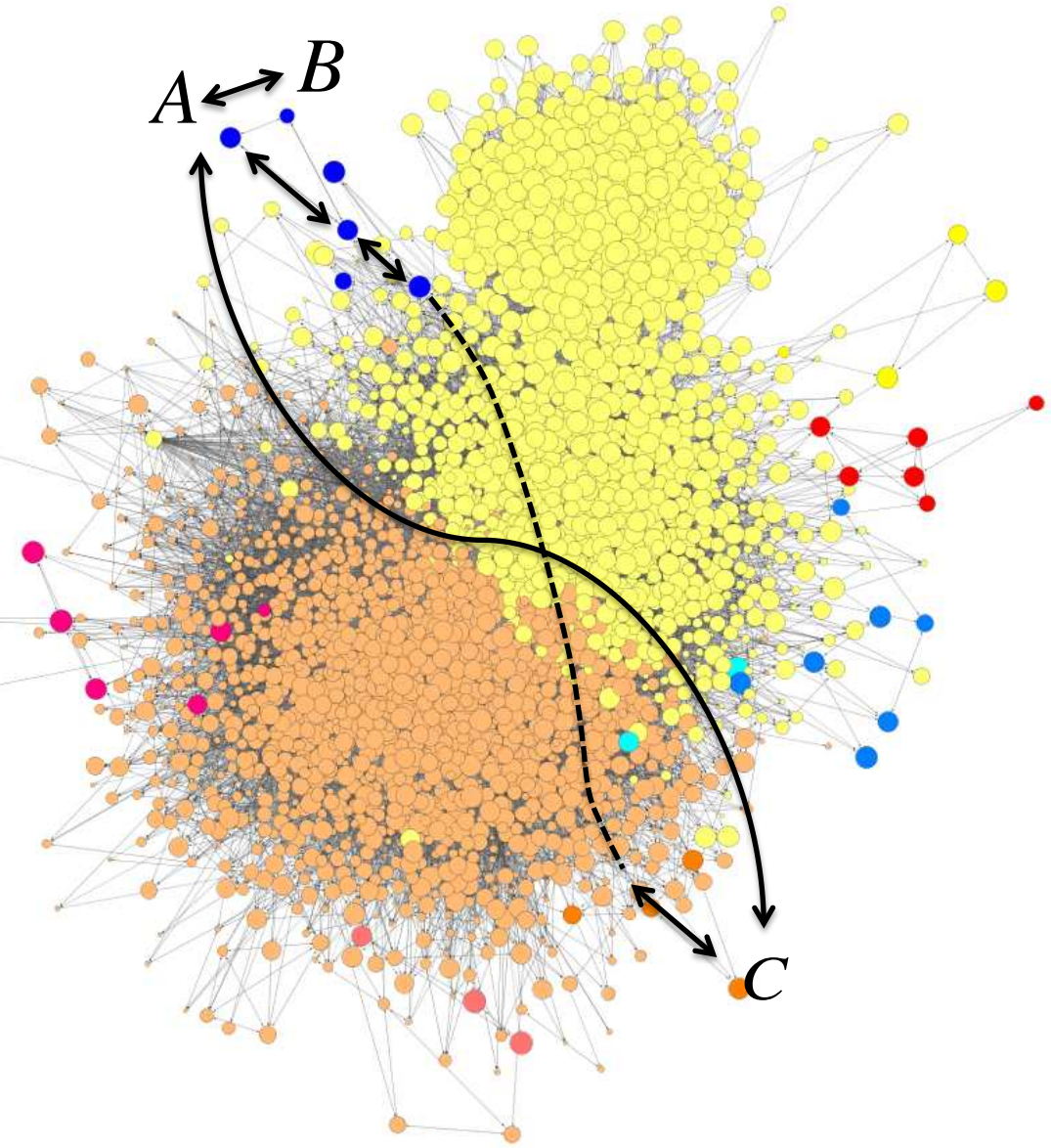


- States and rates are familiar in the context of chemical equilibria
- Complex networks of states and transitions are possible

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

$$i, j = A, B, C, D$$

Long timescale phenomena as series of Markov jump processes



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

$$i, j = [0, 3000]$$

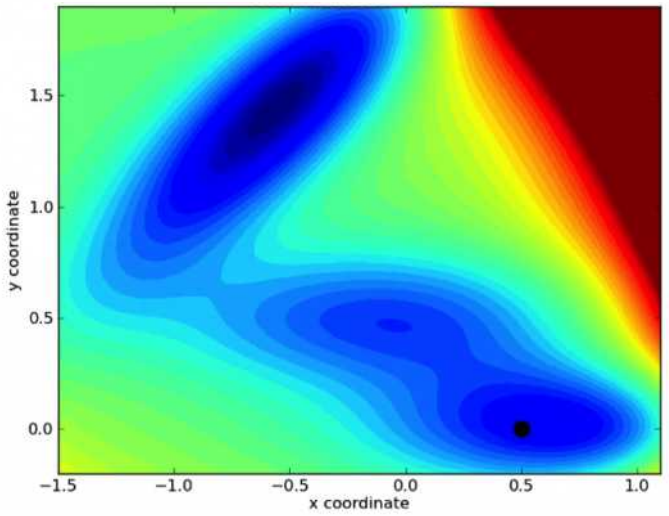
How do we get rates ?

k_{AB} nanoseconds

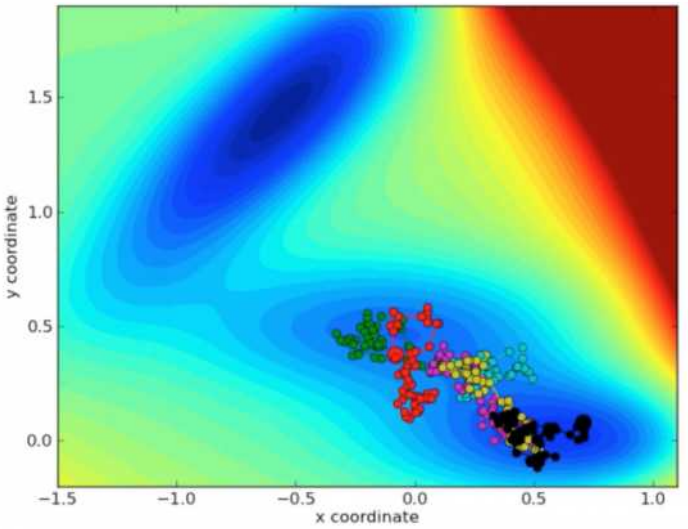
k_{AC} 100's of microseconds

Adaptive sampling of the conformational landscape

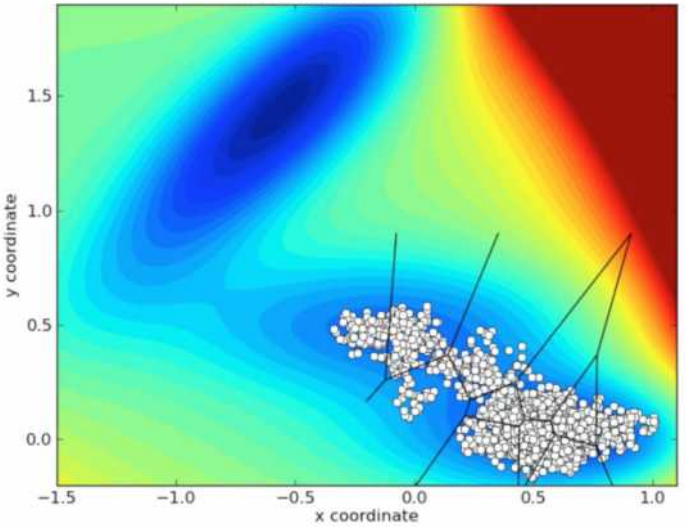
1. Select starting conformation



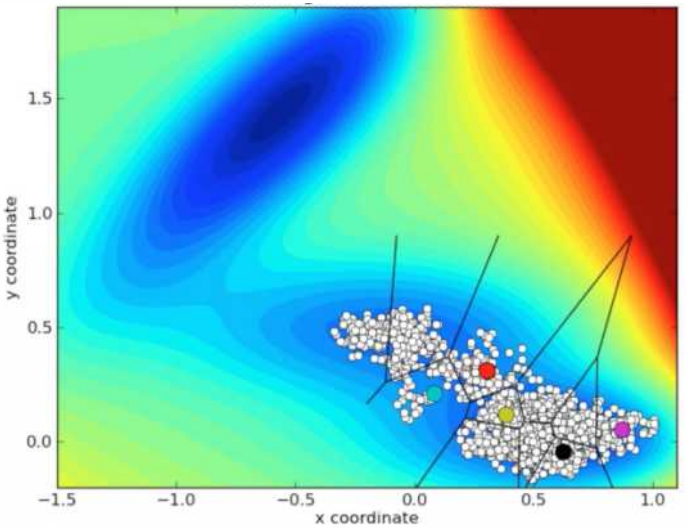
2. Conformational sampling



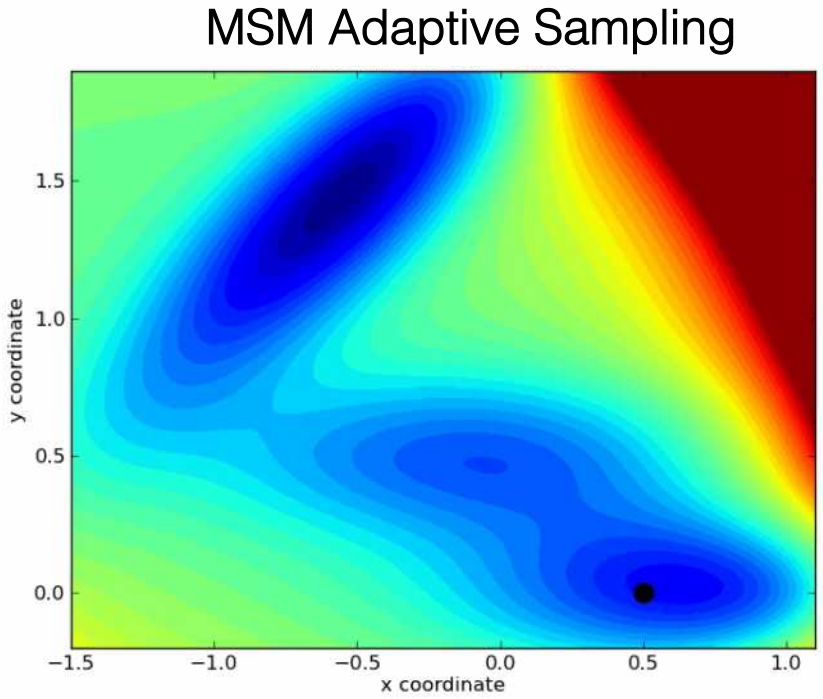
3. Build Markov State Model

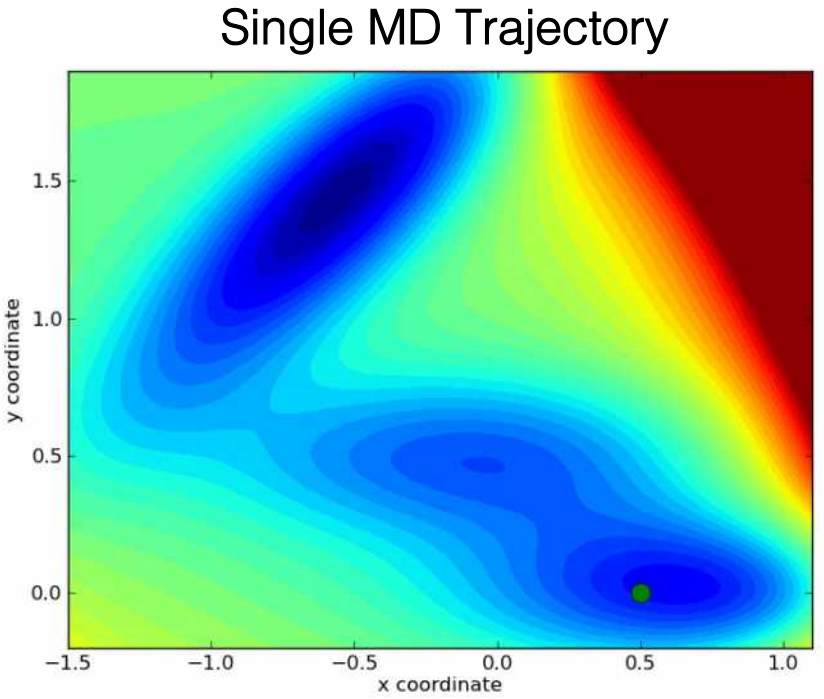


4. Select new starting conformations



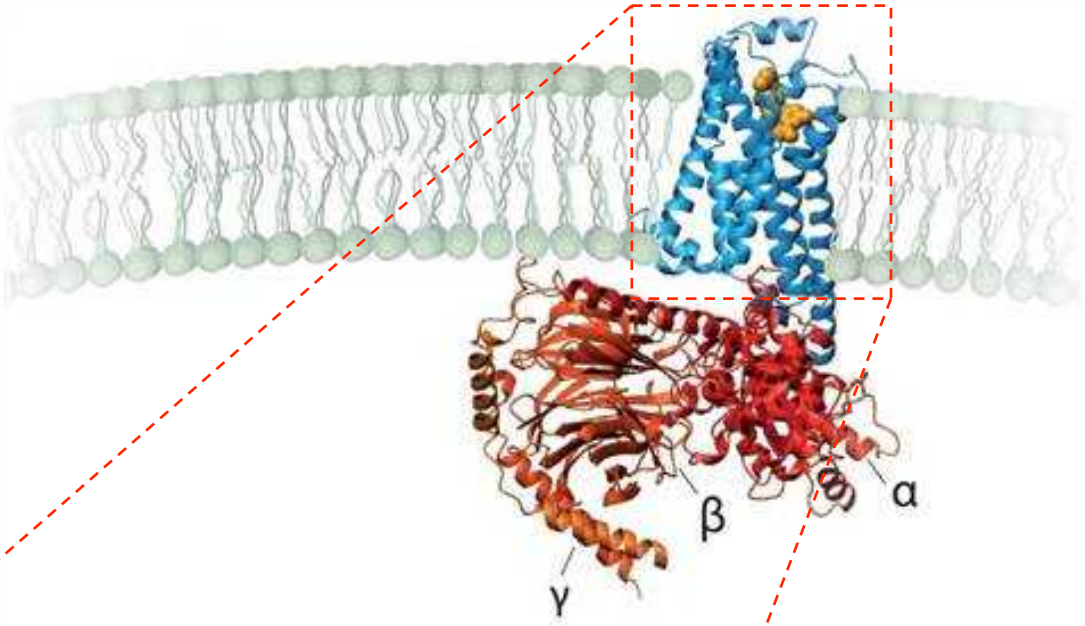
Adaptive sampling of the conformational landscape

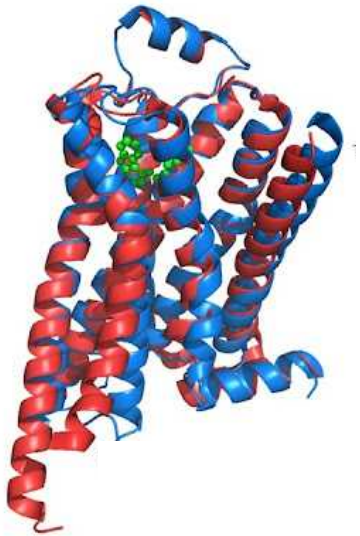


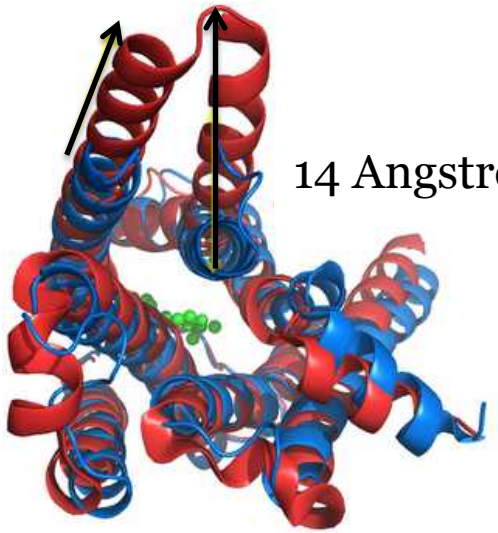


G-Protein Coupled Receptors

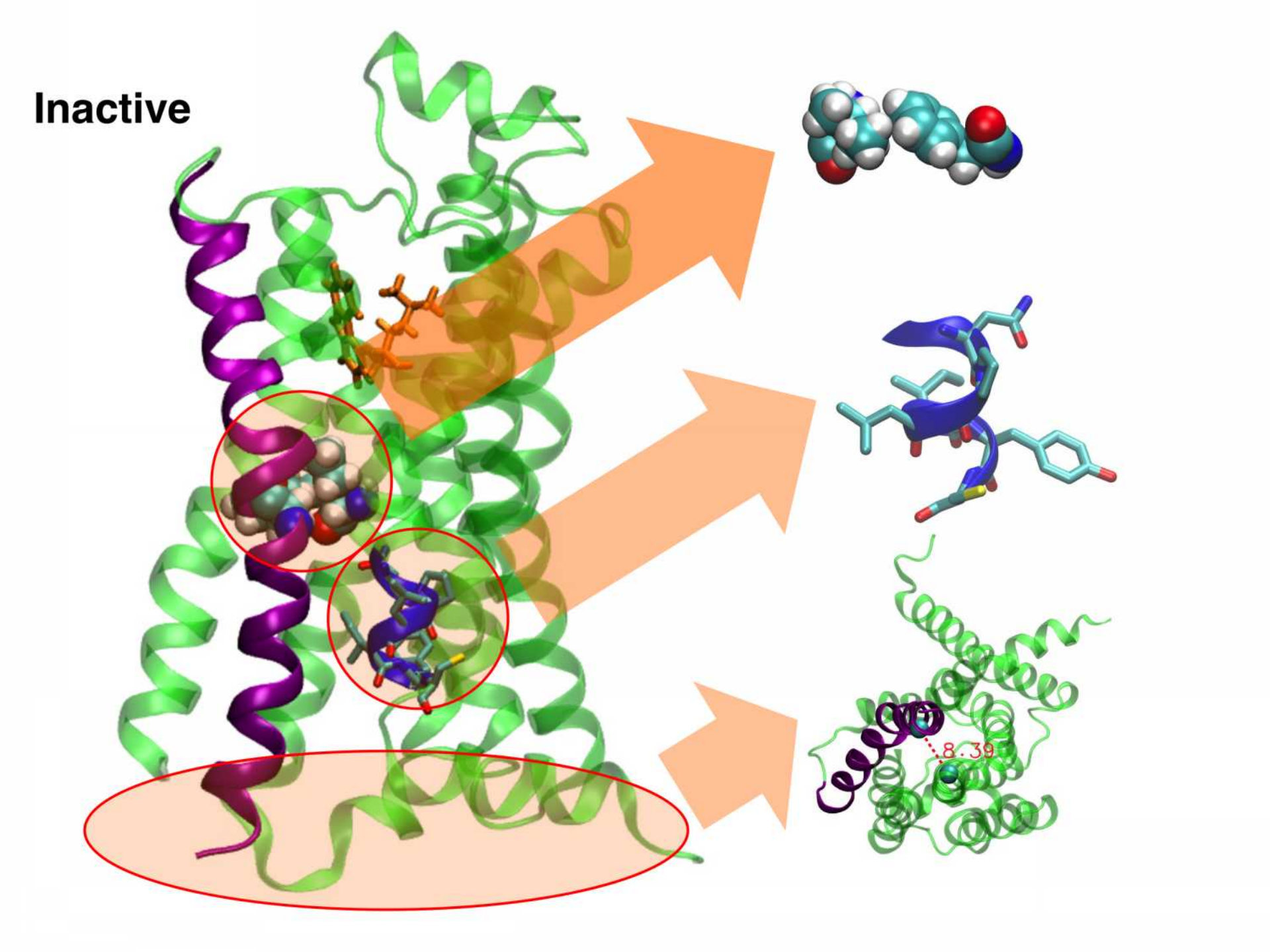
2012 Nobel Prize in Chemistry

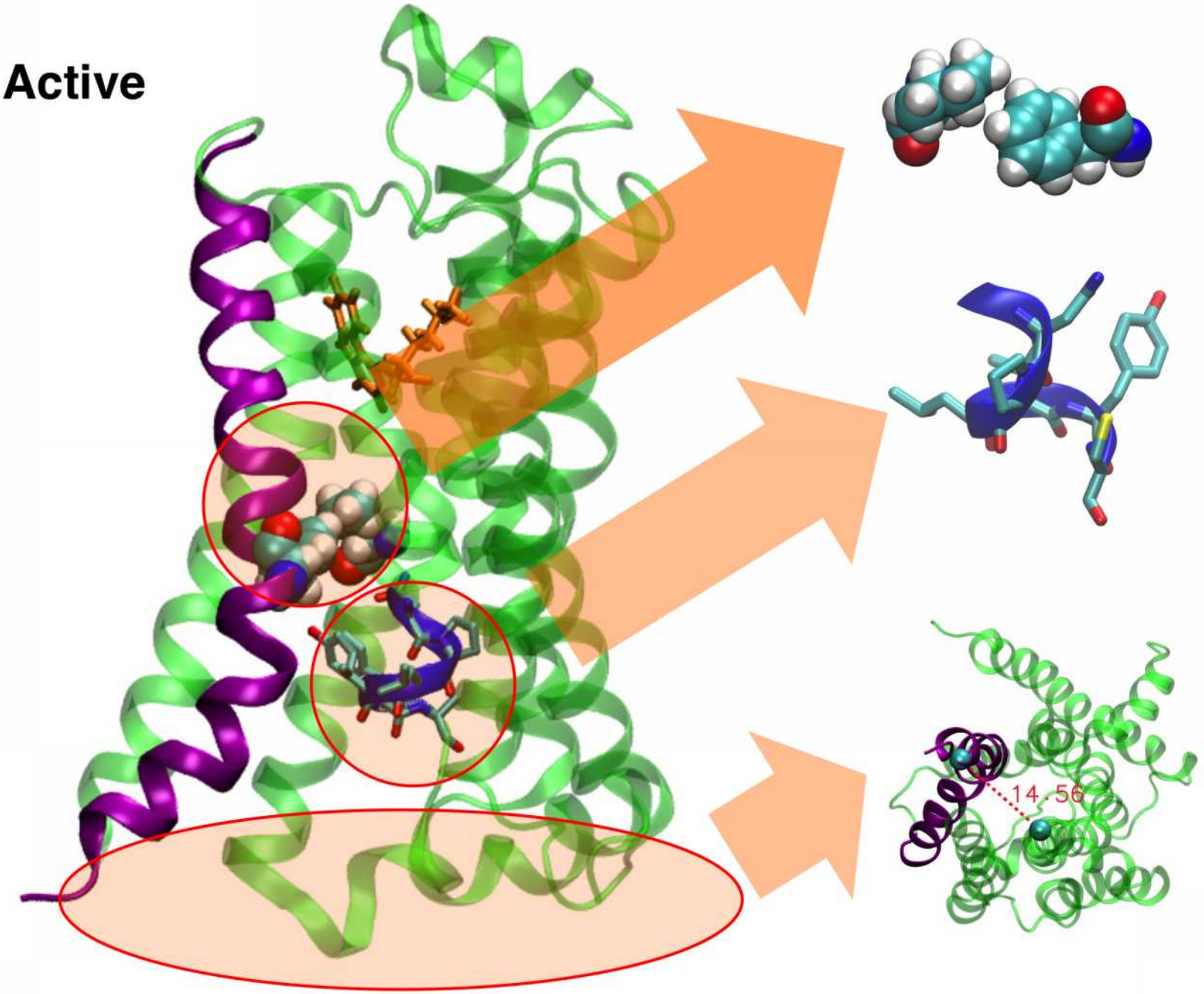




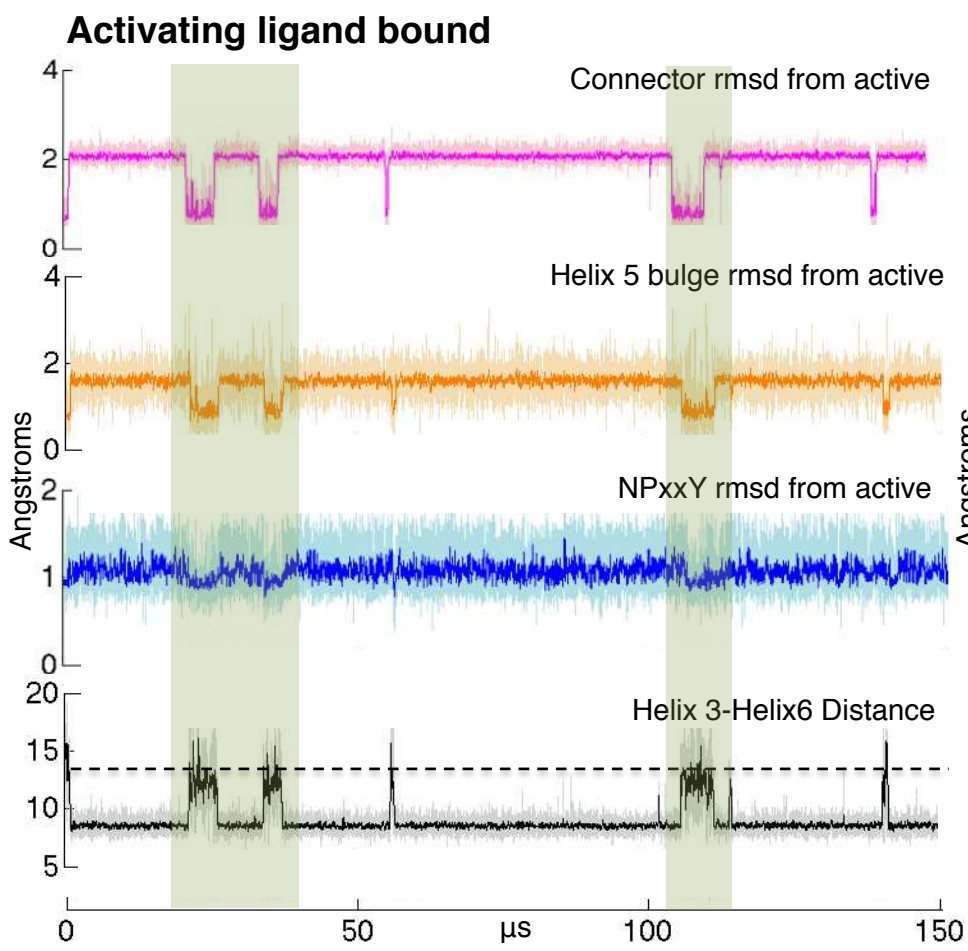


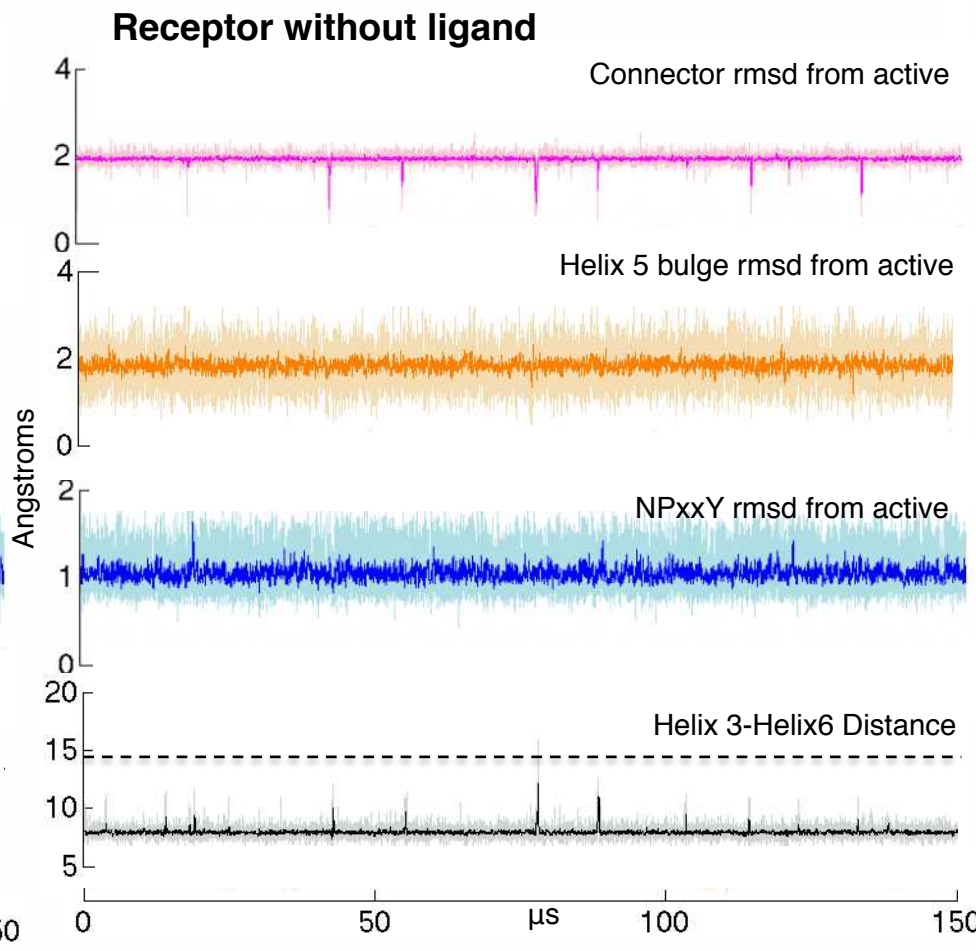
Kobilka and coworkers, Nature, 2011.


Inactive
8.39

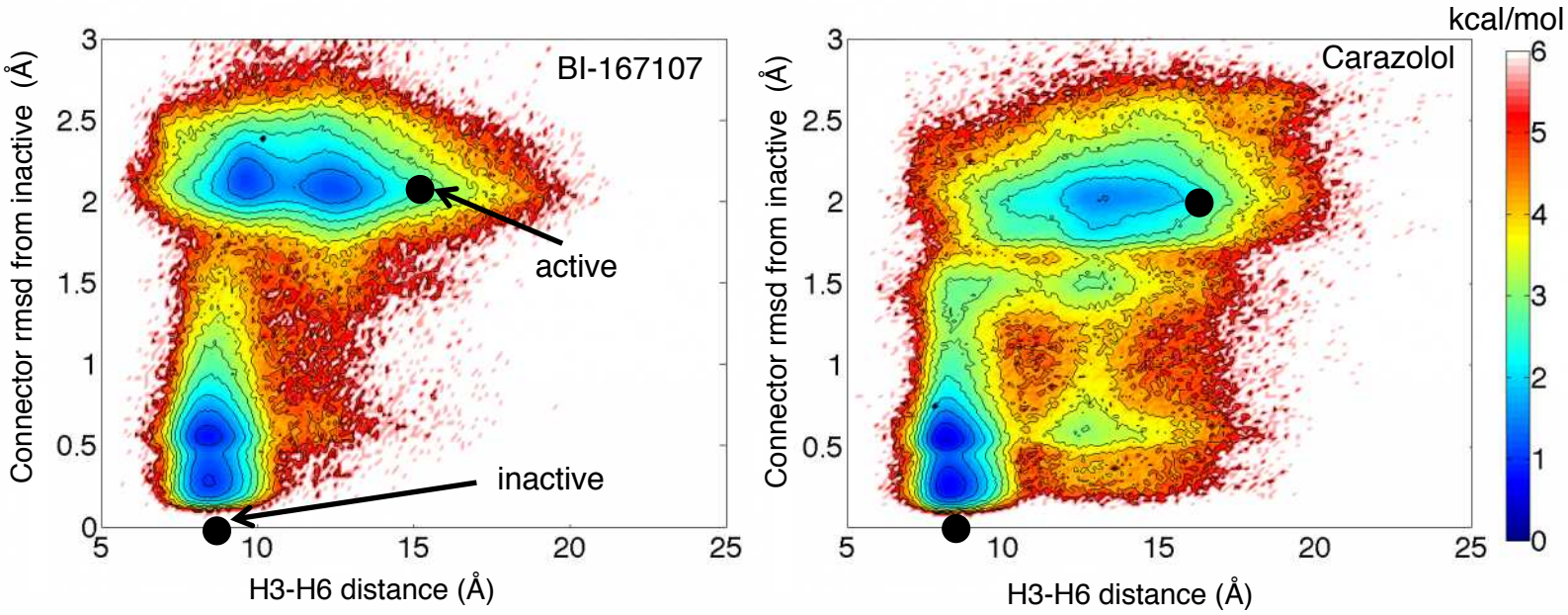

Active
14 - 56

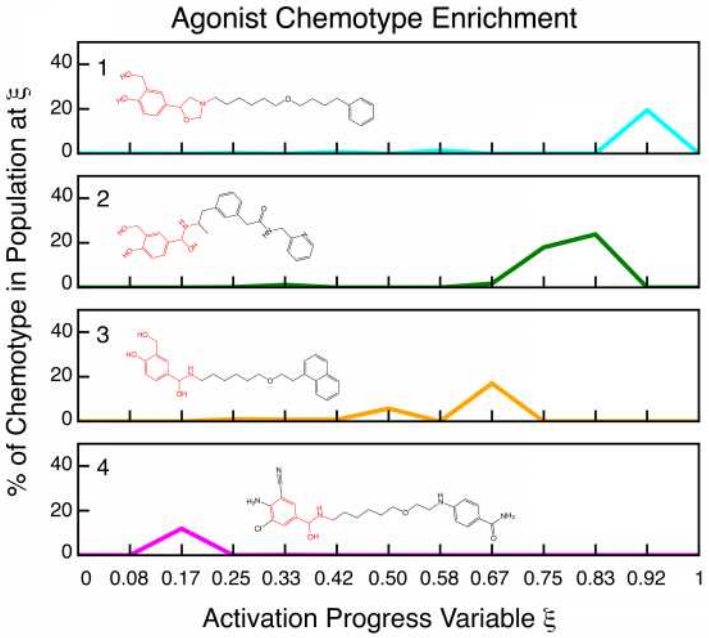
Kinetics of GPCR molecular switches

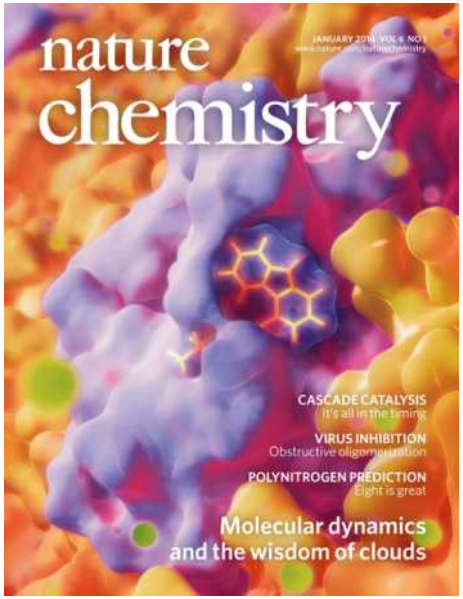




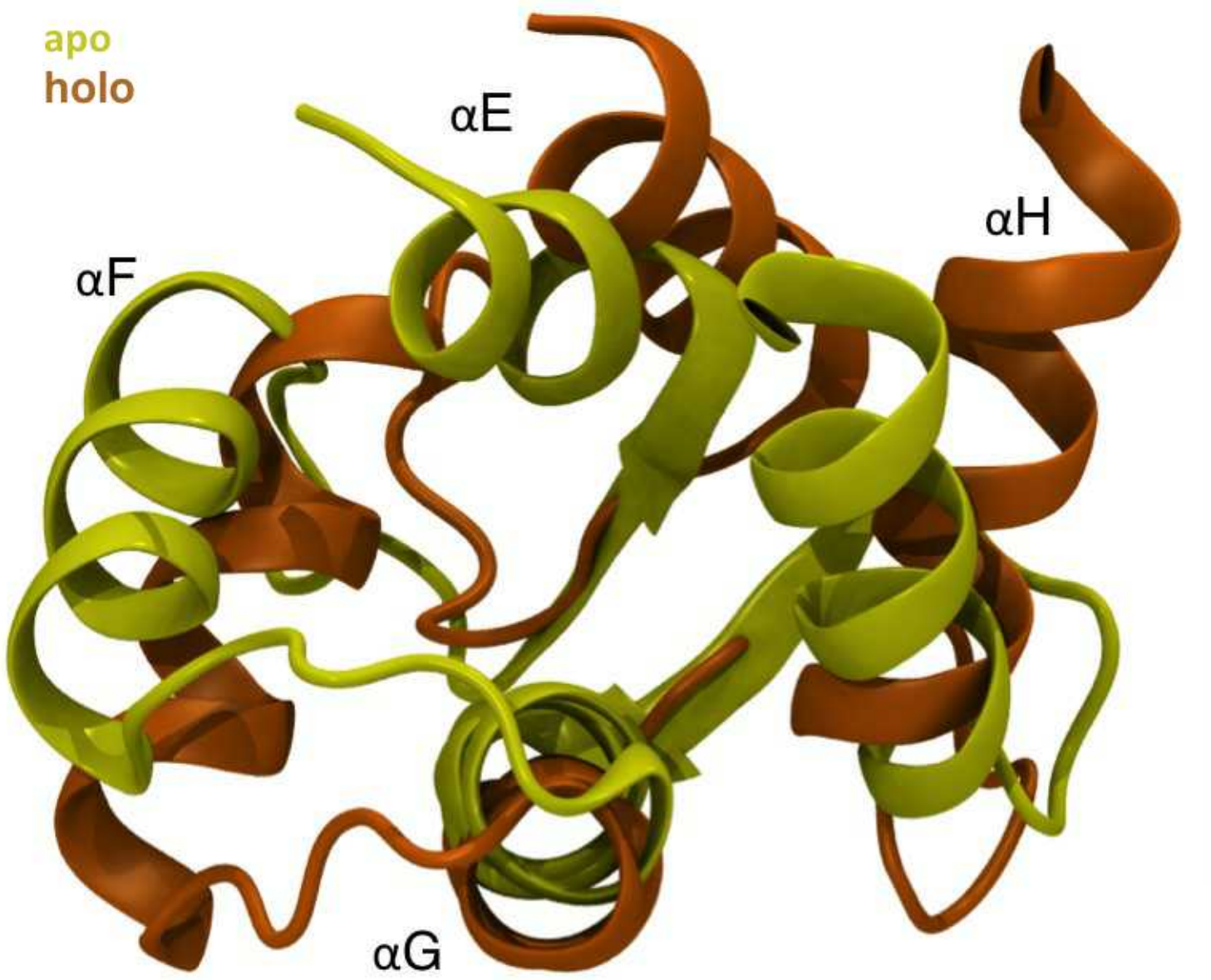
Intermediate states select for novel drug molecules





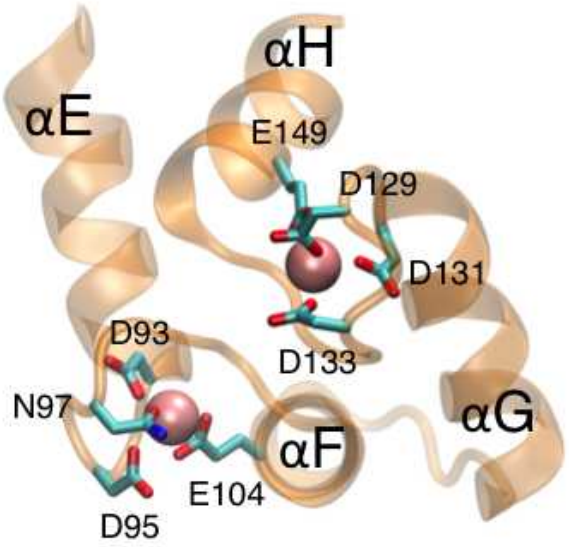


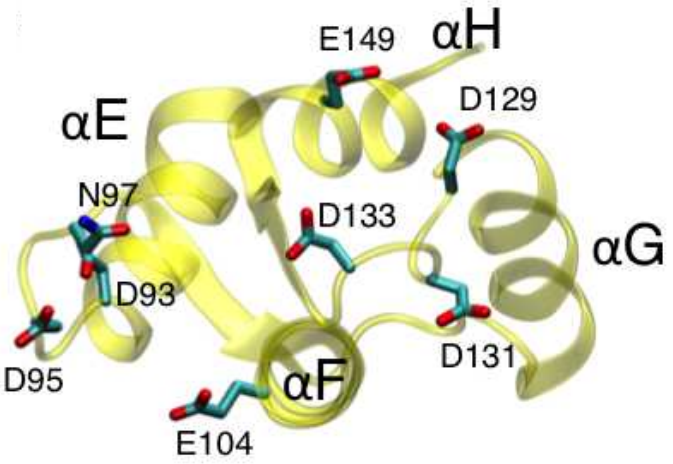
Conformational changes in Calmodulin

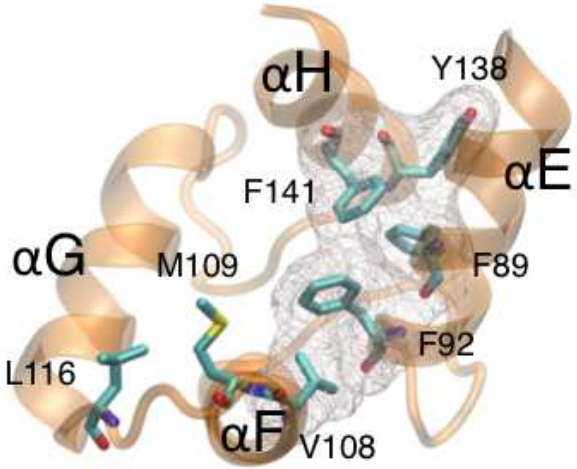


Shukla et al., Nat. Commun., in review, 2015

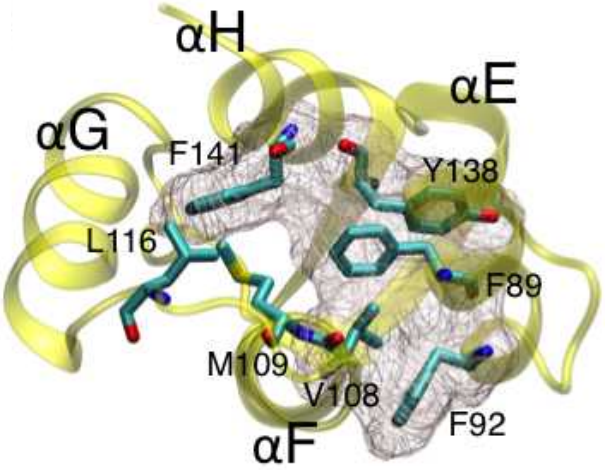
Conformational changes in Calmodulin







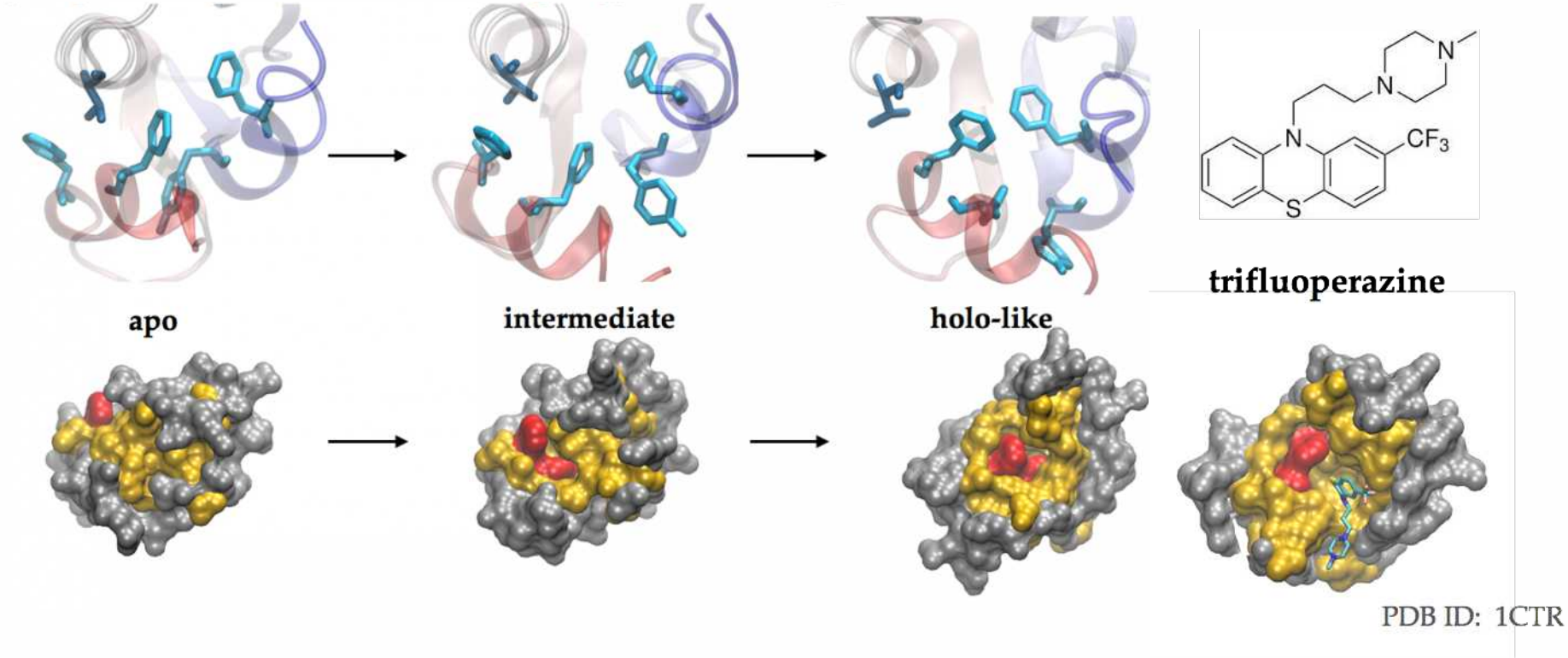
holo-CaM



apo-CaM

Shukla et al., Nat. Commun., In press, 2015

Intermediate states along the highest flux pathway

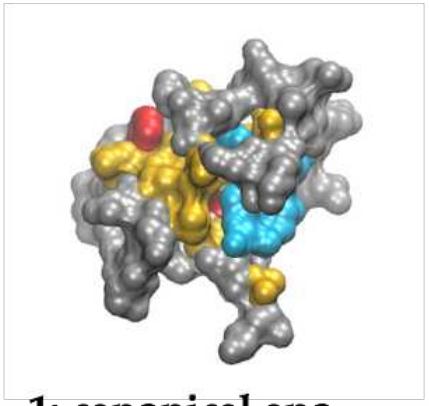


Hydrophobic repacking of the core determines the substrate selectivity

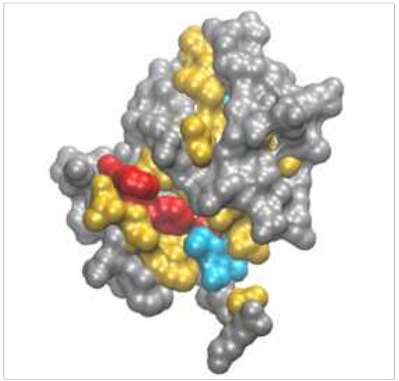
red: Phe, orange: hydrophobic, grey: other

Shukla et al., Nat. Commun., In review, 2015

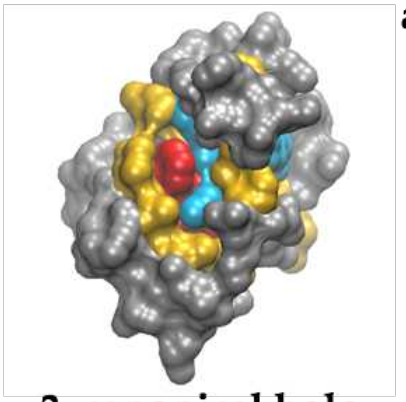
Prediction of chemically and sterically distinct binding interfaces



1: canonical apo topology (58%)

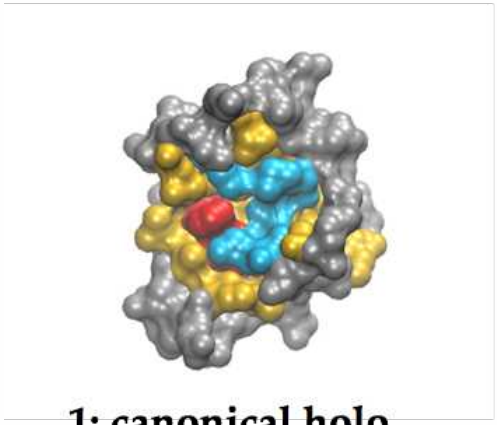


2: Phe-lined groove (7%)

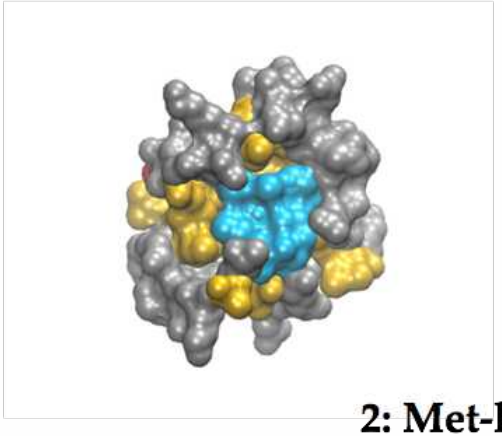


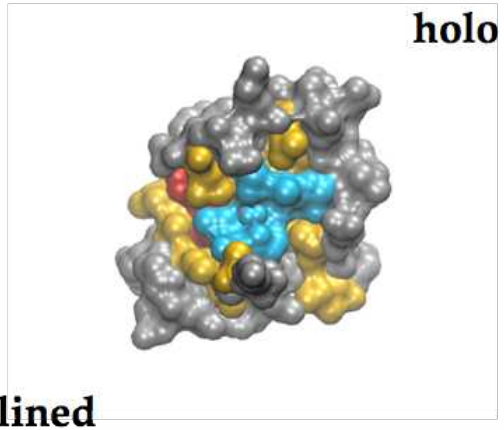
apo

3: canonical holo topology (19%)



1: canonical holo topology (55%)



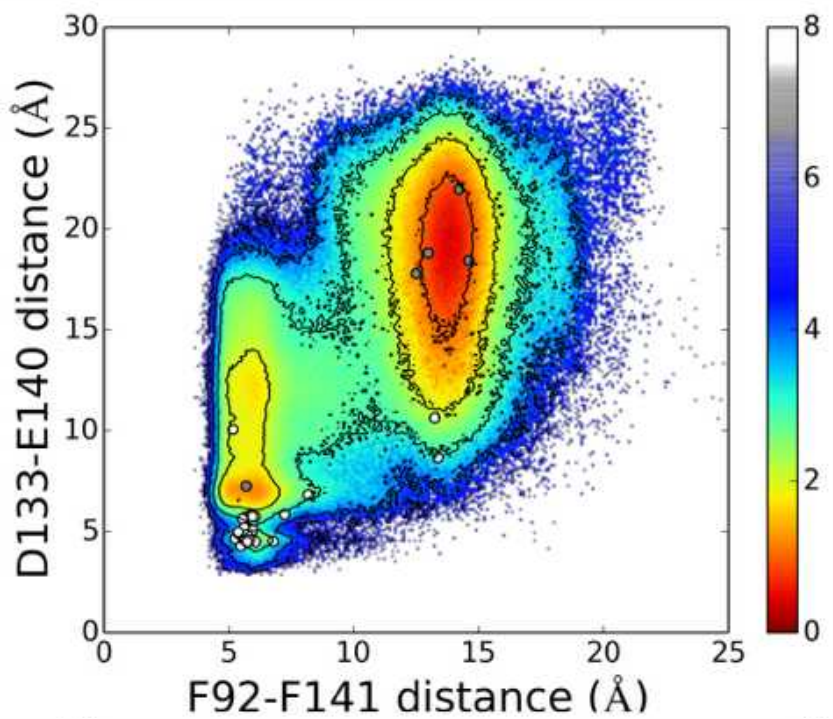


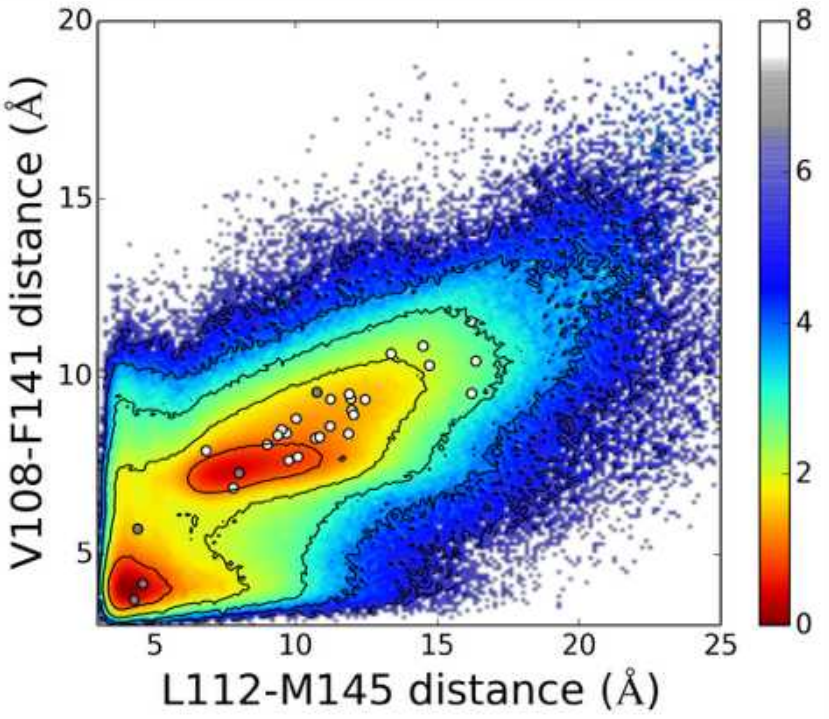
holo

2: Met-lined depressions (38%)

red: Phe; orange: hydrophobic; cyan: Met; grey: other

Prediction of chemically and sterically distinct binding interfaces

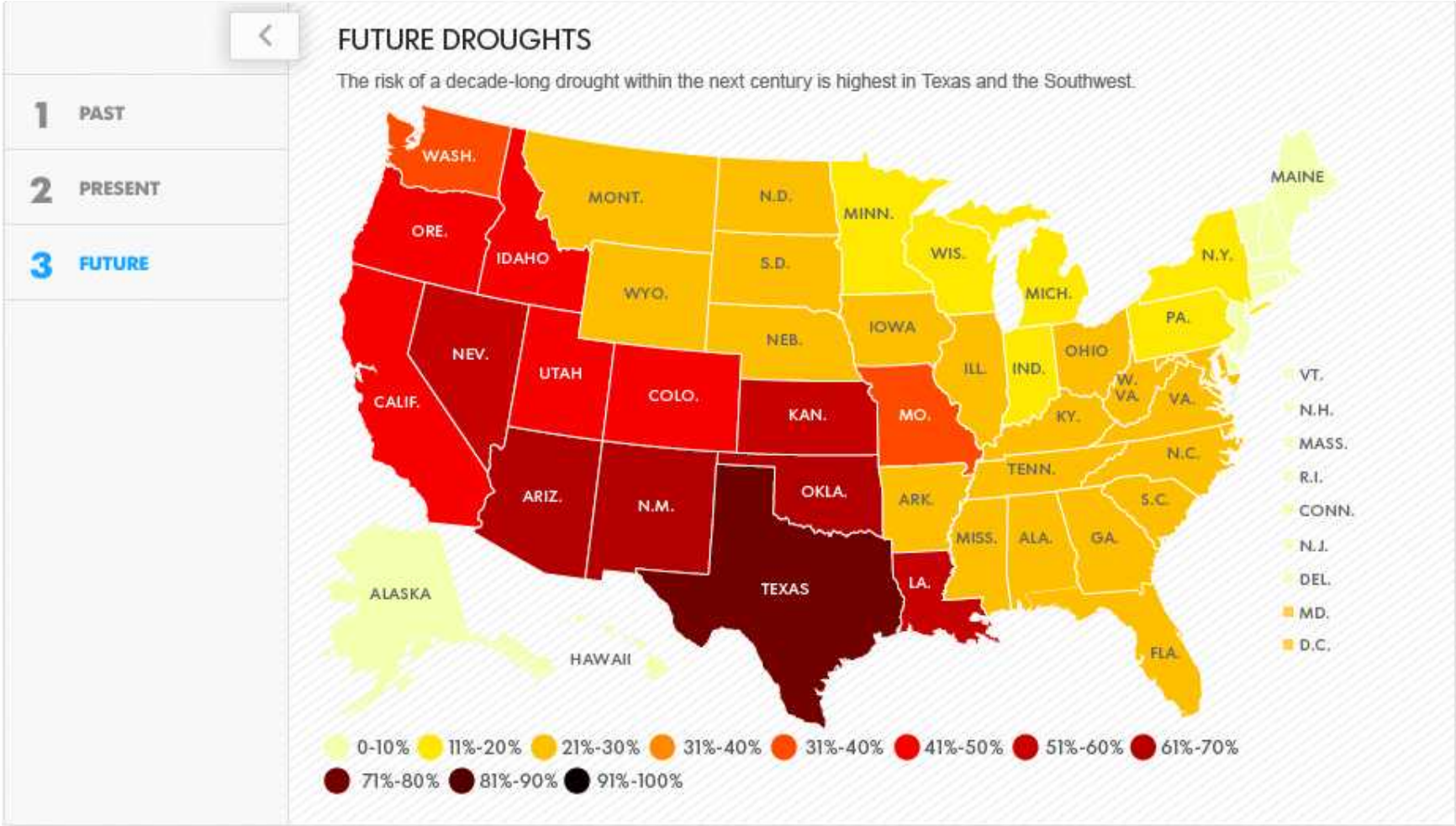




White dots represent the available CaM crystal structures in PDB.
Simulations were started from only two structures of CaM.

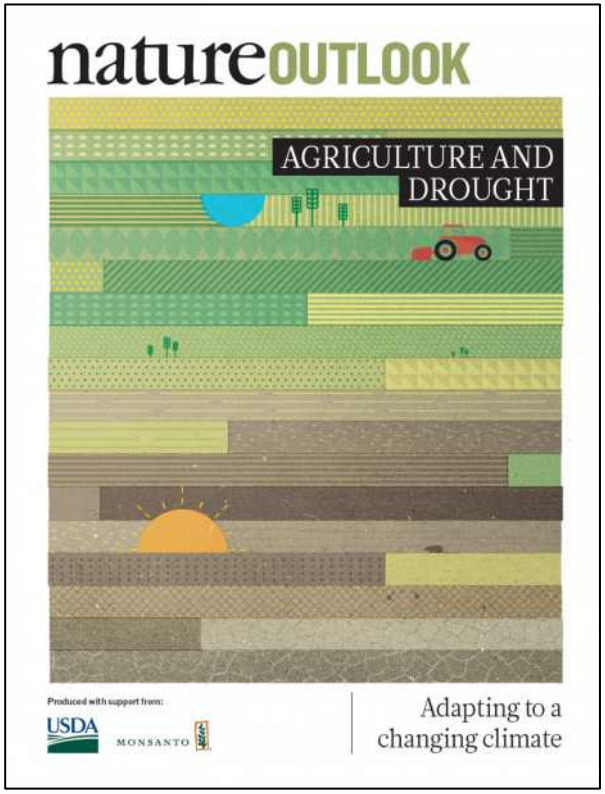
colorbar units: kcal/mol

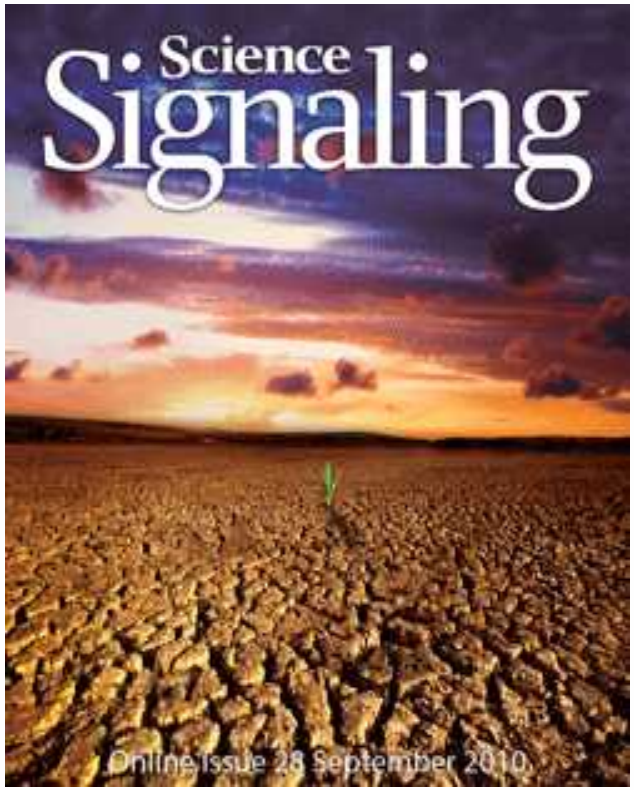
Molecular Design of Drought resistant plants

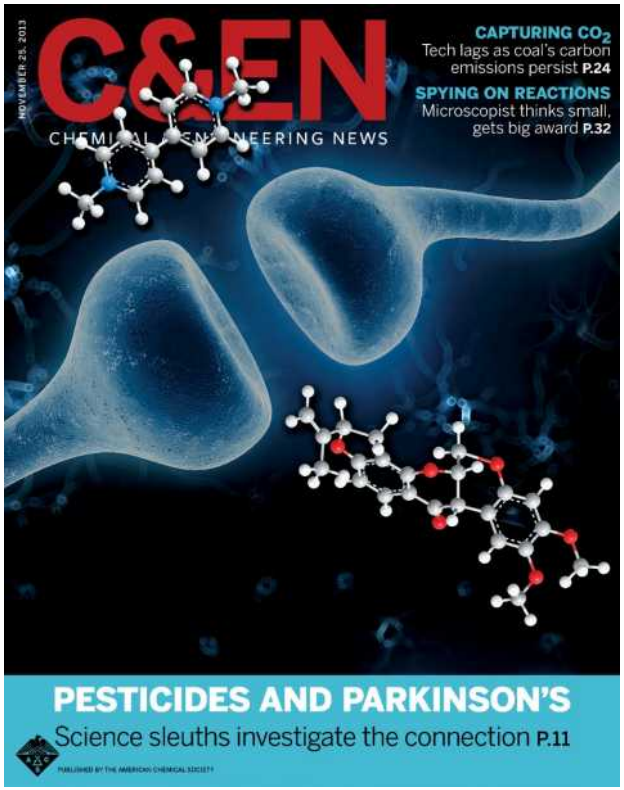


Lamont Doherty Earth Observatory of Columbia University; U.S. Drought Monitor; Cornell University
Doyle Rice, Frank Pompa and Julie Snider, USA TODAY

Fine tuning plants at molecular level

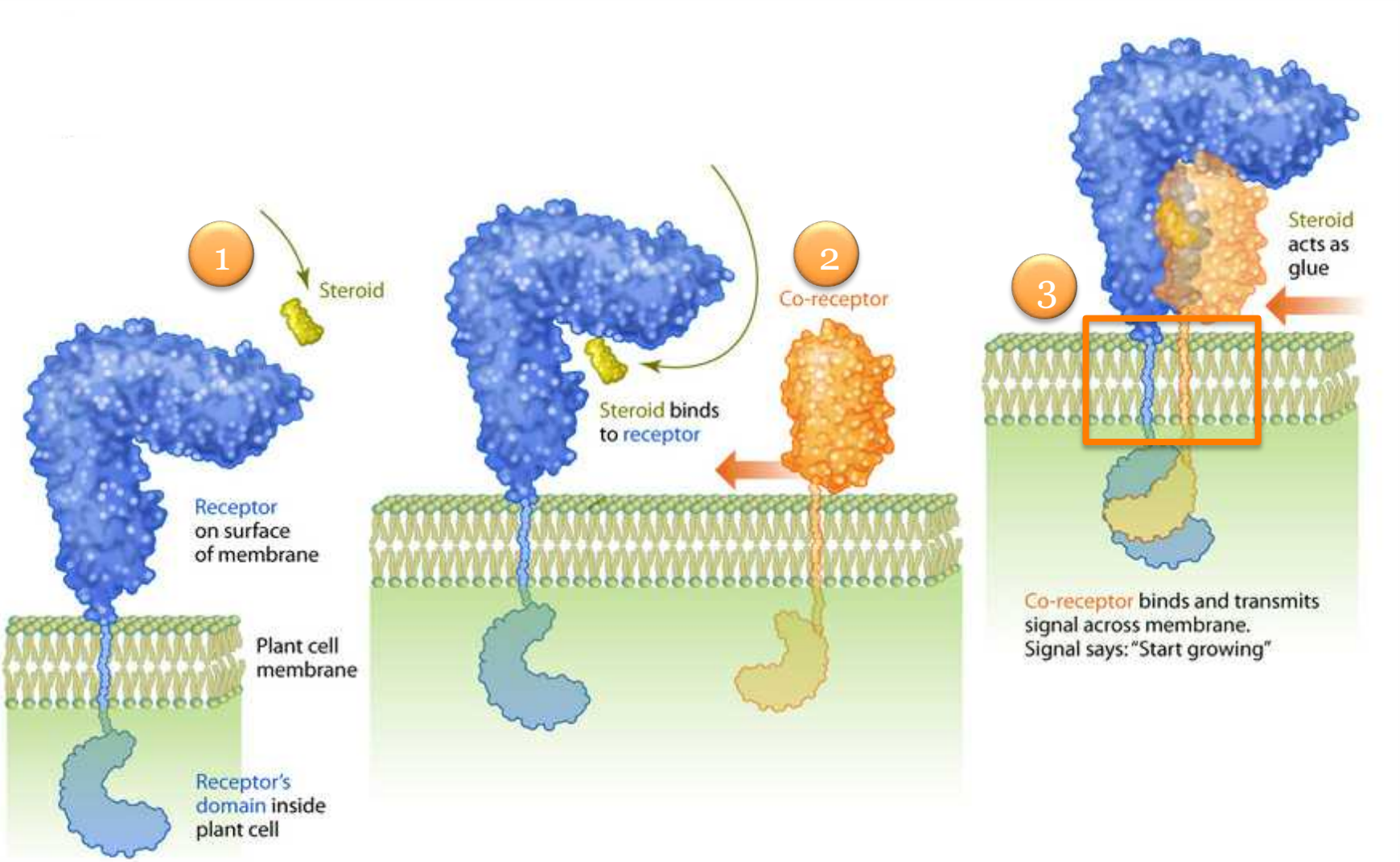




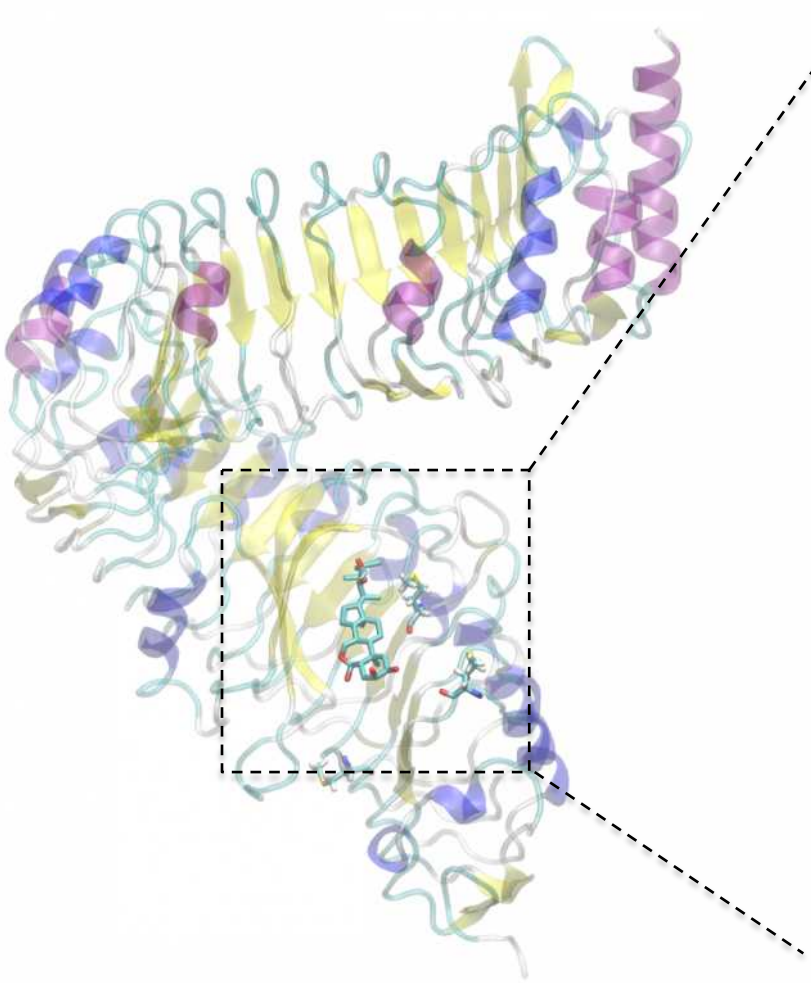


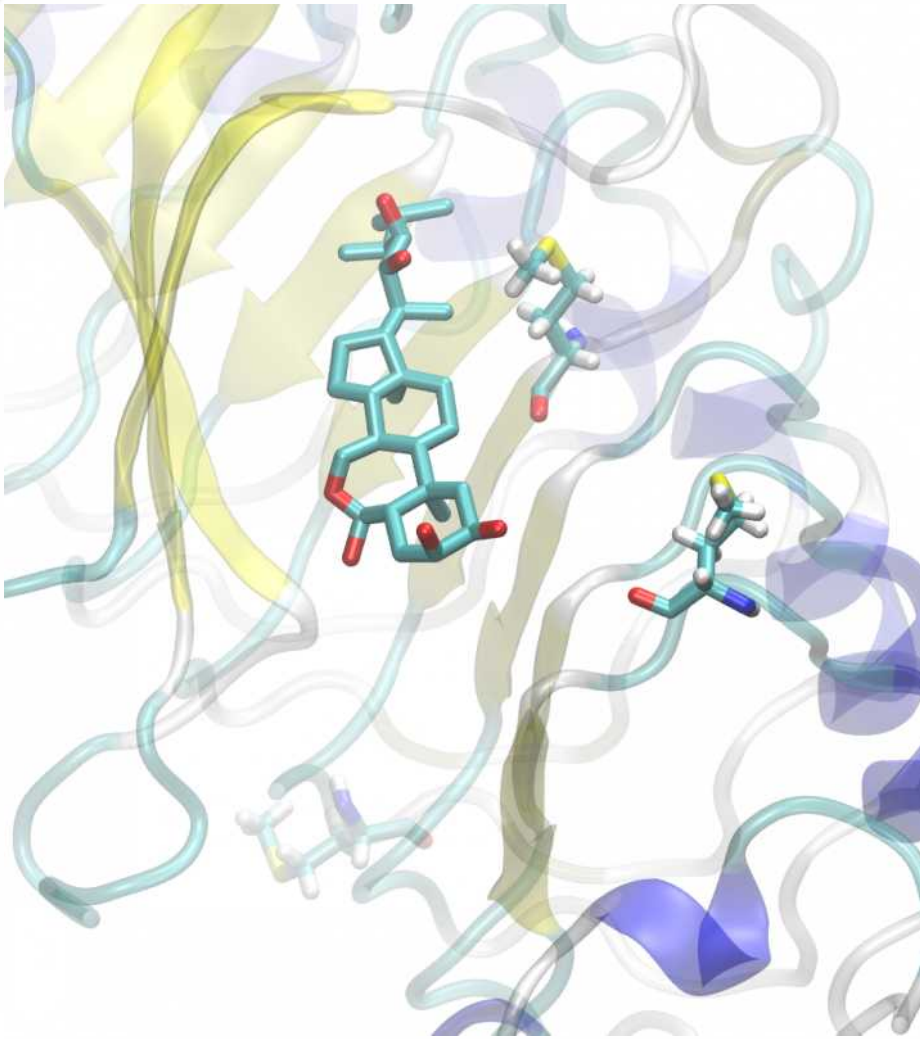
Motivation: Climate Change, Population Growth, Improved Agrochemicals, Links to Human Health

Steroid signaling and plant development

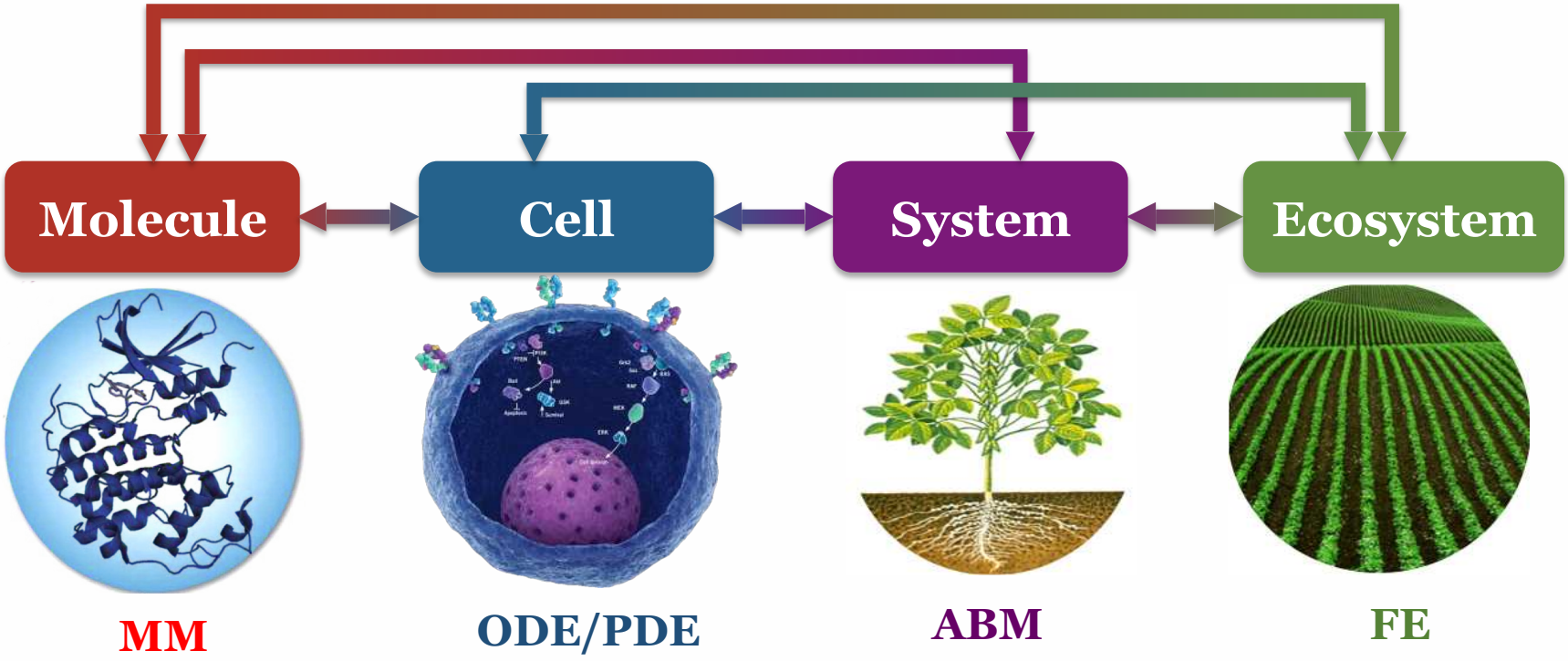


Simulation and experiments for obtaining mechanistic insights in growth signaling





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