
Simulating Functional Cycles and Drug Modulation in Ligand-gated Ion Channels

Opponent's introduction

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Opponent: Grace Brannigan, Rutgers University - Camden

What do all these images have in common?



All involve pharmacology of
pentameric ligand-gated ion channels

Scenario #1

You are going in for surgery.

You see the anesthesiologist when you are taken into the operating room. He tells you he will use an intravenous drug called propofol, which is safer than older inhaled anesthetics.

You ask what makes it safer.

"Well, we don't really know how any of these drugs work," he says casually, right before you lose consciousness.



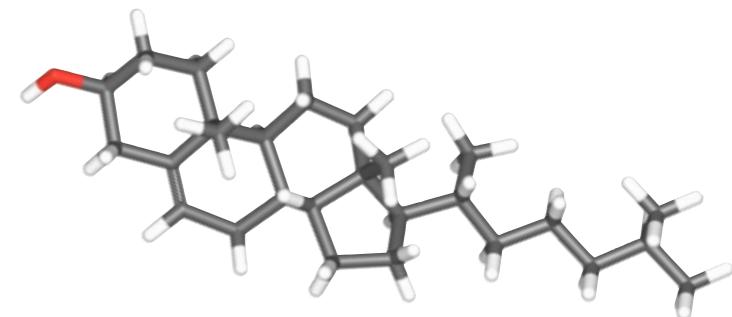
Scenario #2

You've started taking a cholesterol-lowering drug called atrovastatin (Lipitor) for your high cholesterol. After taking the medicine for several days, you notice that your cognition is decreasing.

Your doctor says this can happen and that "it's known that the brain requires a high concentration of cholesterol."

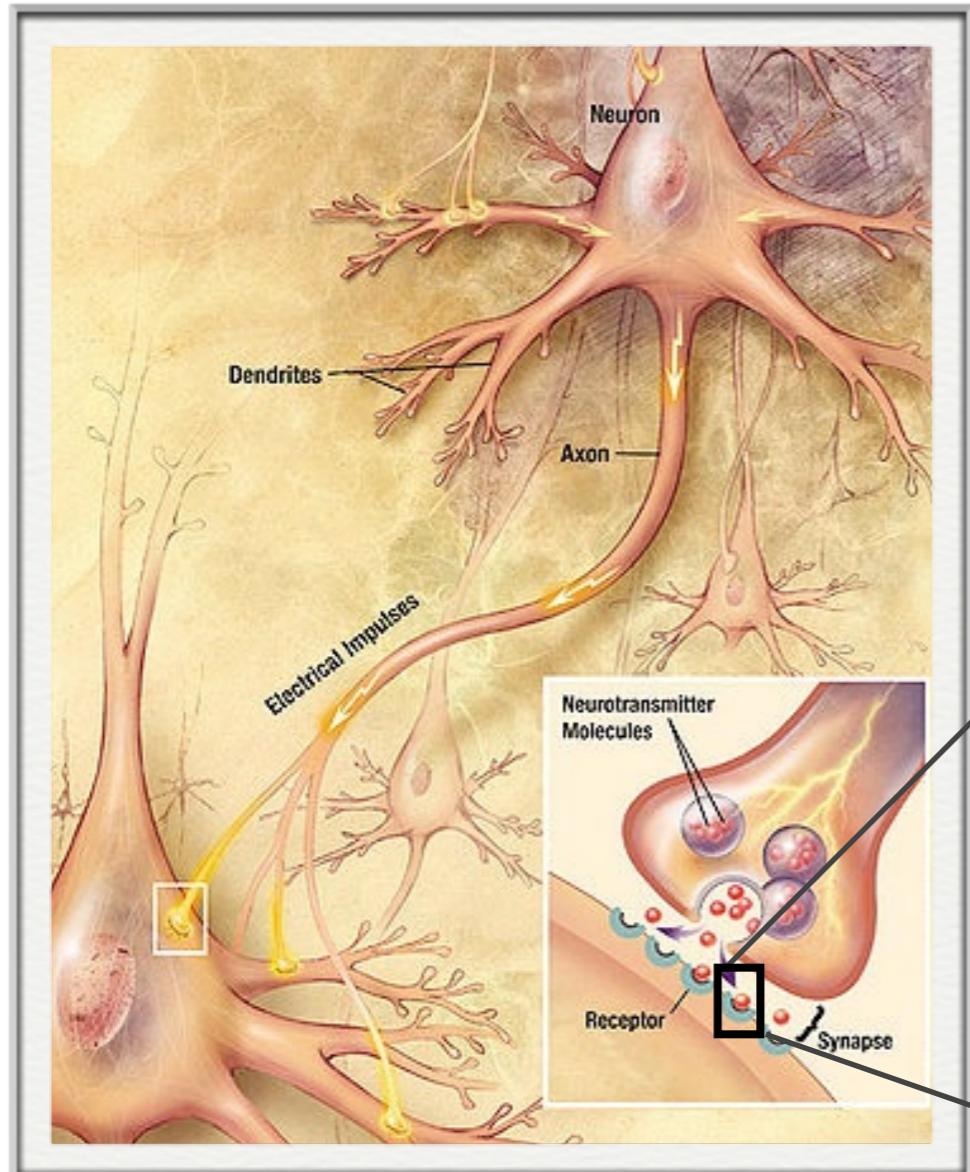
You ask how the drug can be safe to use at all.

"Only some people show cognitive side-effects. We can't yet predict who. We don't know exactly which receptors are affected or why cholesterol is important for those receptors... But most people seem fine."

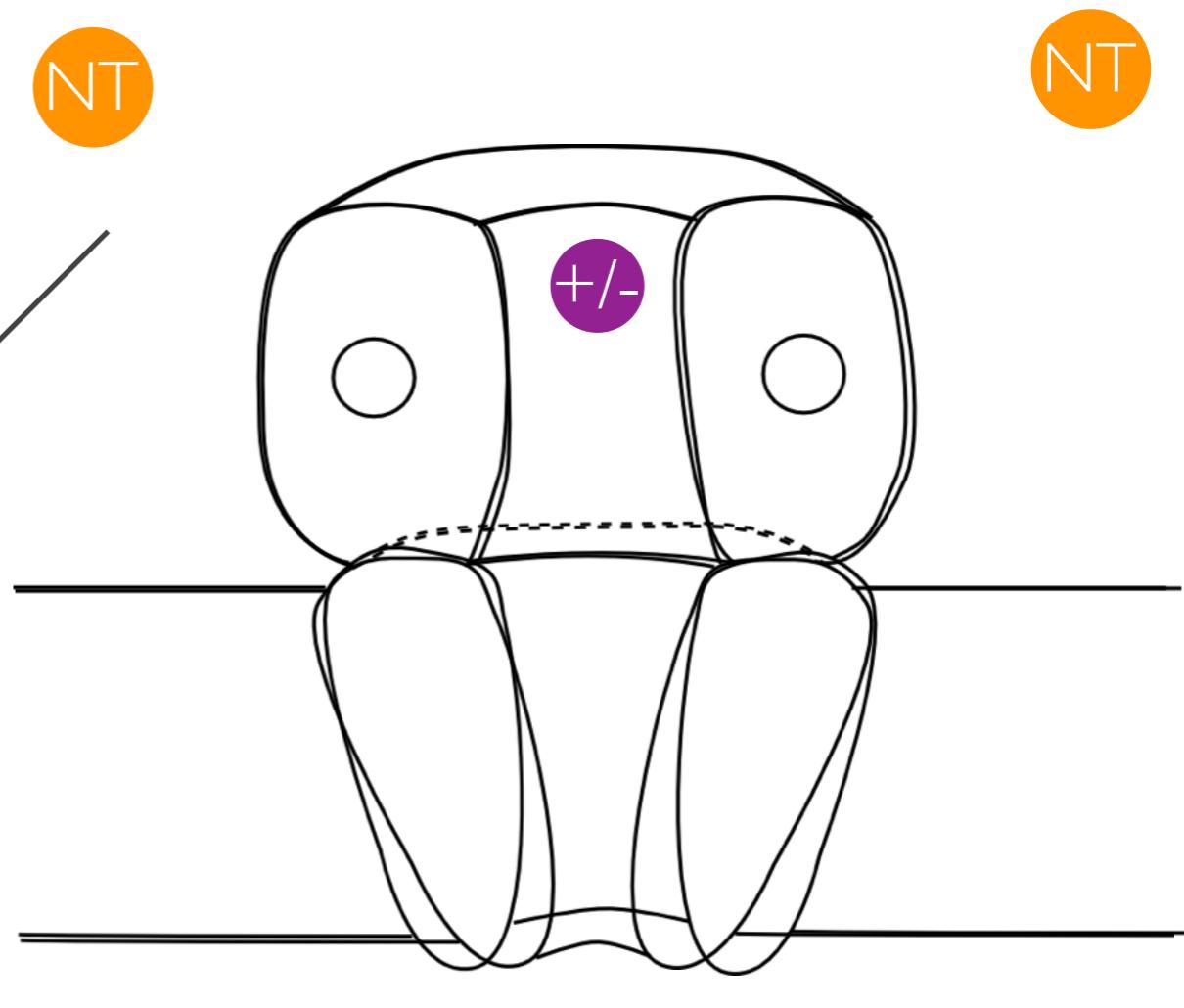


ligand-gated ion channels

Can convert chemical signals (neurotransmitters) into electrical activity.



Desensitized

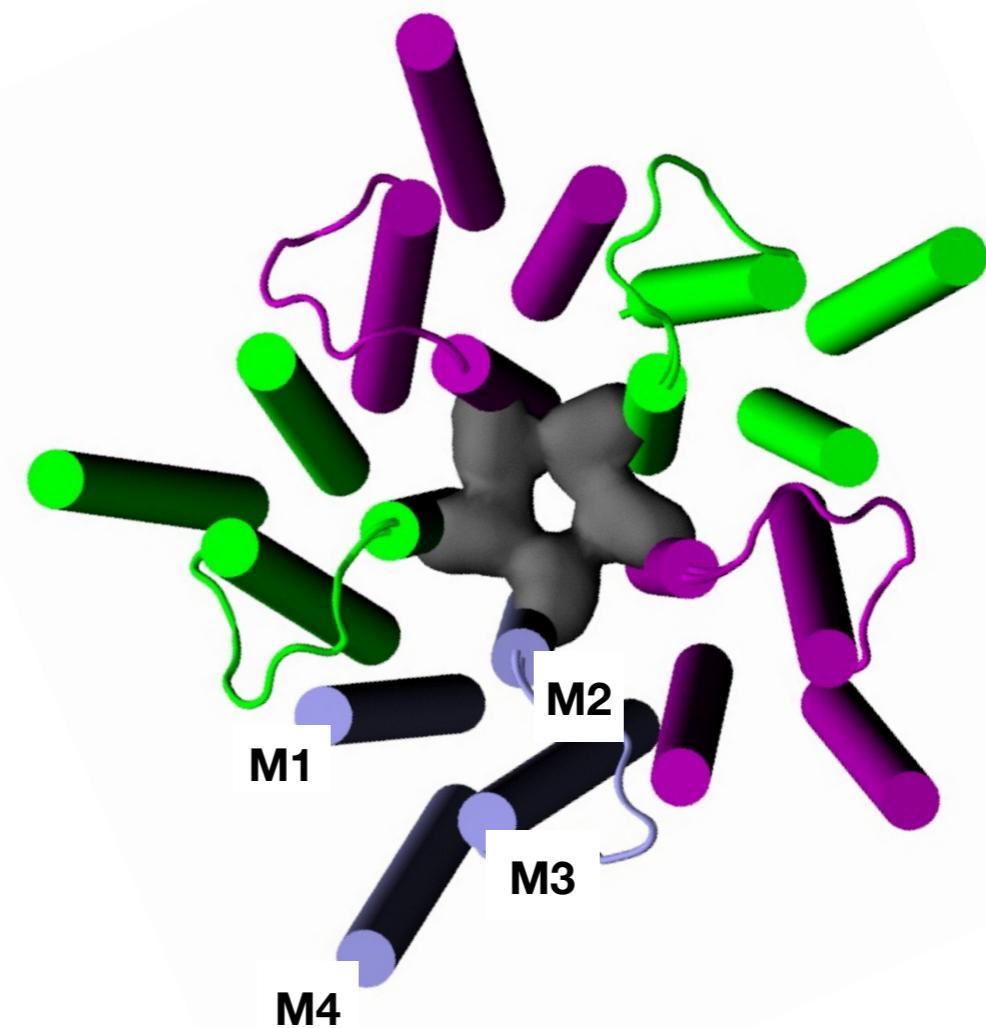
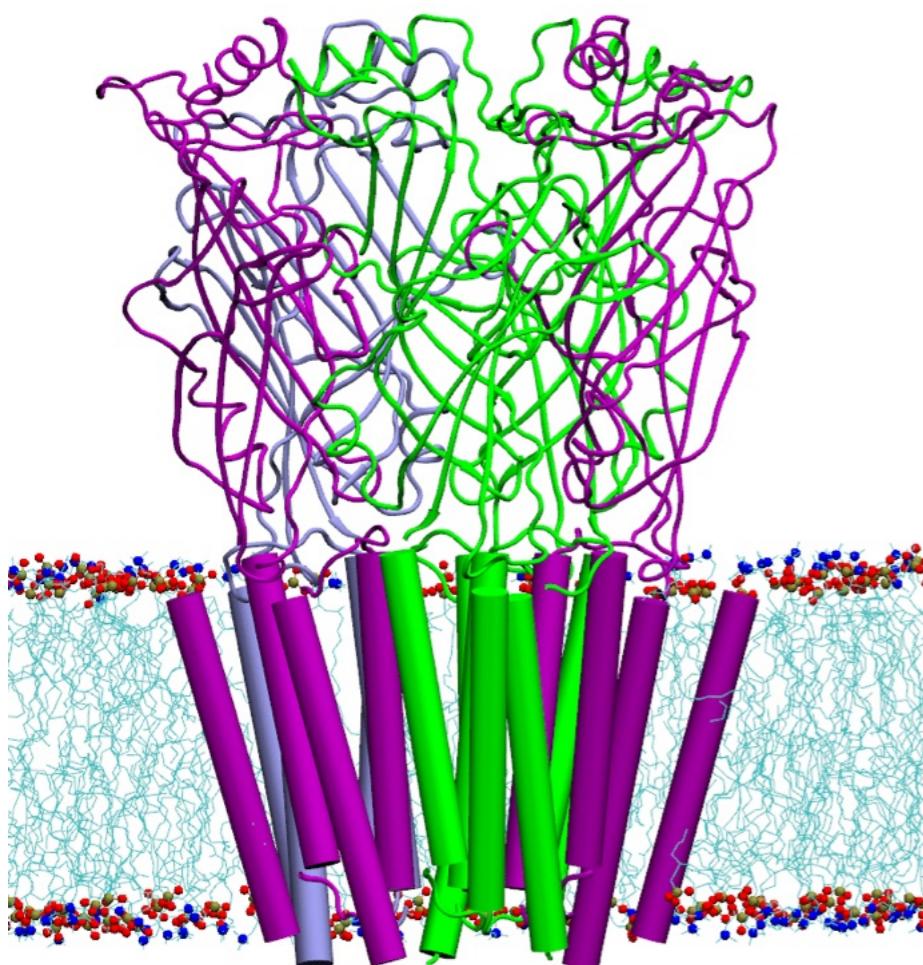


Pentameric ligand-gated ion channels

Five subunits around a central pore

Can be heteromers or homomers

Transmembrane domain: four helix bundles



nicotinic Acetylcholine Receptor



Torpedo electric ray



nicotine



Krait snake



Curare tipped arrow

GABA(A) receptor



Fishberry (picrotoxin)



propofol



pentobarbital



benzodiazapenes



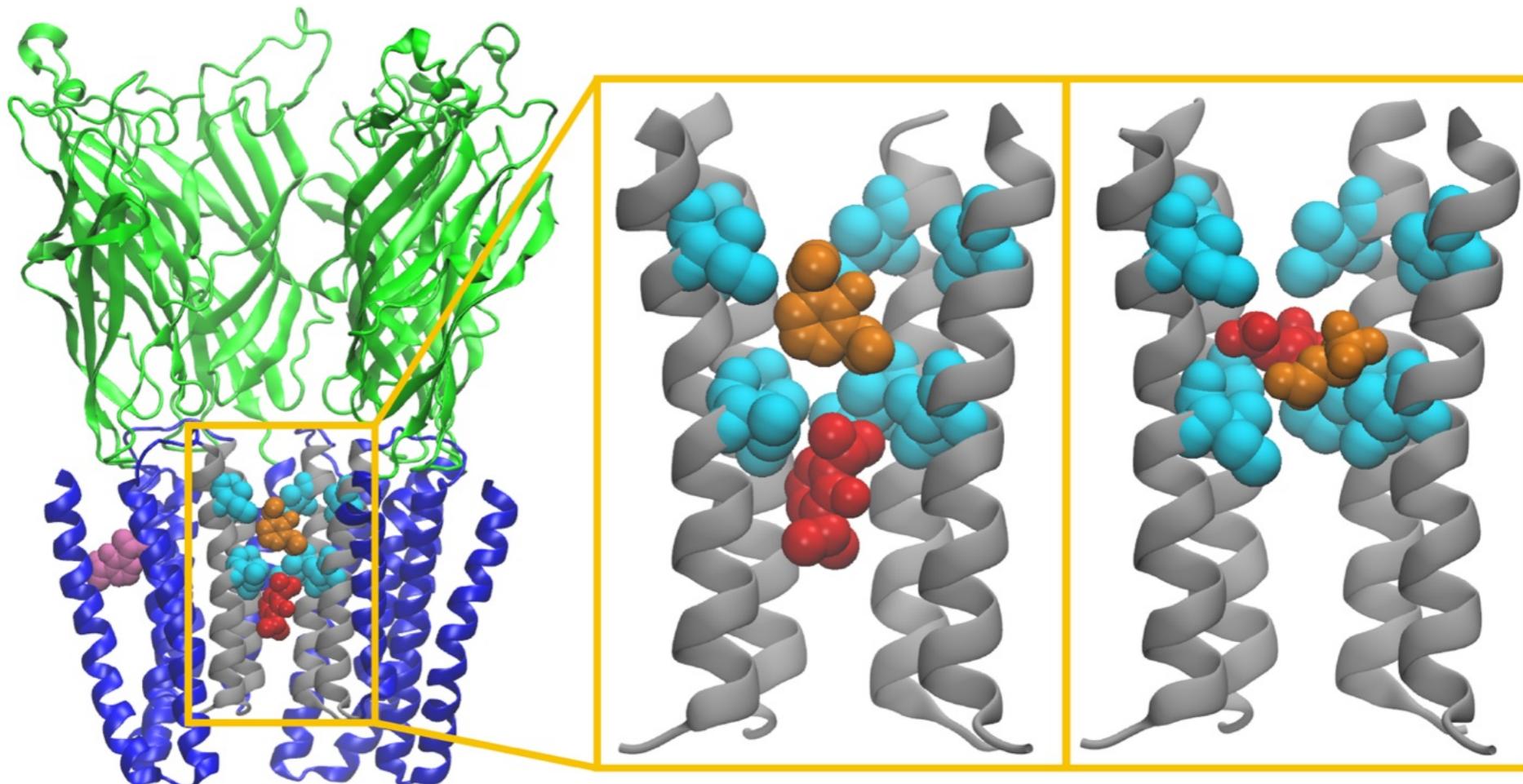
ethanol



methaqualone

Bacterial pLGICs

GLIC : can be modulated by anesthetics but are pH-gated



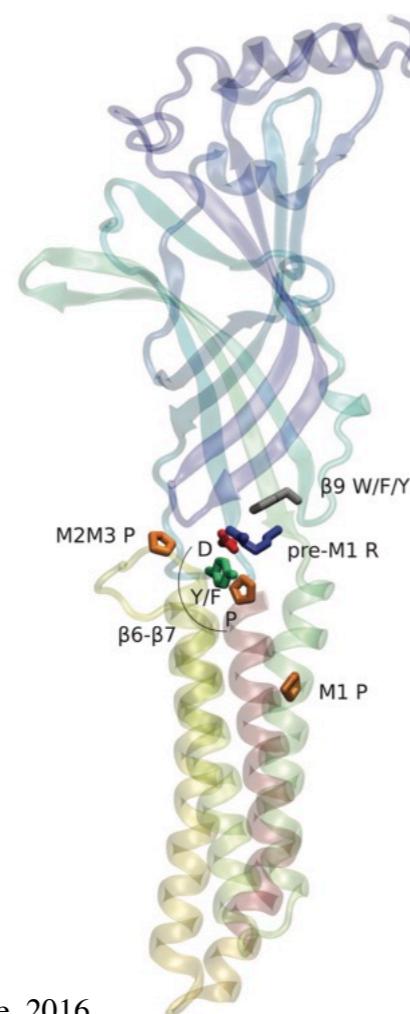
LeBard, Henin, Eckenhoff, Klein, Brannigan, PLOS Comp Bio, 2012

Others (ELIC, etc.) can be activated by neurotransmitters!

Pentameric ligand-gated ion channels

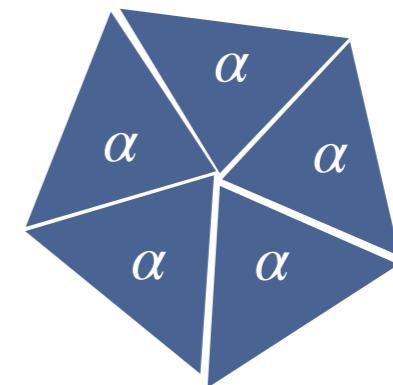
Structure is highly conserved
Sequence isn't!!

Most highly conserved residues
within a single subunit:

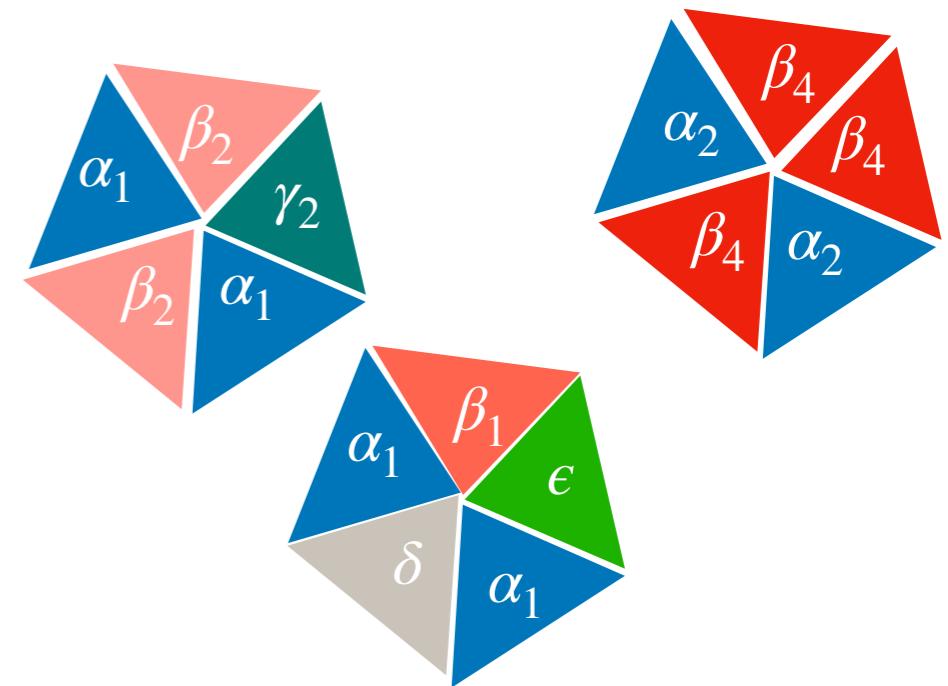


Mix and match sequences

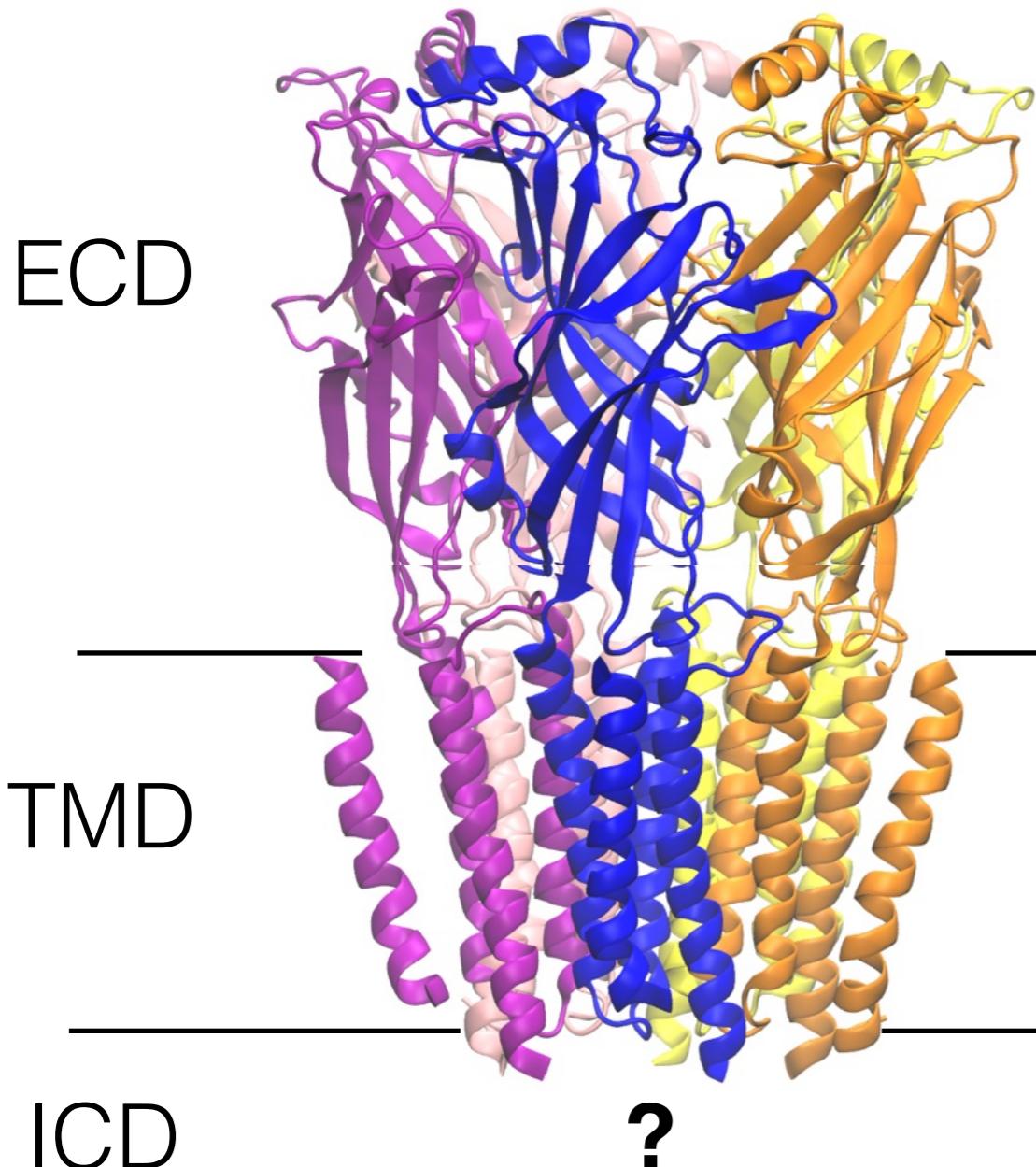
Homopentamer



Heteropentamer



Pentameric ligand-gated ion channels: pharmacology



Neurotransmitters: GABA, acetylcholine, serotonin, glycine

Sedatives and stimulants: benzodiazapenes, nicotine

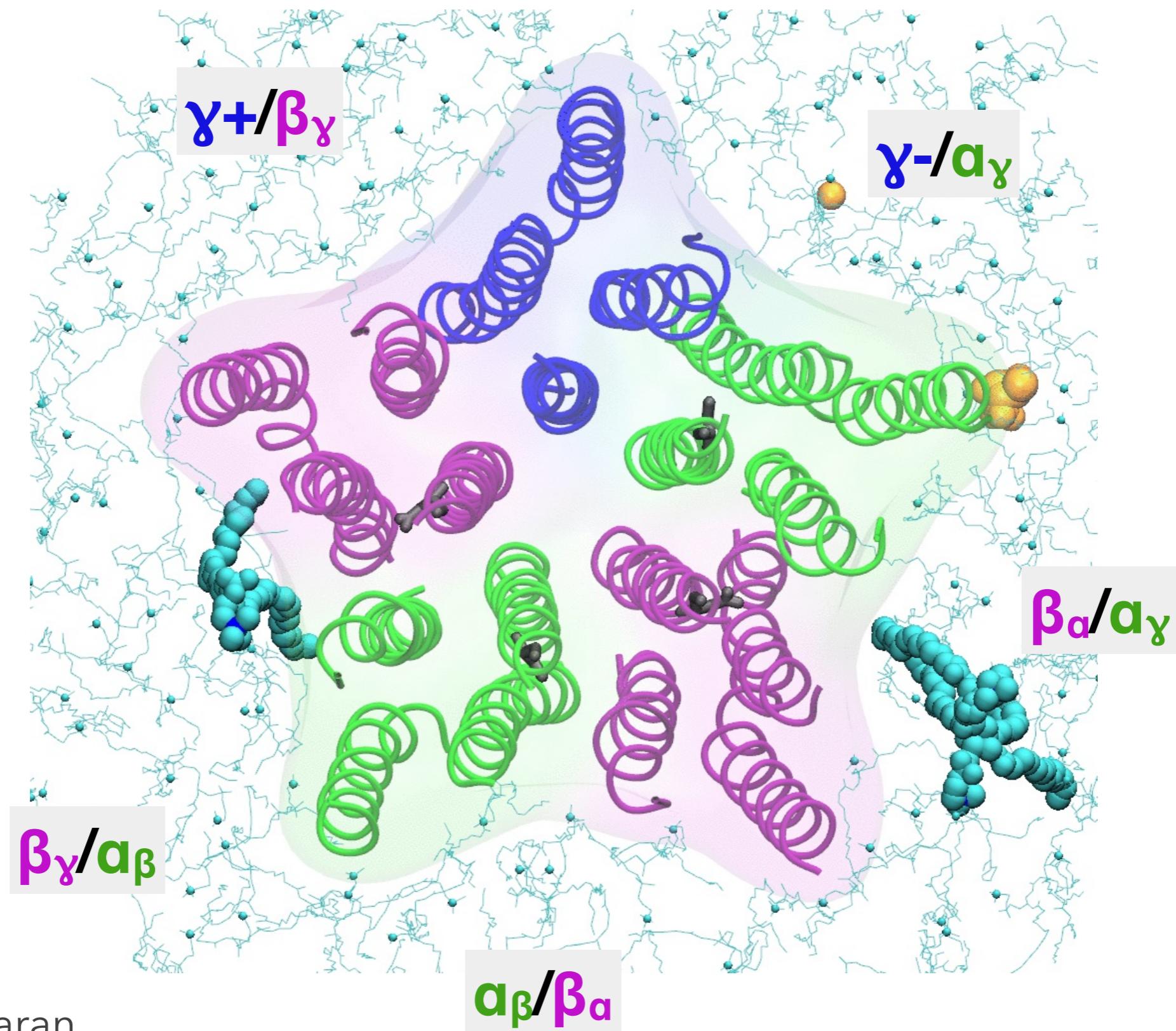
lipophilic modulators: neurosteroids, sterols, phospholipids, hormones

general anesthetics, insecticides, rodenticides

Promiscuous sites, but sequence specificity is critical for minimizing side effects

Drugs are much pickier than sites are!

Flooding the GABA(A) receptor with the general anesthetic sevoflurane (1.5 μ s)



Some open questions

How is ligand binding coupled to pore opening?

Binding modes for lipophilic modulators? Mechanism of effect on conformational equilibrium?

Preferred annular lipids?
Non-annular lipids?
Partitioning domain?

Lipid requirements to yield native pLGIC function?

Which residues confer ion selectivity?

Correspondence between structural and functional states?

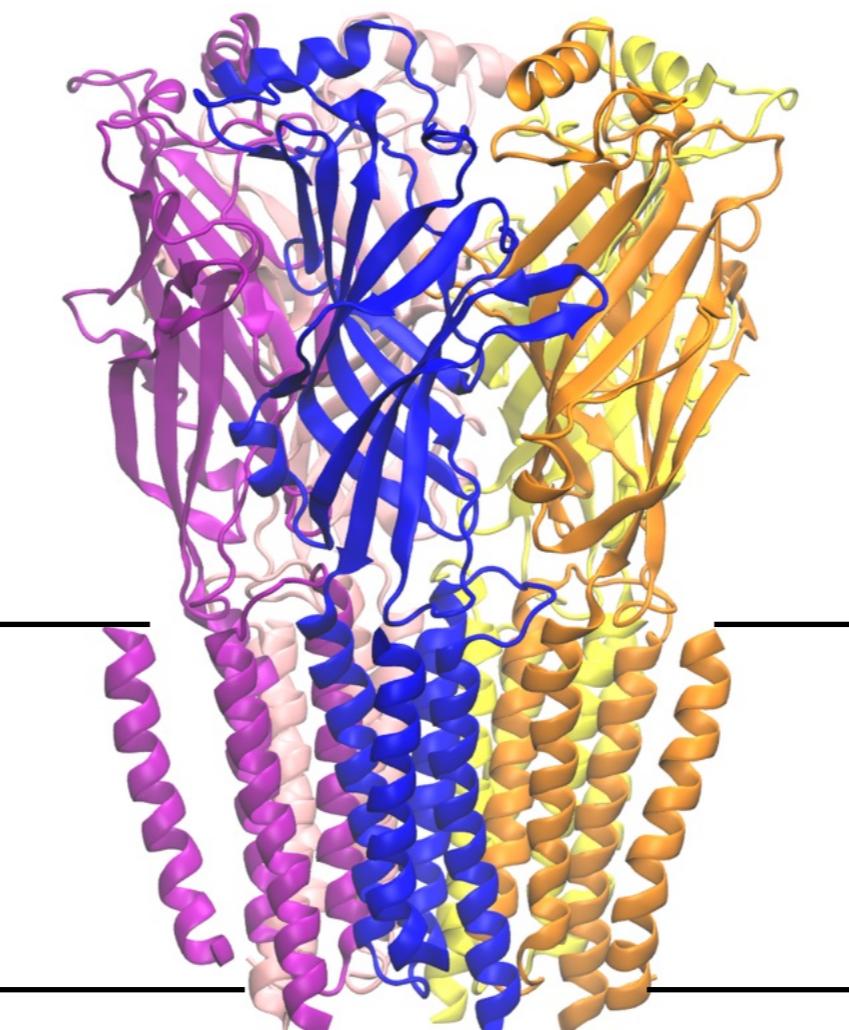
Overlap between pH gating and ligand-gating mechanisms?

Purpose of neurotransmitter receptors - pLGICs - in prokaryotes & archae?

Structure/function of the ICD?

Origins of Sequence Selectivity?

Oligomerization and clustering of pLGICs, especially at NMJ?



Many open questions are about mechanisms

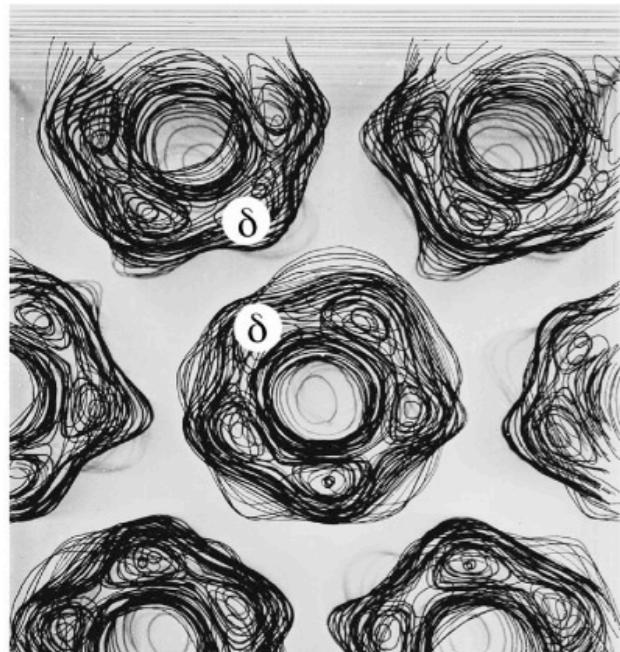
- 1) **Which** molecules are involved : (proteins, lipids/fatty acids, nucleic acids, sugars, water, salt/ions, other small molecules including drugs)
- 2) **How** they interact :

Chemical reactions (breaking and forming of bonds)

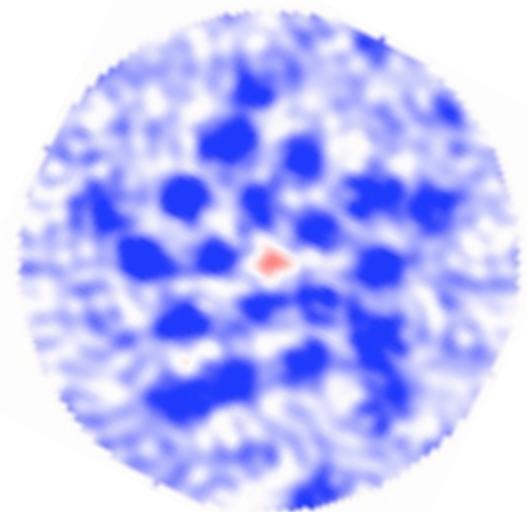
Biophysical interactions (attraction/repulsion) among atoms and molecules.

Determining interactions: Why isn't structural biology "enough?"

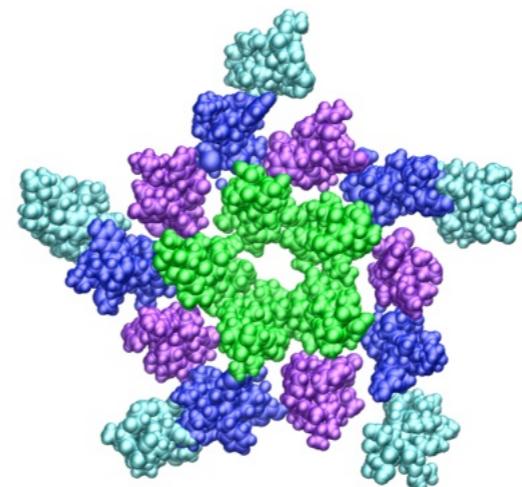
Problem 1: Resolution



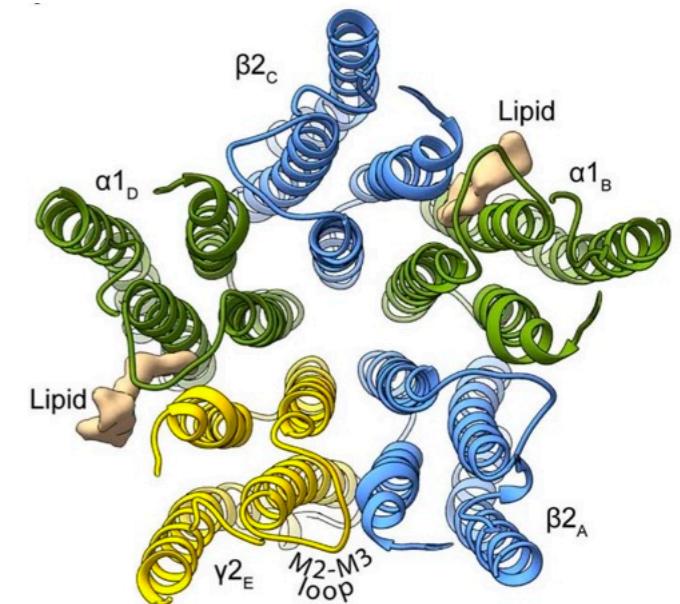
Brisson & Unwin, **1985**)



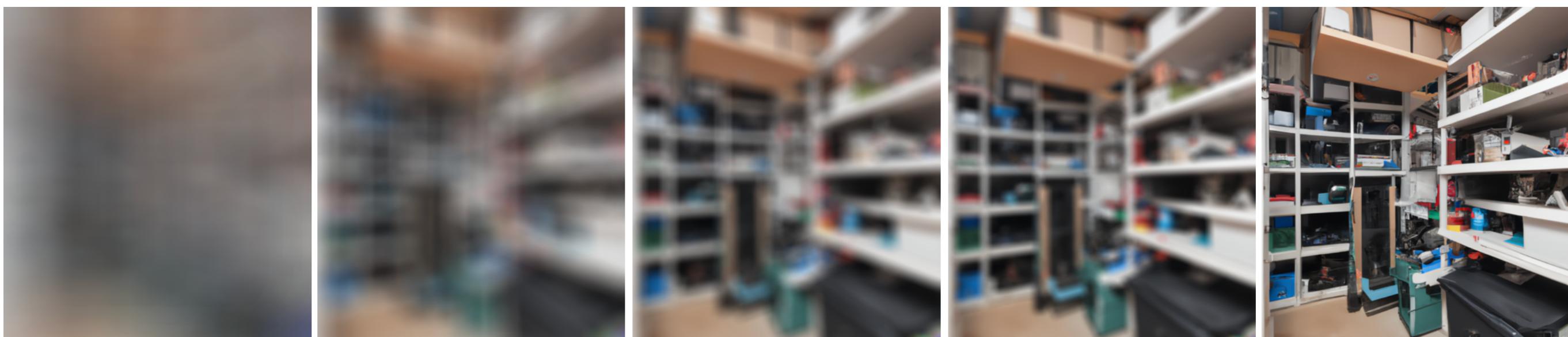
Based on Miyazawa
and Unwin, **2003**



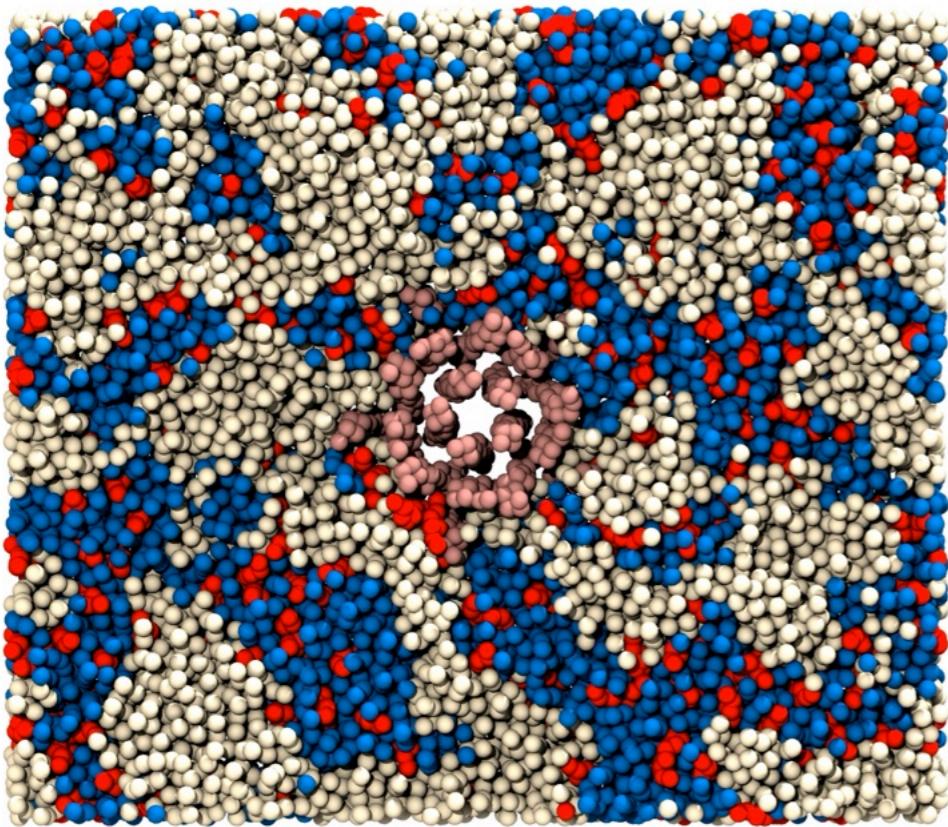
Based on 2BG9,
Unwin, **2005**



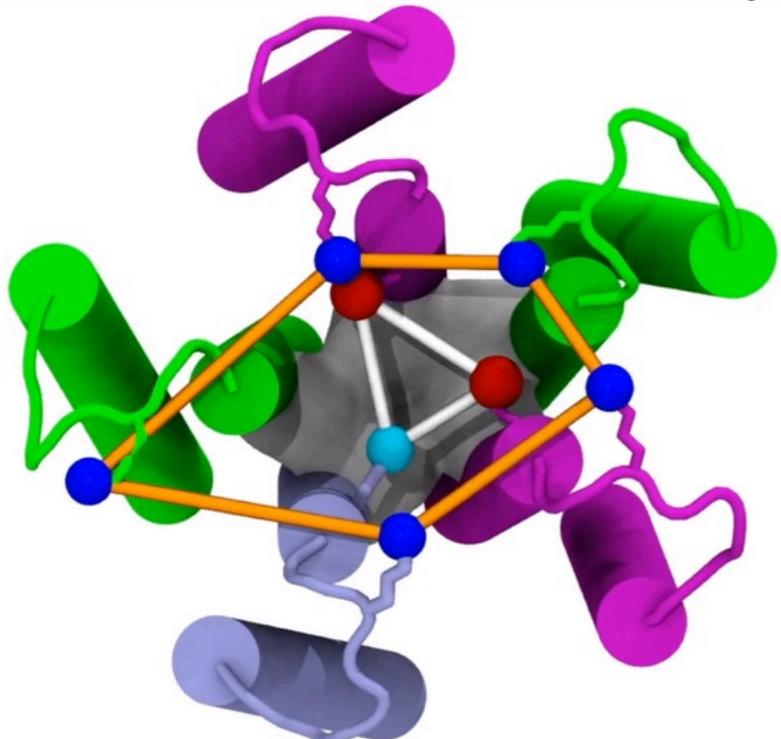
Paper II in this dissertation,
2020



Determining interactions: Why isn't structural biology "enough?"



- Liam Sharp



- Sruthi Murlidaran

Problem 2: Dynamics

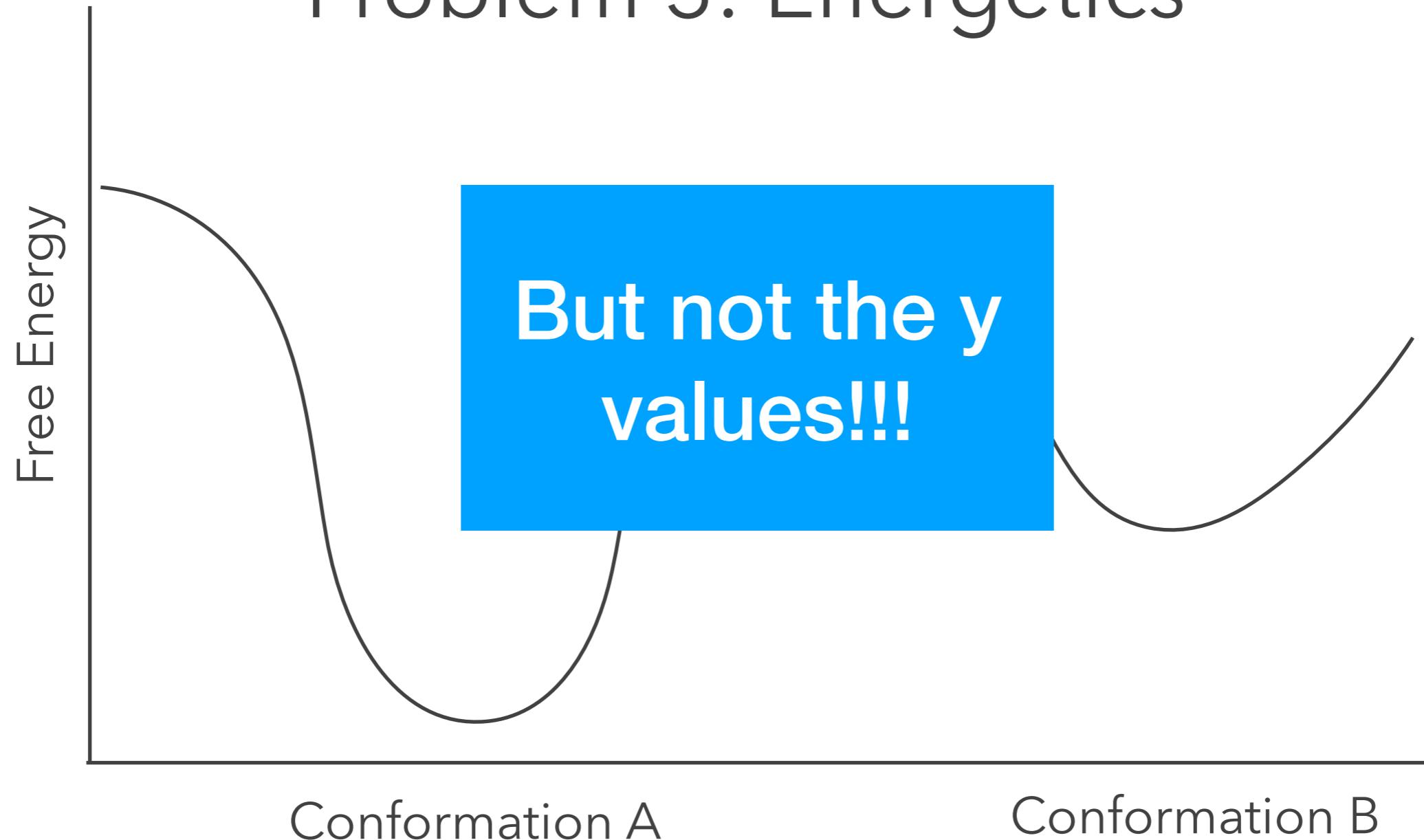
Dynamics are key to function but are lost in static structures



<https://awkwardfamilyphotos.com/category/photos/the-family-portrait/page/4/>

Determining interactions: Why isn't structural biology "enough?"

Problem 3: Energetics



Structural biology gives you the x values

Molecular Simulations Address All 3 of these Problems

Problem 1: Resolution – MD can capture atomistic resolution

Problem 2: Dynamics – MD is run at physiological temperatures with realistic dynamics

Problem 3: Energetics – we have direct access to energy differences (and reasonably direct access to entropy/free energy differences)

Bonus: movies!

Resolution, Dynamics, Free Energies

<https://www.youtube.com/watch?v=FS6e38BtUIw>

Decoupling POPG from ELIC

Audio represents size of free energy difference per window

-Ezry St. Iago-McRae

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