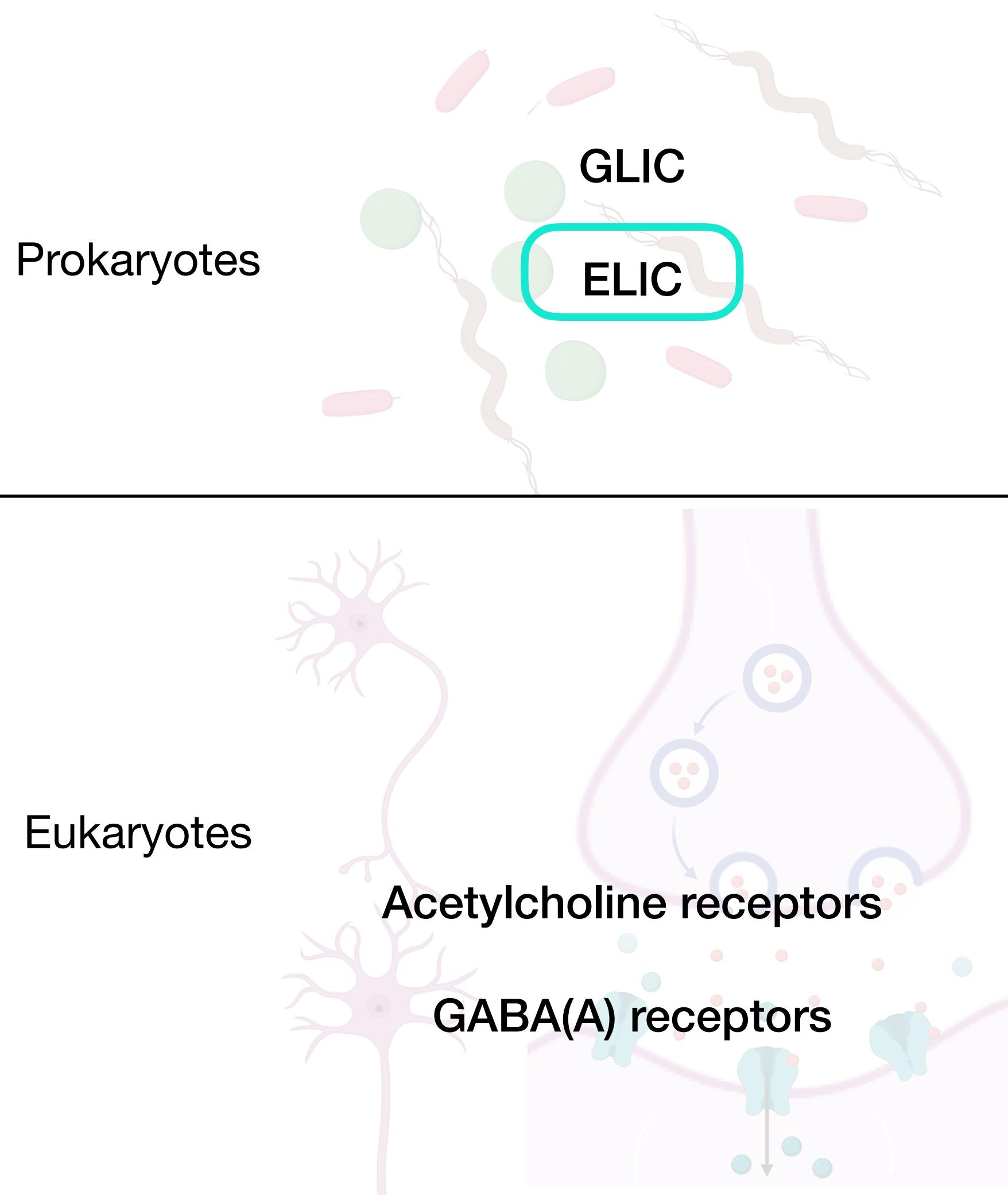


# Lipid Modulation of an Ion Channel, ELIC

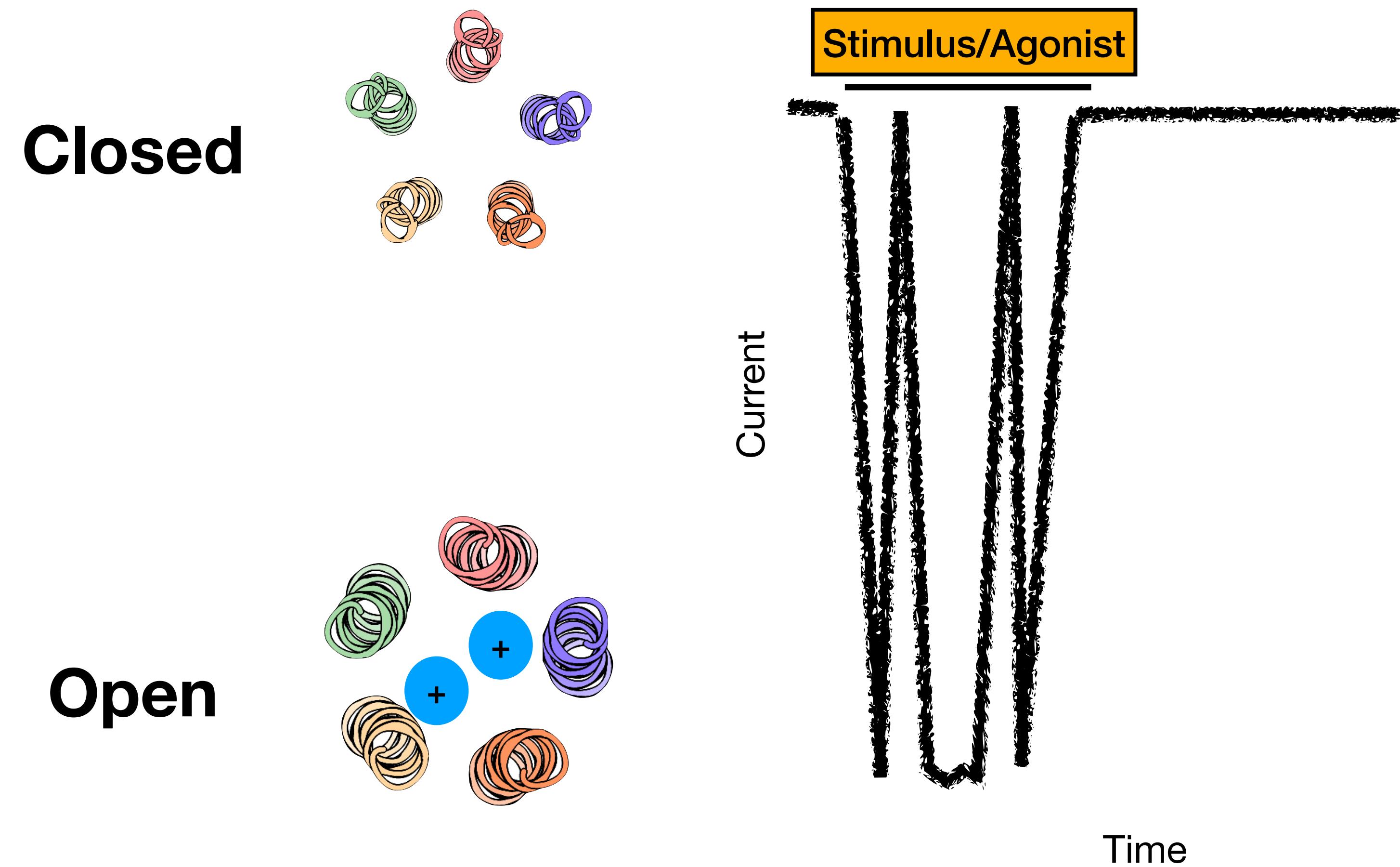
Insights from Free Energy Computation

Ezry Santiago-McRae, Tom Joseph, John T Petroff II, Brandon Tan, Wayland Cheng, Jérôme Hénin, Grace Brannigan

# Pentameric Ligand-Gated Ion Channels (pLGICs) are chemosensors



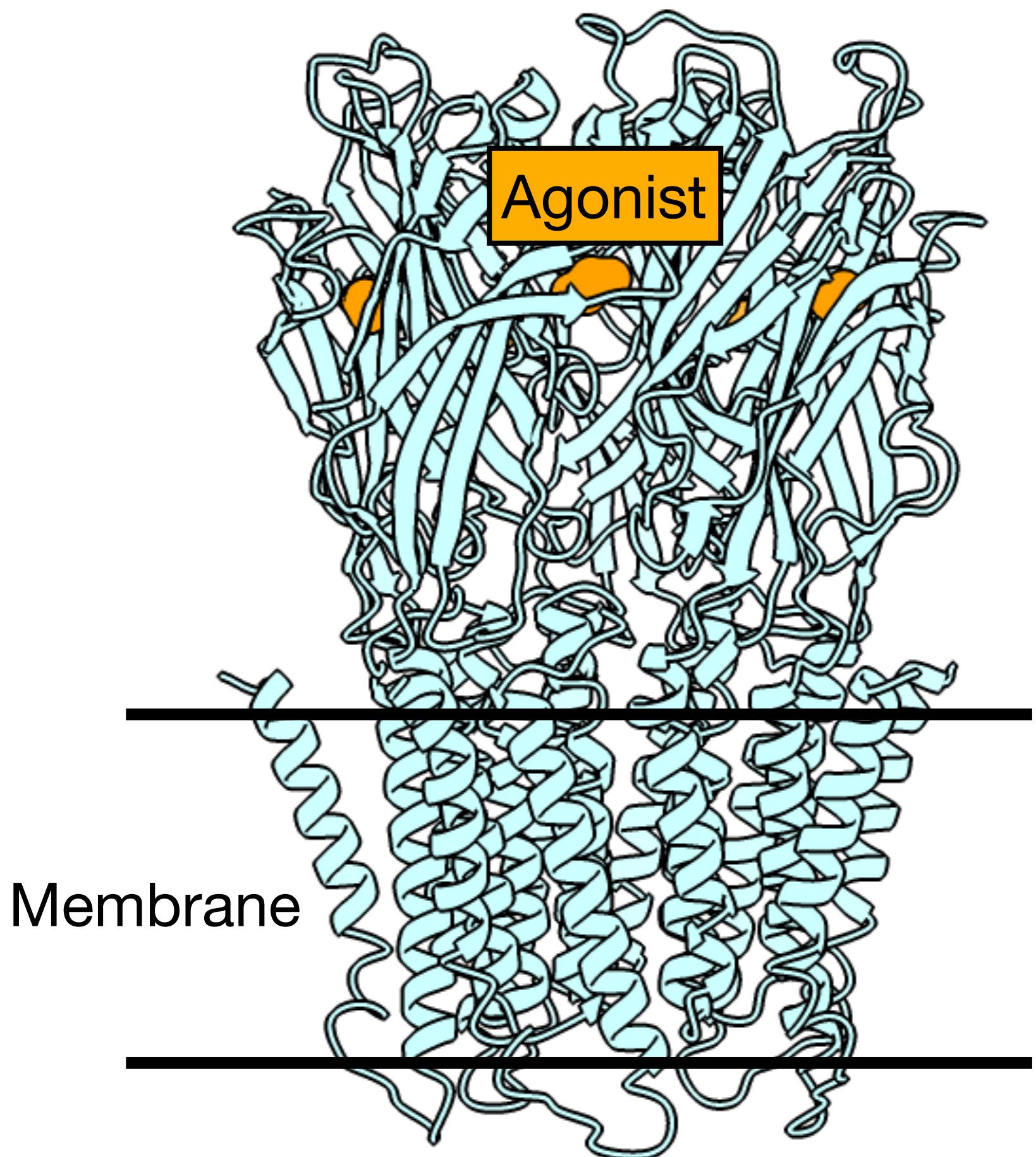
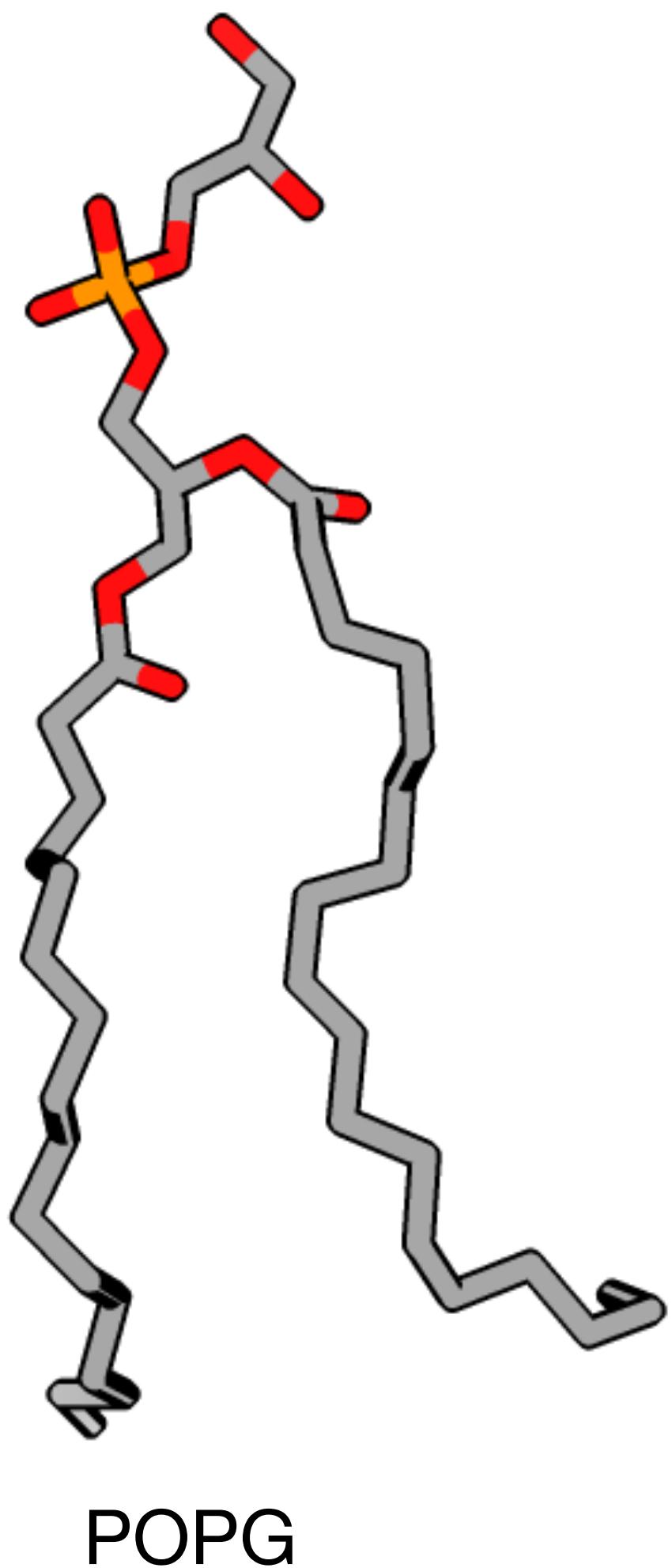
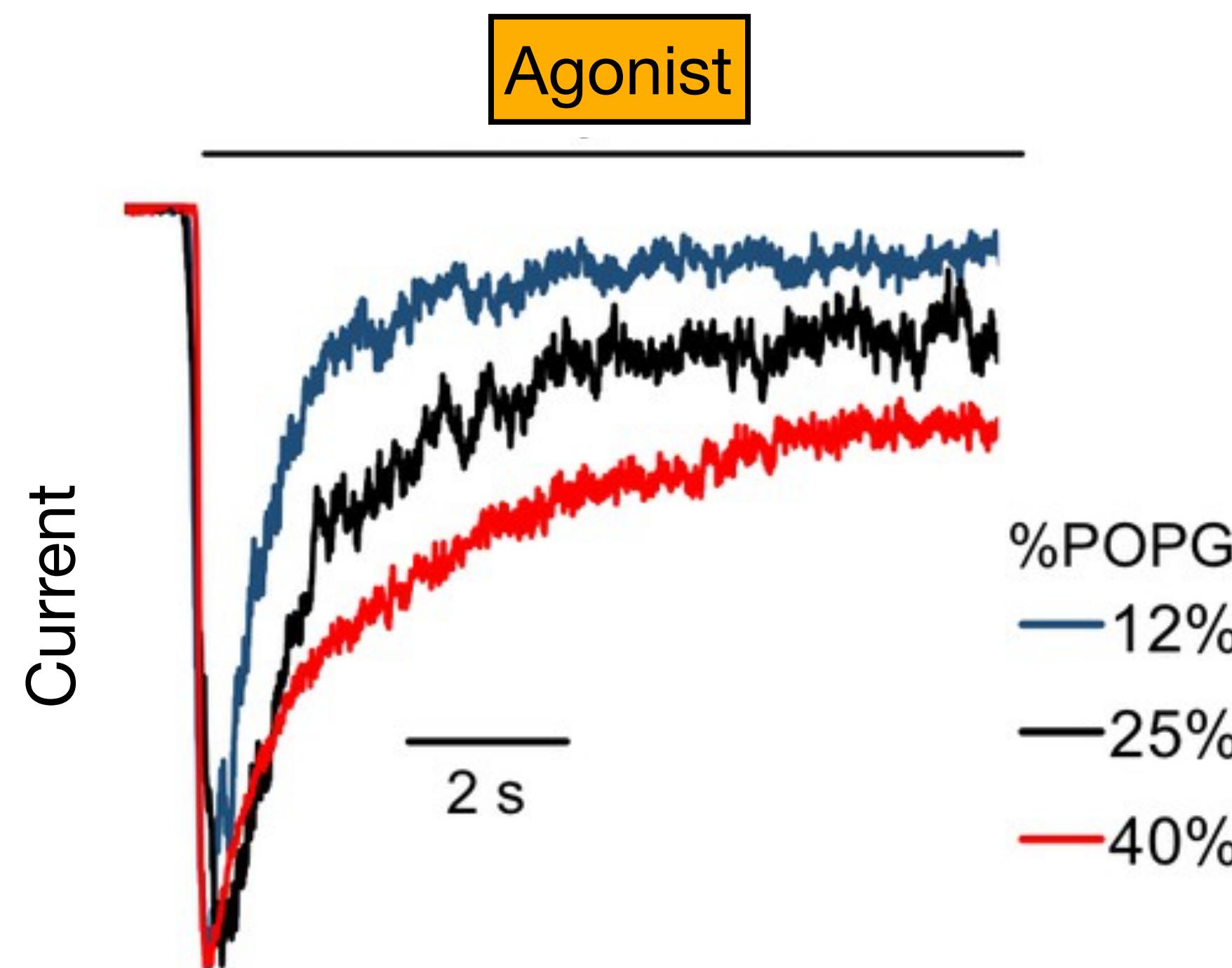
# Gated ion channels have two states:



# Agonist Shifts the Equilibrium to Open

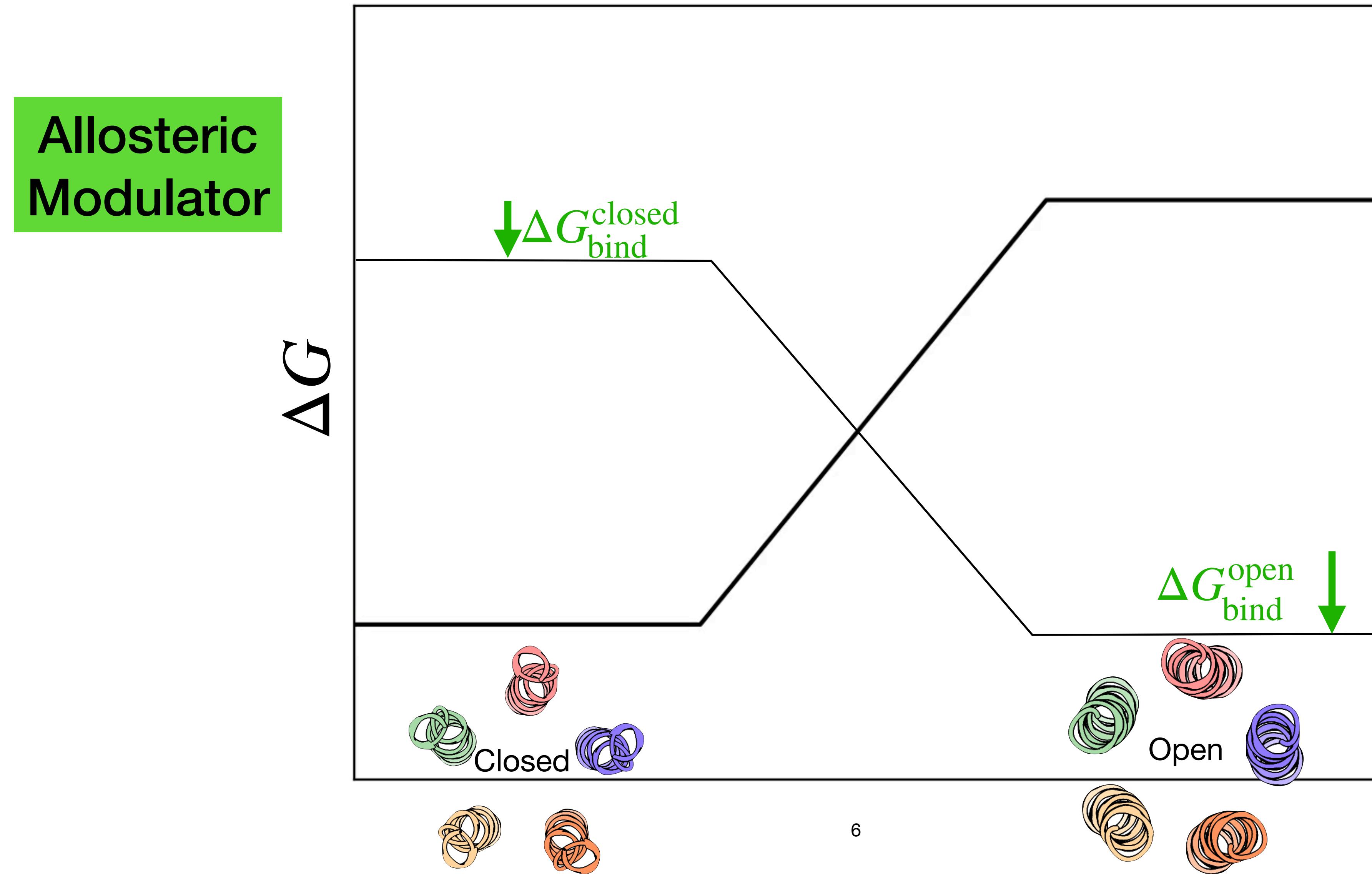
Desensitized

# pLGICs are Lipid-sensitive

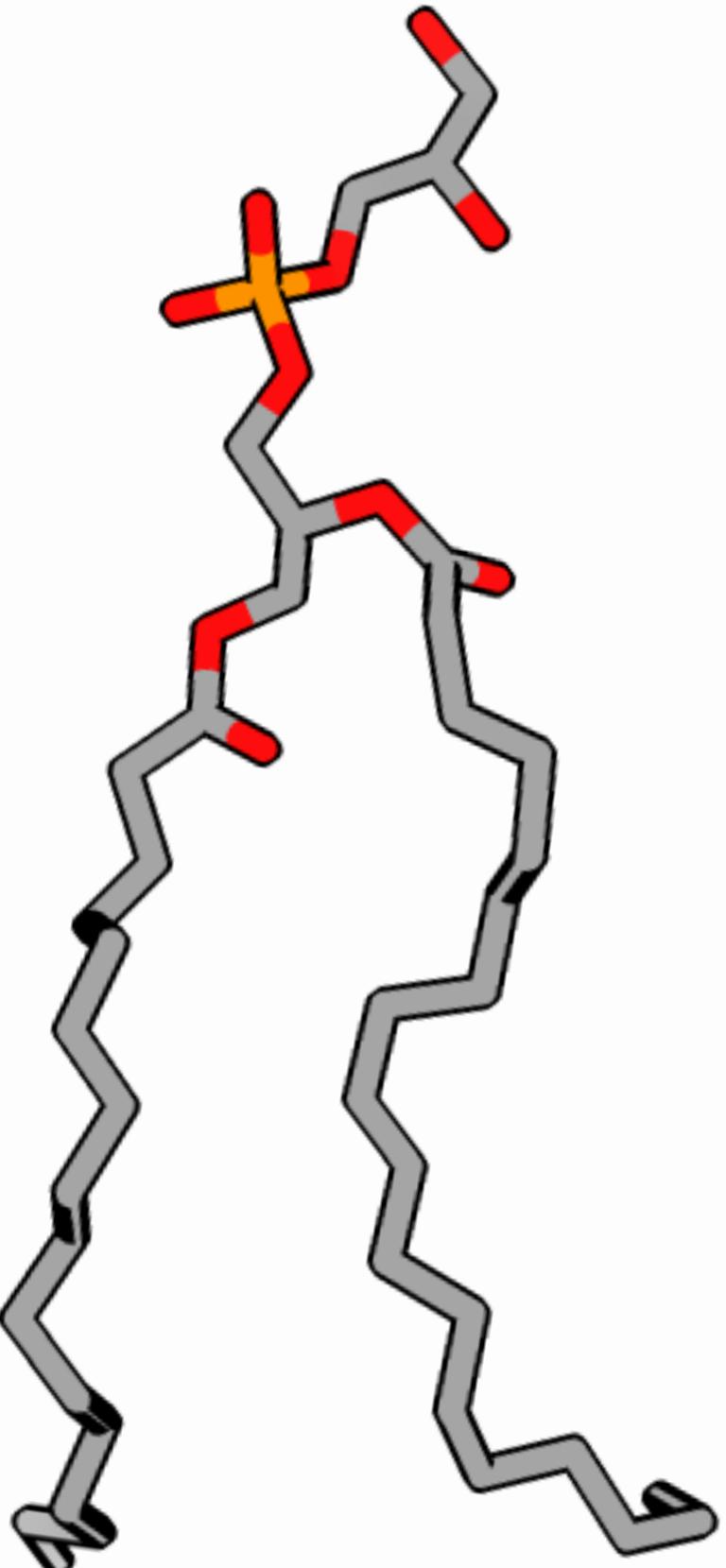


Ailing Tong, John T Petroff II, Liam Sharp, ... ,  
Grace Brannigan, Wayland WL Cheng  
eLife 2019

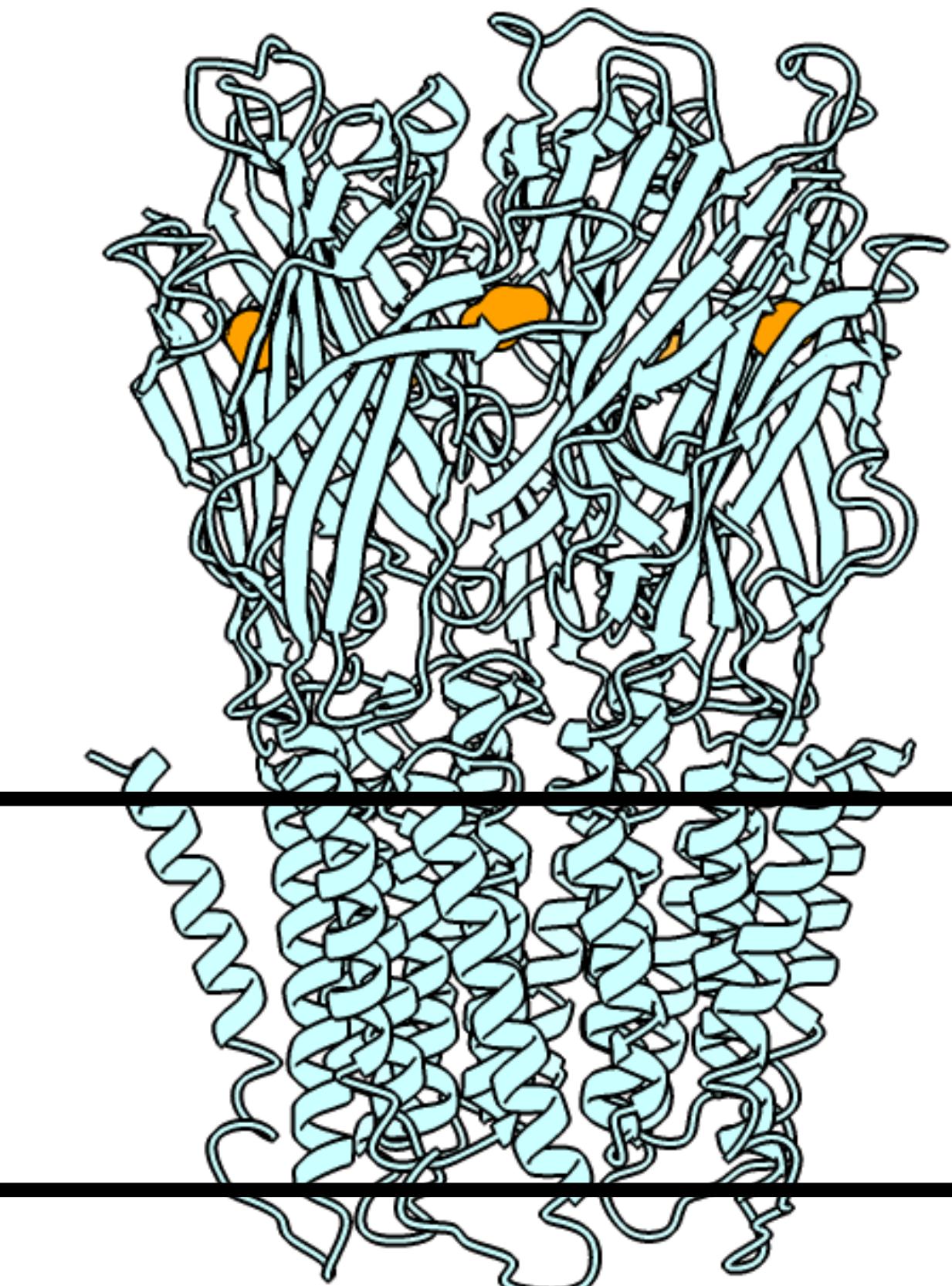
# Allosteric Modulators Shift the Equilibrium



# How does POPG modulate ELIC?

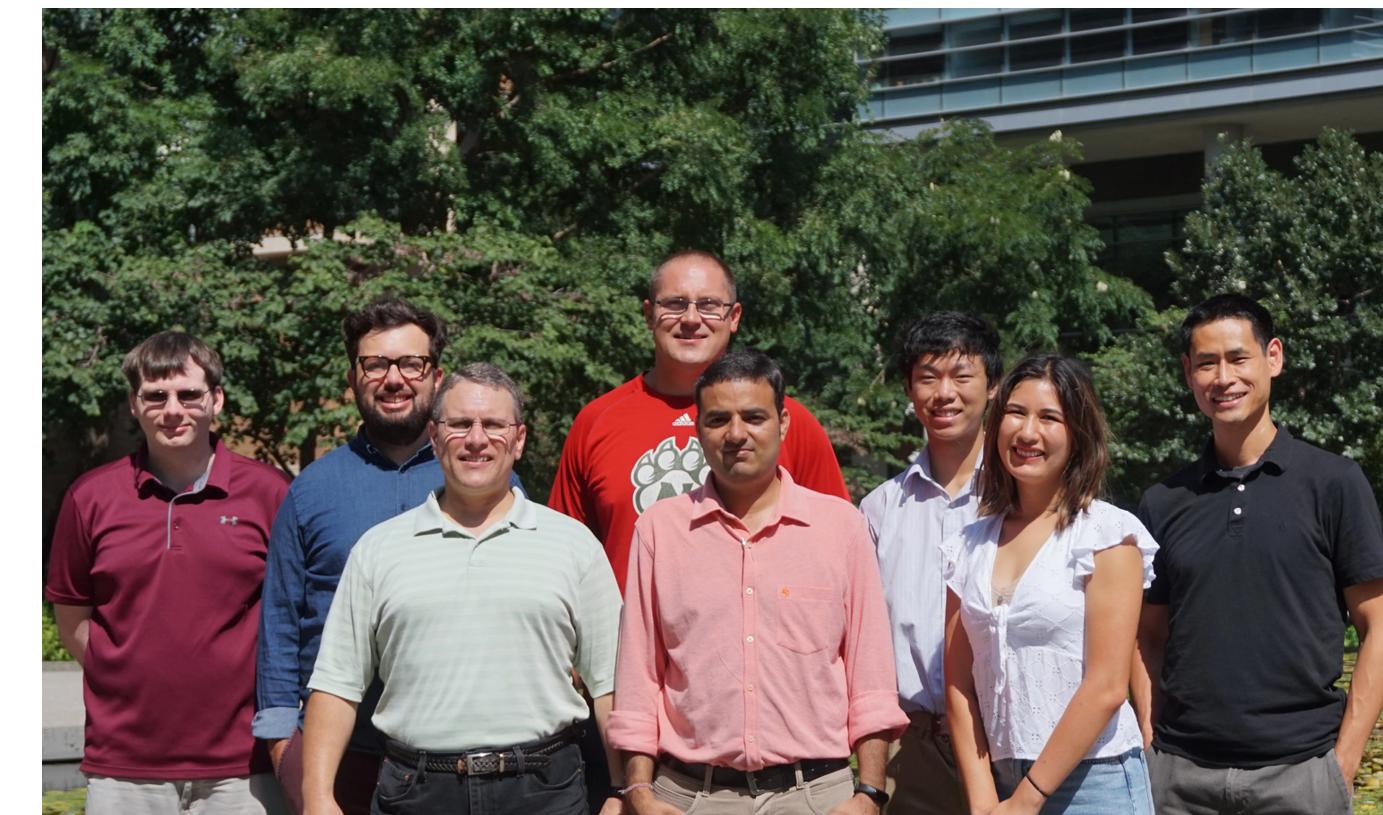
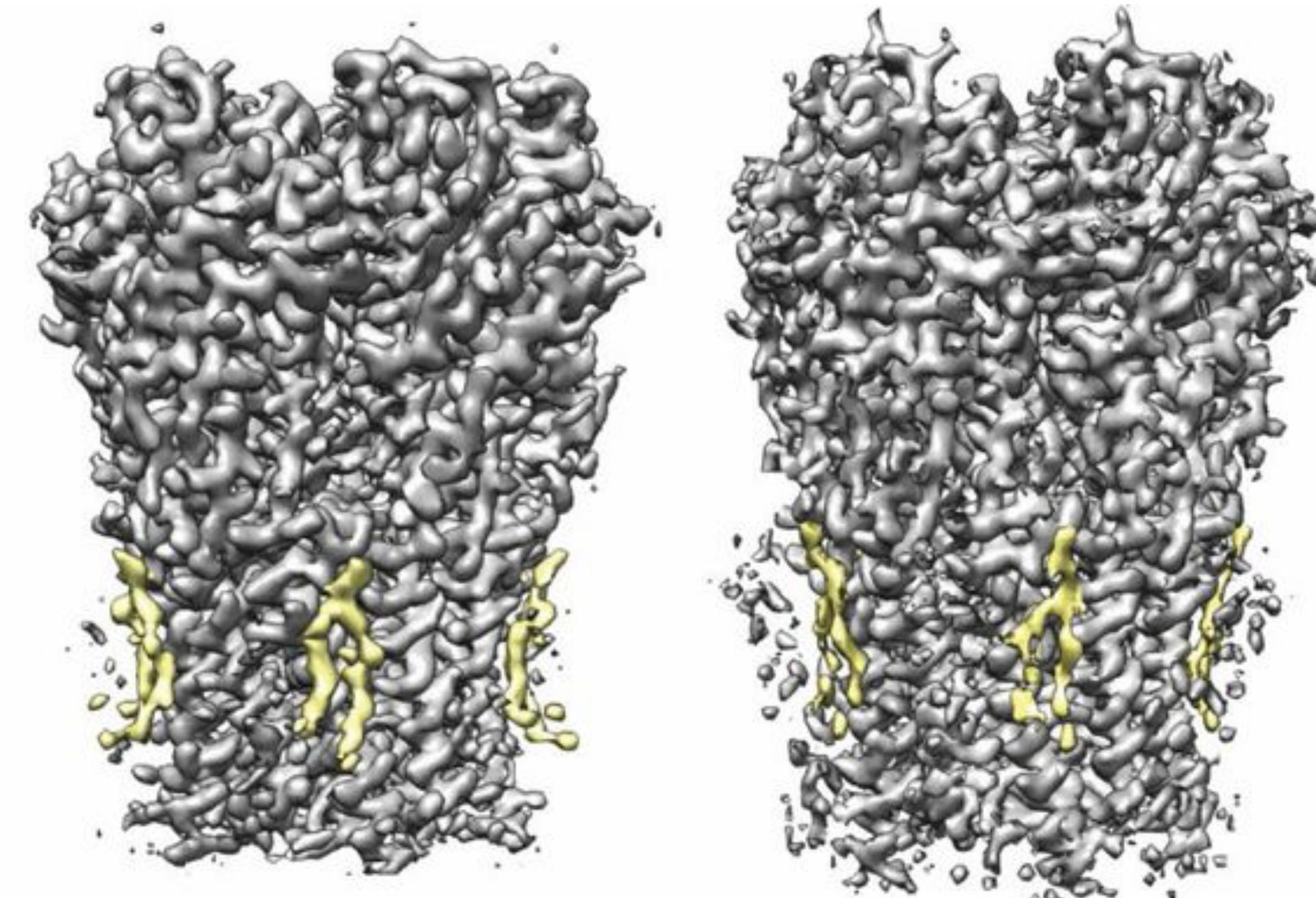


- Does ELIC bind POPG?
- If so, where?
- Is that binding state-dependent? (i.e. allosteric)



# Approach: structure and affinity

- Determine the POPG binding modes
- Obtain open and closed conformations of ELIC
- **Determine affinities for each conformation**



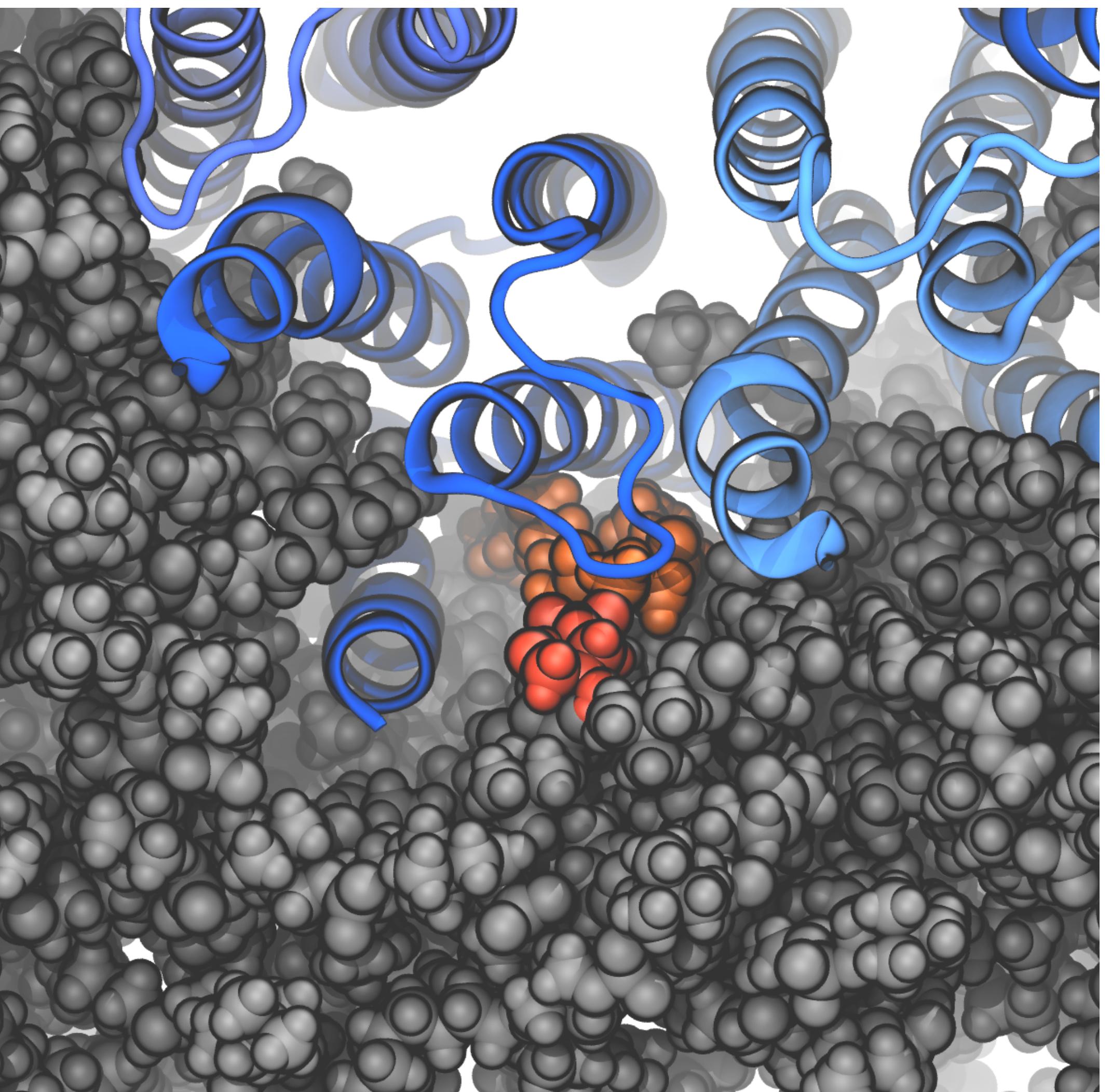
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Grace Brannigan & Wayland W. L. Cheng  
Nature Communications 2022

# Computational Approach: SAFEP

For each structure (open and closed):

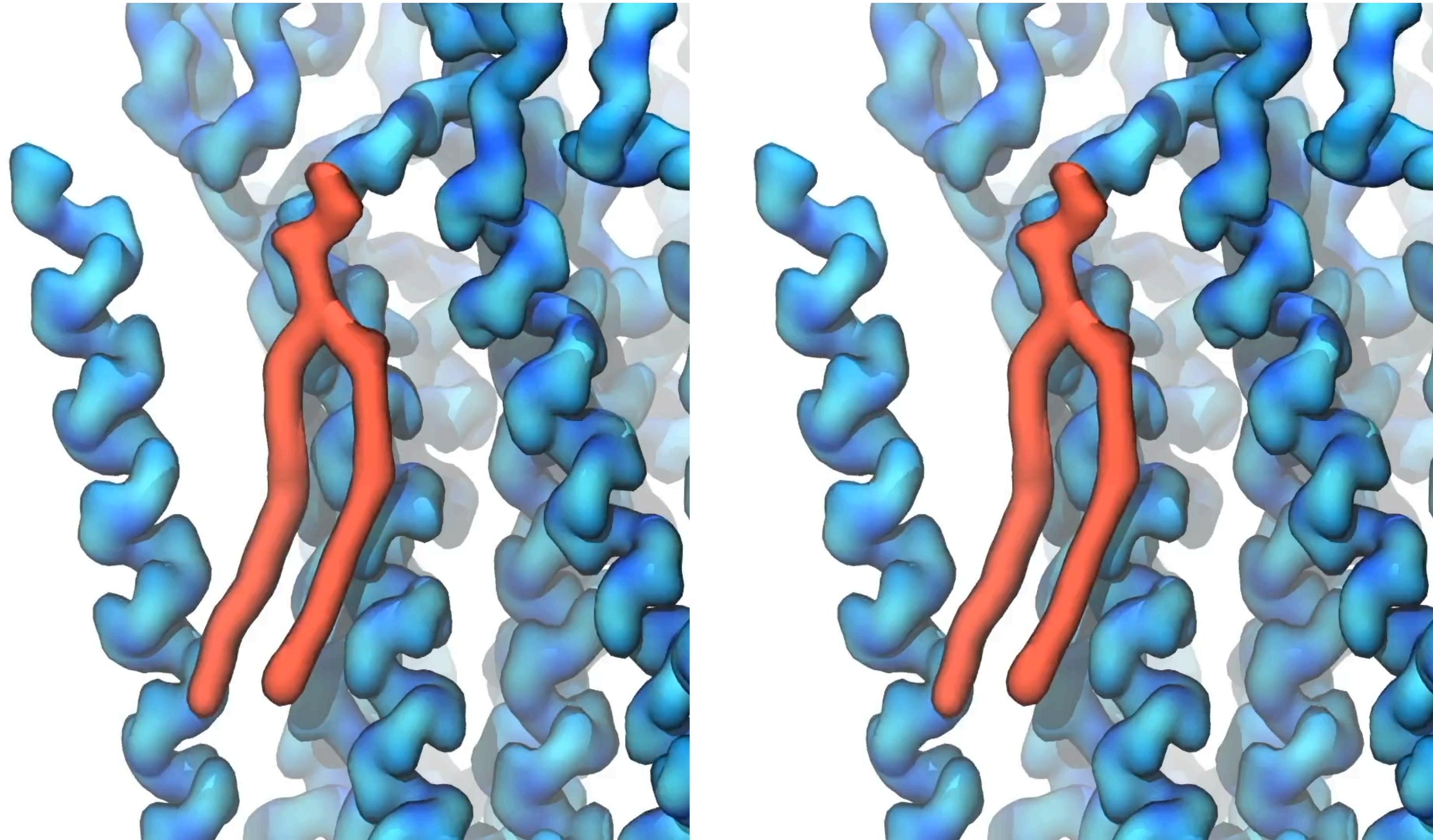
1. “Teleport” POPG out of the site and into the bulk
2. Measure the corresponding free energy
3. Which gets us the probability of occupancy by:

$$\frac{P_{\text{occ}}}{1 - P_{\text{occ}}} = e^{-\Delta G_{\text{bind}}/RT}$$



First accomplished in 2023

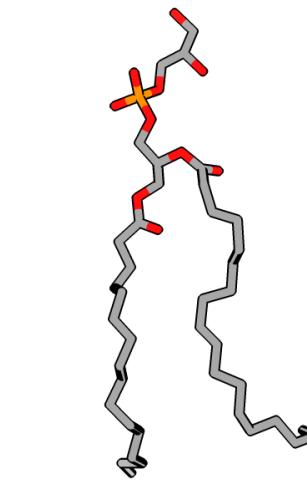
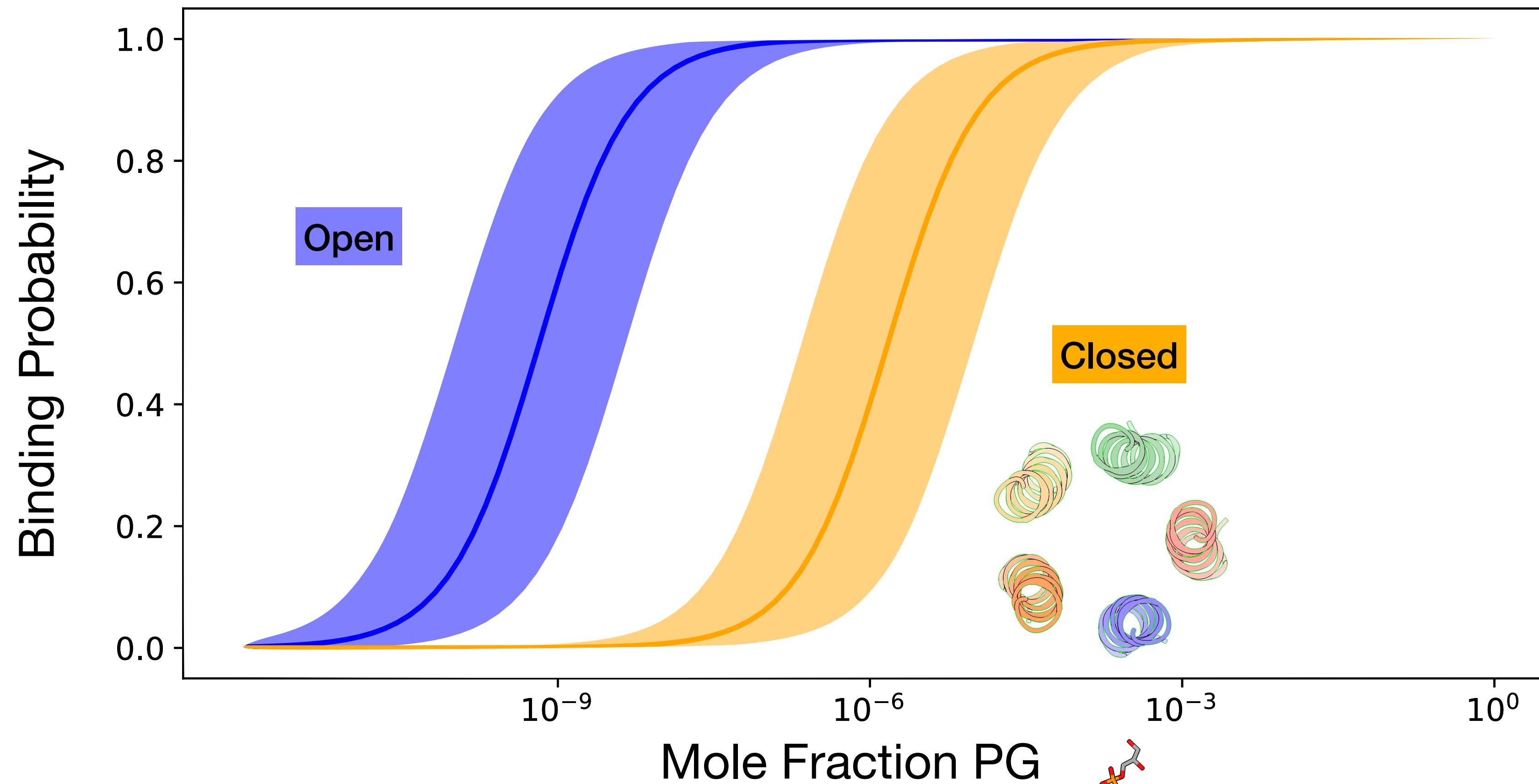
# Computational Approach: SAFEP



Protein's Point of View

POPG's Point of View

# POPG prefers open ELIC



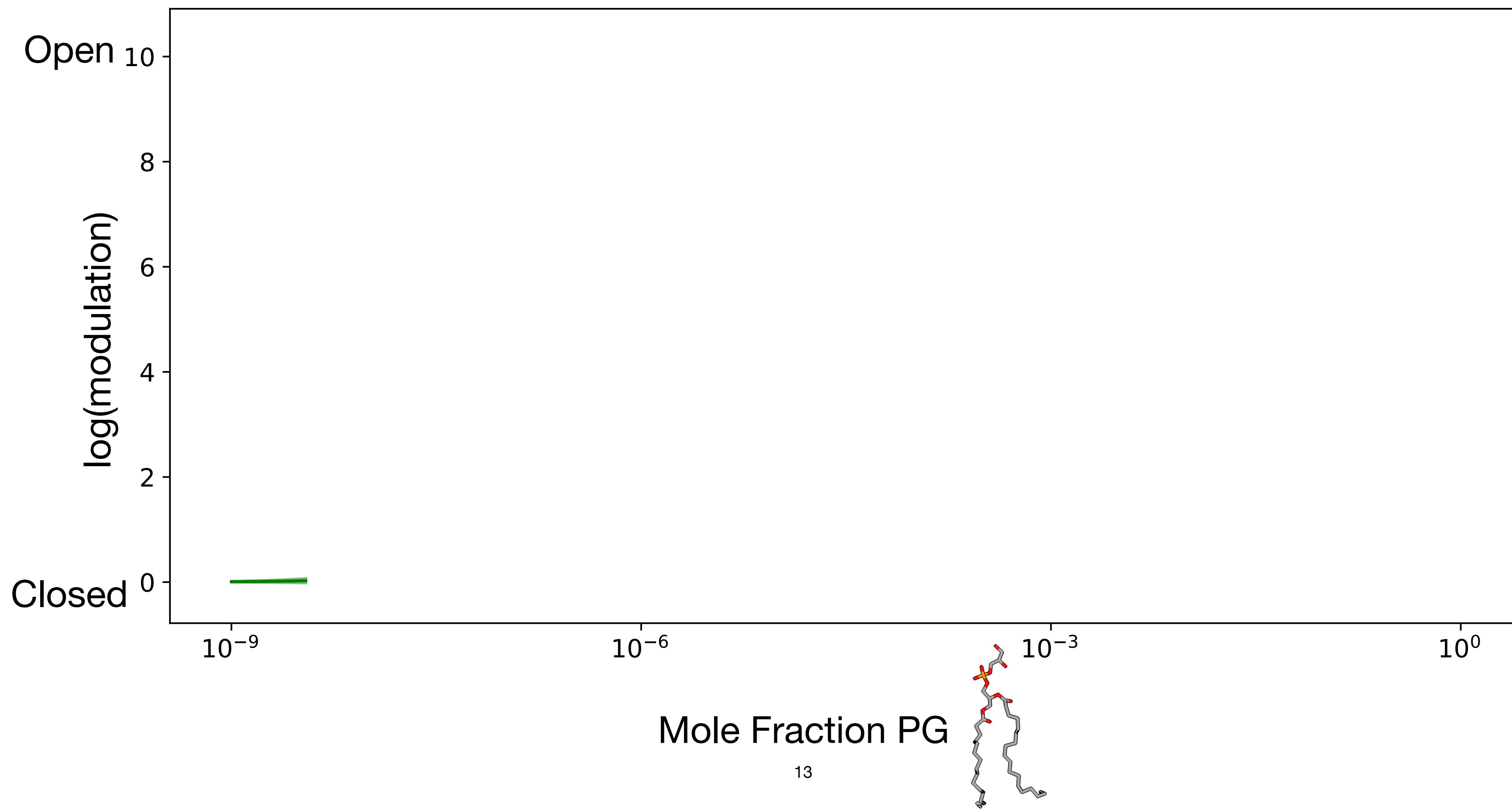
# $\Delta G$ lets us quantify modulation

$$\text{modulation} = \frac{e^{-\Delta G_{\text{bind}}^{\text{open}}/RT} / x_{\text{POPG}} + 1}{e^{-\Delta G_{\text{bind}}^{\text{closed}}/RT} / x_{\text{POPG}} + 1}$$

Affinity of PG for open ELIC      Mole fraction POPG

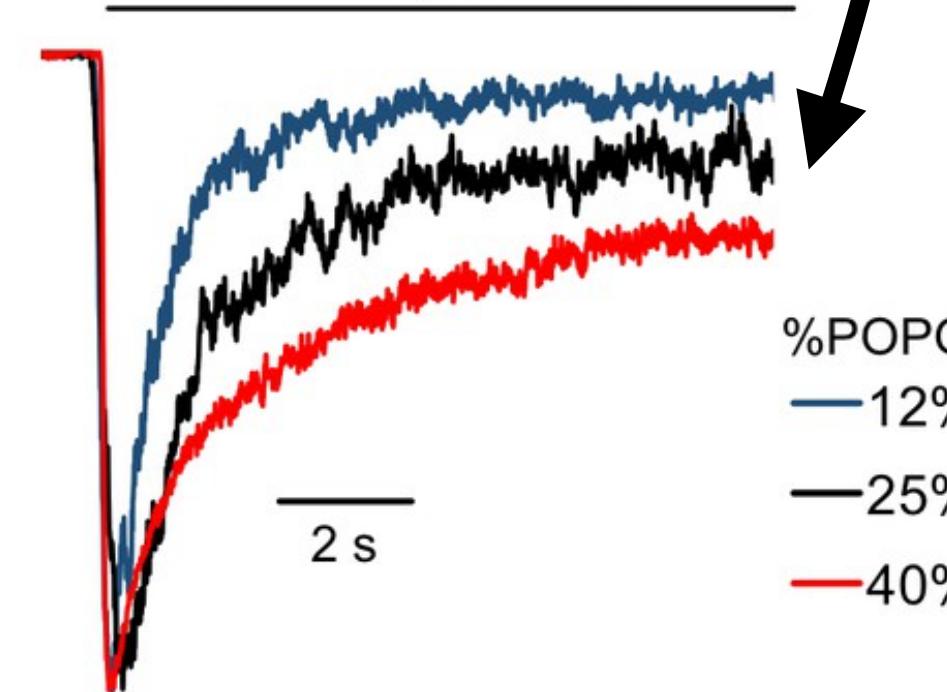
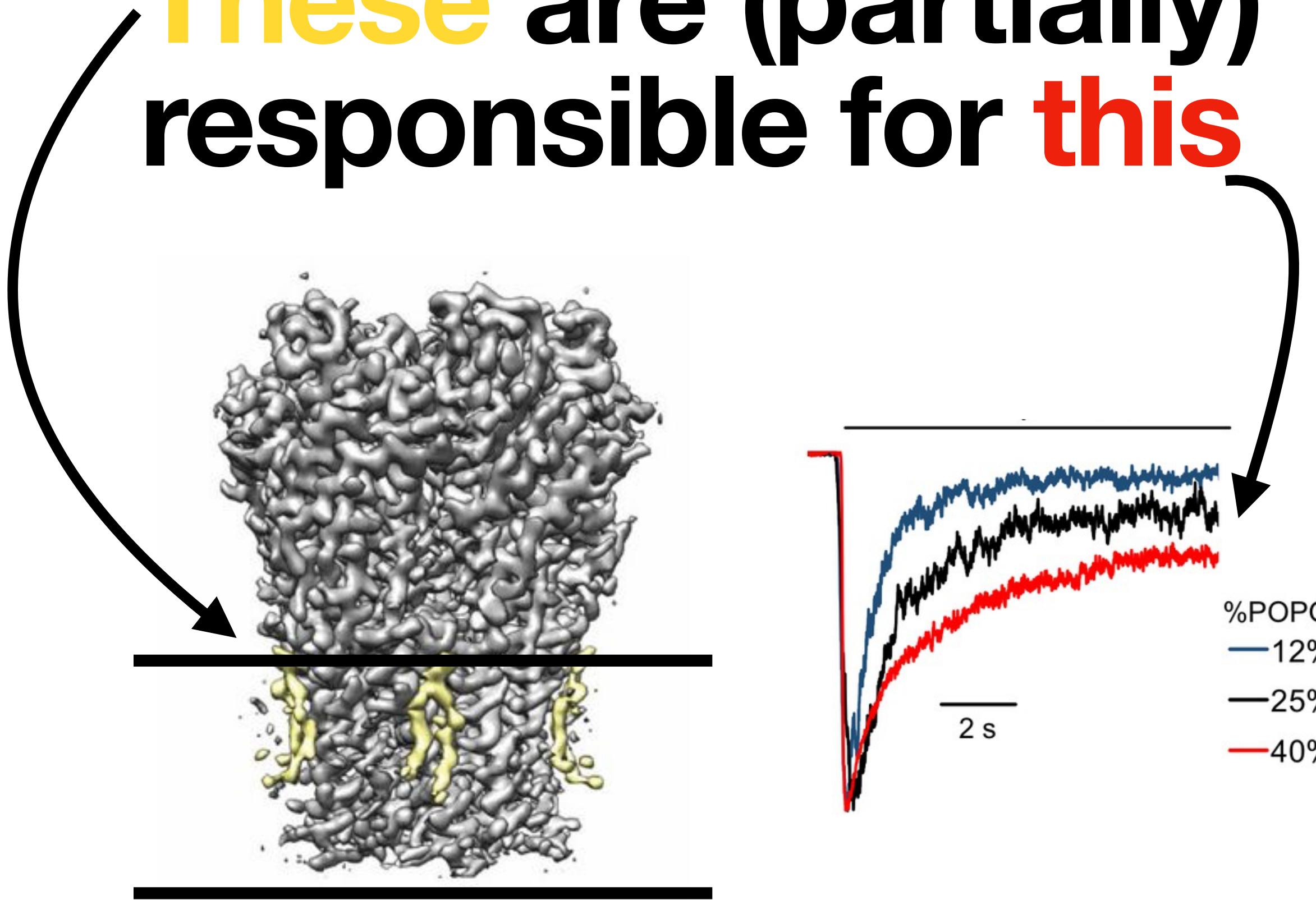
Affinity of PG for closed ELIC

# POPG is a positive modulator

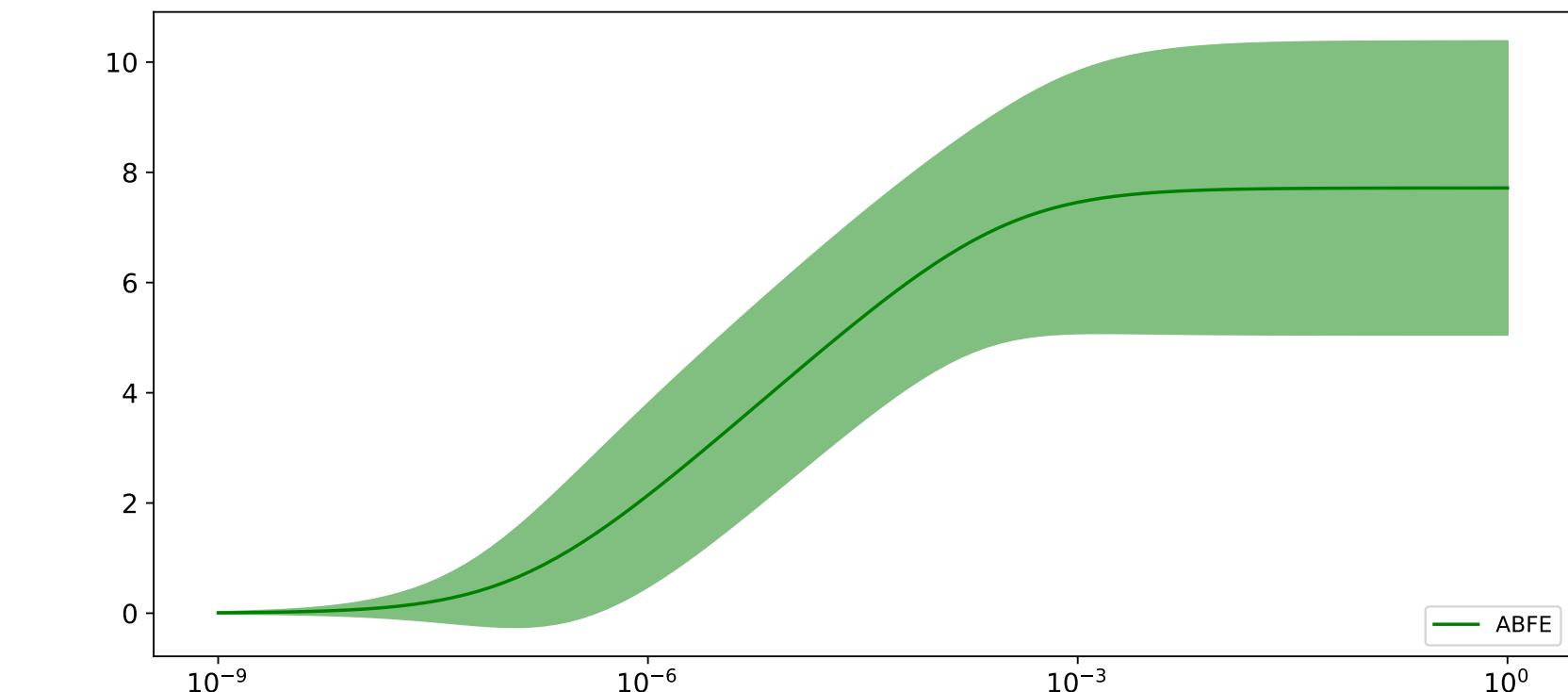


# Summary

These are (partially)  
responsible for this

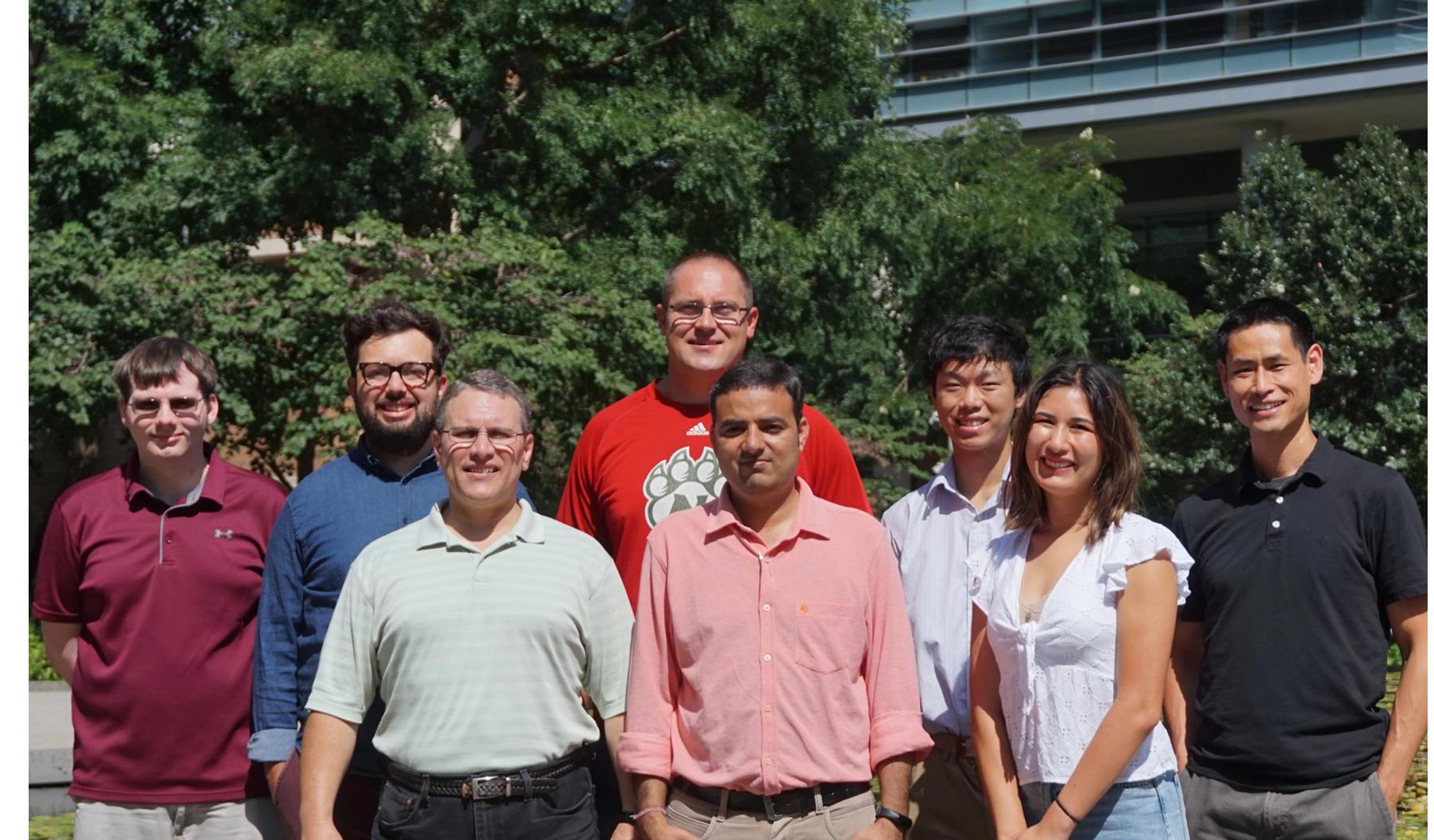


POPG is a positive allosteric modulator



John T. Petroff II, ... Ezry Santiago-McRae, ...  
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Grace Brannigan, Wayland WL Cheng  
eLife 2019



## Brannigan Lab



Reza Salari

## Wayland Cheng's Lab



## Collaborators



Jérôme Hénin

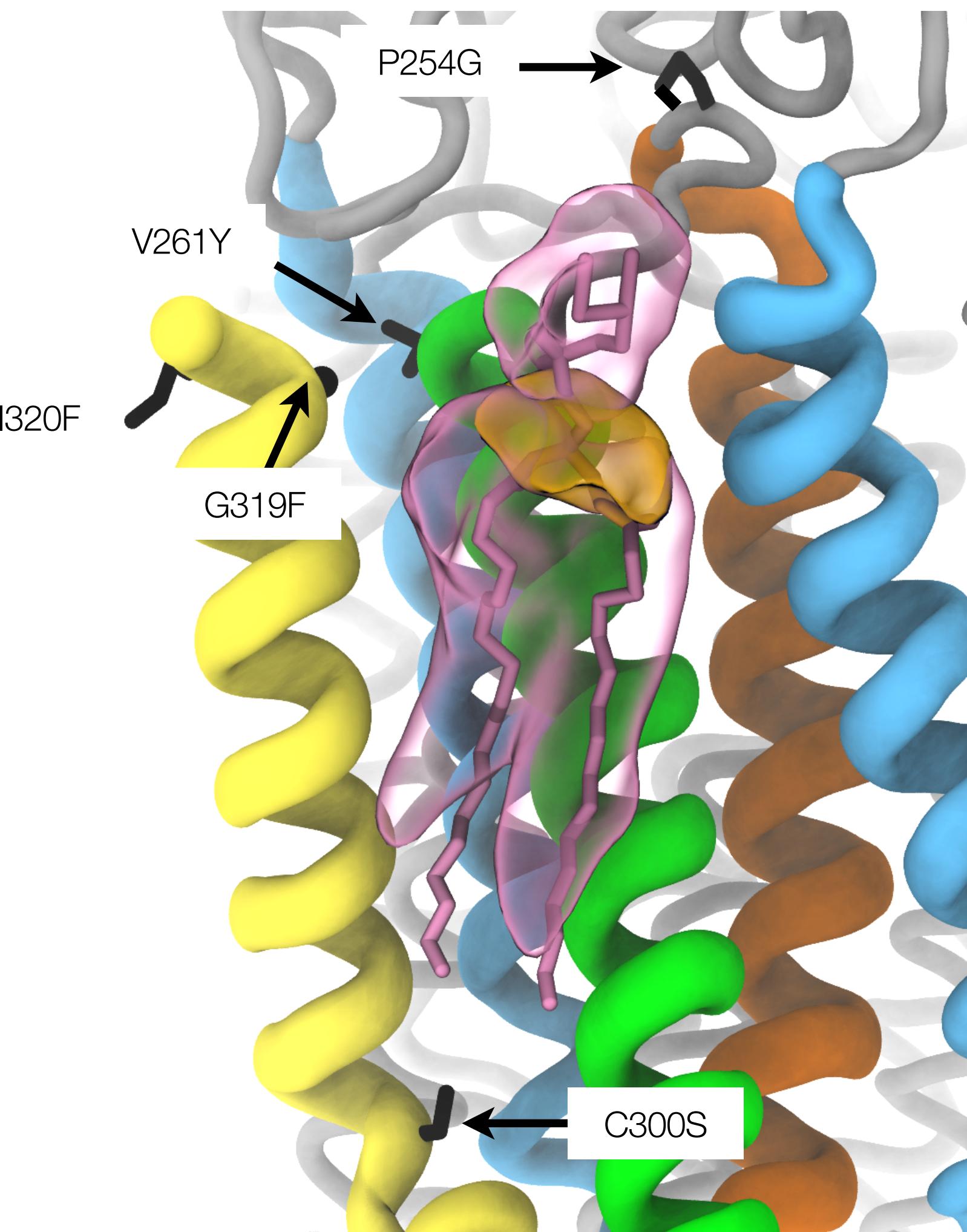


Tom Joseph





# Mutations of ELIC5



# Contacts

