

Hydrophobic Specificity in Lipids, Proteins, and Populations

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Hydrophobic Specificity in Lipids, Proteins, and Populations

1. Lipids

A. Identifying **lipid fragments** from structures

- atomistic
- ELIC + model membranes
- new simulation protocol: SAFEP
- bonus: state dependence!

Ezry St. Iago-McRae



Dr. Jérôme Hénin



Dr. Tom Joseph



B. Quantifying lipid sorting in **complex quasi-native** membranes

- coarse-grained
- new analysis method: density threshold affinity
- nAChR + neuronal membranes

2. Proteins

C. Hydrophobic-to-hydrophobic mutations in **intrinsically disordered proteins**

- Val66Met mutation in the Brain-derived Neurotrophic Factor prodomain
- Massive atomistic simulations
- New analysis method: Blobulation

D. Blobulation as a **generally-useful conceptual tool**

- Protein organization and hierarchy from sequence

3. Populations

- Hydrophobic sequence context of disease-associated mutations
- Population frequency of mutations in particularly hydrophobic blobs

motivation: pentameric ligand-gated ion channels (pLGICs)



recreation



nicotine

sedatives



benzodiazepenes



methaqualone

poisons



rat poison (TETS)



strychnine

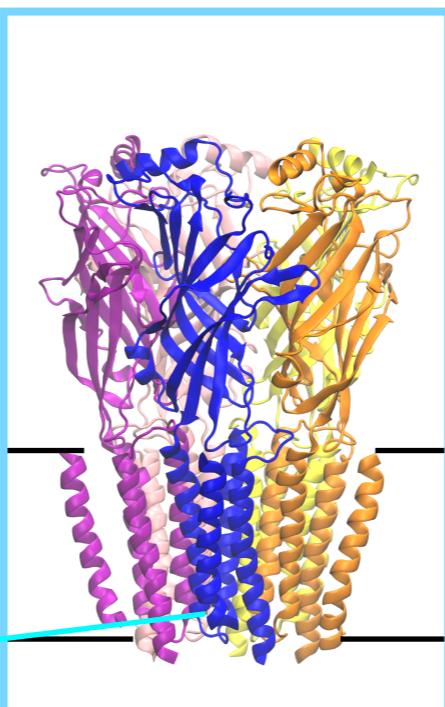
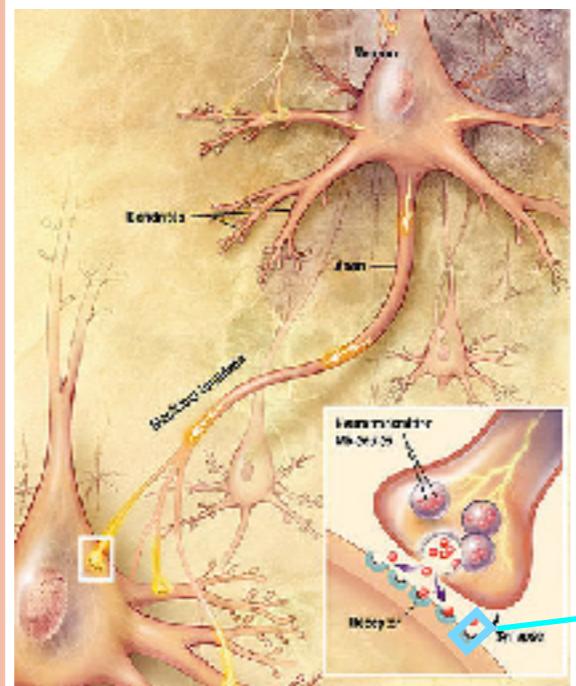


curare



Fishberry (picrotoxin)

nicotinic acetylcholine receptor, GABA_A receptor, glycine receptor, etc



general anesthetics



propofol

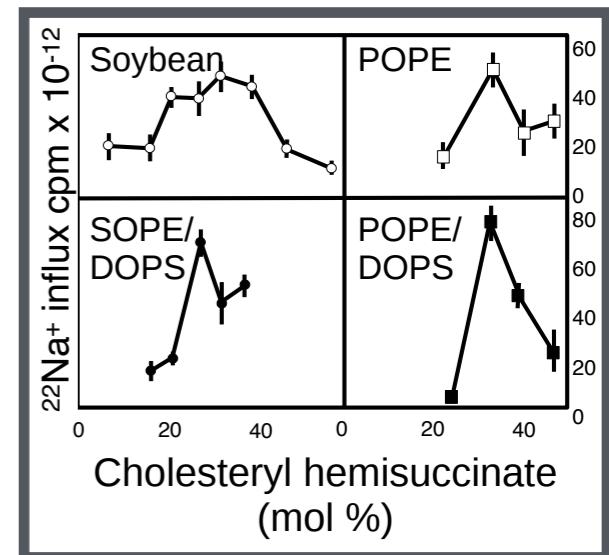


pentobarbital



chloroform

lipids



Criado...Barrantes, 1984, J.Biol.Chem.

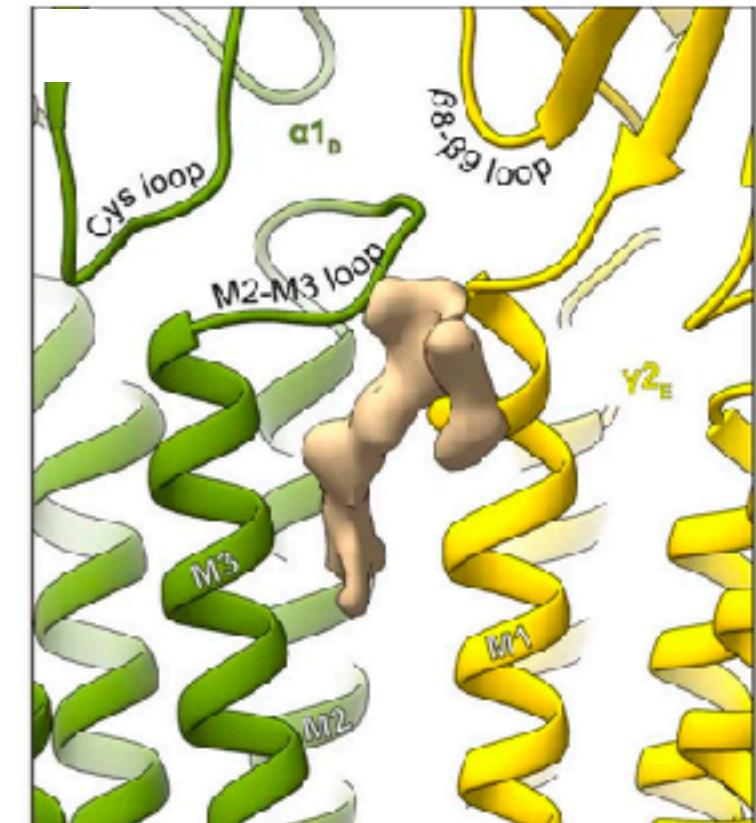
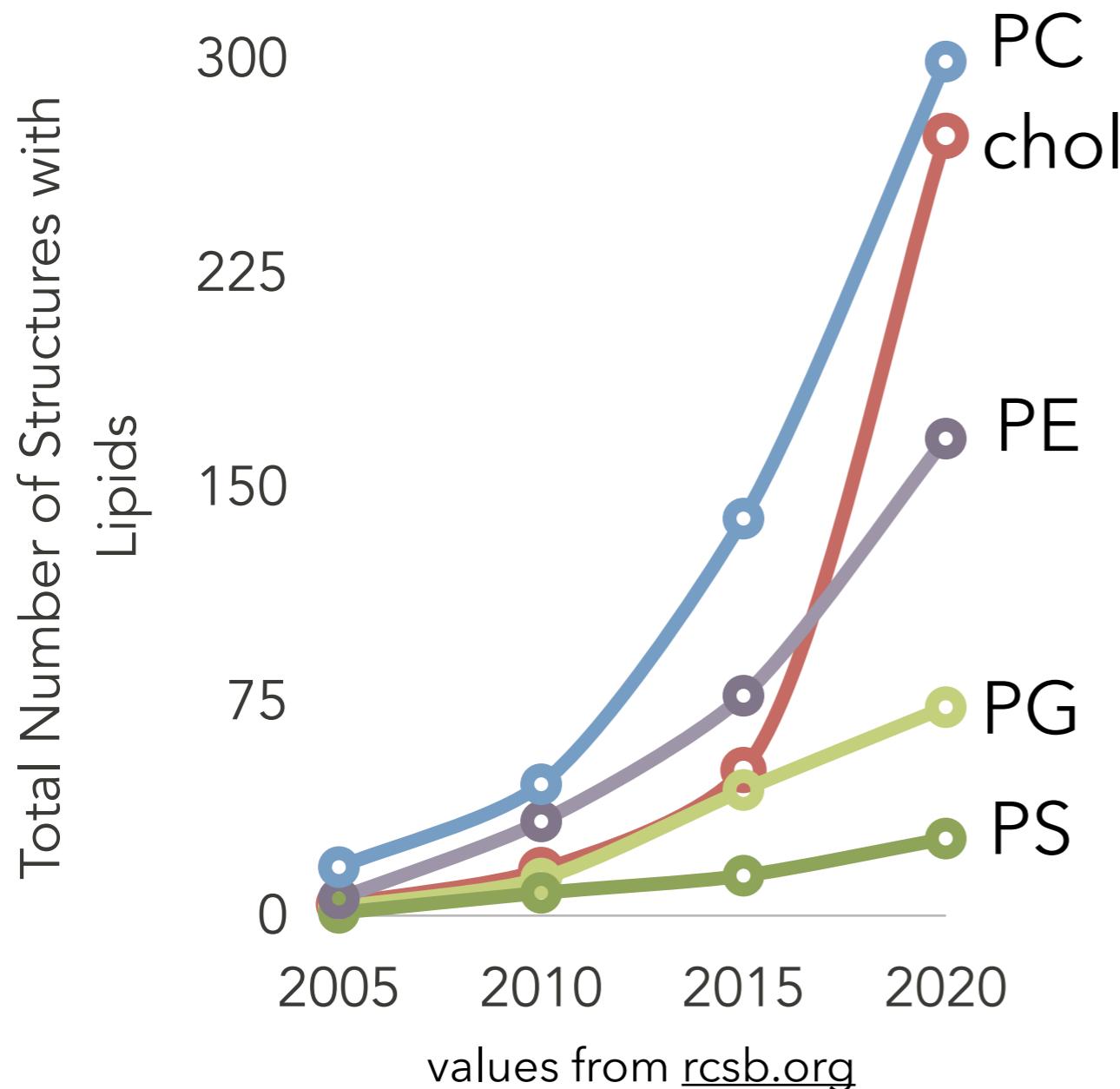
pLGICs are very picky about lipids!



typical membrane protein



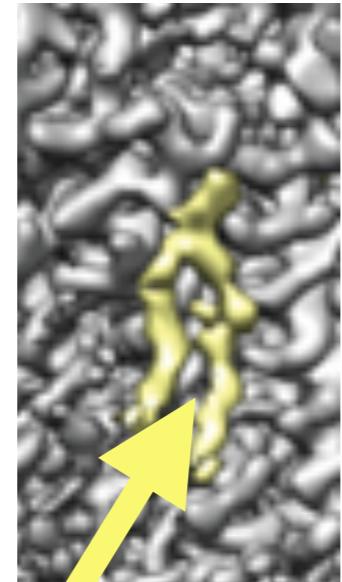
Structures can tell us where lipids bind...



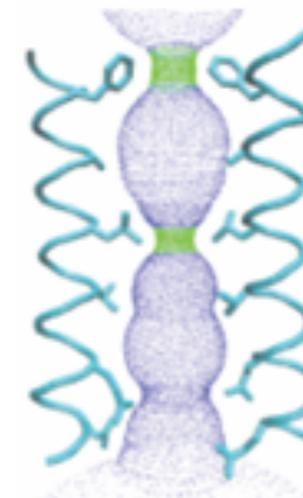
Kim...Hibbs, *Nature*, 2020

...but not (usually) who is binding.

Case of the ELIC modulation site

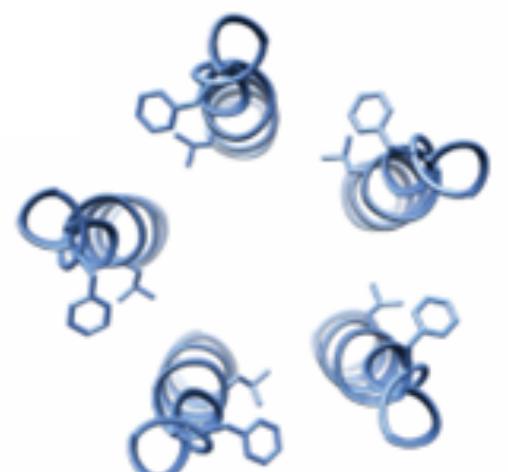
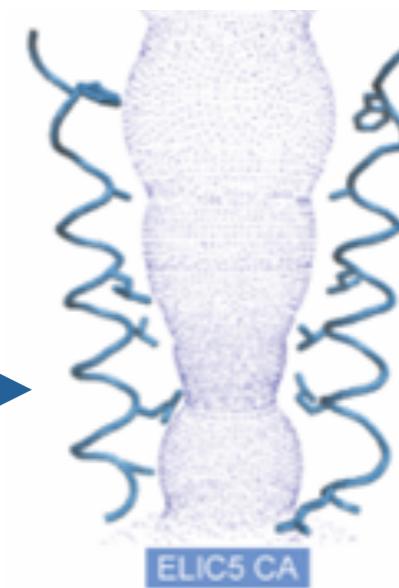


pre-active conformation



WT CA

wide-open conformation



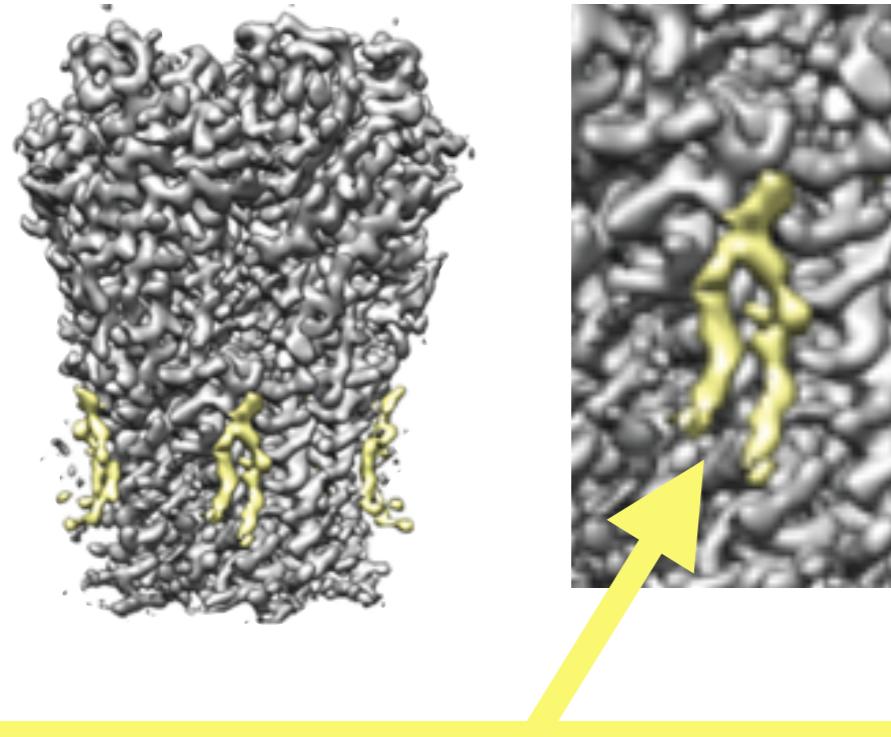
Question 2:
Did they
stabilize this
conformation?



Wayland
Cheng

John T. Petroff II, ... Ezry Santiago-McRae, ... Tom Joseph, Jérôme Hénin, Grace Brannigan & Wayland W. L. Cheng, Nature Communications 2022

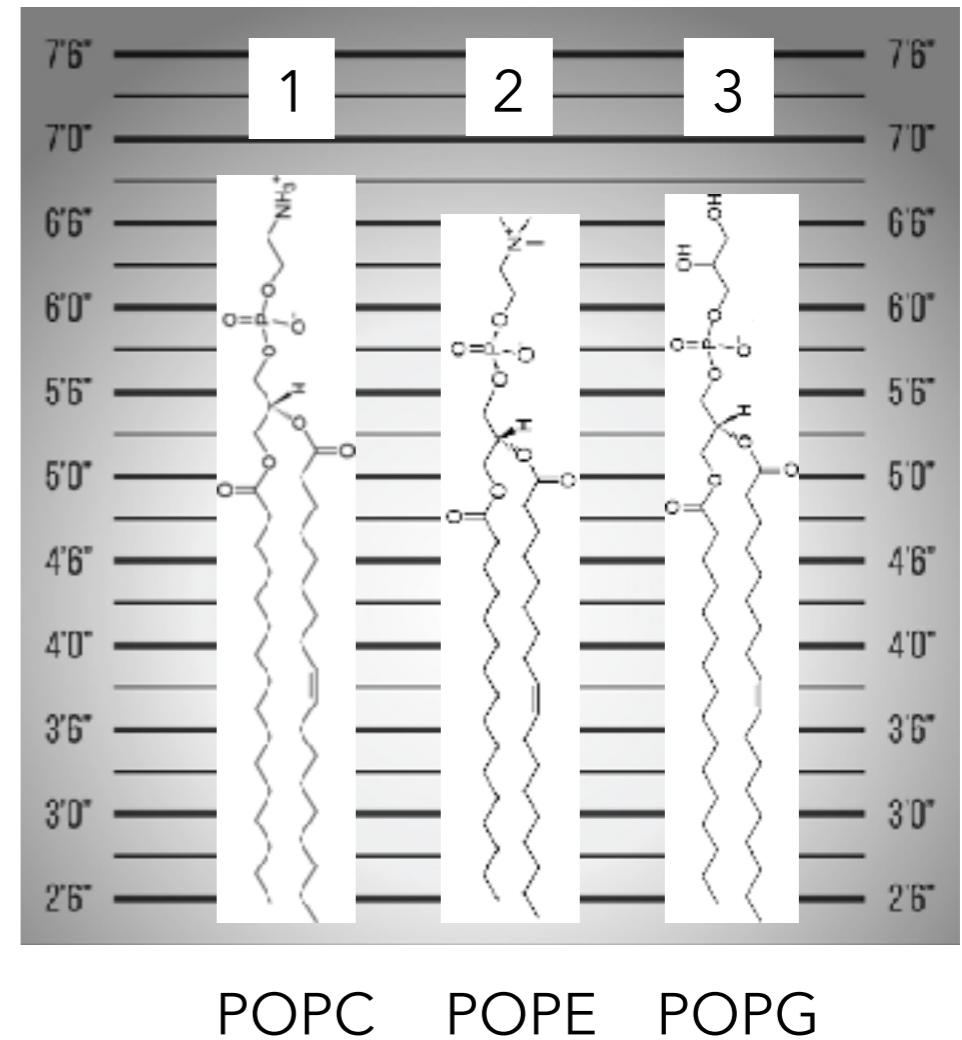
Fragment identification



Question 1: Who is this?

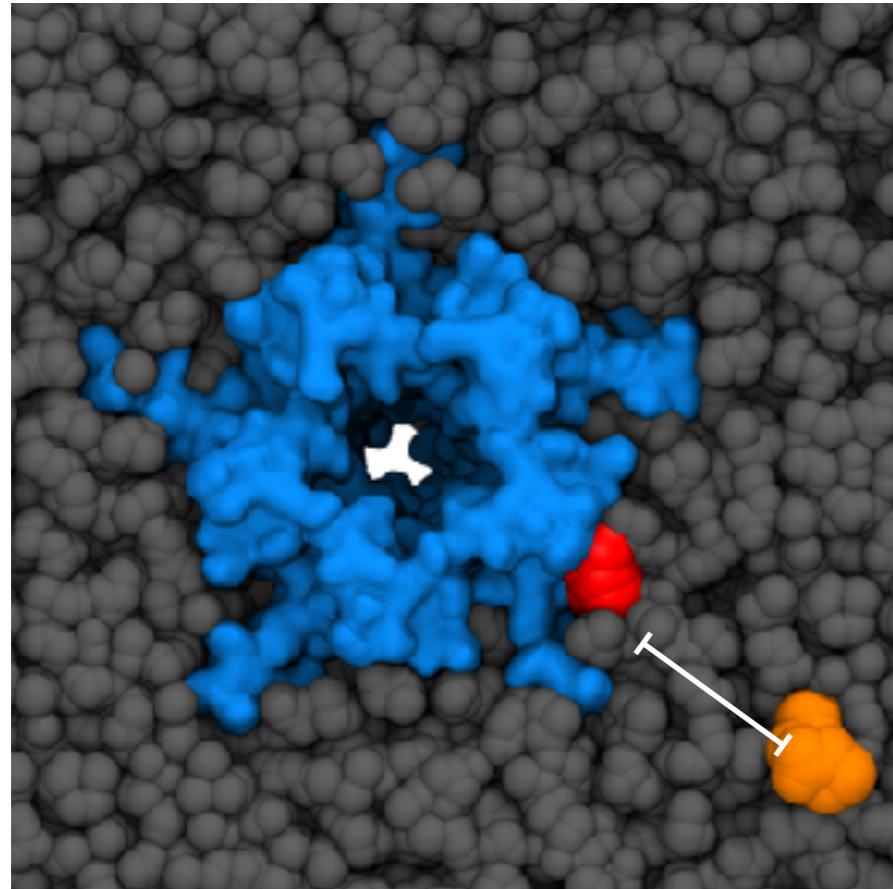
2:1:1 PC:PE:PG nanodisc

Suspects



we're a computational lab...so maybe we should use
"computational microscopy"?

Not so fast!!



in real time....how long would it take the **orange** lipid to exchange with the **red** lipid?

about 4 ms in lipid time or....

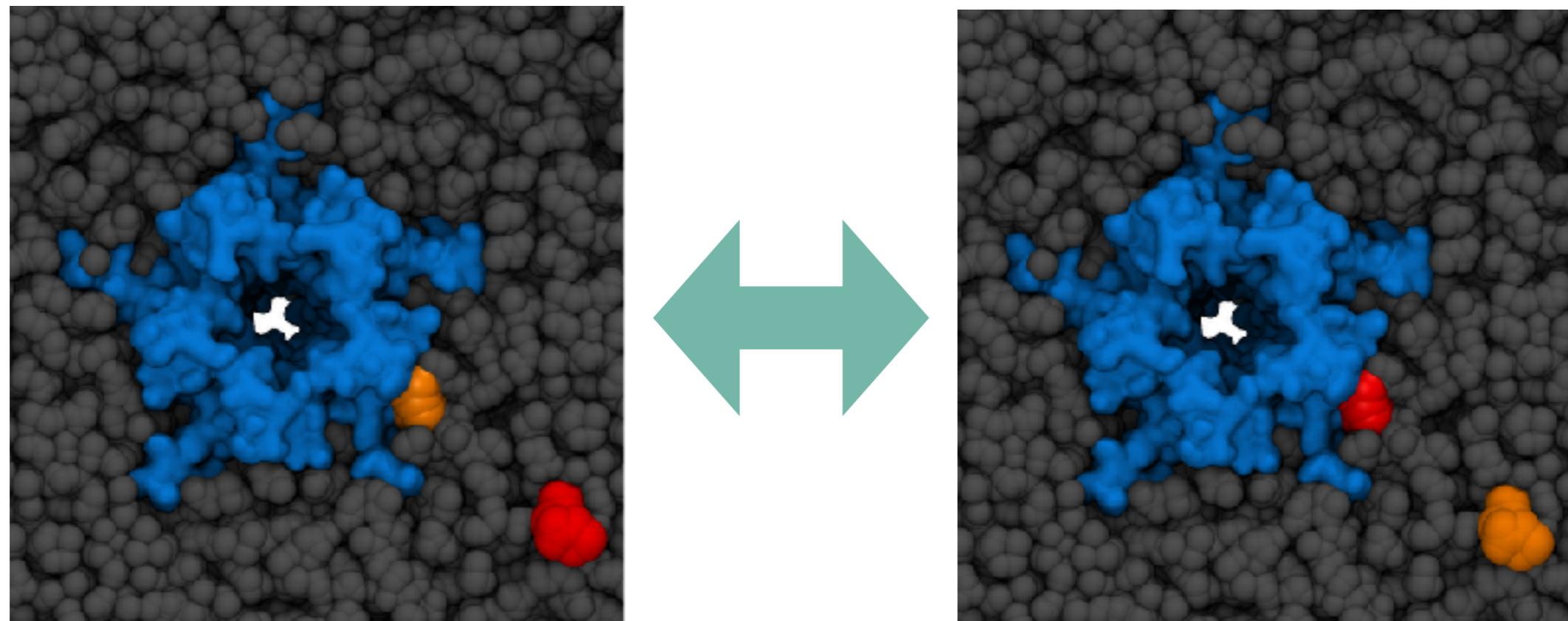
options:

> 100 **years** of MD simulation time

1. Enhanced spatial sampling?
2. Coarse-grained MD?
3. Avoid diffusion altogether?

circumventing diffusion via FEP

"all" we need to know: what is the free energy **difference** between these two states?



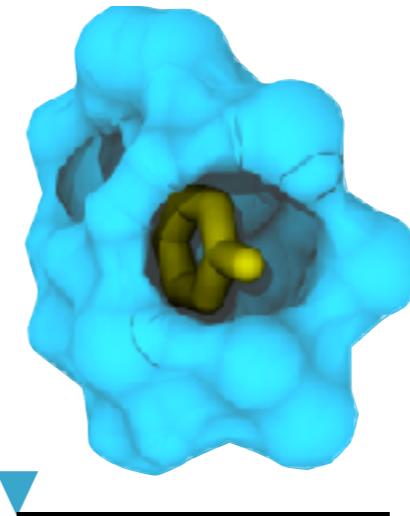
sounds like a job for....alchemical Free Energy Perturbation (FEP)!

two flavors of alchemical FEP

Absolute

How: Gradually **turn off** the interactions between the ligand and everything else; calculate thermodynamic averages

Output: ΔG of binding

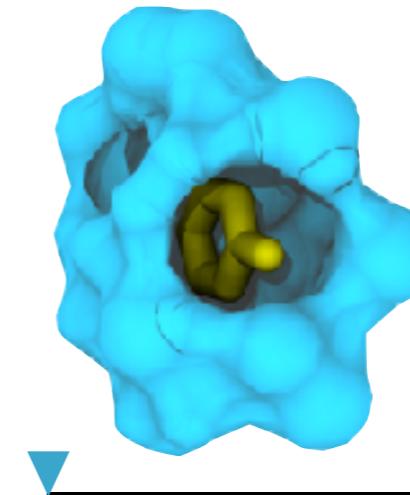


Decoupling Progression

Relative

How: Gradually **transform** one chemical group into another; calculate thermodynamic averages

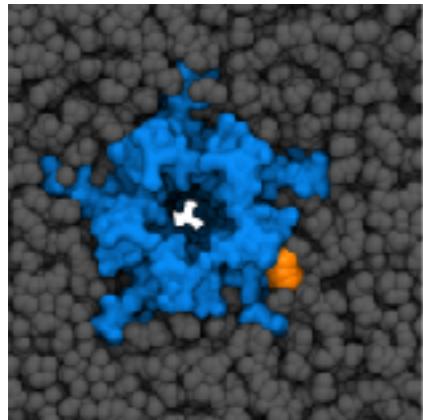
Output: $\Delta\Delta G$ of binding (compare ligands)



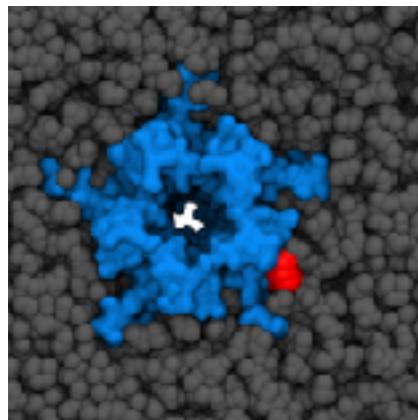
Transformation Progression

initial plan: relative FEP

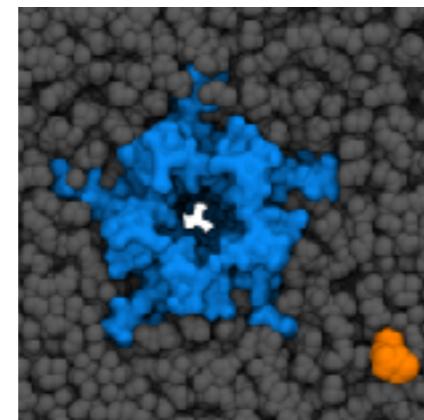
mutate
in site



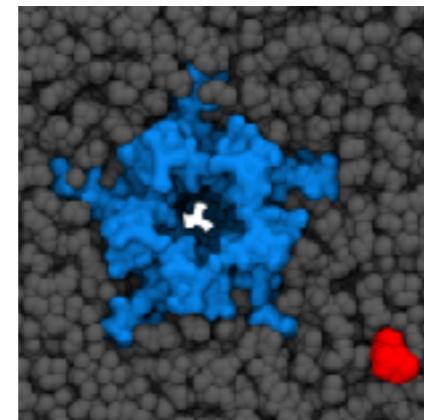
$$\downarrow \Delta G_1$$



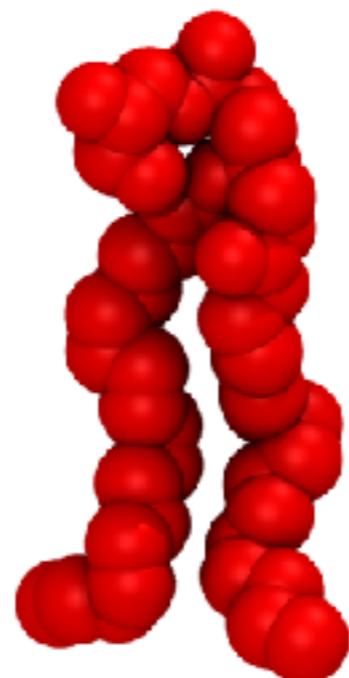
mutate
in bulk



$$\downarrow \Delta G_2$$

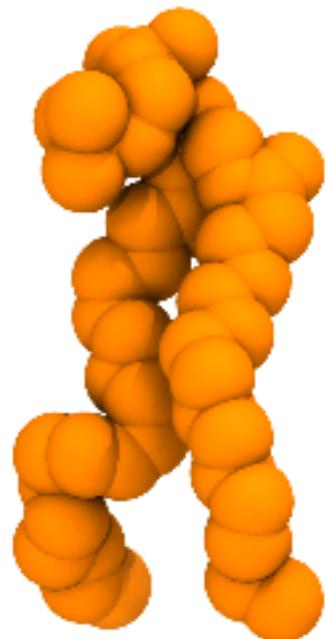


If....
 $\Delta G_1 - \Delta G_2 > 0?$



not guilty!

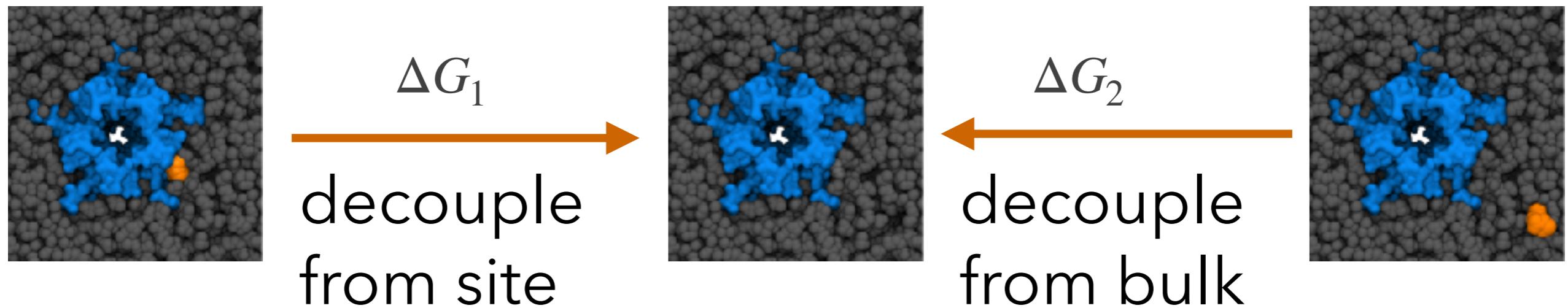
But if....
 $\Delta G_1 - \Delta G_2 < 0?$



not guilty!

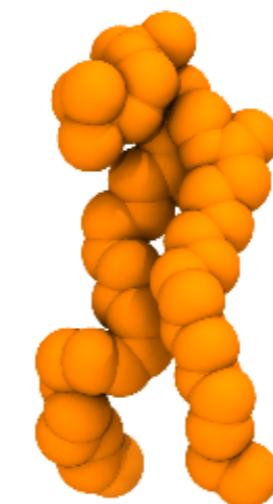
alternate plan: absolute FEP

best option if one of our lipids is low affinity



If....

$$\Delta G_1 + \Delta G_2 \ll 0?$$



guilty if they
have the
opportunity!

SAFEP: a FEP implementation that works in membranes

Streamlined **A**lchemical **F**ree **E**nergy **P**erturbation

FEP but in a site-centered reference frame.

SAFEP introduces the “distance-from-bound-configuration” (DBC): RMSD of the ligand in the site’s reference frame



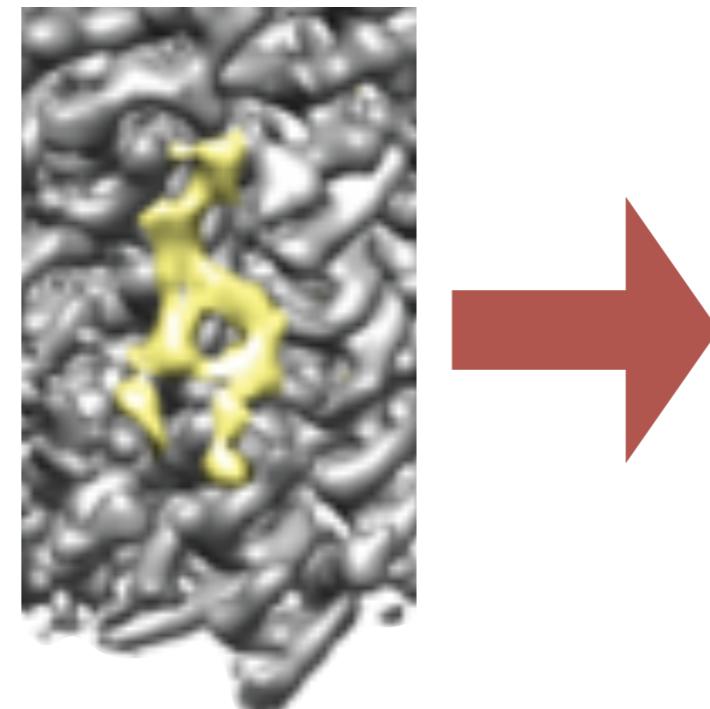
Running FEP while maintaining DBC

bound configuration: EM Density

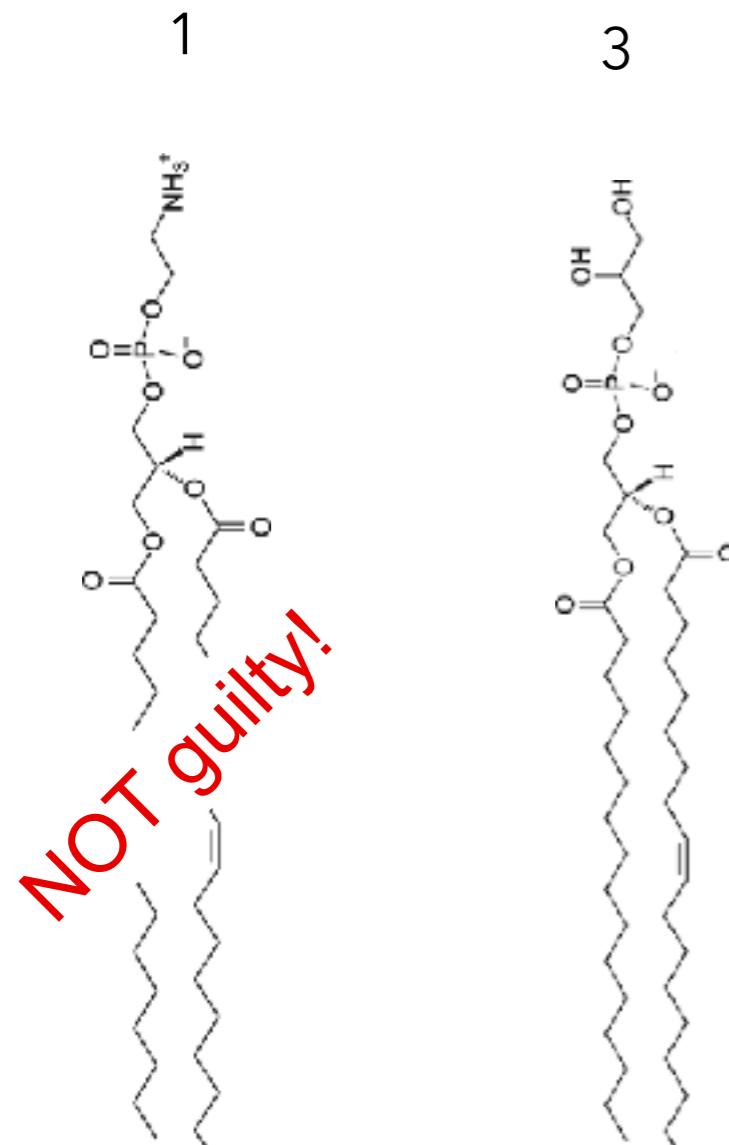
allowable distance-from-bound-configuration: MD

**application of
DBC restraint:**

on-the-fly during
FEP

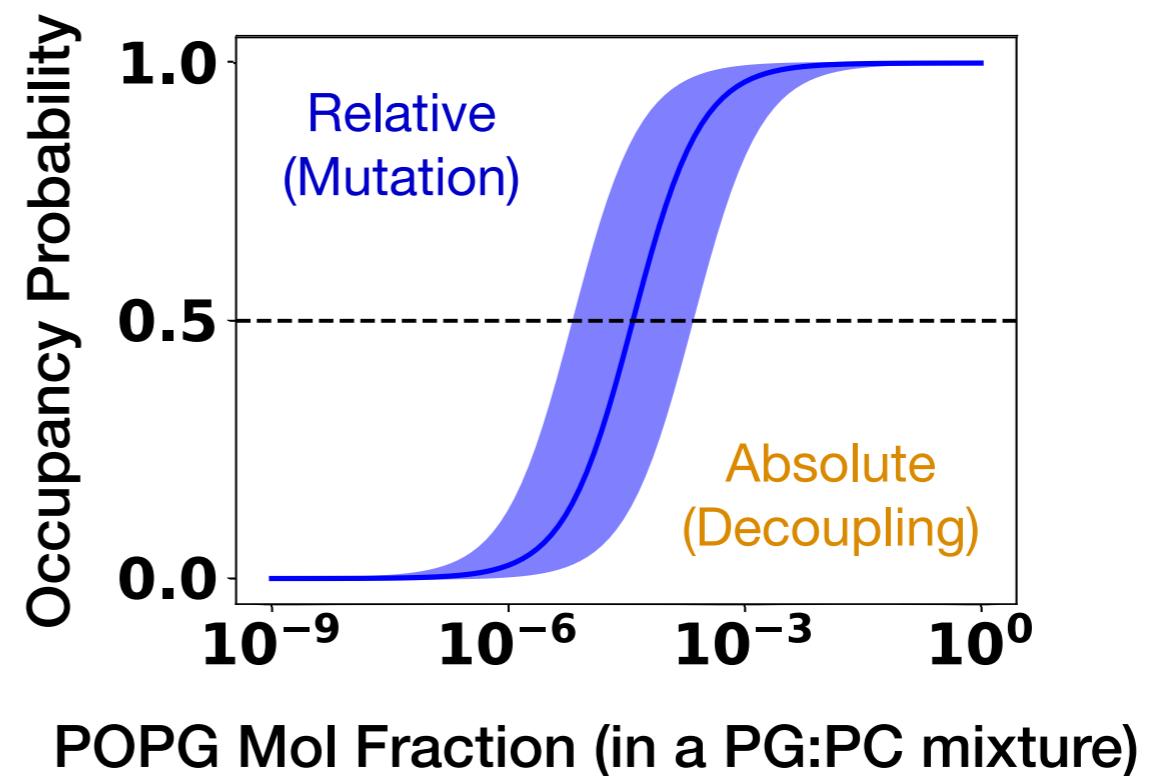


PG vs PC : who is more likely to bind?



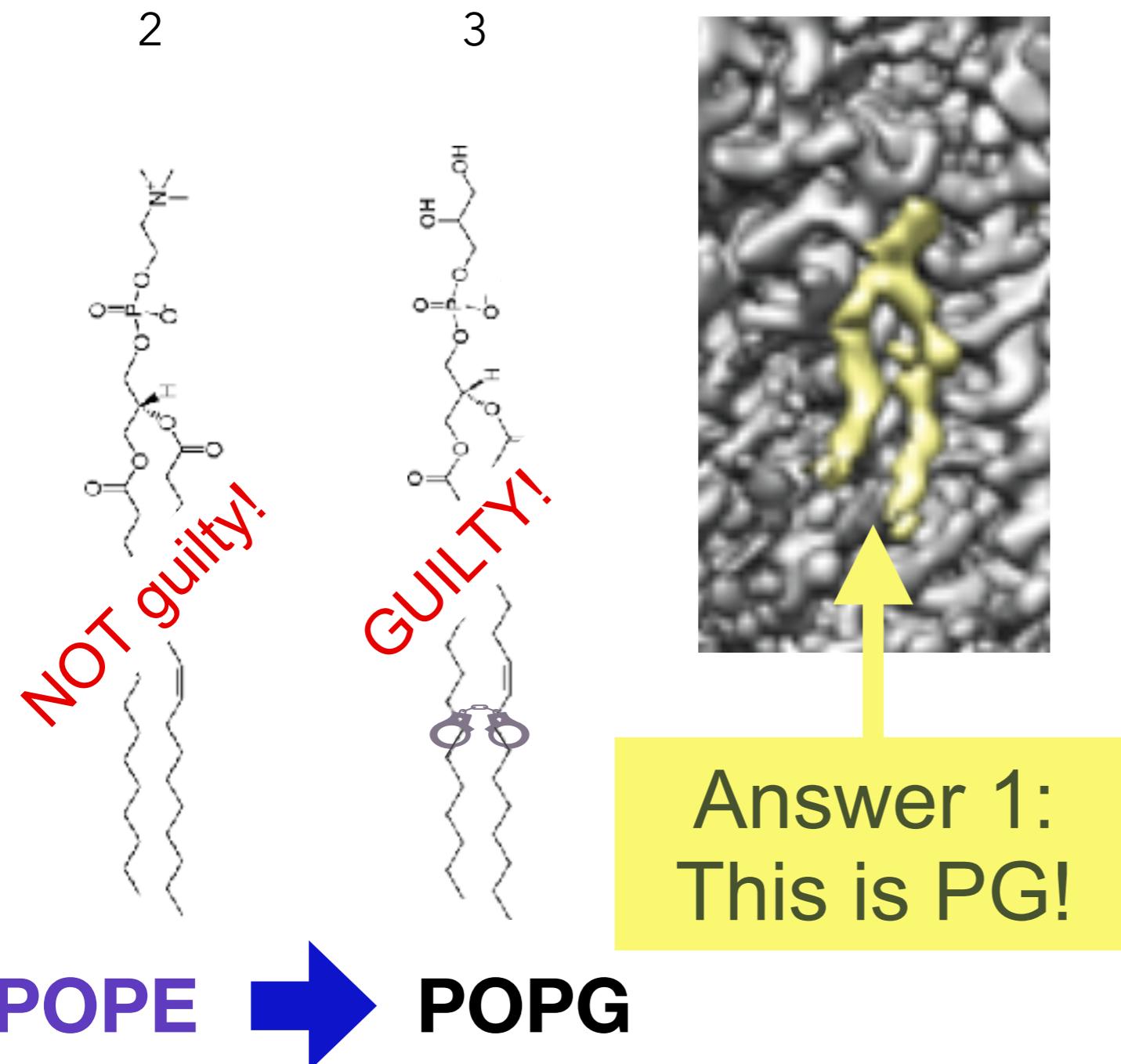
POPC → **POPG**

$$\Delta\Delta G = -6 \text{ kcal/mol}$$

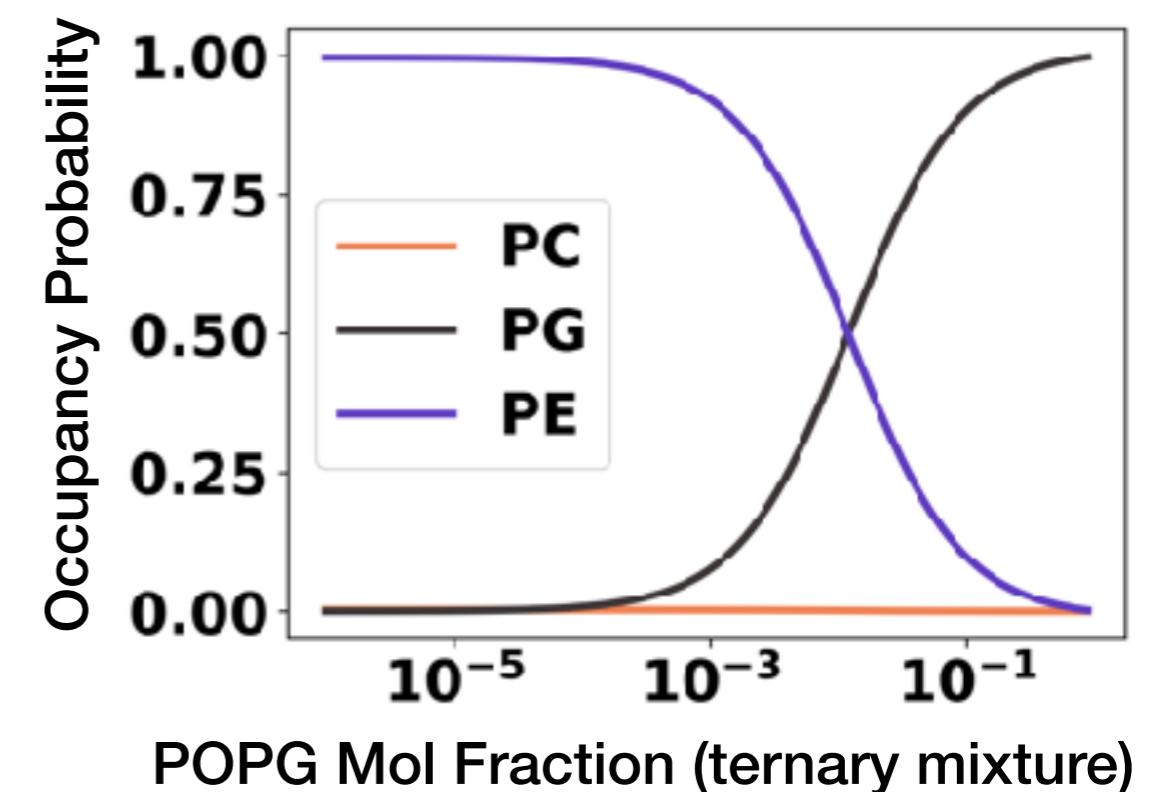


POPC is such a poor “ligand” that it can’t even be used as an endpoint in our relative affinity calculation

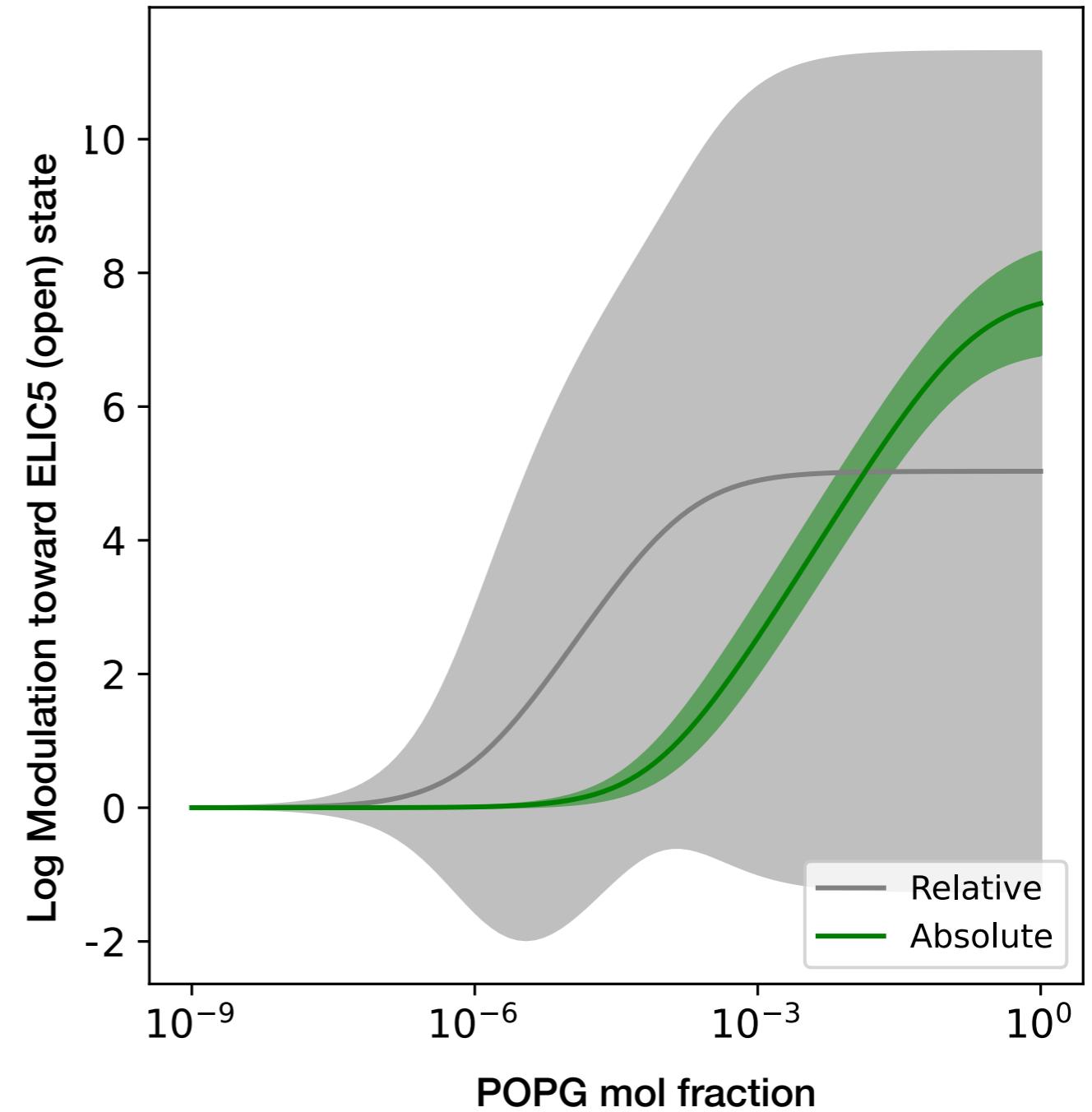
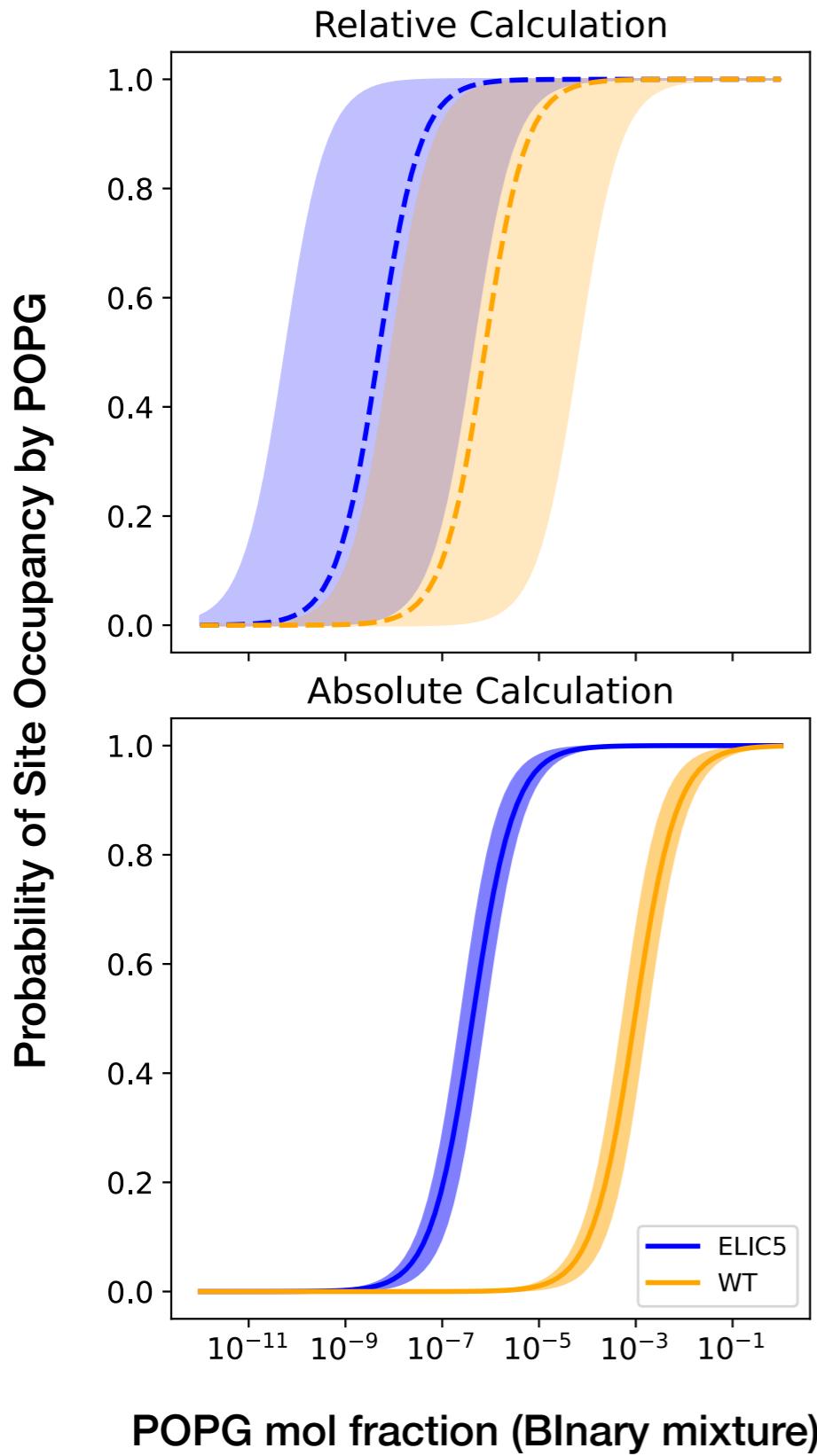
PE vs PG : who is more likely to bind?



$$\Delta\Delta G = -2 \text{ kcal/mol}$$

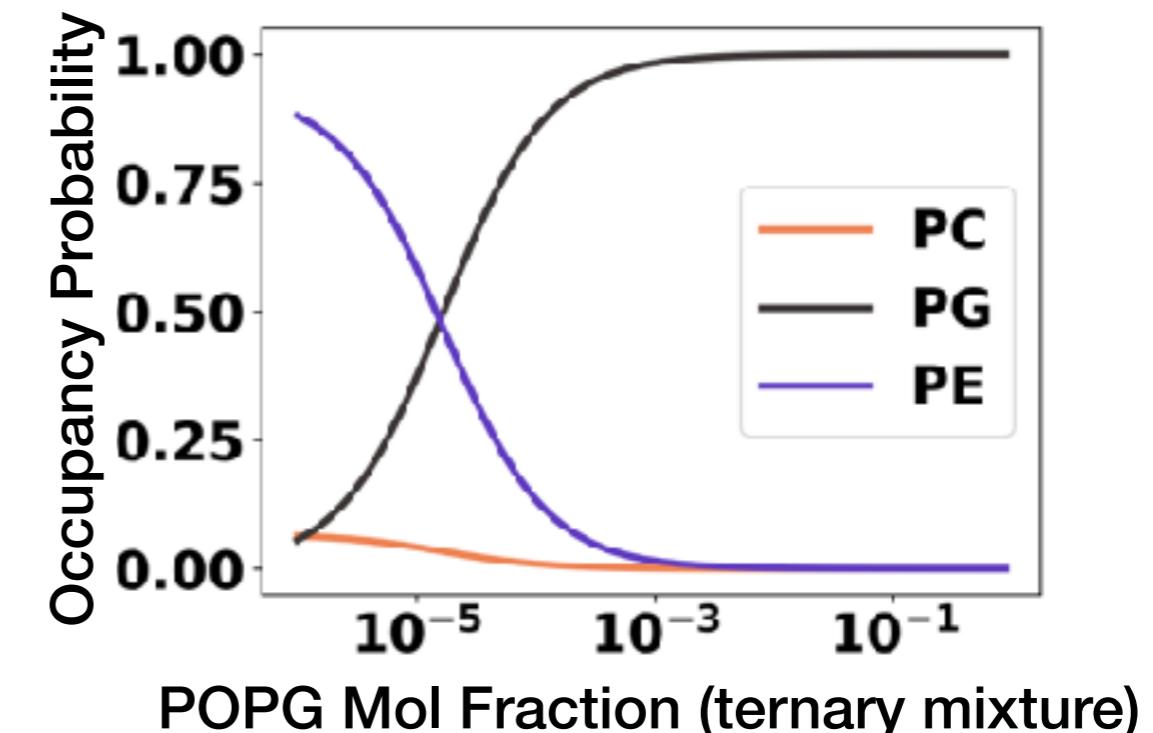
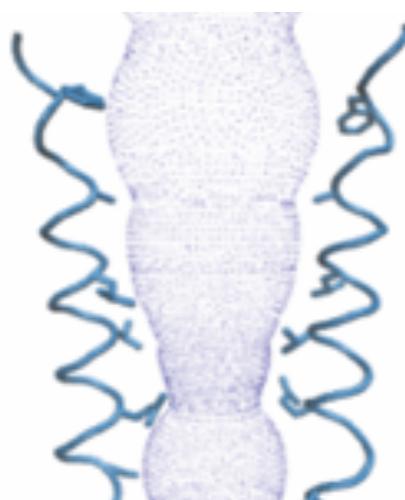
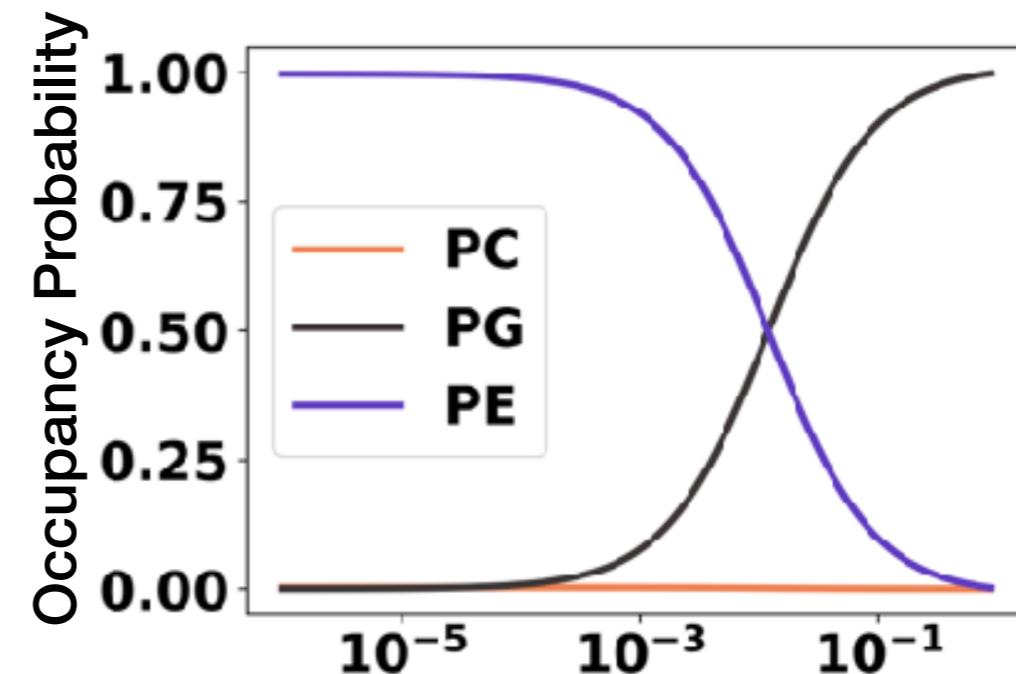
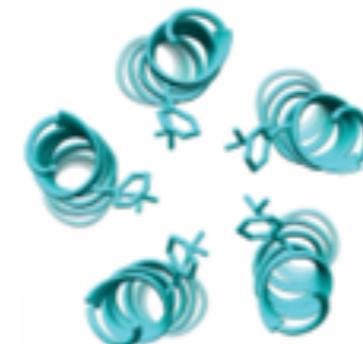
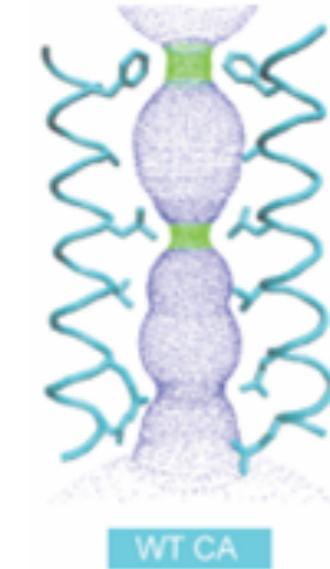


state dependence (binary mixture)



absolute FEP: POPG causes gain of function
relative FEP: ???

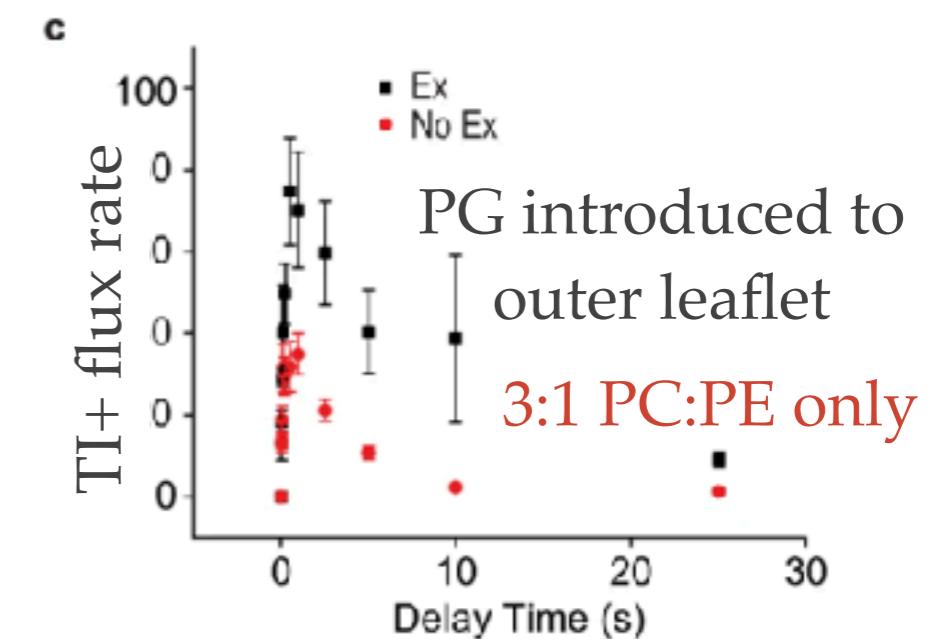
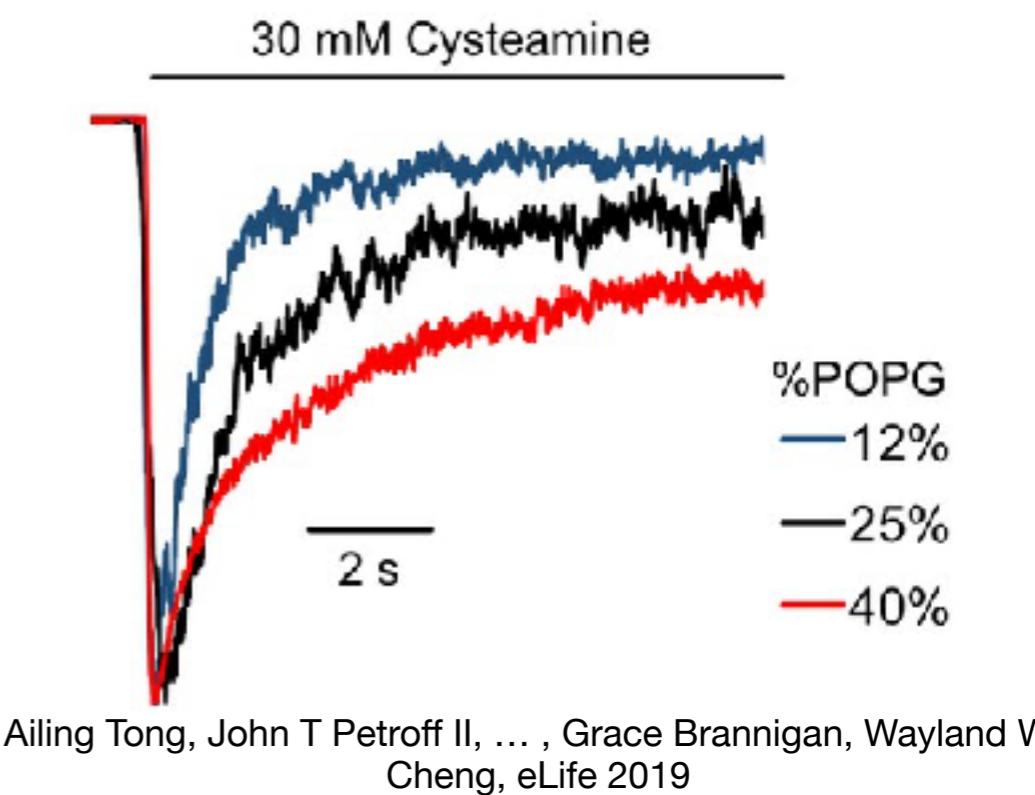
state dependence (ternary mixture)



Answer 2: Yes, PG stabilizes the wide-open conformation!

Summary

- Used SAFEP to identify lipid fragments in structures of ELIC
 - PE and PG can both occupy the observed binding mode; PG starts out-competing PE at less than 1:10 PG:PE
 - Absolute affinity calculations were as straightforward as relative calculations, and less risky
- Also used SAFEP to calculate state dependence of lipid binding
 - yes, PG has a higher affinity for the wide open ELIC5 conformation!
 - Consistent with functional data



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1. Lipids

A. Identifying **lipid fragments** from structures

- atomistic
- ELIC + model membranes
- new simulation protocol: SAFEP
- bonus: state dependence!

Dr. Liam Sharp



B. Quantifying lipid sorting in **complex quasi-native** membranes

- coarse-grained
- new analysis method: density threshold affinity
- nAChR + neuronal membranes

2. Proteins

C. Hydrophobic-to-hydrophobic mutations in **intrinsically disordered proteins**

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- New analysis method: Blobulation

D. Blobulation as a **generally-useful conceptual tool**

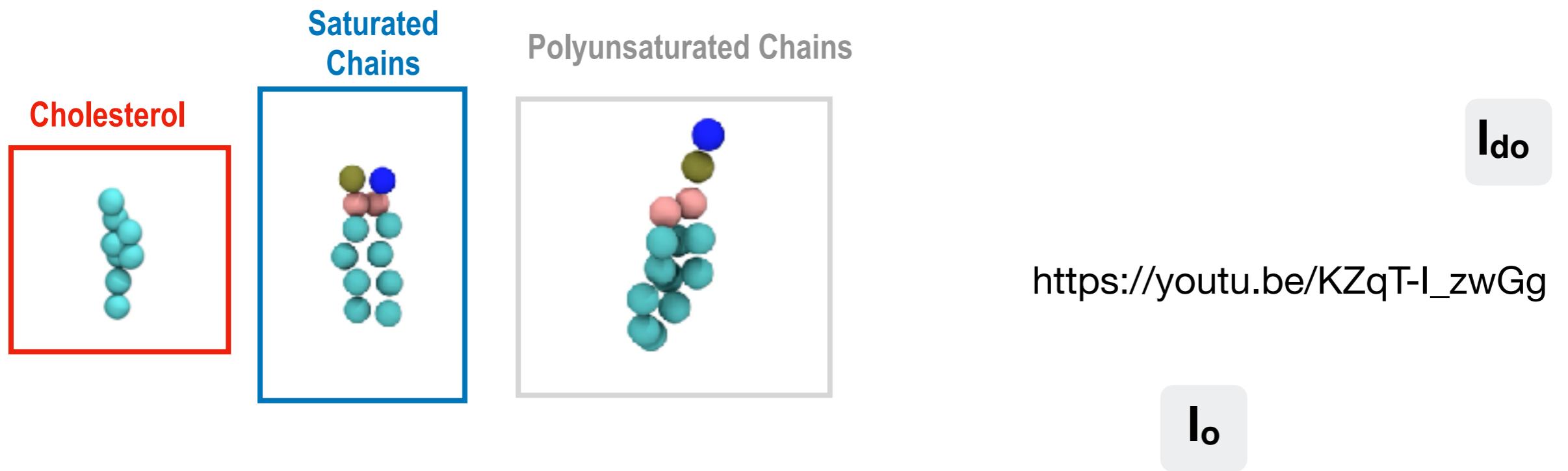
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3. Populations

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- Population frequency of mutations in particularly hydrophobic blobs

Computational Microscopy

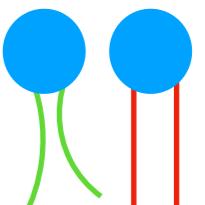
via coarse-grained molecular dynamics simulation (MARTINI)



<https://youtu.be/0qqXHvJUupk>

$\sim 2 \text{ us}$ $75 \times 75 \text{ nm}^2$

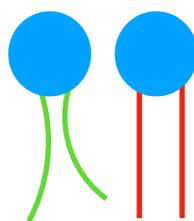
Homo-Acidic
Domain Forming



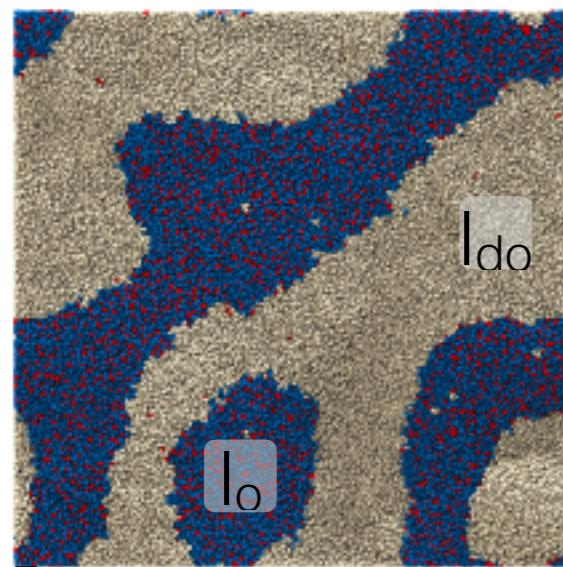
surprise: nAChR partitions to a cholesterol-poor domain

simulations in a quasi-native membrane

Homo-Acidic Domain Forming



Model Membrane



25 Å

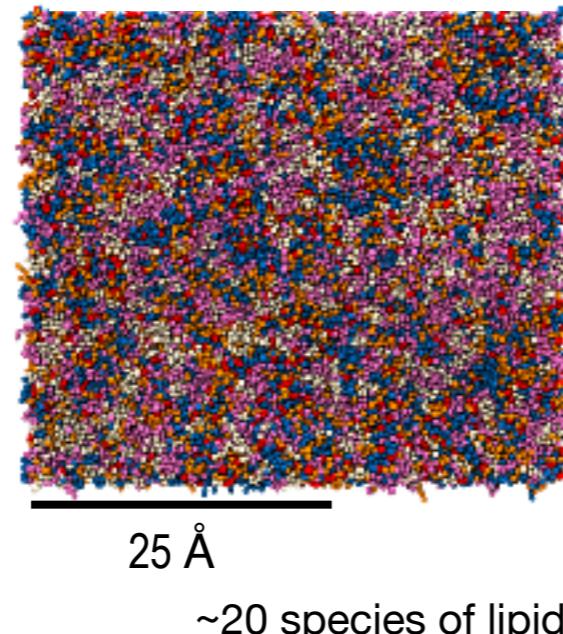
Sharp, Salari, Brannigan 2019

Woods, Sharp, Brannigan 2019

Hetero-Acidic Non-Domain Forming



Native Membrane



~20 species of lipid

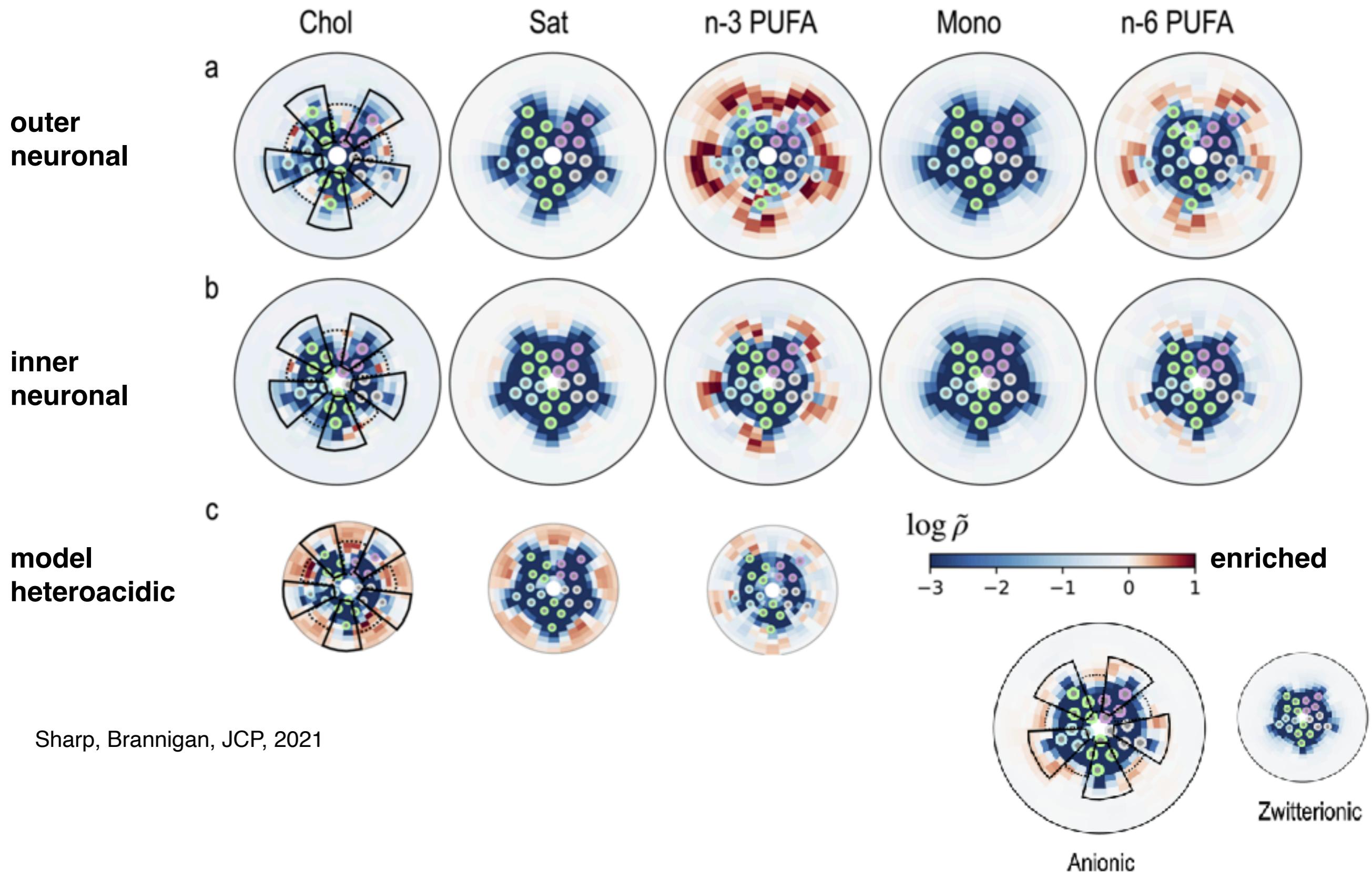
Table S1 Lipid composition^a

Helgi I Ingólfsson et al, 2017

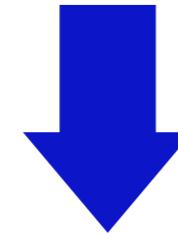
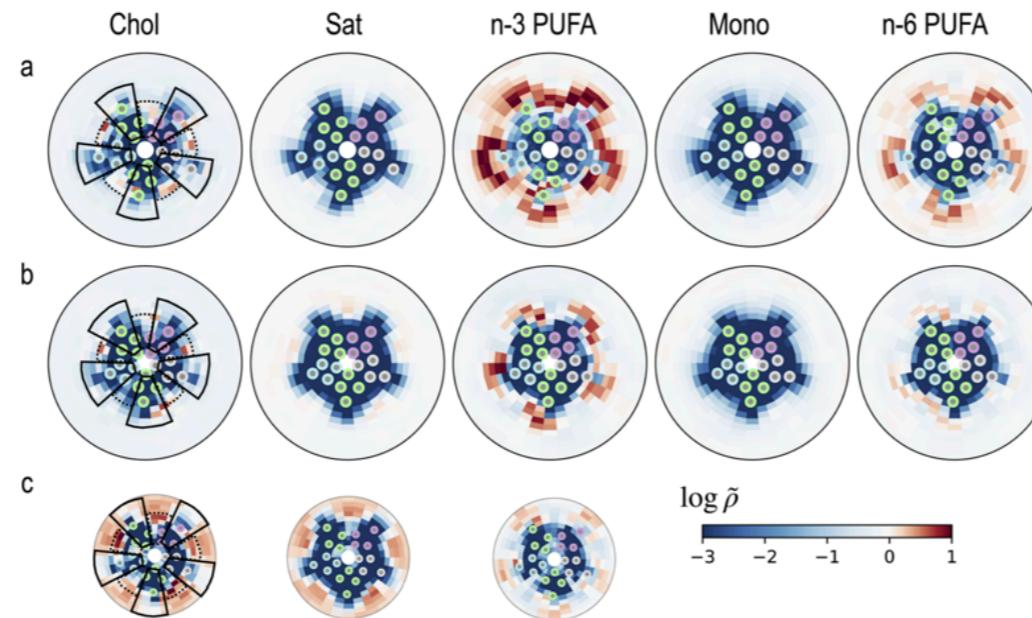
nAChR in a post-synaptic membrane

<https://youtu.be/PJZnIBCPe2s>

boundary lipids: post-synaptic membrane



can we convert all these maps to numbers?



yes! “density-threshold affinity”

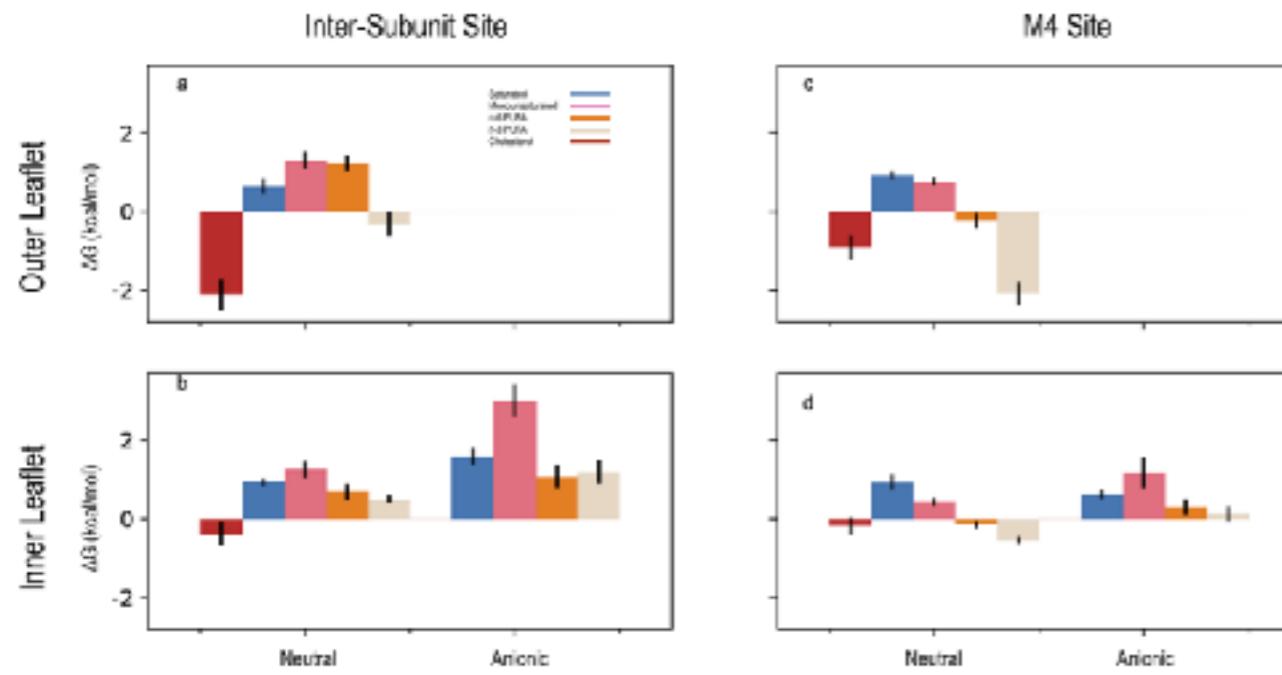
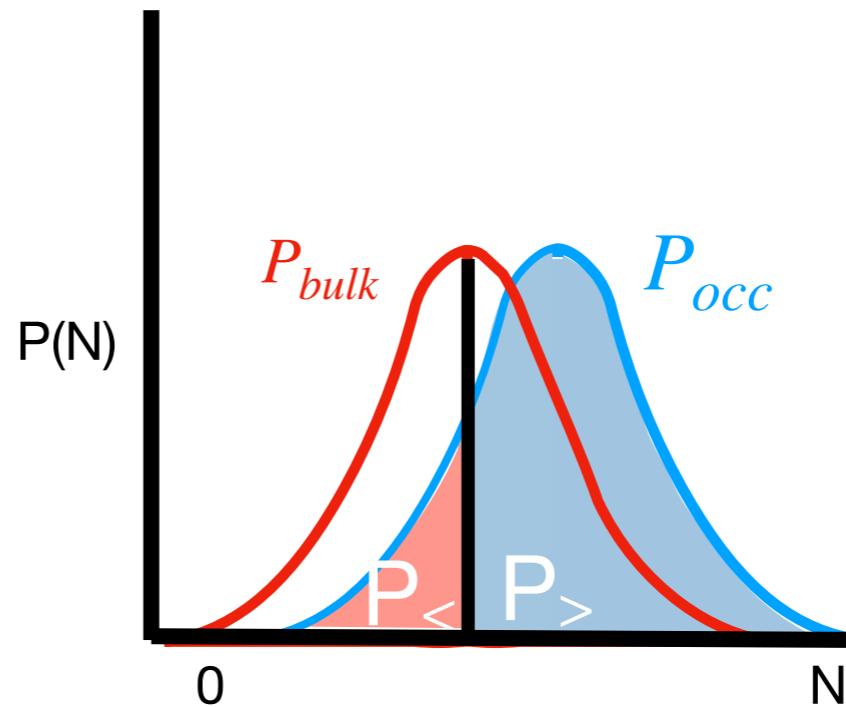
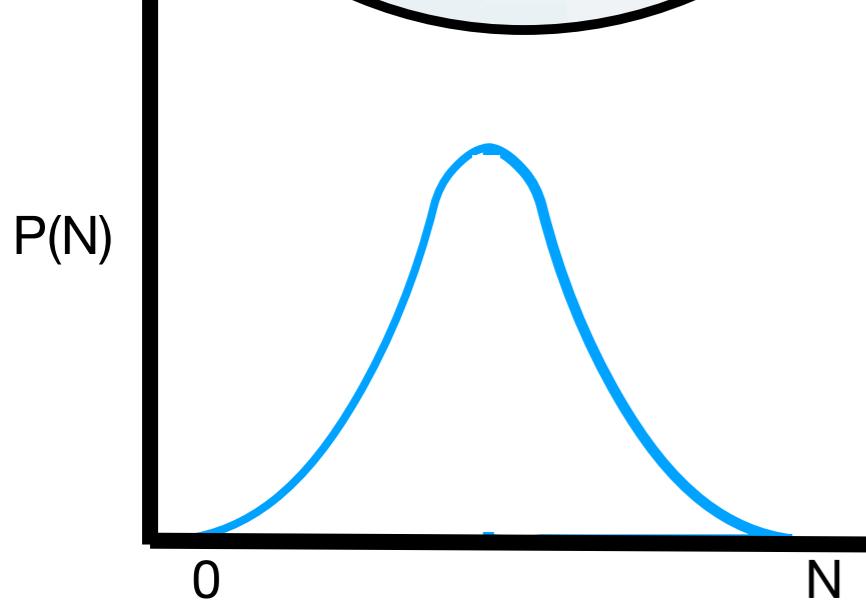
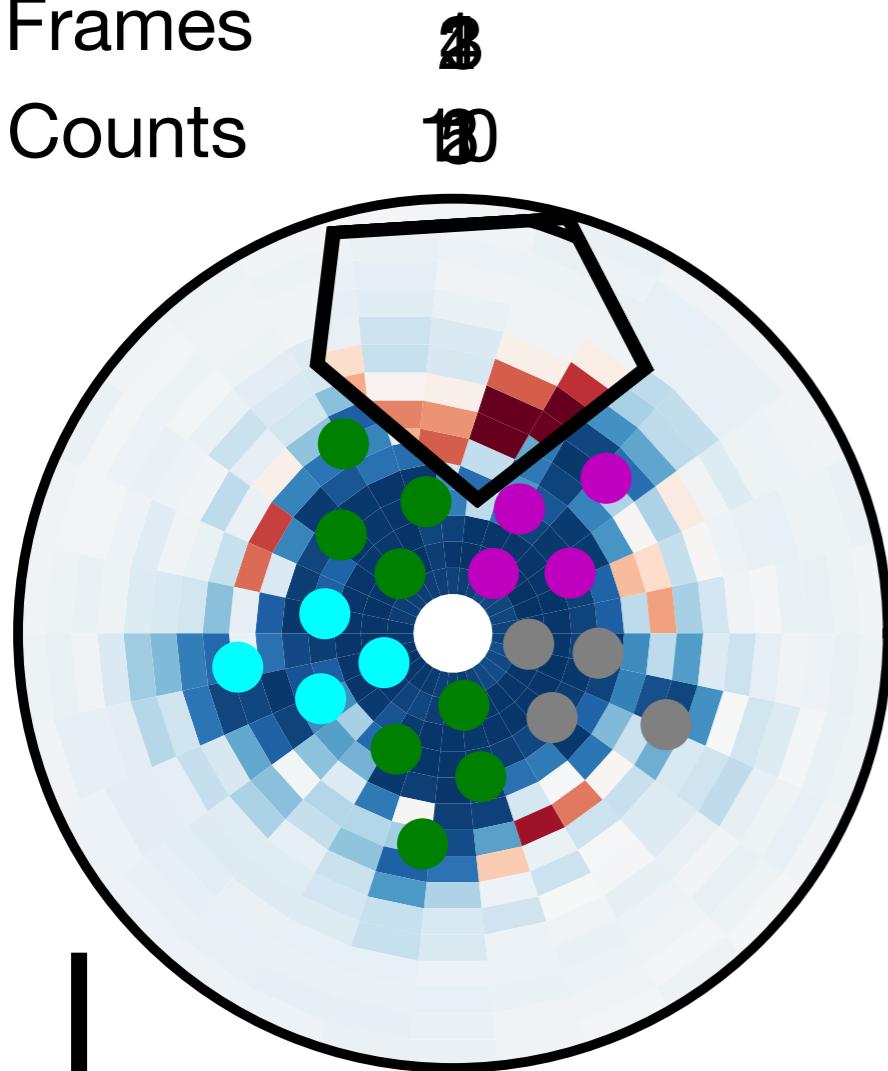


TABLE II. Density-threshold affinities of neutral and anionic lipids for both sites in the inner leaflet, by headgroup. Values are sorted by strength of affinity for inter-subunit sites. Errors are standard errors ($n = 10$ independent replicas).

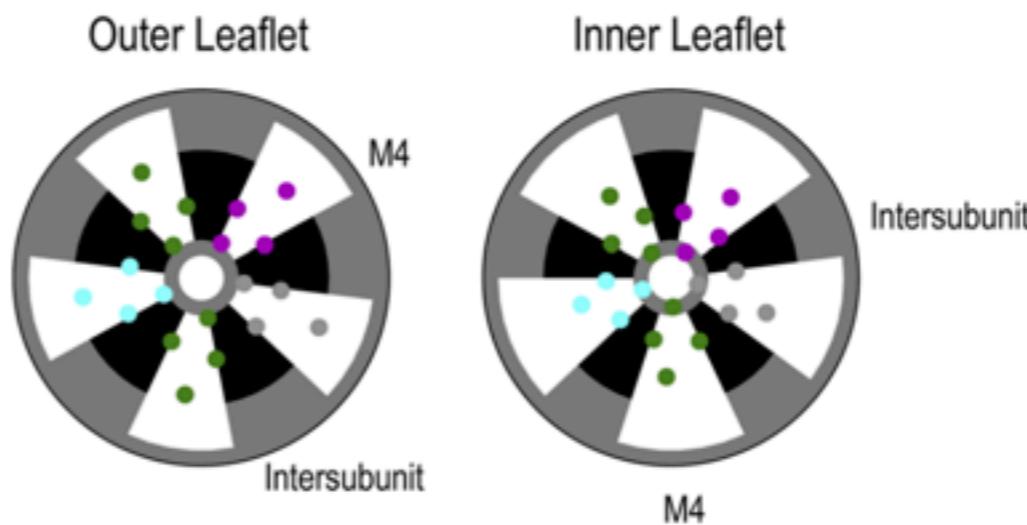
	Inner inter-subunit sites ΔG (kcal/mol)	Inner M4 sites ΔG (kcal/mol)
PE	0.3 ± 0.2	-0.2 ± 0.1
PI	1.4 ± 0.3	0.3 ± 0.1
PS	1.4 ± 0.2	0.5 ± 0.2
PC	1.3 ± 0.3	0.8 ± 0.1
PIP3	3.1 ± 0.5	2.4 ± 0.4
PIP2	2.4 ± 0.3	1.3 ± 0.4
PIP1	2.2 ± 0.3	1.3 ± 0.4
PA	2.8 ± 0.3	1.9 ± 0.4

density threshold affinity

Frames
Counts

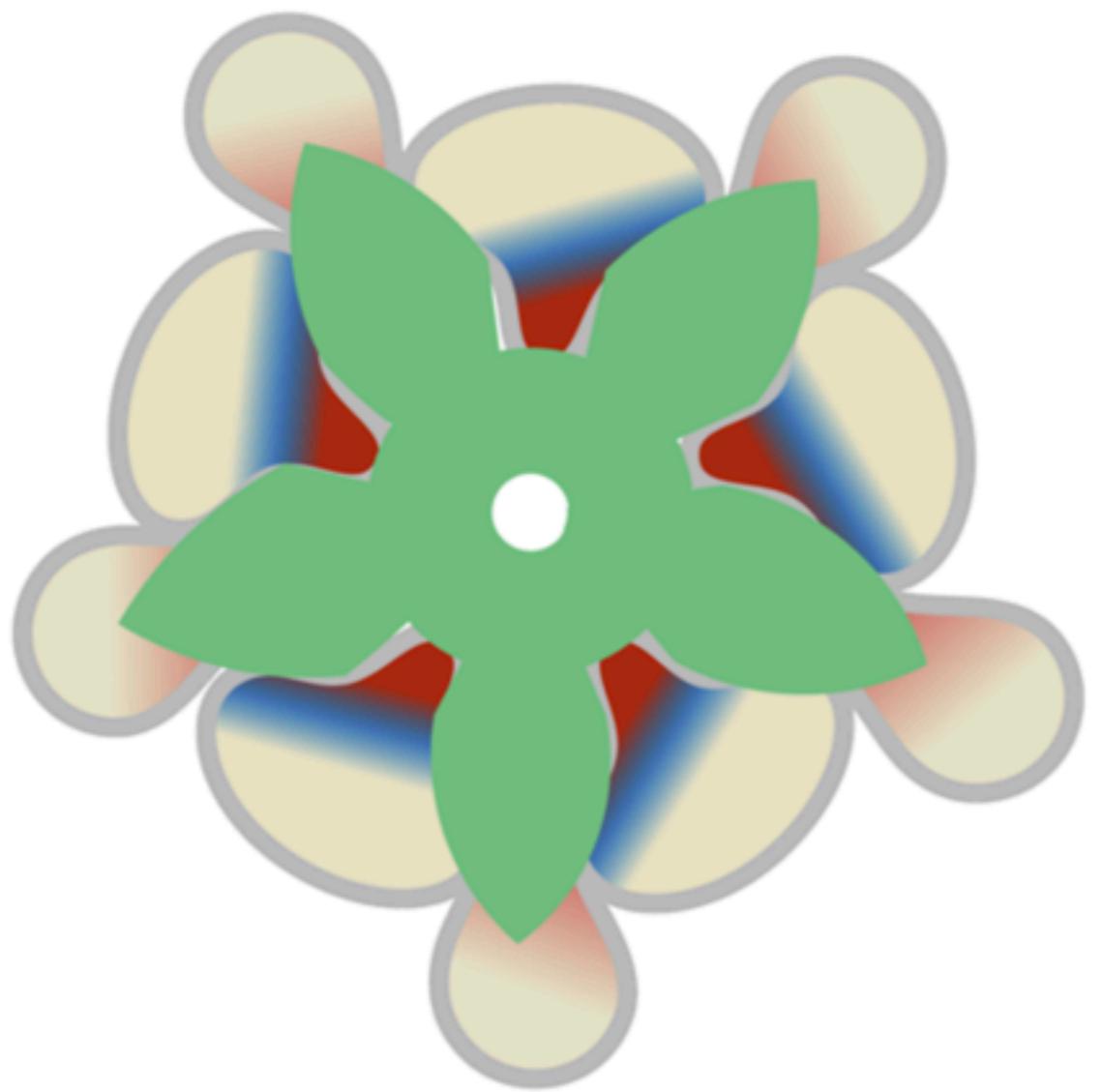


$$\Delta G = -RT \ln \frac{P_>}{P_<}$$

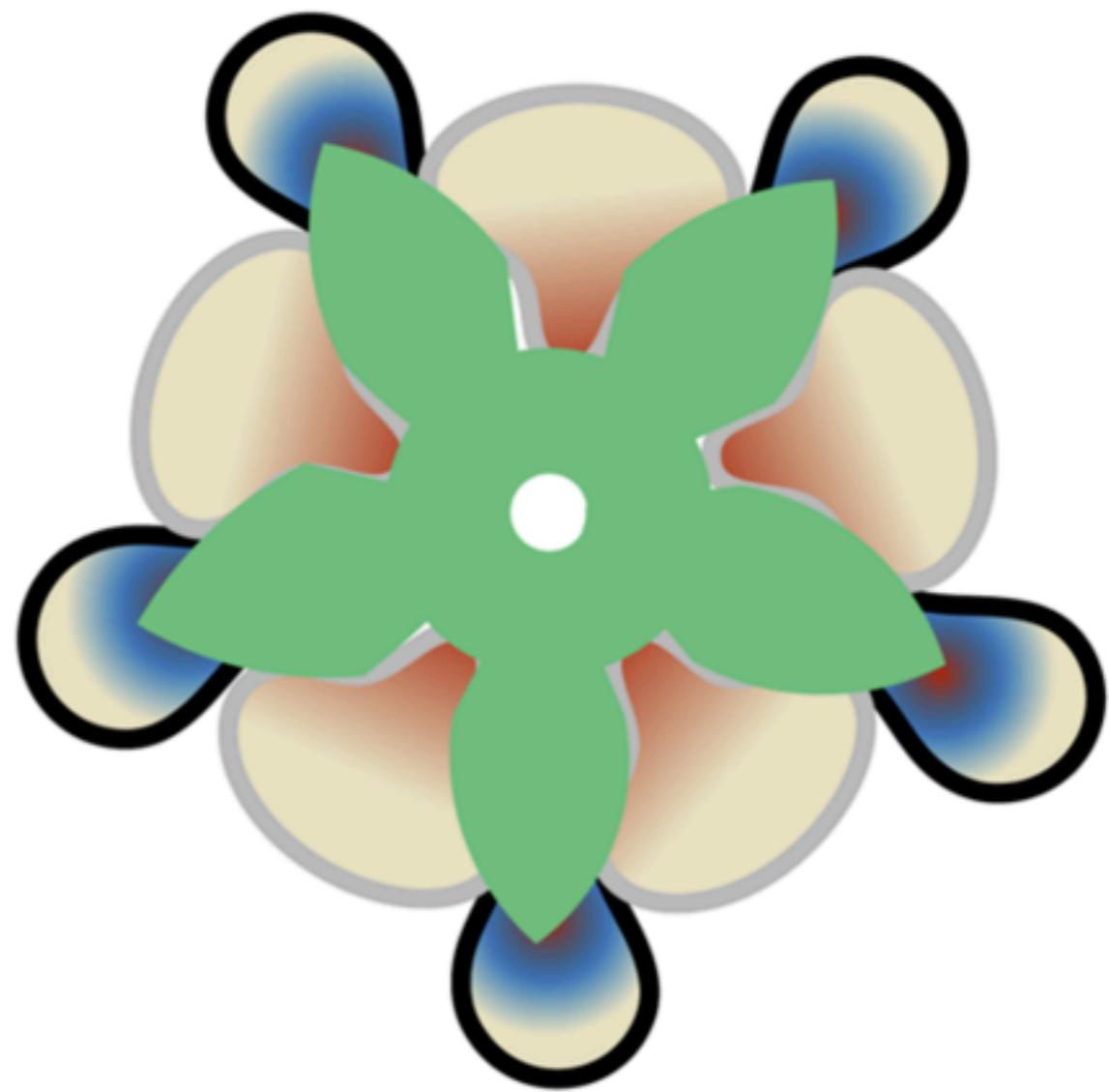


outcome: nAChR boundary lipids in a quasi-neuronal membrane

Outer Leaflet



Inner Leaflet



PUFA

Saturated

Cholesterol

Neutral

Anionic

Part II: Summary

- nAChRs bind cholesterol **but avoid** cholesterol-rich domains
 - We now know that domain formation in post-synaptic membrane is unlikely anyway
- Densities can yield affinities!
- Lipid selectivity in a quasi-native neuronal membrane:
 - Outer leaflet:
 - rigid groups (chol and saturated chains) occupy the concave regions
 - flexible chains (PUFAs) pack the convex regions
 - Inner leaflet:
 - saturated acyl chains shift from concave regions to convex regions (pack around M4)
 - Anionic lipids occupy M4 sites in the inner leaflet

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Dr. Ruchi Lohia



D. Blobulation as a **generally-useful conceptual tool**

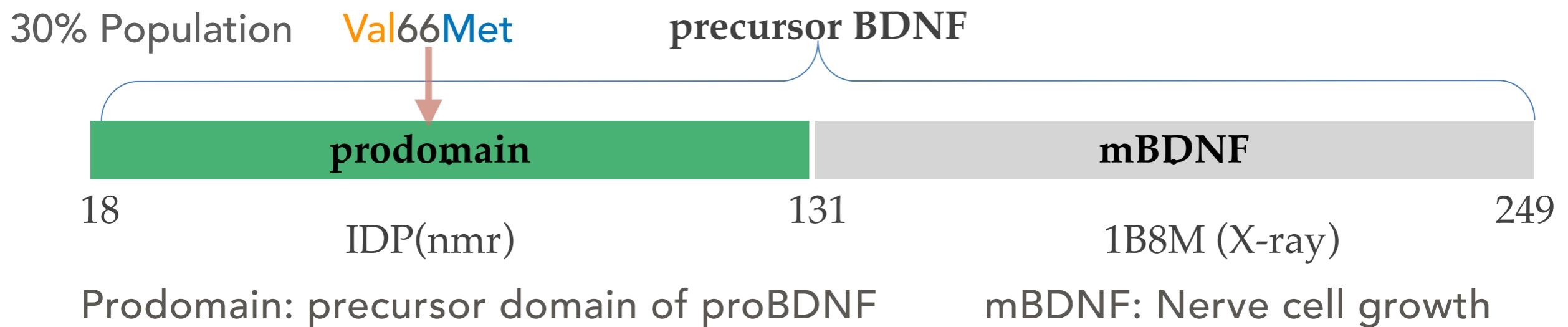
- Protein organization and hierarchy from sequence

3. Populations

- Hydrophobic sequence context of disease-associated mutations
- Population frequency of mutations in particularly hydrophobic blobs

That's weird...

Brain-derived neurotrophic factor :



Brief Communication

The Brain-Derived Neurotrophic Factor (BDNF) Val66Met Polymorphism and Variation in Human Cortical Morphology

Lukas Pezawas, Beth A. Verchinski, Venkata S. Mattay, Michael E. Egan, Andreas Meyer-Lindenberg, and Daniel Weinberger^{1,2}
Genes, Cognition, and Psychosis Program, National Institute of Mental Health, Bethesda, Maryland 20892, USA

Brain-Derived Neurotrophic Factor (BDNF) Gene Polymorphisms and Psychiatric Disorders: New Studies Confirm Association with Major Depressive Disorder, Eating Disorders, and Alcoholism

Mònica Gratacòs, Juan R. González, Josep M. Martí, and Xavier Estivill

Cell

Volume 112, Issue 2, 24 January 2003, Pages 257-266

Article
The BDNF val66met Polymorphism Alters Activity-Dependent Secretion of BDNF and Human Memory and Hippocampal Function

Michael F. Egan¹, Masami Kojima^{2,4,5,6}, Joseph H. Callicott^{7,1}, Terry E. Goldberg^{7,1}, Bhaskar S. Kolachana¹, Alessandro Bertolino¹, Eugene Zaitsev⁴, Bert Gold³, David Goldman², Michael Dean³, Bai Lu^{4,8,9}, Daniel R. Weinberger^{*1,2,3}

© 2010 Nature Publishing Group. All rights reserved 1546-1353/10/010099-04 \$30.00
www.nature.com/mp

ORIGINAL ARTICLE

Meta-analysis of the *BDNF* Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity

M. Verhagen¹, A. van der Meij¹, P.A.M. van Deurzen^{1,2}, J.G.E. Janzing¹, A. Arias-Vásquez^{1,3,4}, J.K. Buitelaar^{1,2} and B. Franke^{1,5}

A Genetic Variant BDNF Polymorphism Alters Human Hippocampal Formation Volume in Both

Vita,^{1,2} Rebecca M. Jones,^{1,2}
Amso,^{1,2} Leah H. Somerville,^{1,2}
Coston,^{1,2} Theresa Teslovich,^{1,2}

Human Hippocampal Formation Alters Human Behavior

Sandro Ieraci,¹ Tanvir Khan,¹
Lingwen Yang,⁵ Bruce S. McEwen,⁶

(2005) 10, 631–636
© 2005 Nature Publishing Group. All rights reserved 1362-4886/05 \$30.00
www.nature.com/mp

so much activity on
a hydrophobic-to-
hydrophobic
mutation in a long
IDP!!!

66met polymorphism and volume of the hippocampal formation

PR Szeszko^{1,2}, R Lipsky³, C Mentschel⁴, D Robinson^{1,2}, H Gunduz-Bruce⁵, S Sevy^{1,2}, M Ashtari⁶, B Napolitano¹, RM Bilder⁷, JM Lane^{1,2}, D Goldman⁸ and AK Malhotra^{1,2}

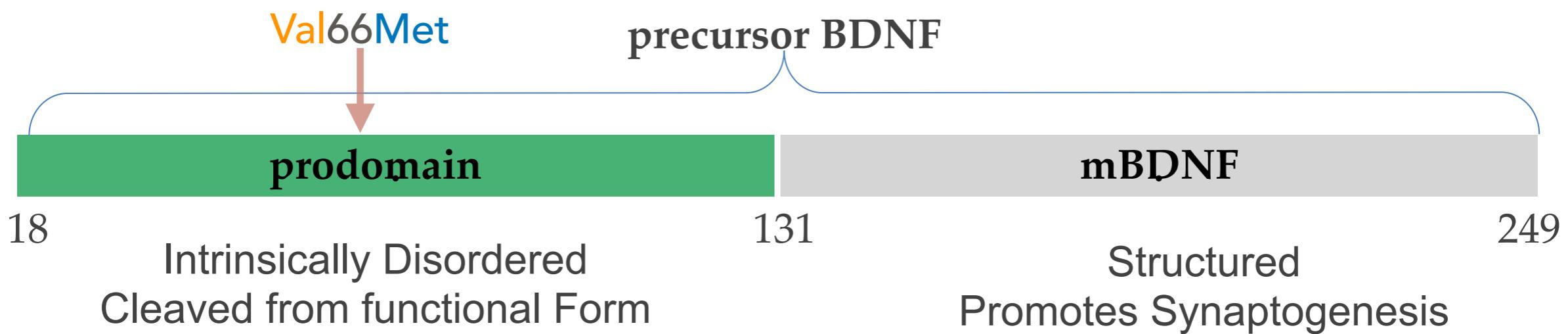
Results: 2,258

(from Web of Science Core Collection)

You searched for: TOPIC: (Val66Met)
...More

Weird Part #1

Residue 66 is not part of mature BDNF



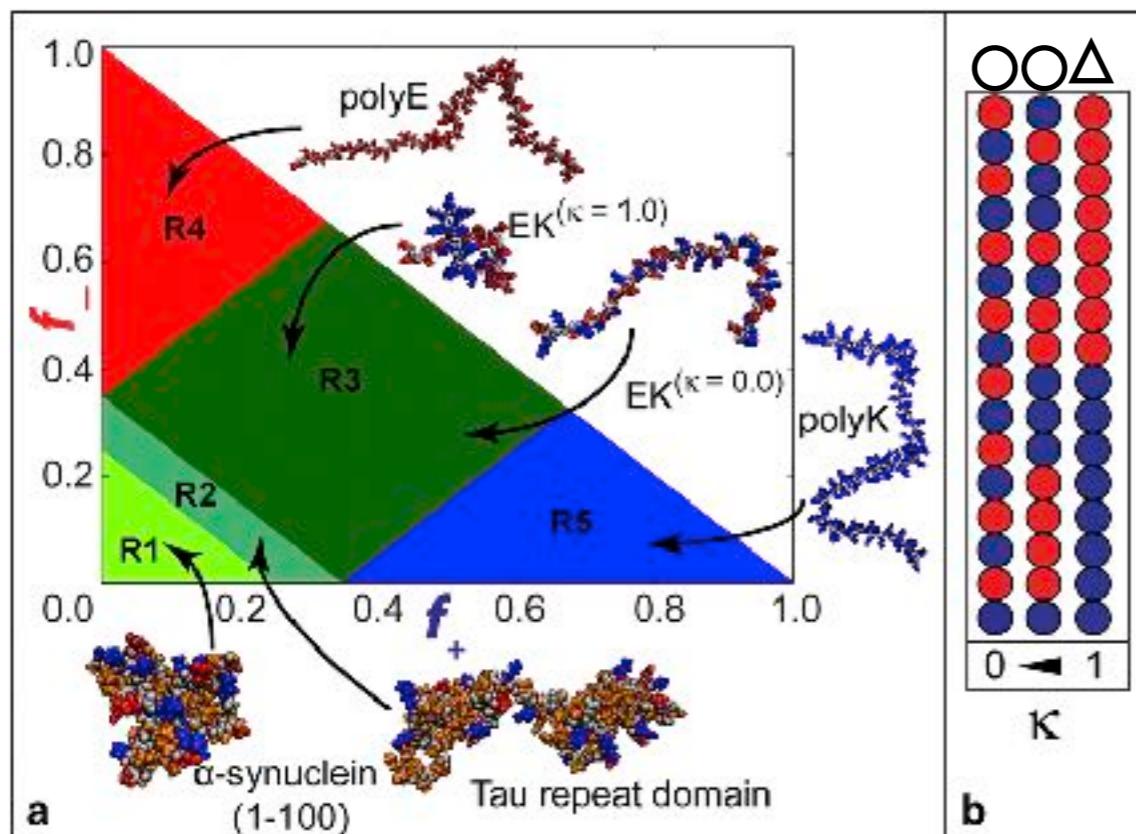
Why is the non-functional form having physiological effects?

Likely answer: Only the ancestral/wildtype form is non-functional

Met66 prodomain has a **new receptor** (SorCS2)!

Weird Part #2

prodomain is intrinsically disordered, "should" be sensitive to charged mutations



(Das et al., PNAS, 2013)

f_+ fraction of positively charged residues
 f_- fraction of negatively charged residues
 κ sequence distribution of oppositely charged residues

● negatively charged ● positively charged OΔ uncharged residues

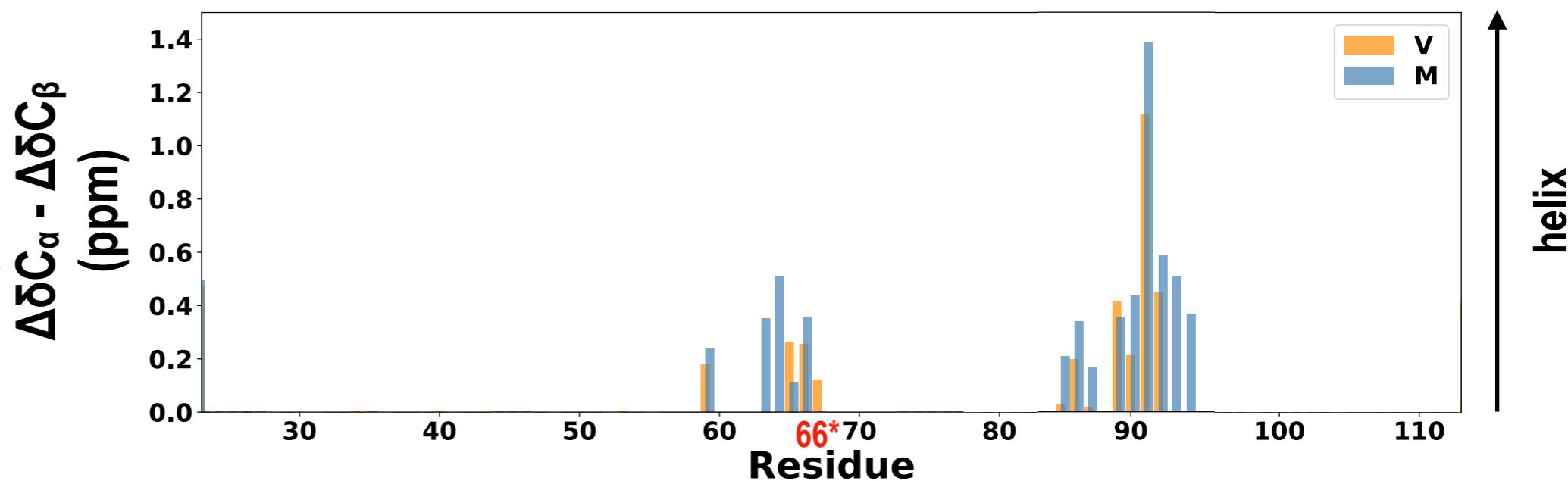
- Weak polyampholytes & polyelectrolytes:
Globules & tadpoles
- Janus sequences:
Collapsed or expanded - context dependent
- Strong polyampholytes:
Coils, hairpins, & chimeras
- Negatively charged strong polyelectrolytes:
Swollen coils
- Positively charged strong polyelectrolytes:
Swollen coils

Why is ensemble or function sensitive to charge-neutral mutation?

Weird Part #3

prodomain is intrinsically disordered, but mutation changes non-local secondary structure

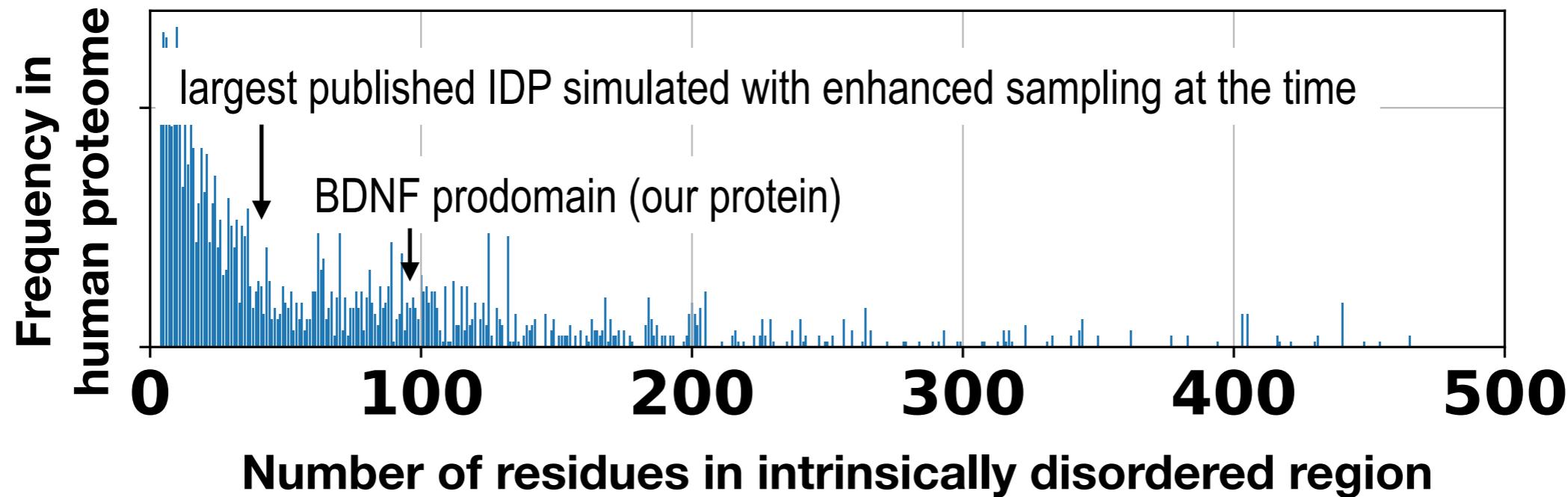
Same study
detects effects of
Val66Met on
residual secondary
structure



(Anastasia et al., Nat Commun., 2013)

How can this happen without tertiary interactions?

Massive simulations



- Longest IDPs previously simulated with explicit solvent, replica-exchange accuracy are much shorter (~40) than average IDP length
- Number of contacts increases as N^2 but frequency of each contact also decreases!
- 256 μ s (2 μ s x 64replicas) explicit solvent temperature replica exchange simulation (300K - 385K) of each prodomain; using GROMACS
- Amber99SB*-ILDN with TIP4PD water

Experimental Validation

MD is in agreement with NMR diffusion Rh and chemical shifts, and...

Dear [REDACTED]

Experimentalist

I hope you're well! I'm writing about your paper.

Publication with NMR data

For directly comparing our V66 and M66 prodomain simulation results with your data, we have relied on your chemical shifts deposited at BMRB. One reviewer of our manuscript has asked about apparent differences between your chemical shifts as they appear in our paper and your Fig S6.

I asked Ruchi to directly generate your Fig S6 with the chemical shifts obtained from BMRB. Her version (below) looks very similar to Fig S6. All but one of the discrepancies extend to both sequences and can be explained by variations in random coil values (we used those from POTENCI, Nielsen & Mulder, 2018).

Unfortunately, there is still one stubborn and dramatic discrepancy at R93 that only affects the V66 sequence. BMRB has

Hi Grace,

That is clearly a typo!

Thank you for bringing this to my attention!

I'll have [REDACTED] get this corrected!

Best regards,

Experimentalist

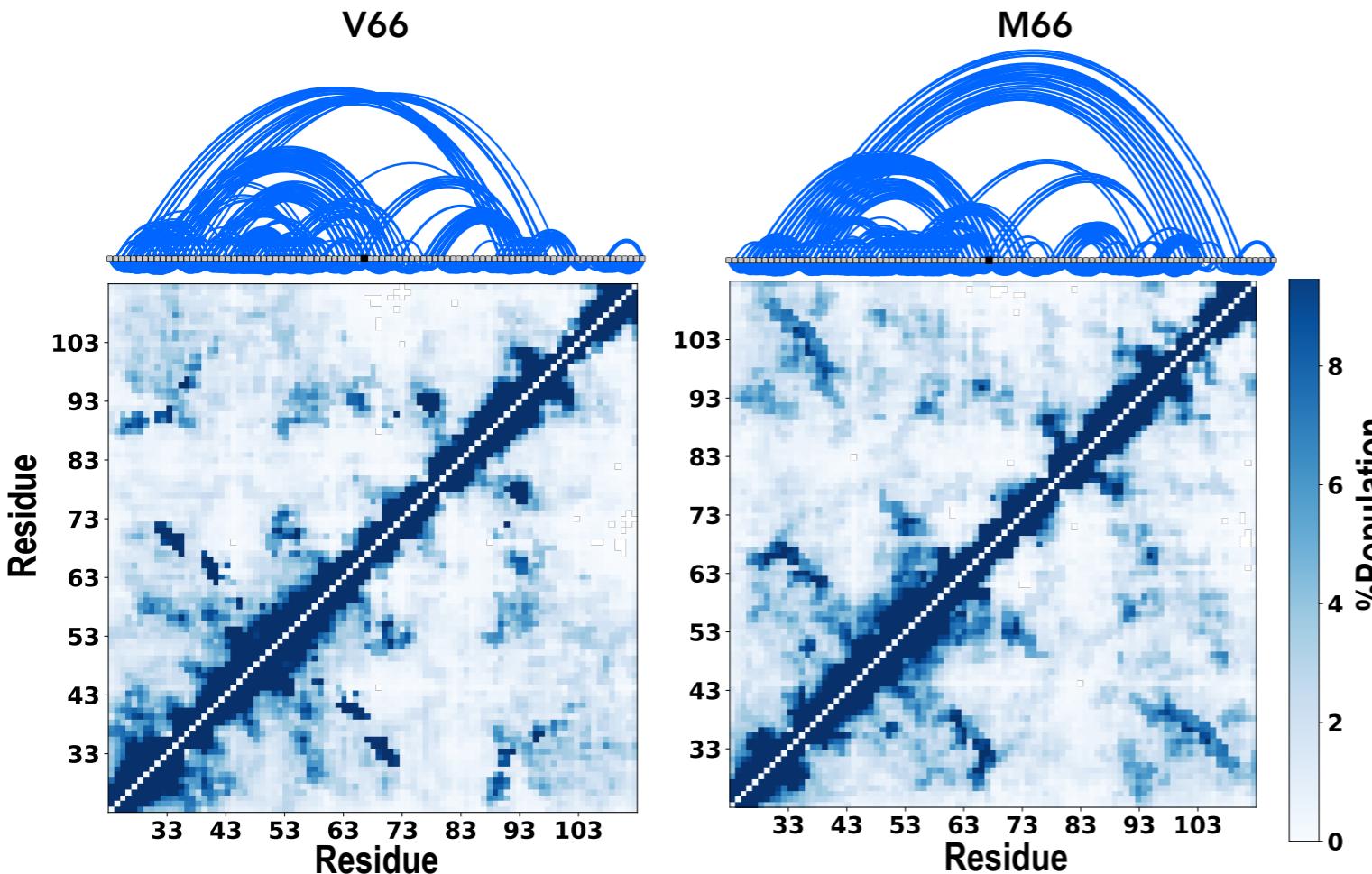
From me:

Experimentalist:

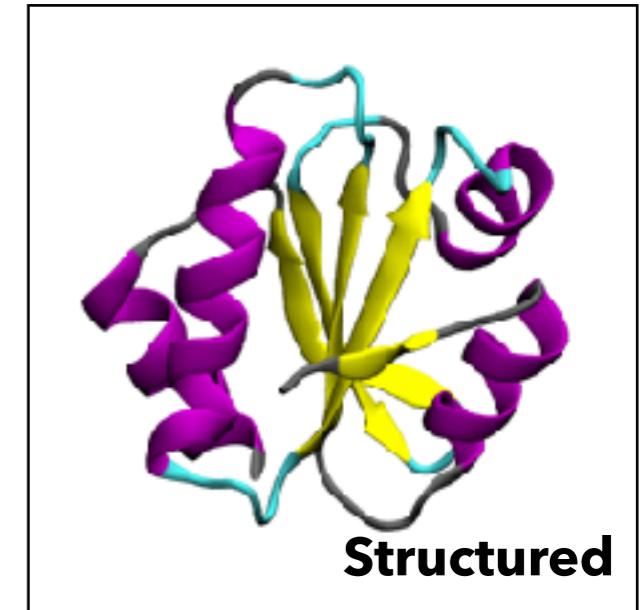
...the one discrepancy turned out to be an error in the experimental data file!

How can we possibly analyze this?

Step 1: try analyzing changes in contacts:



Structured : $O(N)$ Possible contacts

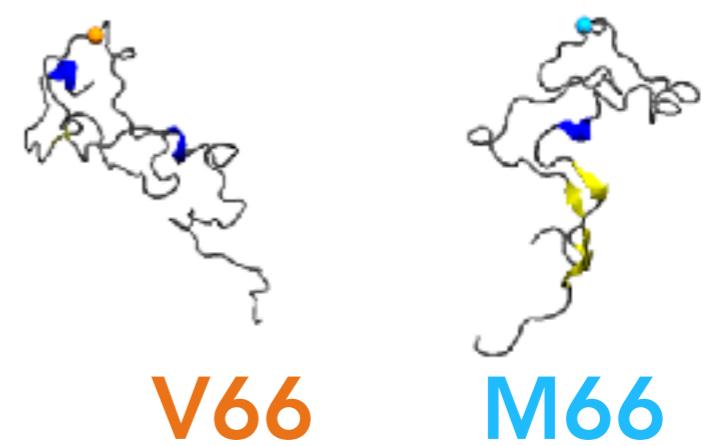


PDBID: 2N5A yeast Thioredoxin

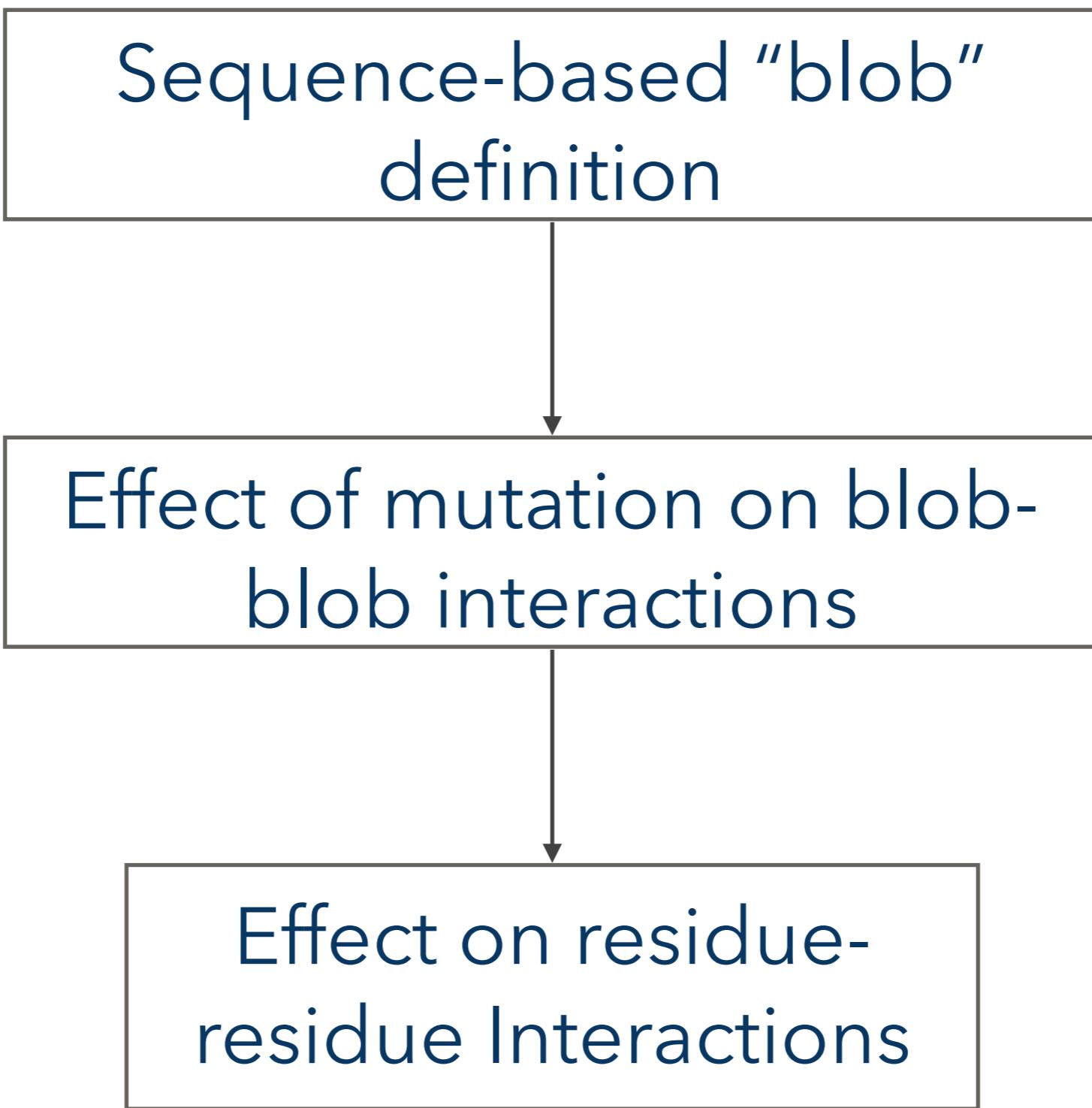
This is a statistical nightmare!

Solution : coarse-grain analysis
of atomistic simulation

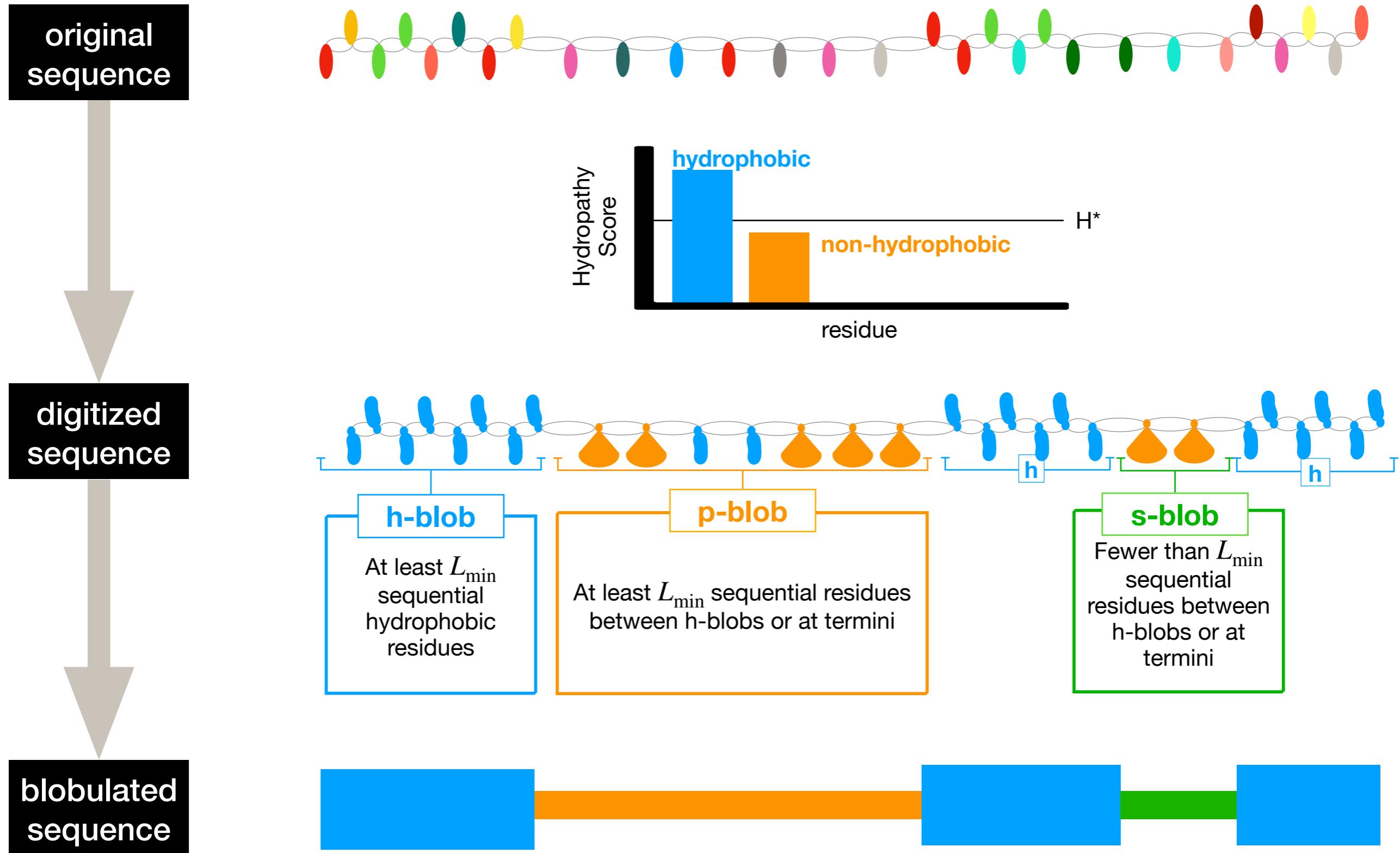
IDP: $O(N^2)$ Possible contacts



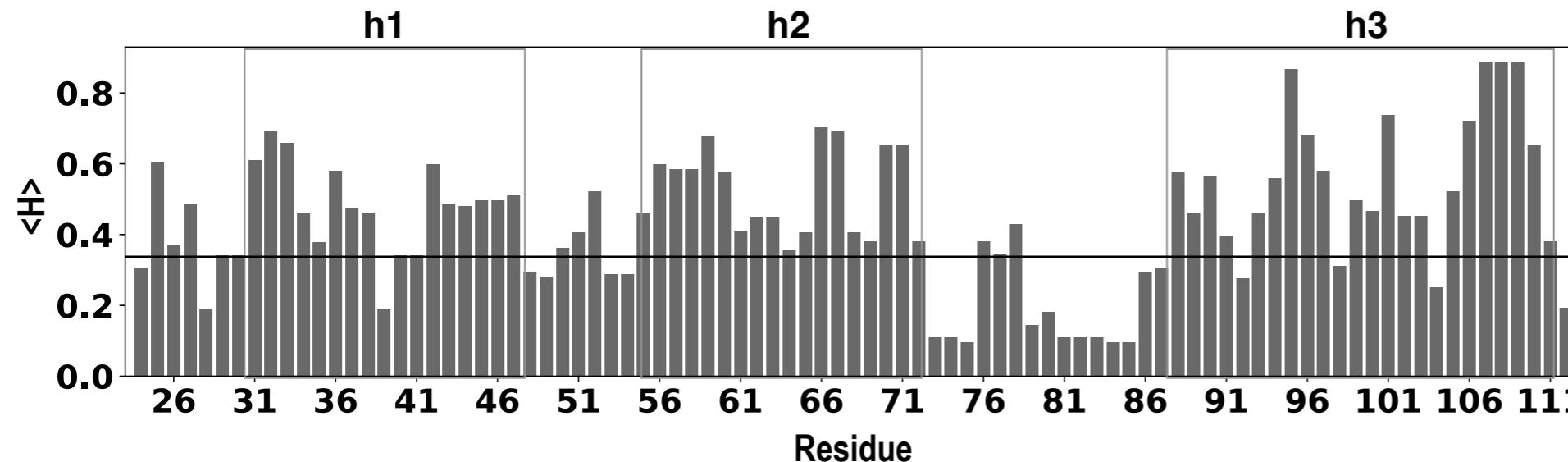
Hierarchical Analysis



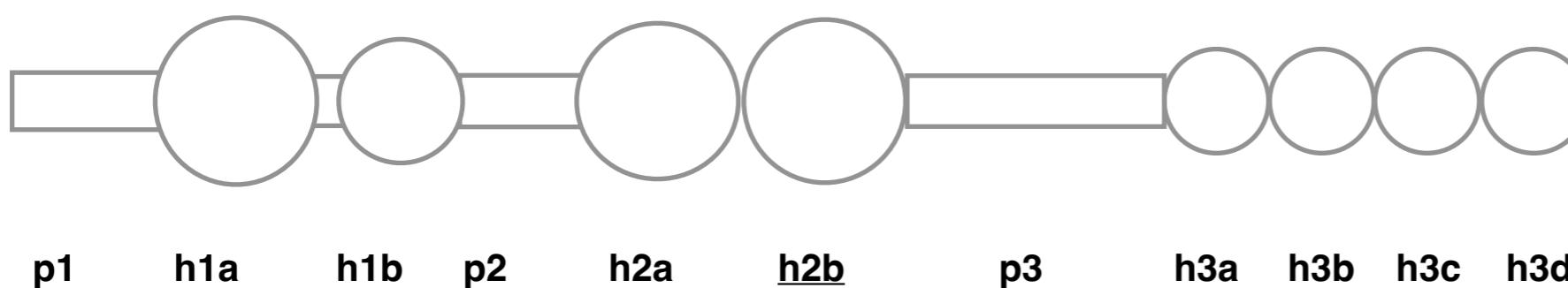
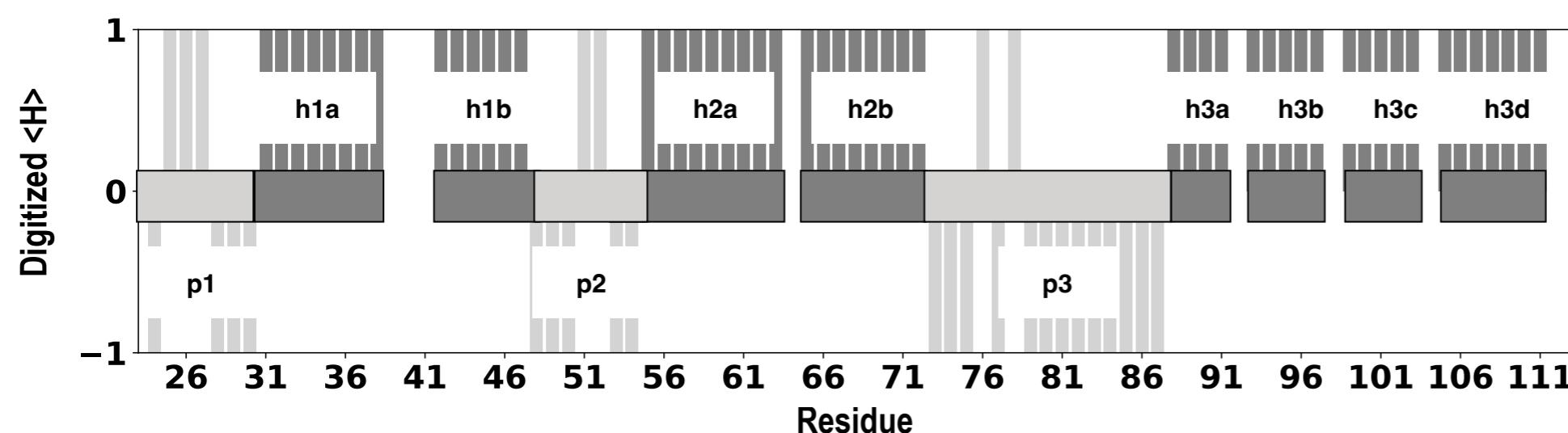
introducing blobulation



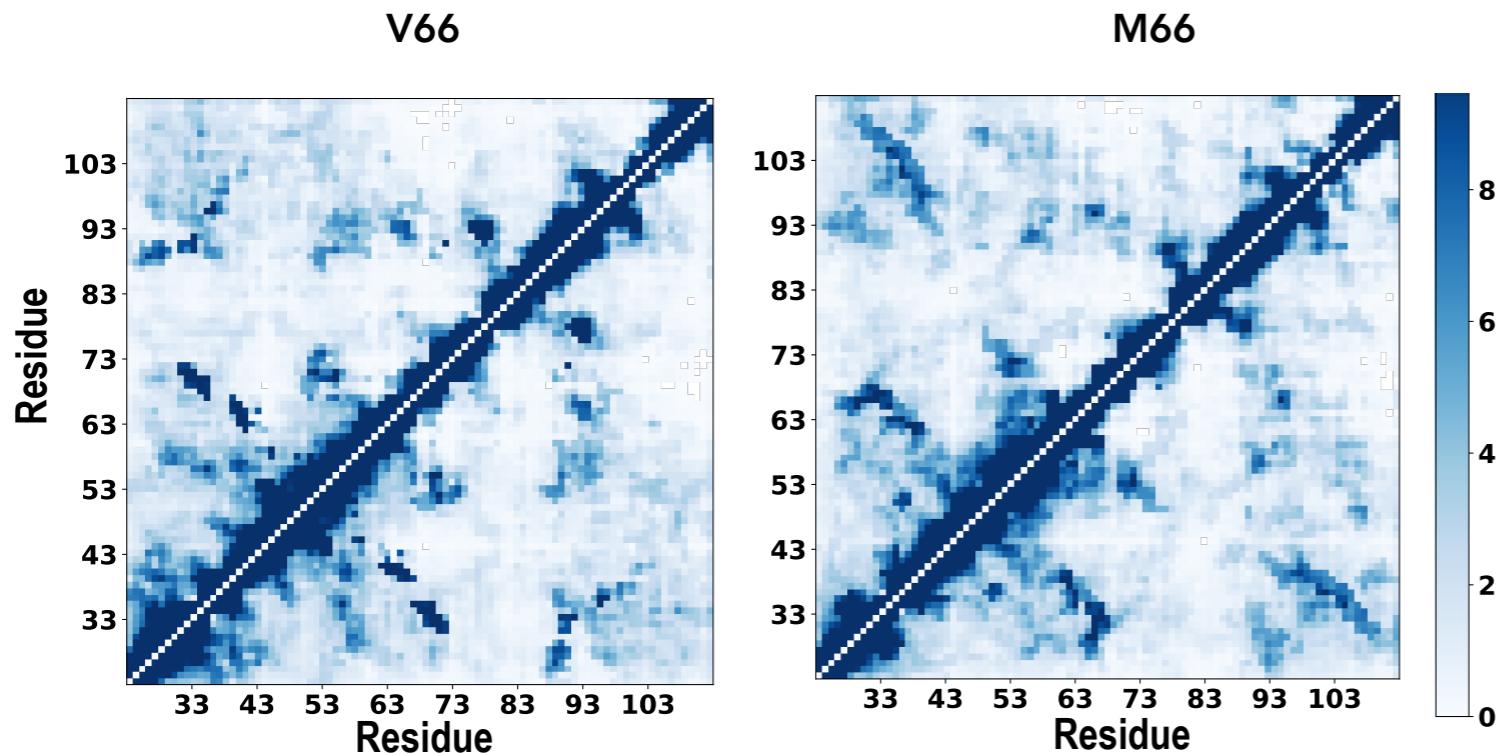
Sequence-based blob identification



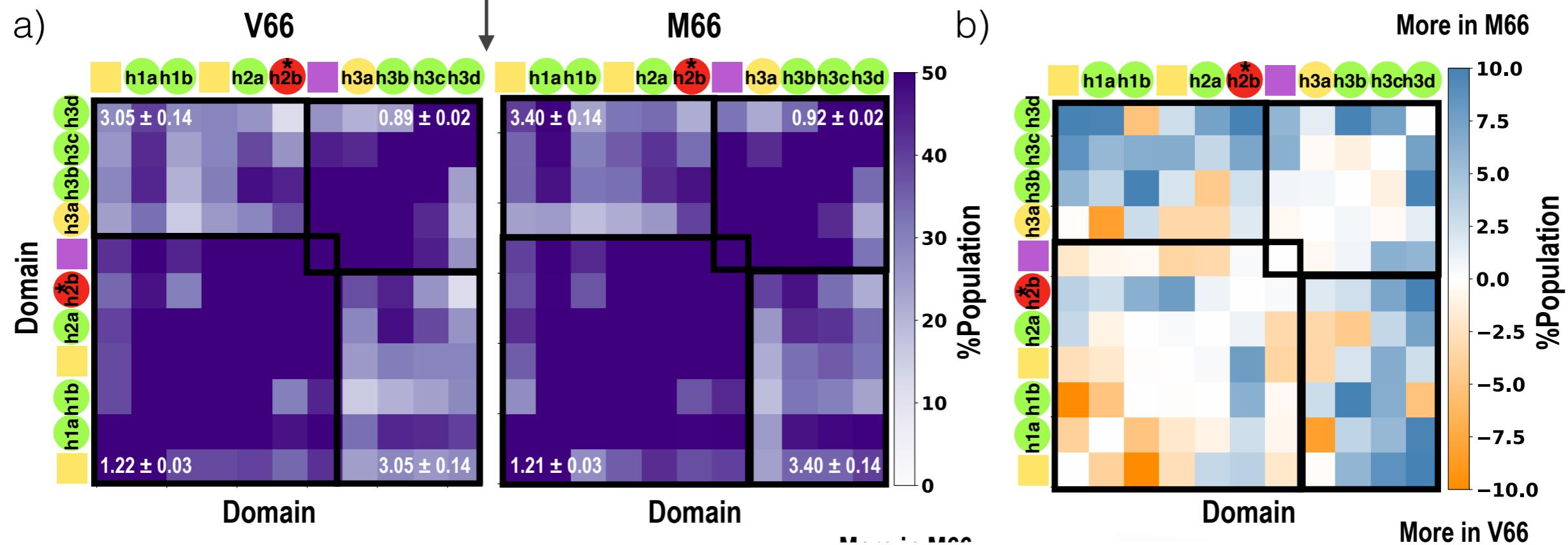
- Blob identification is purely based on sequence hydrophobicity
- Reduced total number of possible contacts : 91^2 vs 11^2



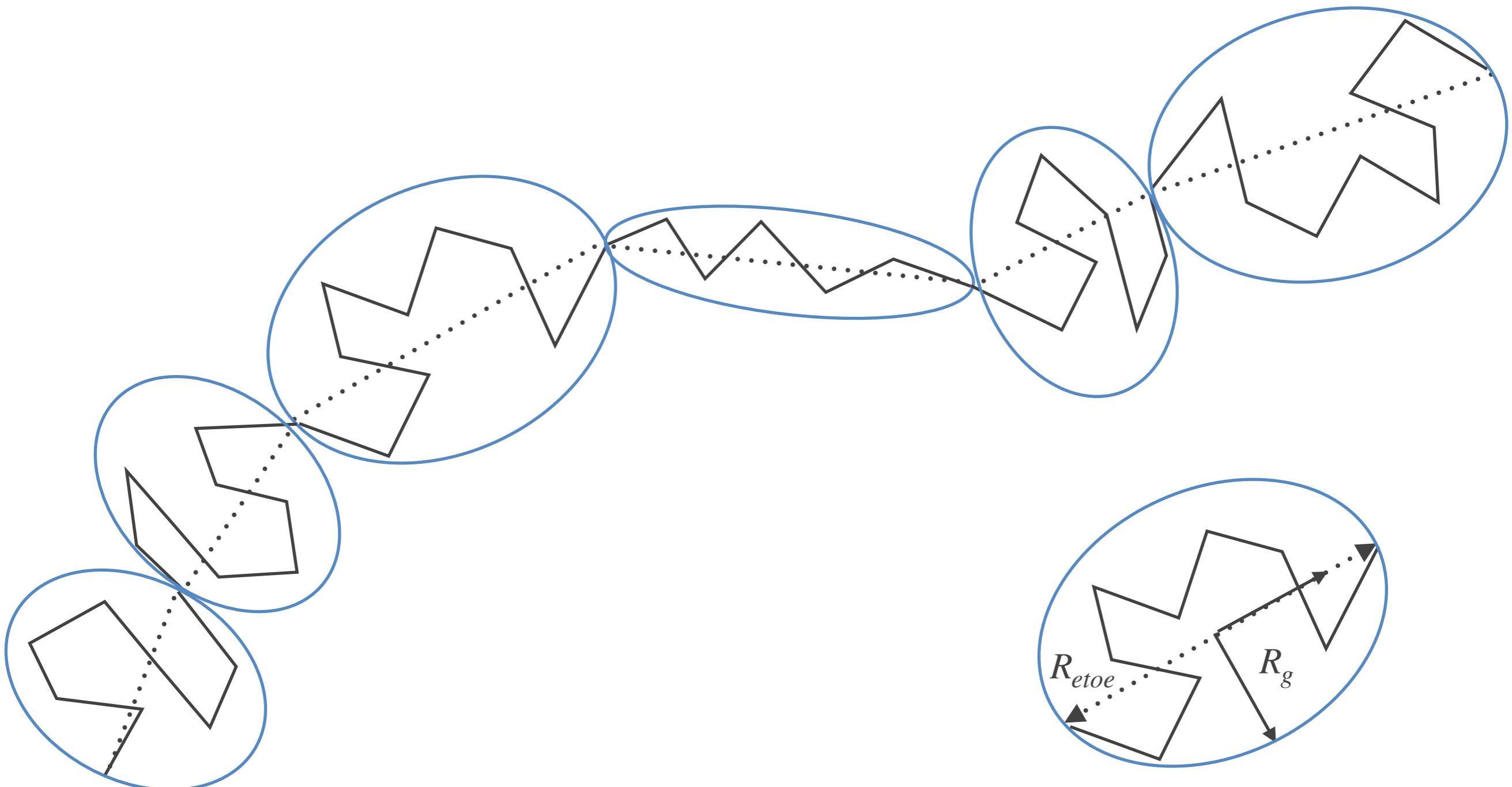
Blob-blob Interactions



How "should" blob interactions depend upon separation along chain, for an ideal heteropolymer?

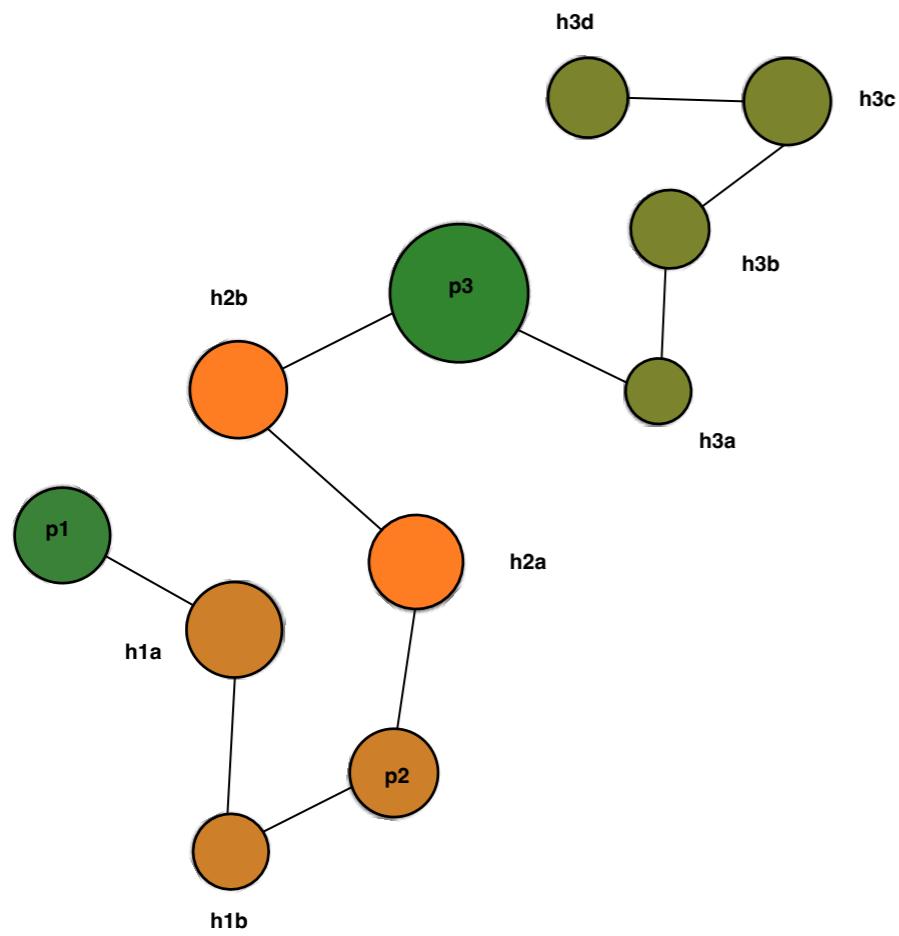


Monte Carlo Model of Self-avoiding heteropolymer



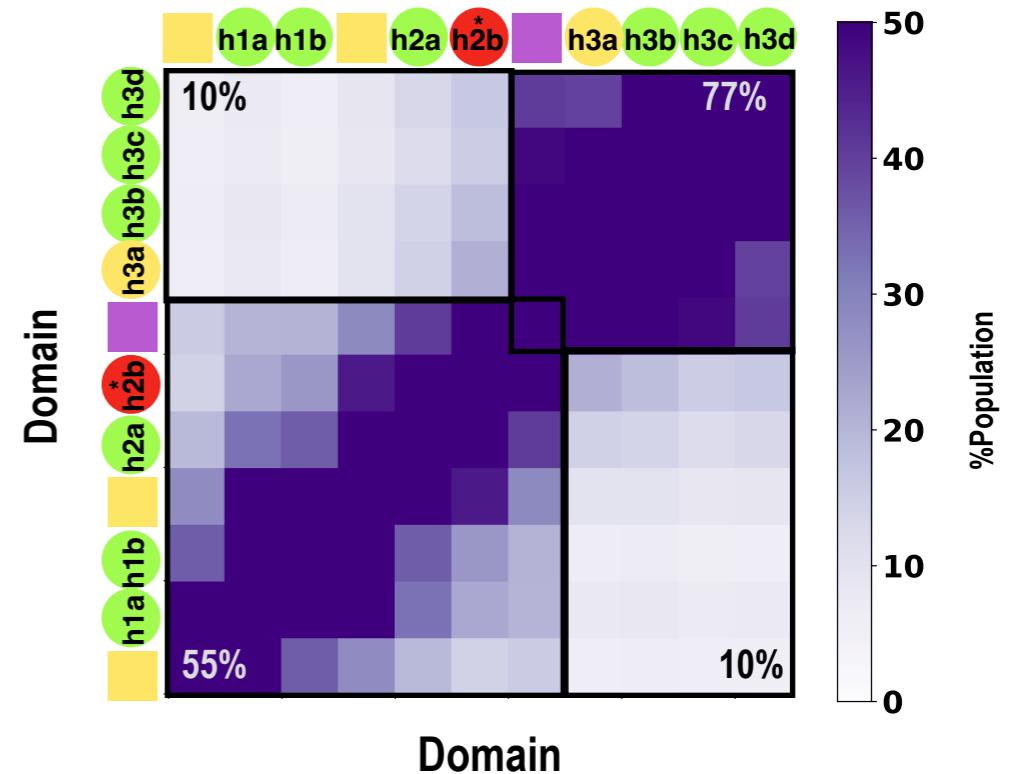
Mean values of R_{etoe} and R_g
calculated from T-REMD of full protein

Domain contacts in an ideal heteropolymer

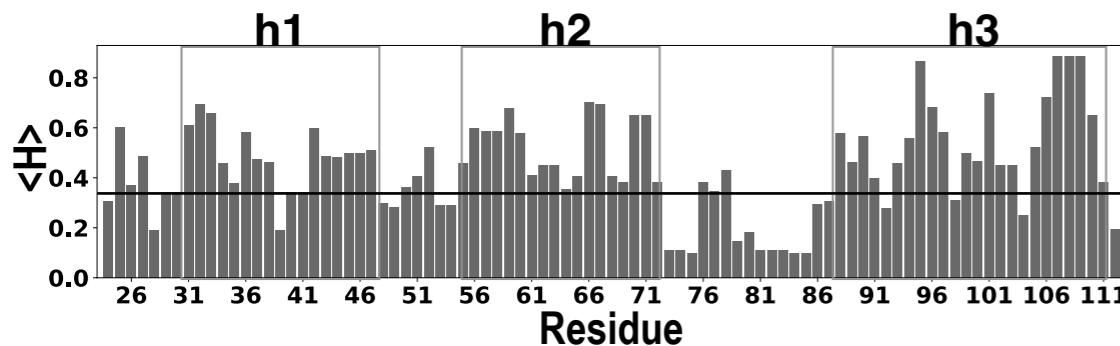


Probability of Contact

Self-avoiding 11-mer

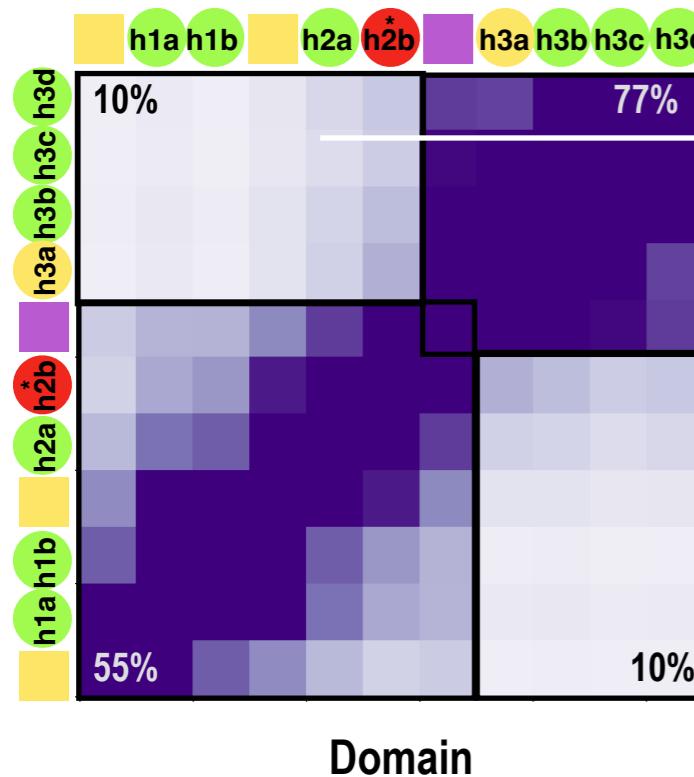


prediction : Large extended domain would effectively split the protein into two segments that don't interact

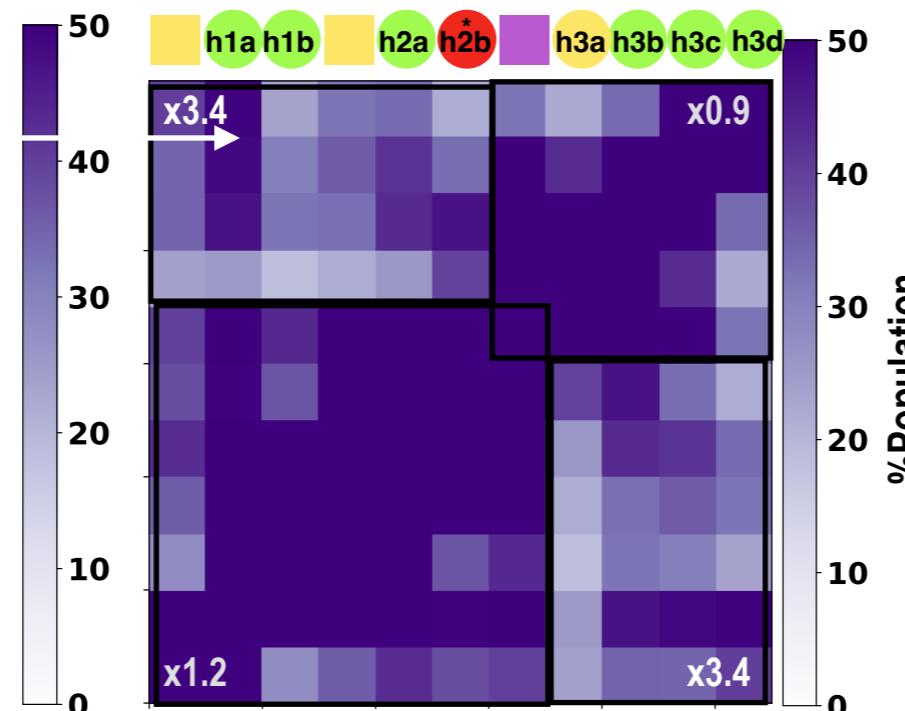


Self-avoiding heteromer vs. Real Protein

Self-avoiding heteromer



Prodomain



Visible boundary in our data also, but prodomain has 3-fold enrichment between N-terminal and C-terminal side

high hydrophobicity

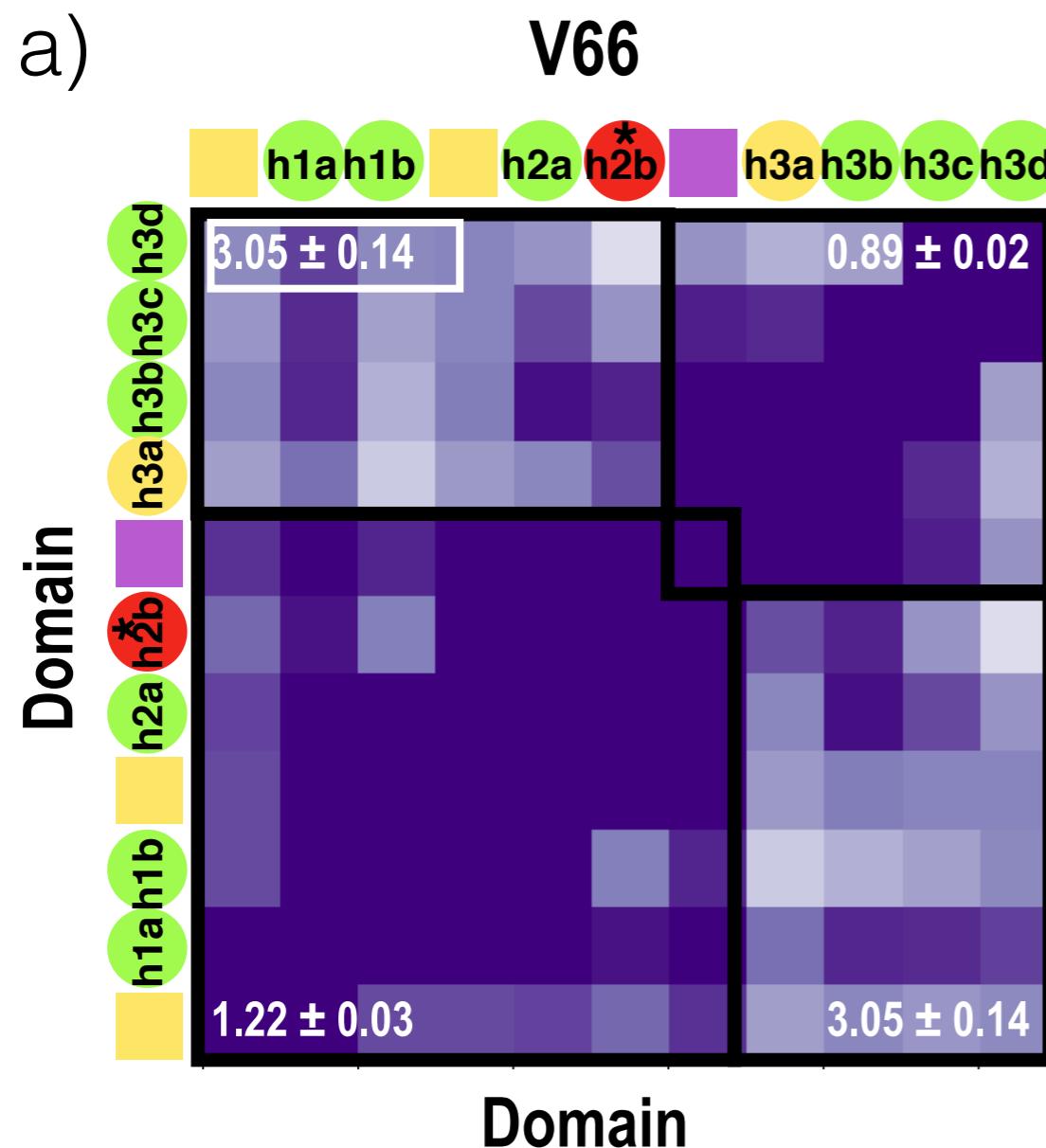


low hydrophobicity

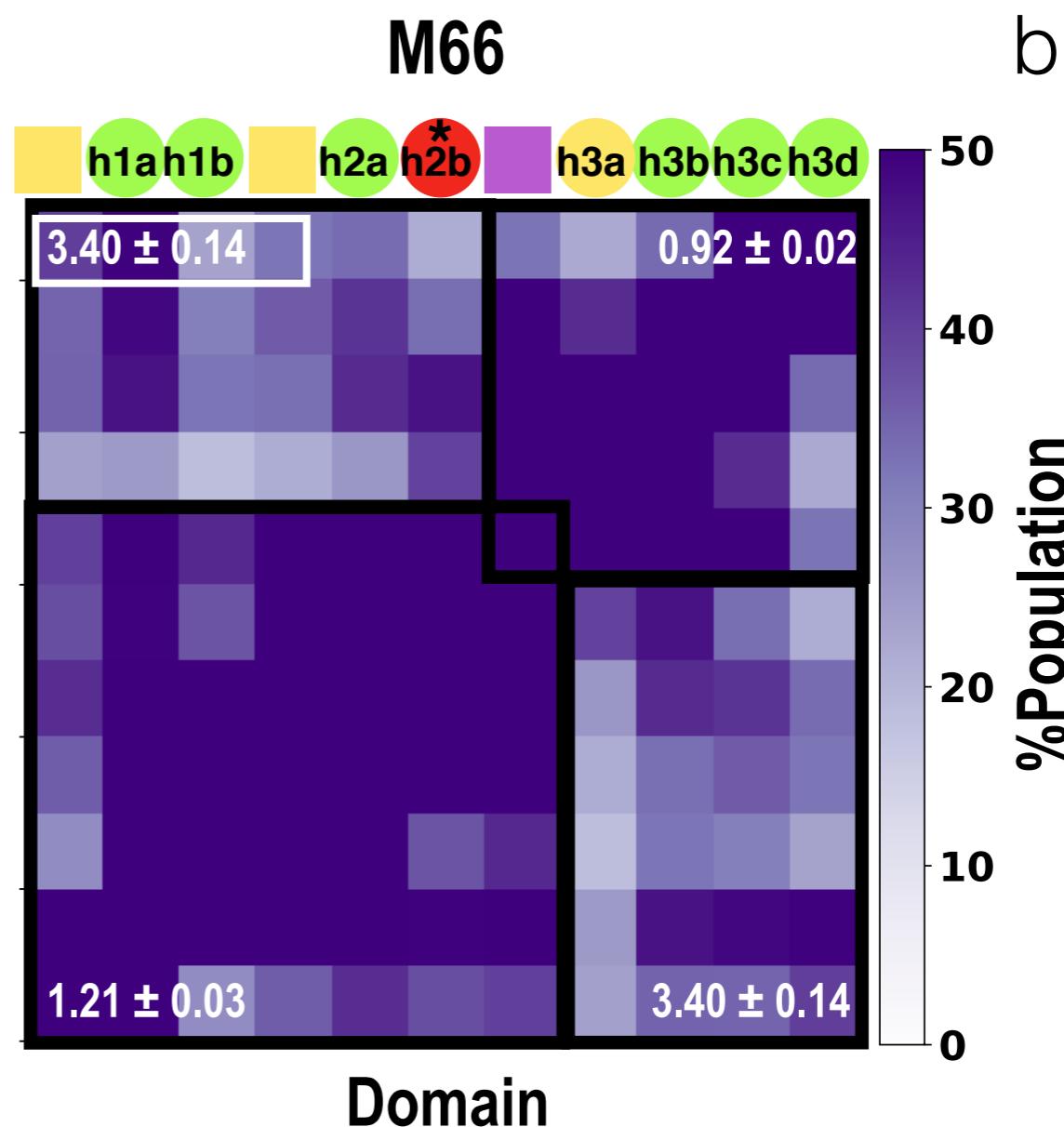


Effect of Val66Met

a)



M66



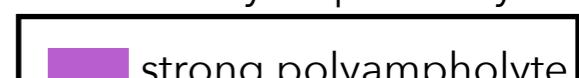
b)

Met66 : two ends interact more with each other!

high hydrophobicity

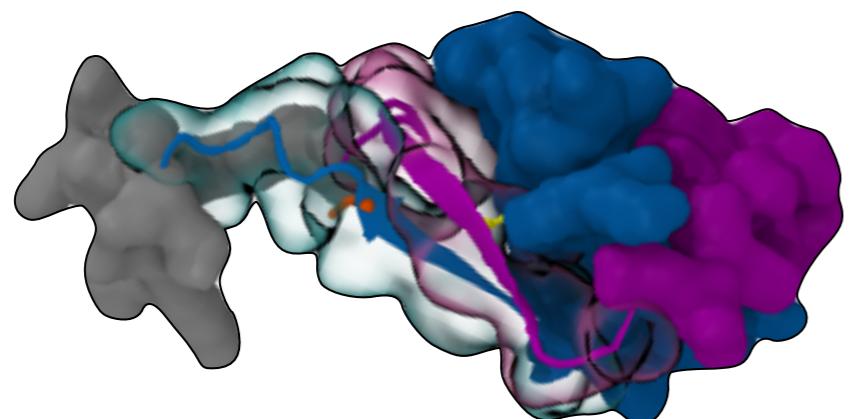


low hydrophobicity

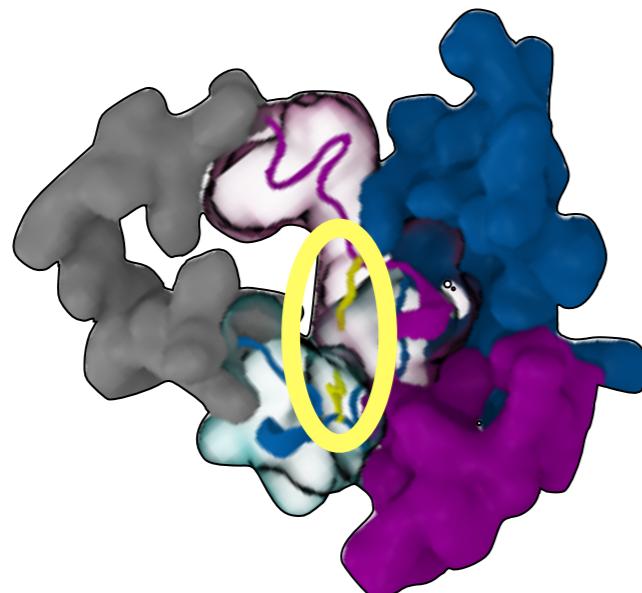


Why?: Met-Met interactions

V66



M66

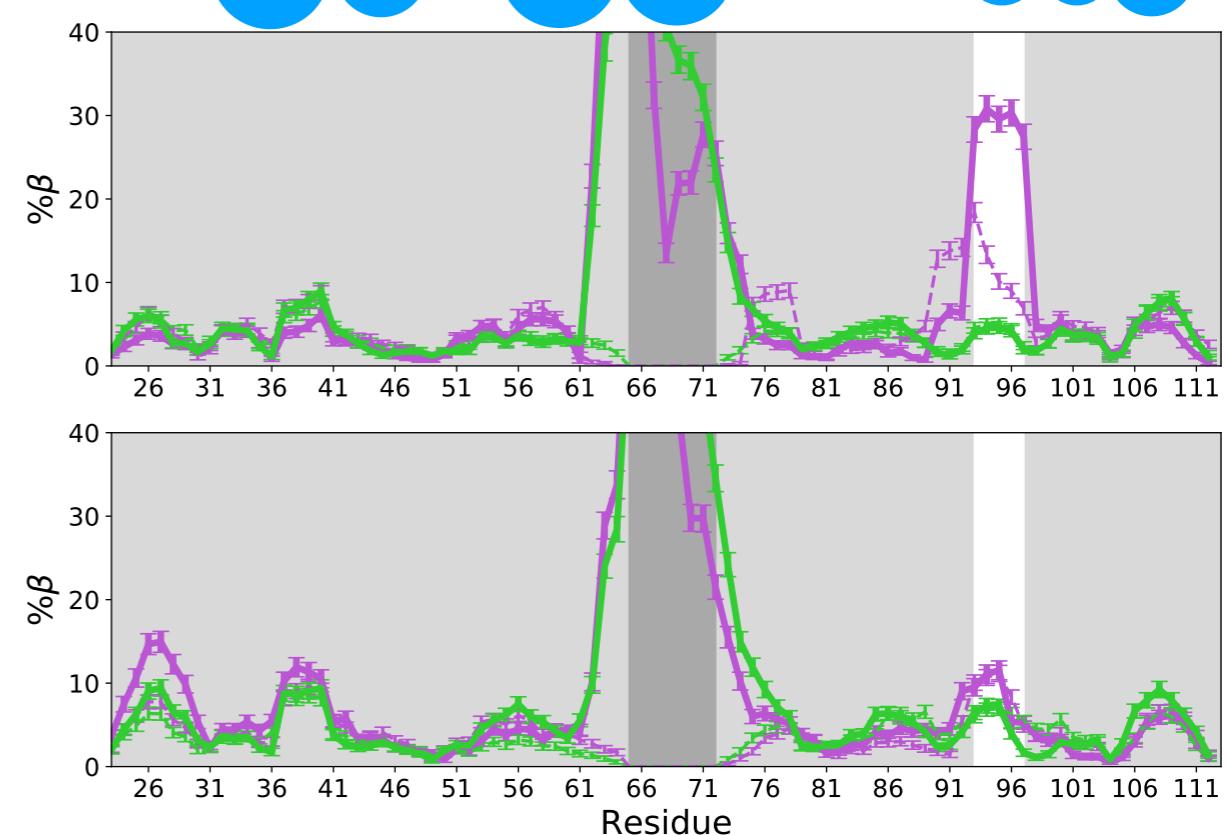


Met-Met
Interactions switch
backbone-
backbone to
sidechain-sidechain

V66

M66

only other Met in sequence



PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Sequence specificity despite intrinsic disorder:
How a disease-associated Val/Met
polymorphism rearranges tertiary
interactions in a long disordered protein

Ruchi Lohia¹, Reza Salari^{1*}, Grace Brannigan^{1,2*}

Hydrophobic Specificity in Lipids, Proteins, and Populations

1. Lipids

A. Identifying **lipid fragments** from structures

- atomistic
- ELIC + model membranes
- new simulation protocol: SAFEP
- bonus: state dependence!

B. Quantifying lipid sorting in **complex quasi-native** membranes

- coarse-grained
- new analysis method: density threshold affinity
- nAChR + neuronal membranes

2. Proteins

C. Hydrophobic-to-hydrophobic mutations in **intrinsically disordered proteins**

- Val66Met mutation in the Brain-derived Neurotrophic Factor prodomain
- Massive atomistic simulations
- New analysis method: Blobulation

D. Blobulation as a **generally-useful conceptual tool**

- Protein organization and hierarchy from sequence

3. Populations

- Hydrophobic sequence context of disease-associated mutations
- Population frequency of mutations in particularly hydrophobic blobs



Connor
Pitman

Dr. Ruchi
Lohia

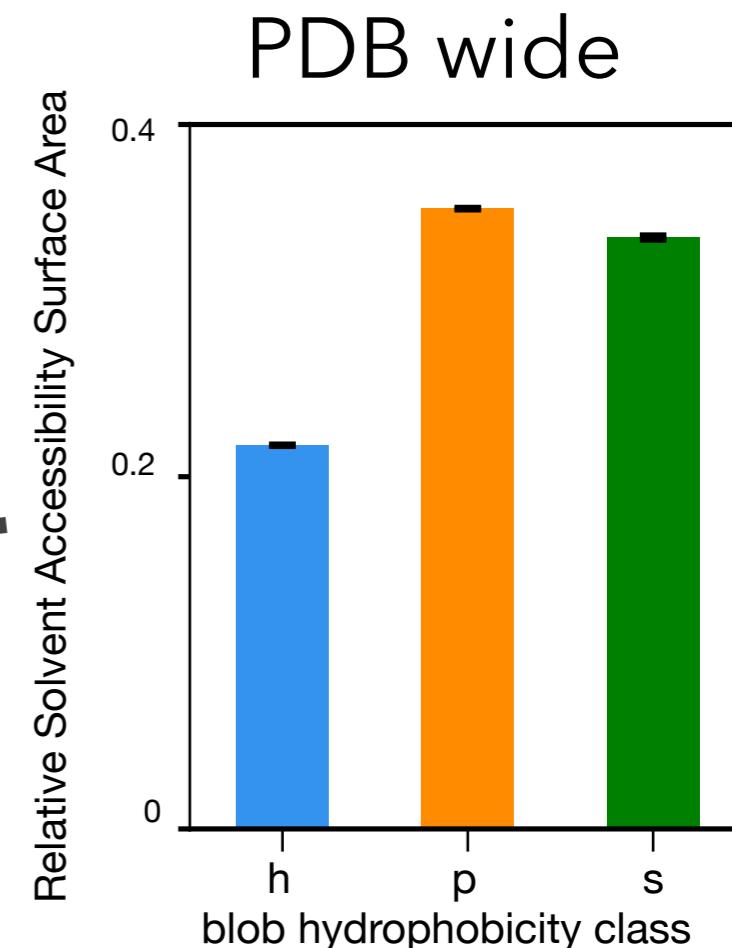
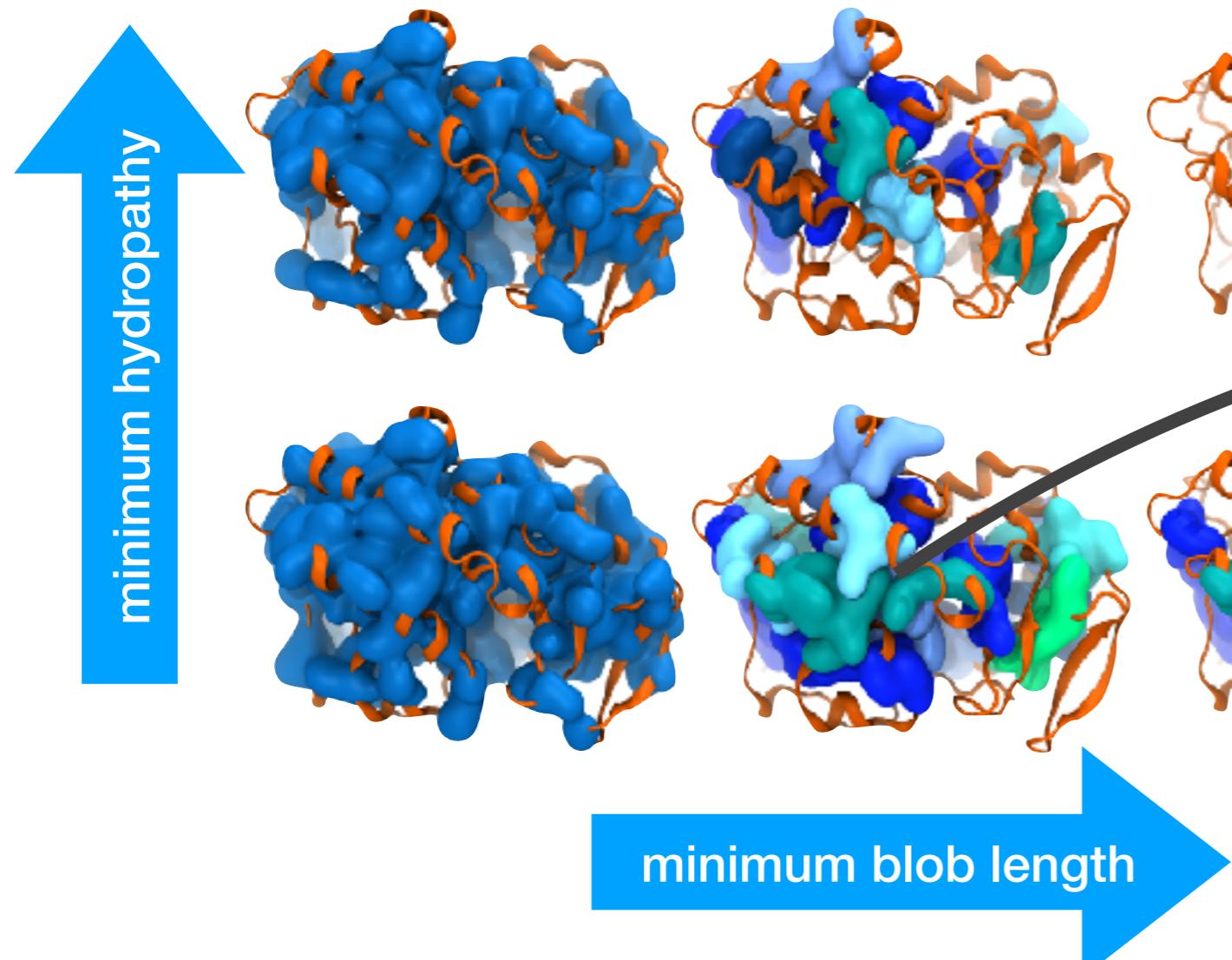
Dr. Matthew
Hansen

Dr. Tom
Hansen

Ezry St.
Joseph Iago-McRae

is blobulation a meaningful generic sequence-analysis approach?

example: cytochrome C peroxidase



PNAS

RESEARCH ARTICLE

BIOPHYSICS AND COMPUTATIONAL BIOLOGY



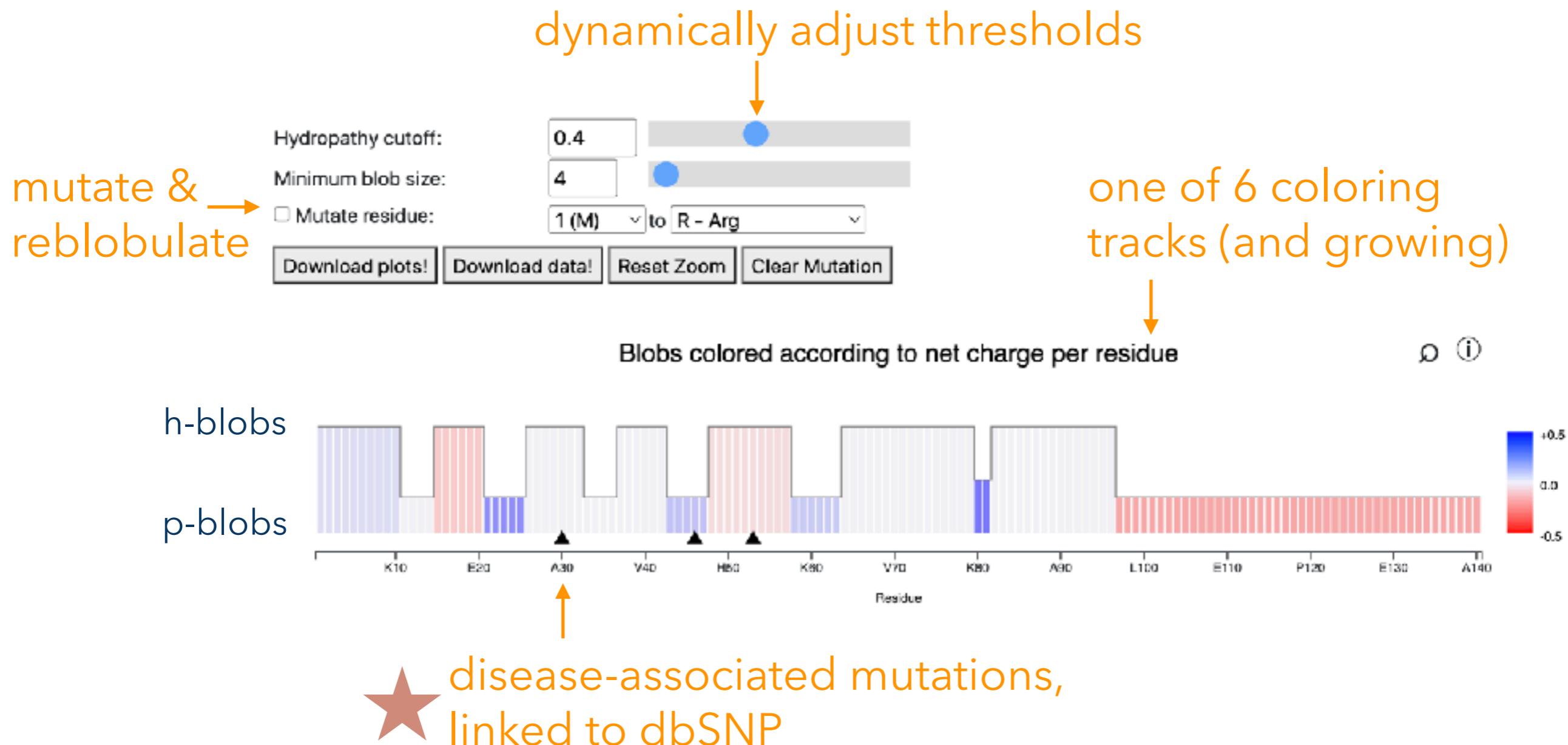
Contiguously hydrophobic sequences are functionally significant throughout the human exome

Ruchi Lohia^{1,2}*, Matthew E. B. Hansen¹*, and Grace Brannigan^{1,2}†

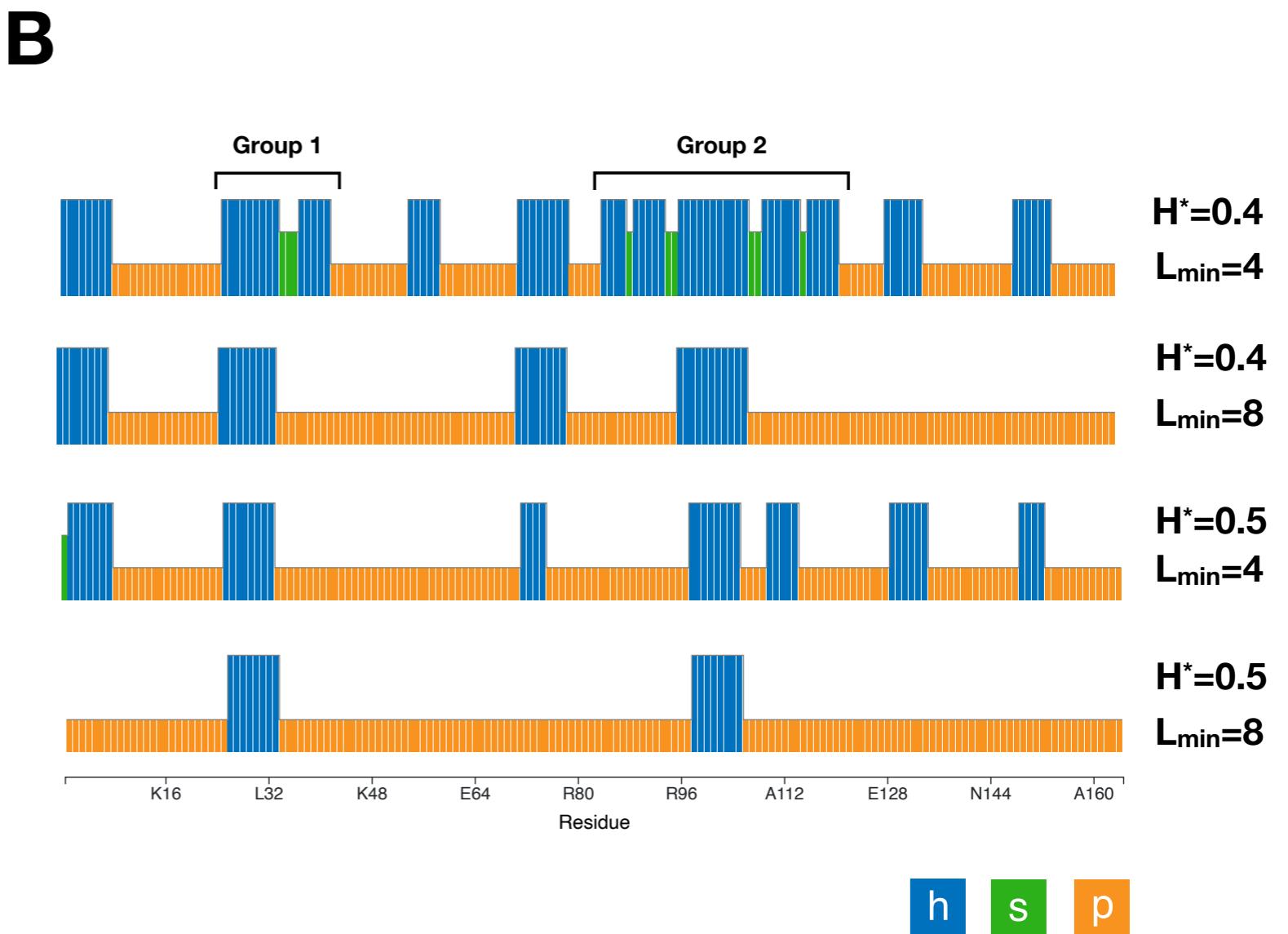
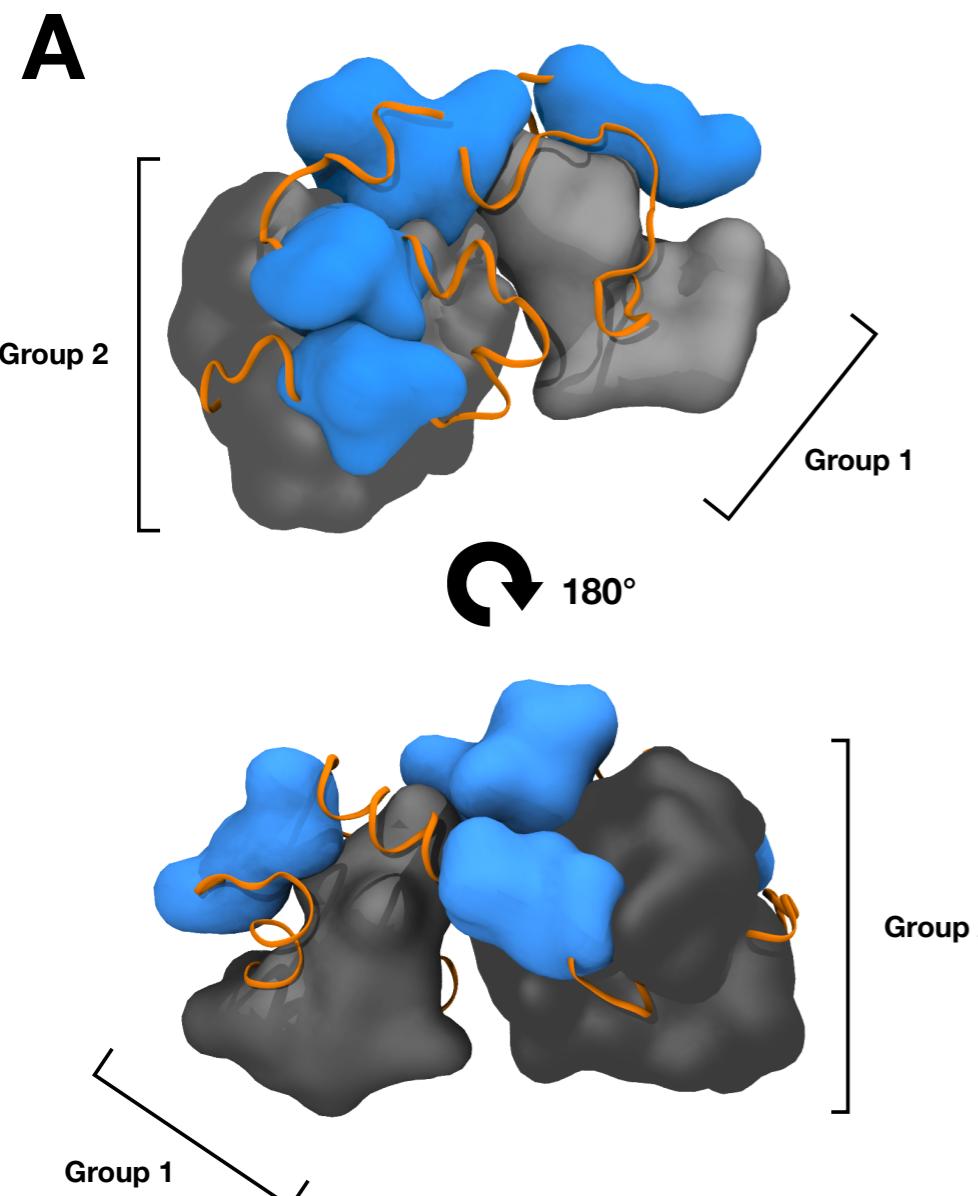
Edited by Ken Dill, Stony Brook University, Stony Brook, NY; received September 12, 2021; accepted February 2, 2022

blobulator.branniganlab.org

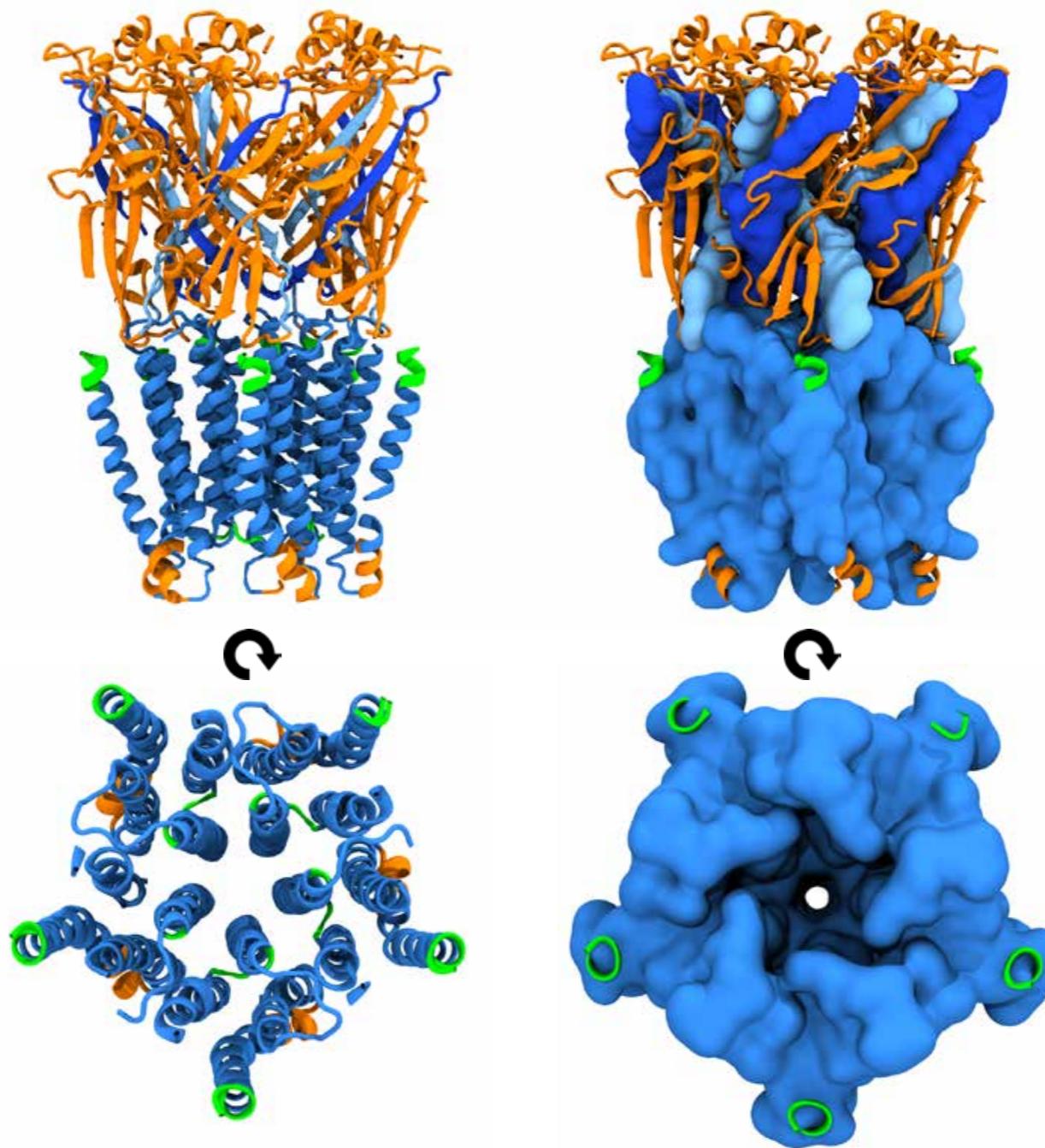
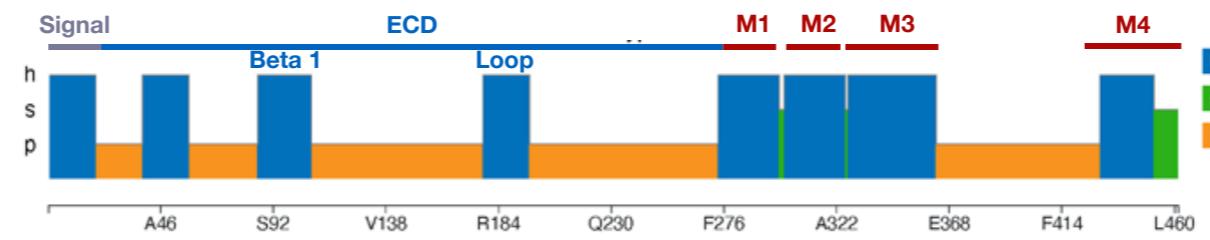
Detect and visualize blobs in your own sequence



Higher order groupings in lysozyme

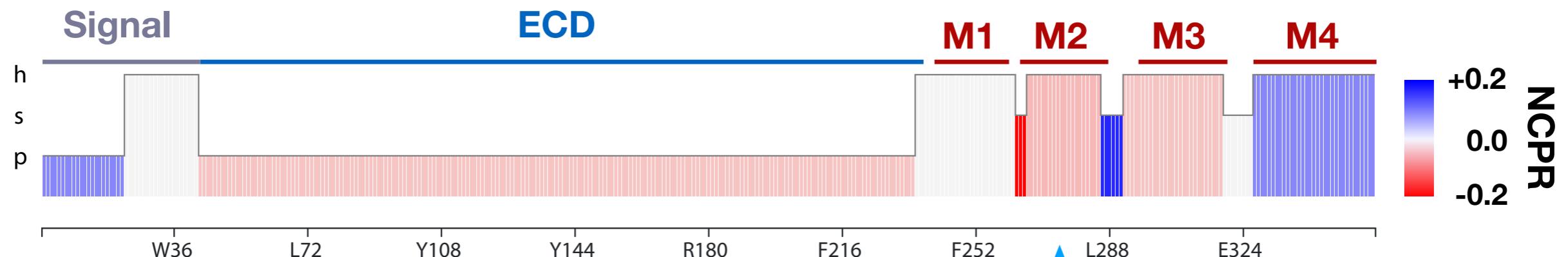


blobulation of GluCl

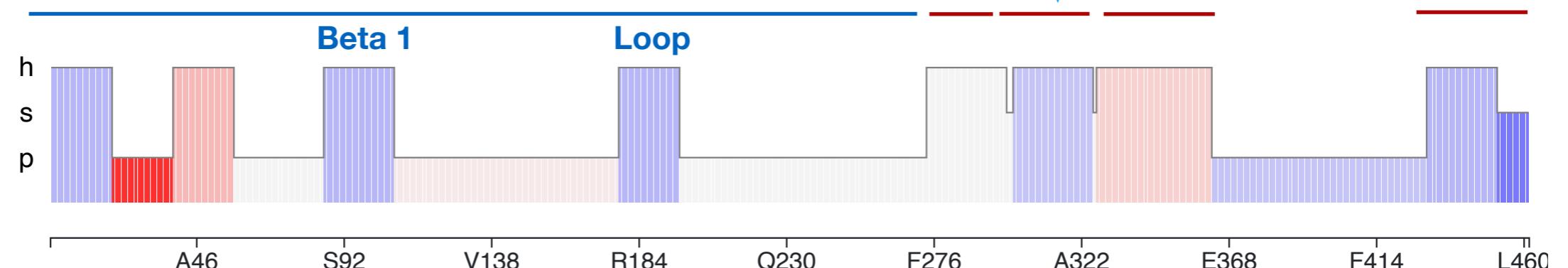


Net charge per residue of M2 “blob”

GLIC (conducts cations)

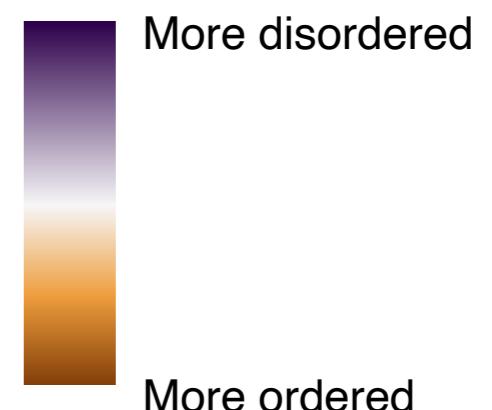
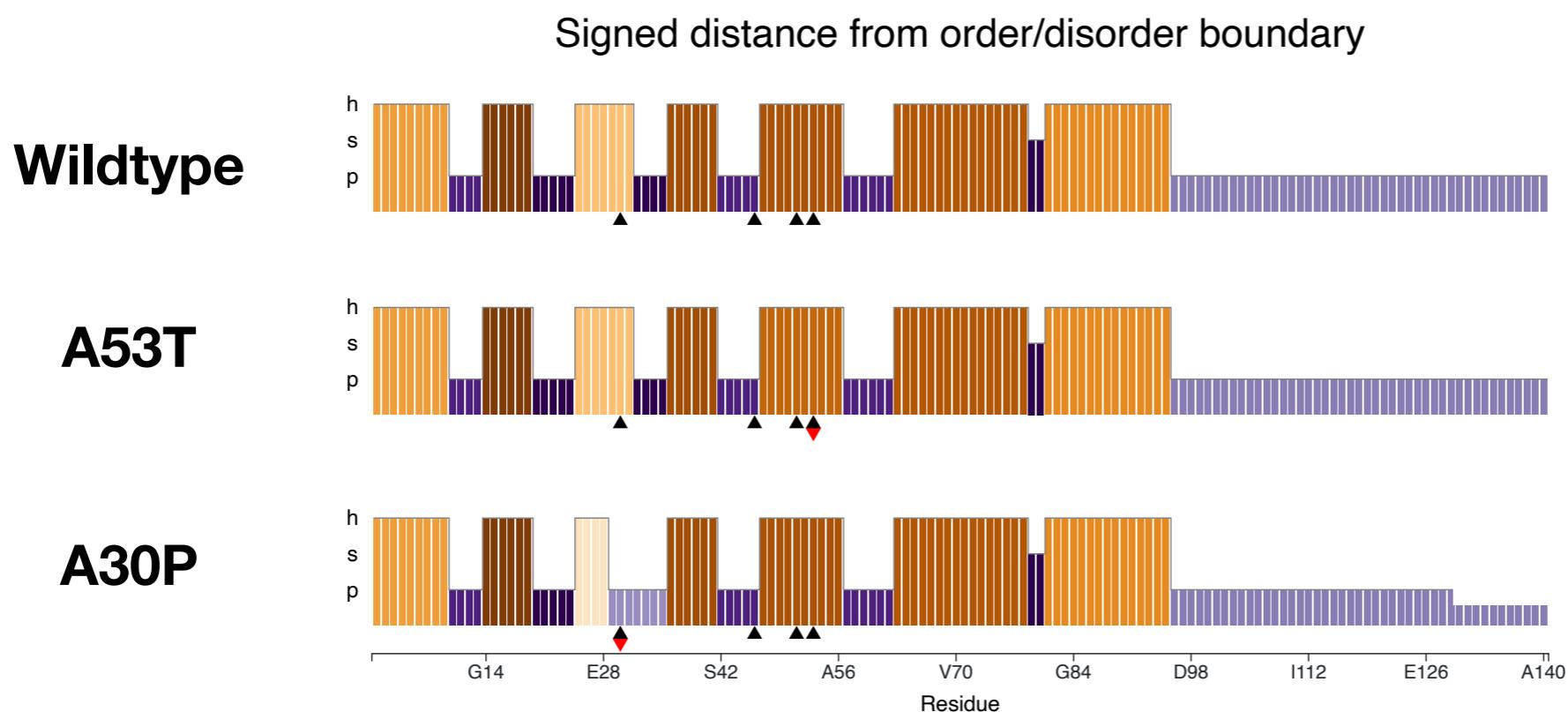
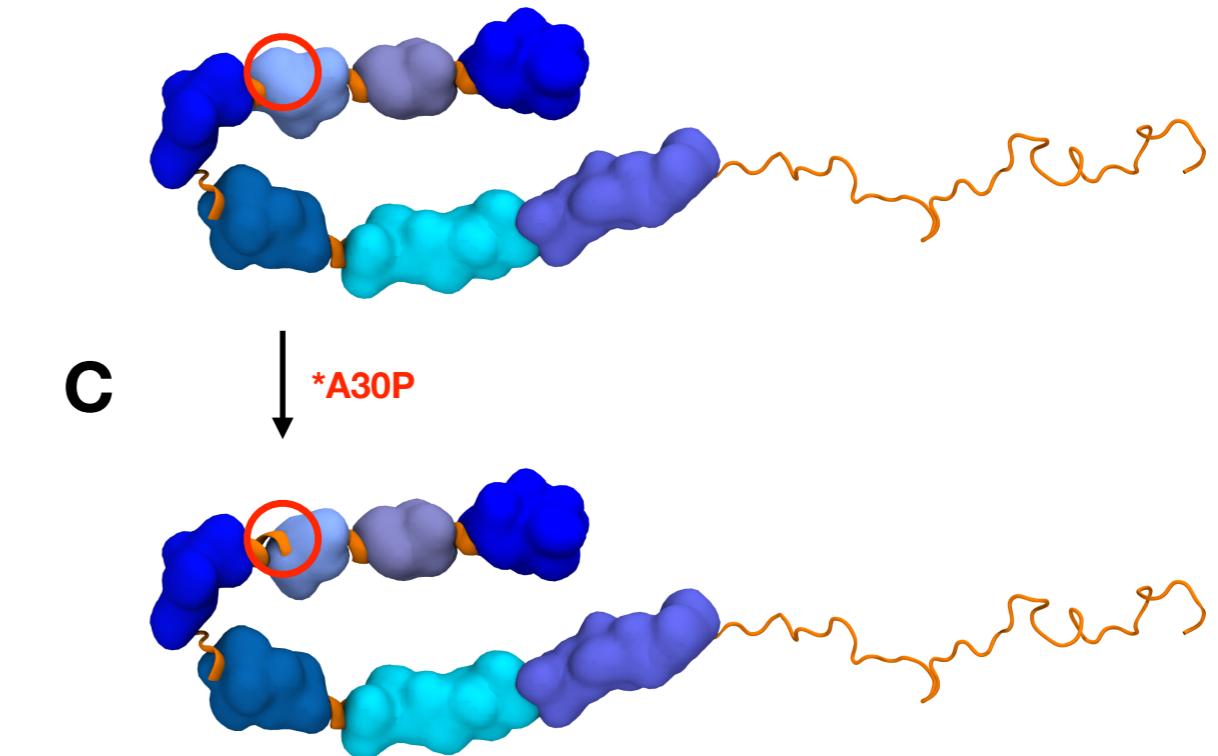
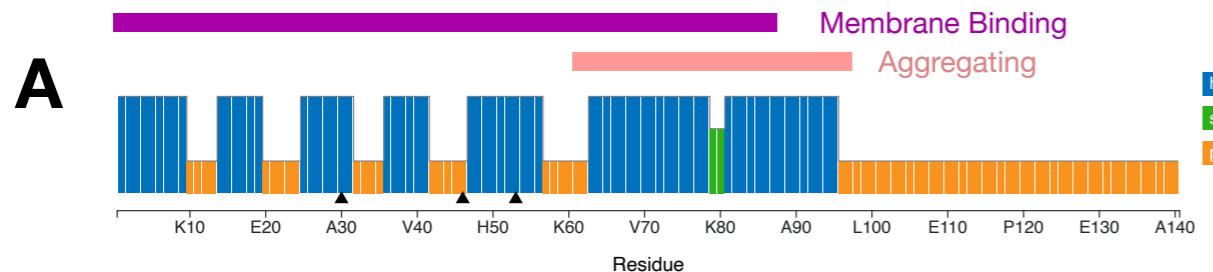


GluCl (conducts anions)



$$L_{\min}=19, H^*=0.33$$

Blobulation of alpha synuclein



Hydrophobic Specificity in Lipids, Proteins, and Populations

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- Population frequency of mutations in particularly hydrophobic blobs

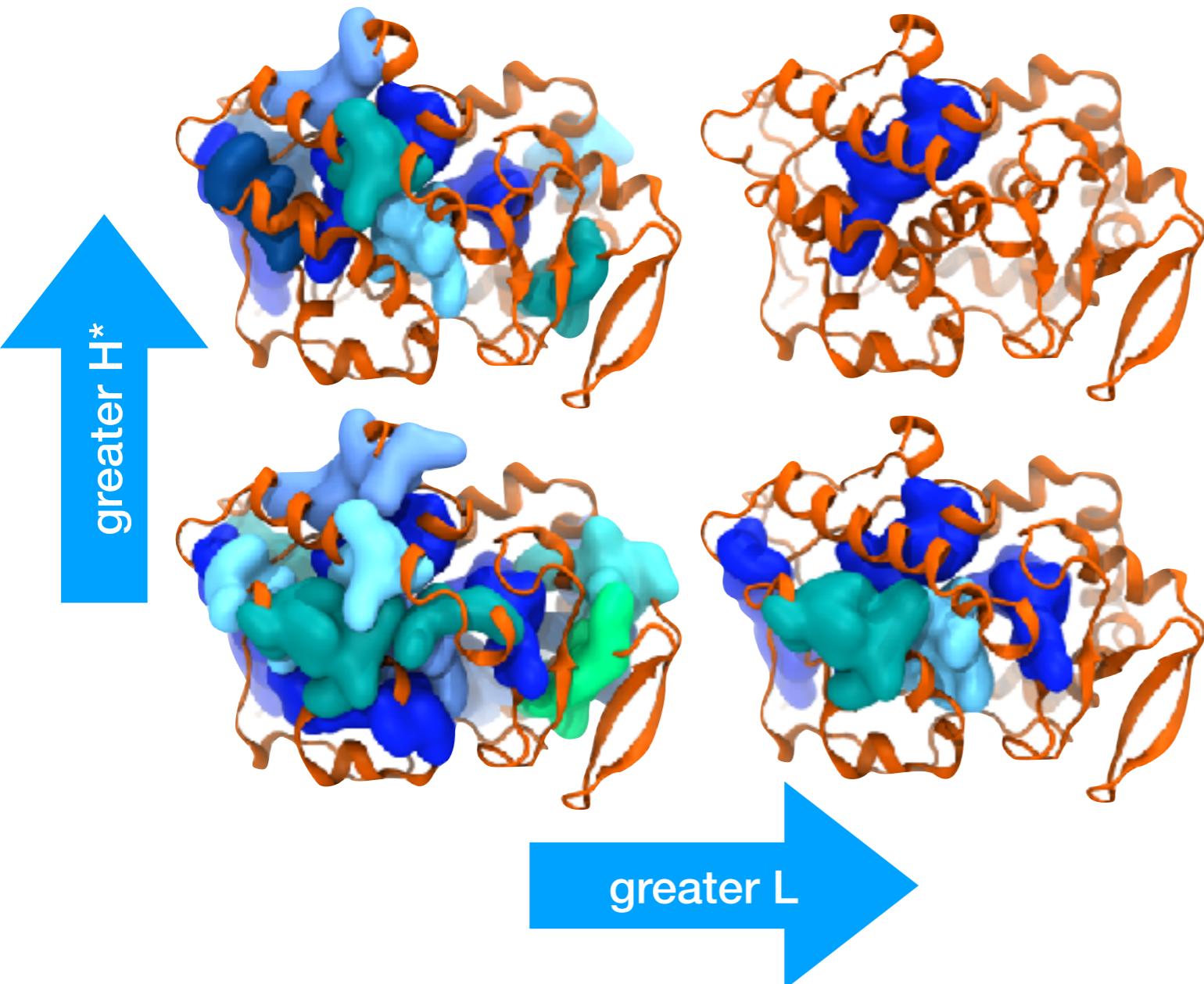


Connor
Pitman

Dr. Ruchi
Lohia

Dr. Matthew
Hansen

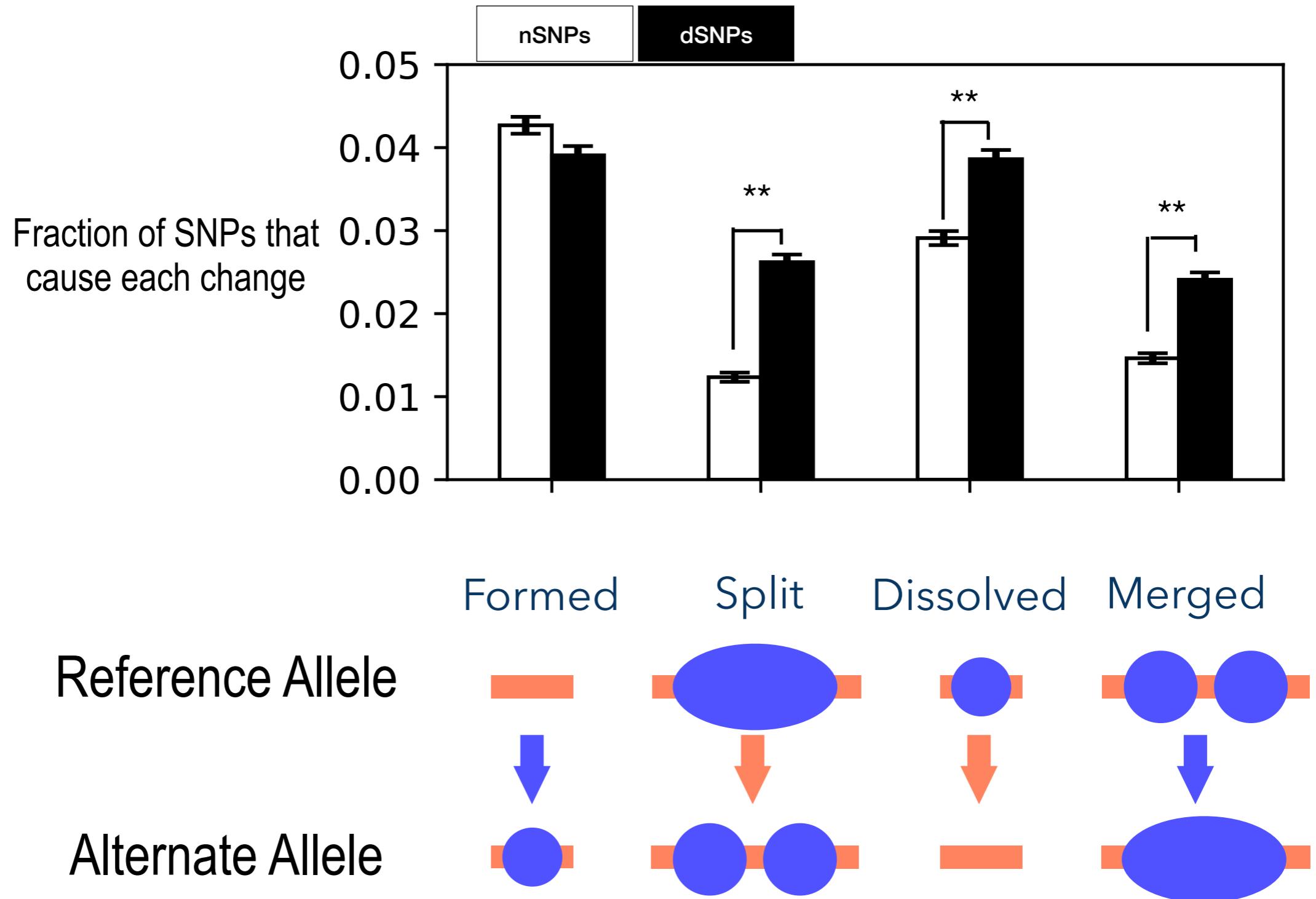
Hypothesis: h-blobs will be more mutation sensitive...



...and the more hydrophobic the blob, the more sensitive it will be

Approach: test for h-blob enrichment of human disease-associated SNPs

disease-causing mutations change blob topology

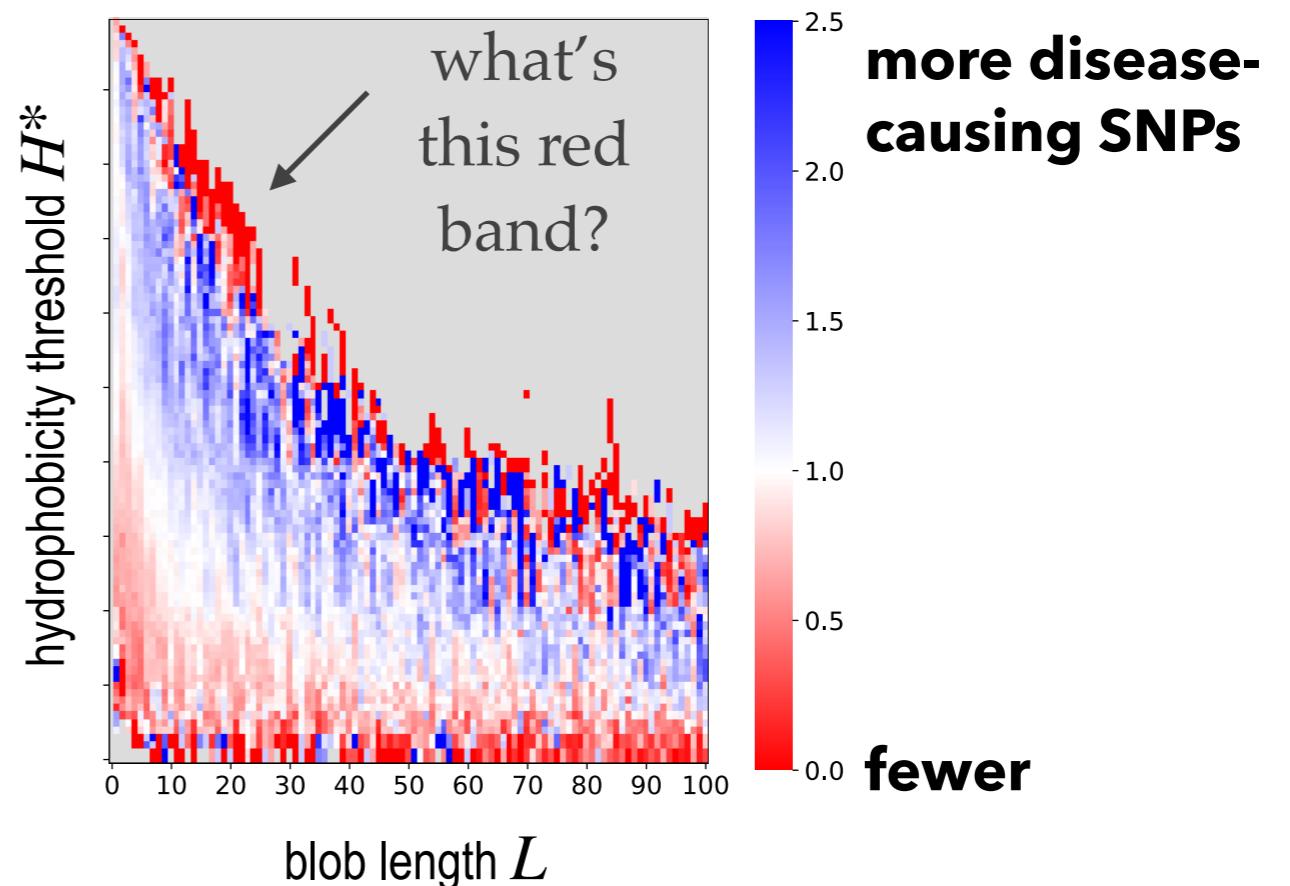


enrichment of disease-associated SNPs (dSNPs)

For any threshold H^* , how many disease-causing mutations are in h-blobs of length L ? How many non disease-causing mutations?

Calculated L for ~70K missense variants (UniProtKB)

- 57% "likely benign or benign" (nSNPs)
- 43% "likely pathogenic or pathogenic" (dSNPs)



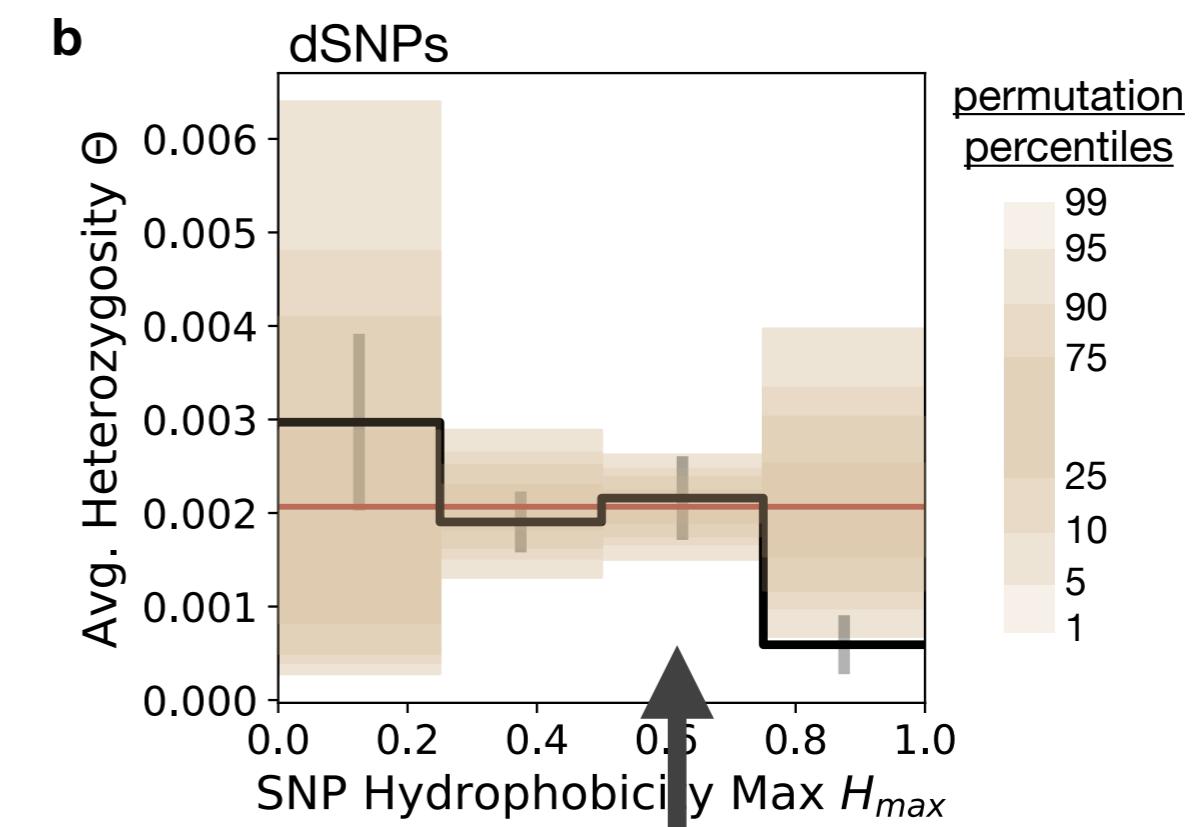
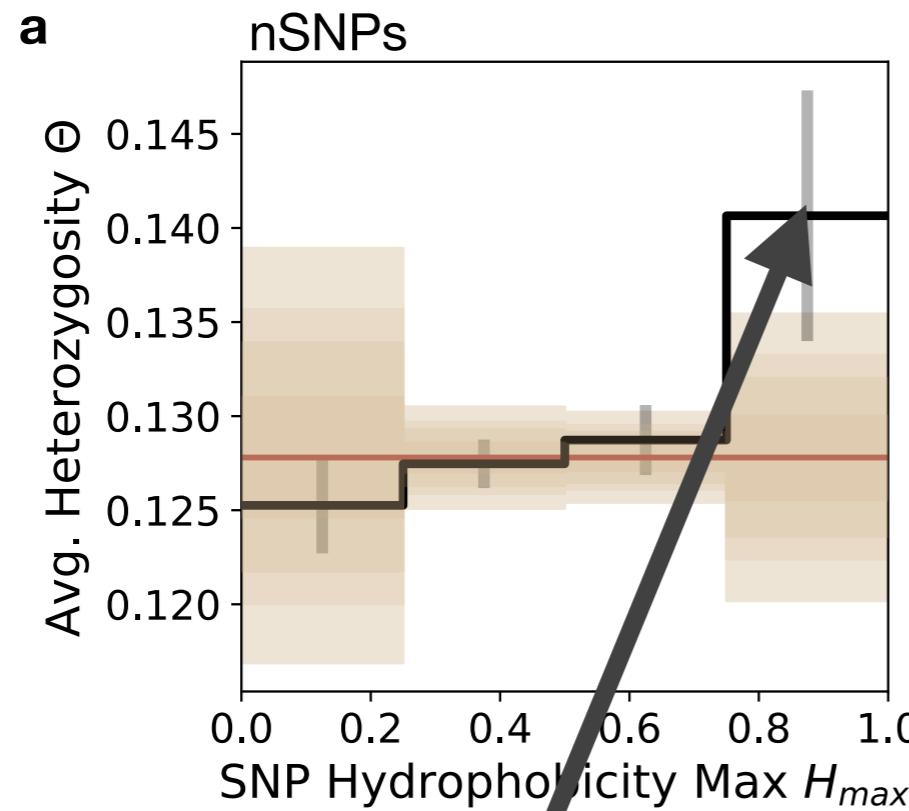
mutations in very long **or** very hydrophobic blobs: most likely to be disease-associated

Why the exception to the trend?

dSNPs/nSNPs plunges for most extreme blobs:

- ✓ Possibility 1: more nSNPs (SNPs are functional, but not deleterious)
- ✓ Possibility 2: fewer dSNPs (so deleterious, they are not observed)

gnomAD : non-Finnish Europeans



ex: olfactory receptors

ex: transporters

Summary

- blobulation yields interesting and useful **trends across the human exome** (not just in one protein)
- results are consistent with h-blobs as **physical interaction nodes**
- resulting odds ratios **could be used as priors** in prediction of causal SNPs
- **evidence for selection** on SNPs in most extreme h-blobs
- SNPs that **split h-blobs** are 3 times as likely to be **disease-associated**
- blobulation GUI at **blobulator.branniganlab.org**

SAFEP protocol, tutorial, tools

Computing Absolute Binding Affinities by Streamlined Alchemical Free Energy Perturbation (SAFEP)

Ezry Santiago-McRae^{1†}, Mina Ebrahimi^{2,3,4‡}, Jesse W. Sandberg¹, Grace Brannigan^{1,5‡}, Jérôme Hénin^{3,4‡}

In press at LiveCOMS, available now at Bioarxiv!

"I commend the authors on the clarity of the protocol and ease with which it can be followed" - Reviewer 1

Density threshold affinity

The Journal of Chemical Physics

ARTICLE

scitation.org/journal/jcp

Spontaneous lipid binding to the nicotinic acetylcholine receptor in a native membrane

Citation: J. Chem. Phys. 154, 185102 (2021); doi: 10.1063/5.0046313
Submitted: 2 February 2021 • Accepted: 18 April 2021 • Published Online: 13 May 2021

Liam Sharp¹ and Grace Brannigan^{1,2*}



New implementation coming soon to *nougat*; Until then I suggest coding yourself, it's straightforward!

Resources...

SAFEP applied to lipids

JCTC
Journal of Chemical Theory and Computation
© 01 Mar 2018, 14, 1850–1873

A Streamlined, General Approach for Computing Ligand Binding Free Energies and Its Application to GPCR-Bound Cholesterol
Reza Salari,^{1,2} Thomas Joseph,^{1,3} Ruchi Lohia,¹ Jérôme Hénin,^{1,4} and Grace Brannigan^{1,2*}

nature communications

Article
<https://doi.org/10.1038/s41467-022-04863-6>
Open-channel structure of a pentameric ligand-gated ion channel reveals a mechanism of leaflet-specific phospholipid modulation

Received: 21 June 2022

Accepted: 8 November 2022

Published online: 17 November 2022

Check for updates

John T. Petroff II¹, Noah M. Dietzen¹, Ezry Santiago-McRae², Brett Deng¹, Maya S. Washington¹, Lawrence J. Chen¹, K. Trent Moreland¹, Zengqian Deng^{1,4}, Michael Rau^{1,5}, James A. J. Fitzpatrick^{1,6,7}, Peng Yuan^{1,8}, Thomas T. Joseph^{1,9}, Jérôme Hénin^{1,9}, Grace Brannigan^{1,2,*} & Maryland W. L. Cheng^{1,10}

Expensive IDP trajectory (deposited)

200 μ s of 91 residue IDP MD, atomistic resolution, explicit solvent, expt validation, forcefield comparison, temperature REMD



RESEARCH ARTICLE
Sequence specificity despite intrinsic disorder: How a disease-associated Val/Met polymorphism rearranges tertiary interactions in a long disordered protein

Ruchi Lohia¹, Reza Salari^{1*}, Grace Brannigan^{1,2*}

blobulation GUI & references

branniganlab.org/blobulator

Bonus: biophysicist-friendly viewer for known pathogenic mutations in any human protein!

This and other talks

github.com/BranniganLab/Communications

Acknowledgments

From the Lab (past & present)

Ezry St. Iago-McRae

Connor Pitman

Jesse Sandberg

Liam Sharp (Fairfield University)

Ruchi Lohia (Cold Spring Harbor)

Reza Salari (Washington University - St Louis)



XSEDE
Extreme Science and Engineering
Discovery Environment



Collaborators

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Matthew Hansen (University of Pennsylvania)

Thomas Joseph (University of Pennsylvania)

Wayland Cheng and Lab
(Washington University - St. Louis)