

Connor Pitman¹, Ezry Santiago-McRae¹, Ruchi Lohia, Kaitlin Bassi, Matthew E.B. Hansen², Thomas T. Joseph³, and Grace Brannigan^{1,4}

¹Center for Computational and Integrative Biology, Rutgers–Camden, NJ, 08102, USA ²Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA ³Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, PA, 19104, USA
⁴Department of Physics, Rutgers–Camden, NJ, 80102, USA

Background

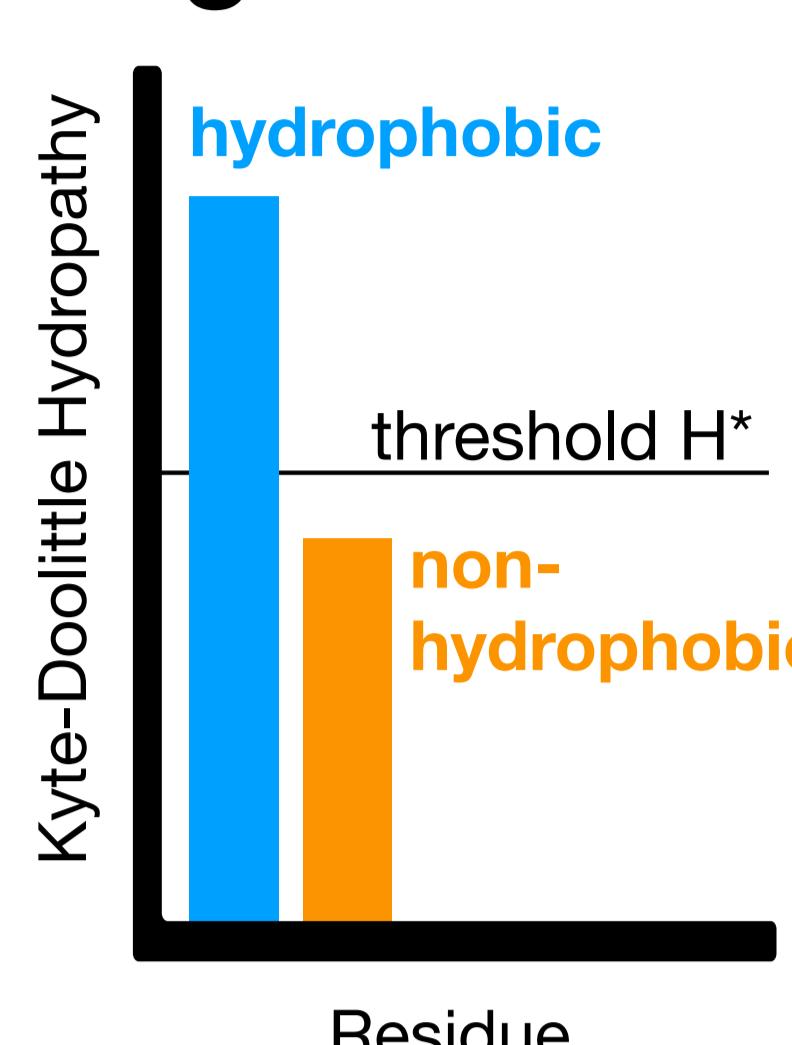
- Hydrophobic interactions are critical for protein structure
- Contiguous hydrophobic residues act cooperatively to create stable globular regions
- This is true even in disordered proteins and amphipathic polymers
- Many mutation prediction methods incorporate an arbitrarily defined local sequence
- Blobulation adaptively determines local sequence by clustering residues based on their hydrophobicity
- Blobulation can be used to generate hypotheses about the functional effects of mutations, including human disease-causing mutations [1]
- The Blobulator is an interactive GUI for Blobulation

Vision Statement:

Provide researchers with an interactive and intuitive interface to detect intrinsic modularity in any protein sequence based on hydrophobicity

Algorithm

Digitization



Clustering

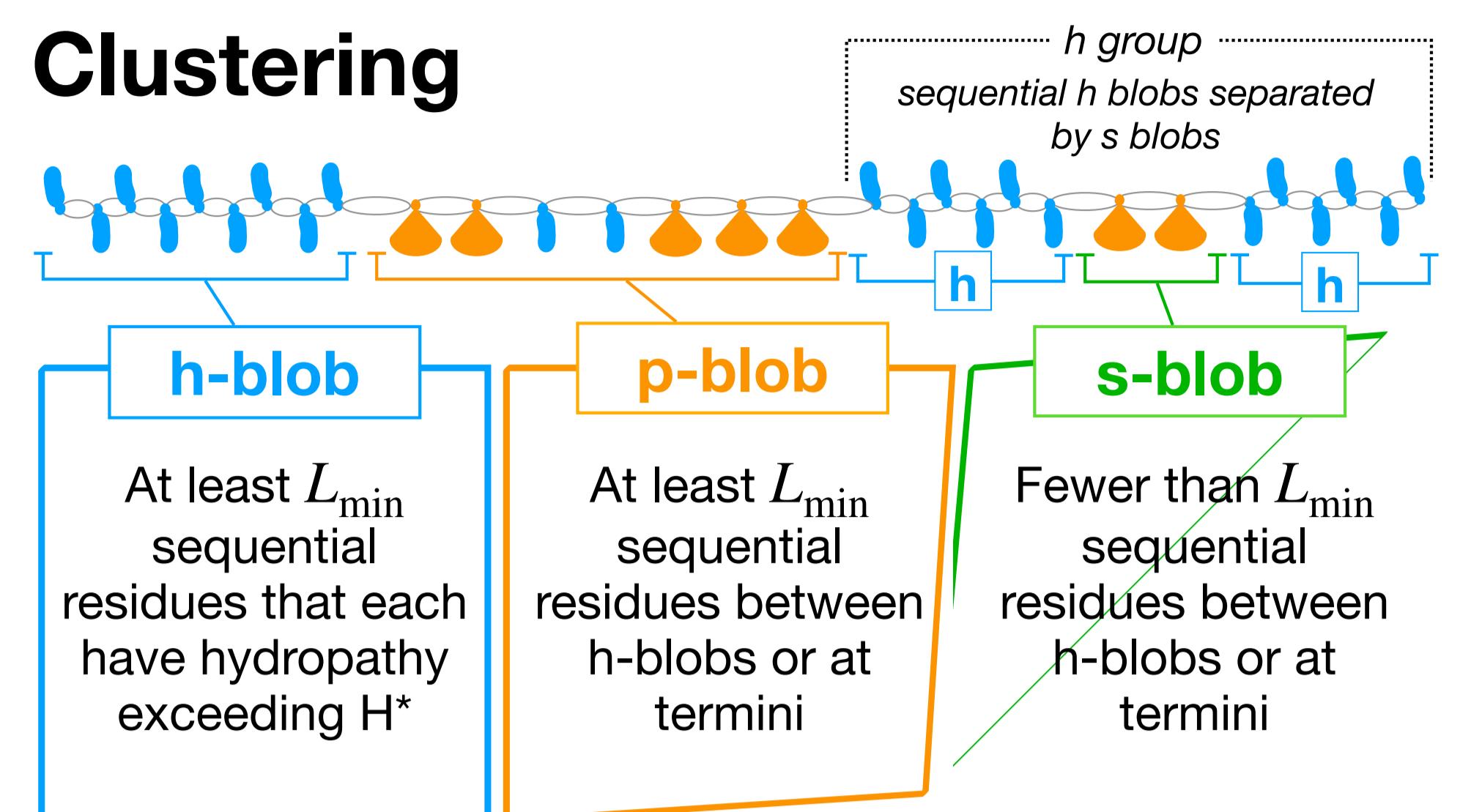
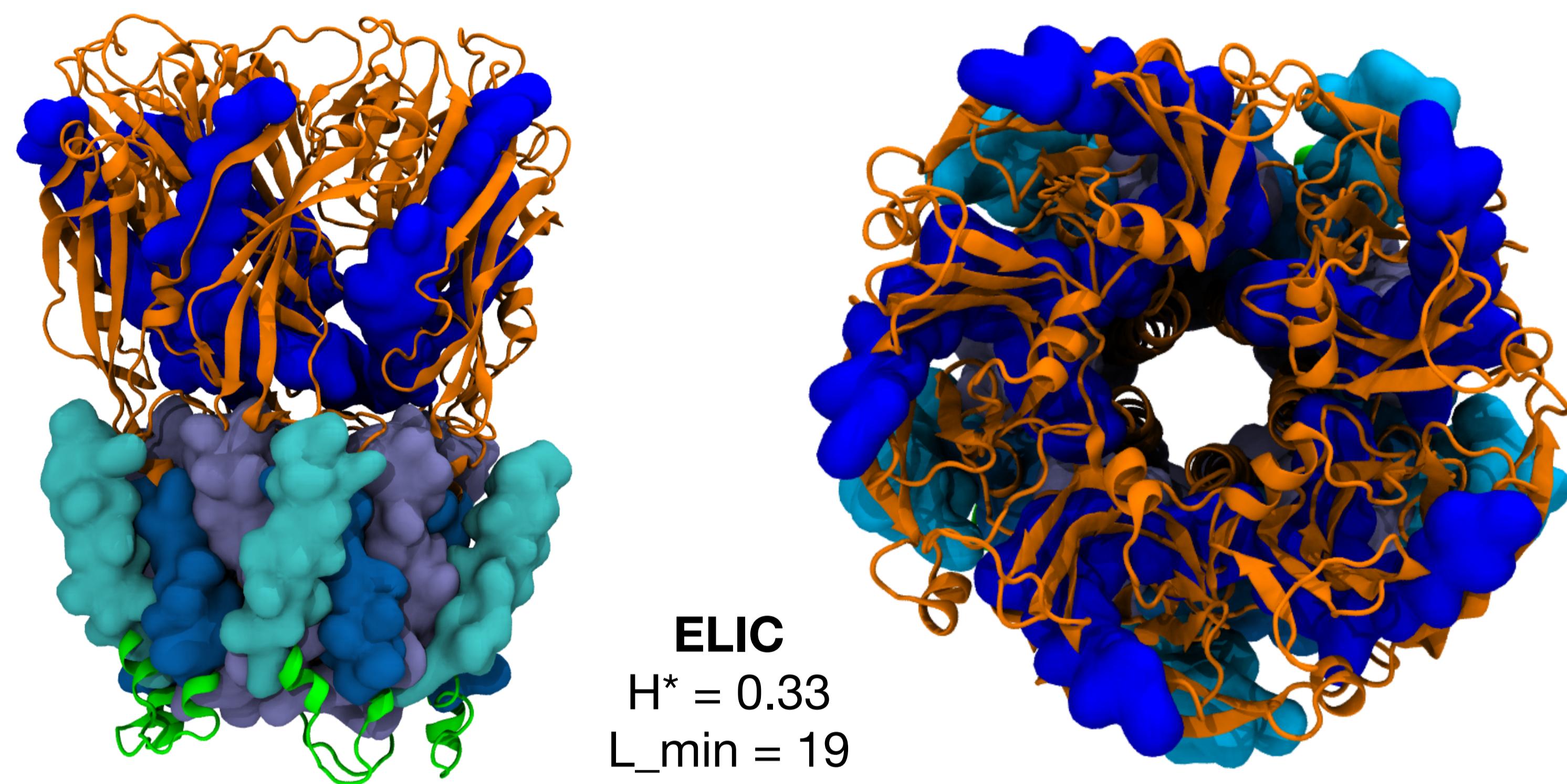


Figure 1: Blobulation, our sequence-based algorithm for identifying contiguous hydrophobic regions, involves two steps: digitization (left), which classifies individual residues as either hydrophobic or hydrophilic based on a cutoff H^* ; and identification of clusters (right) at least L_{\min} residues long. “H,” “P,” and “S” refer to “hydrophobic,” “polar,” and “short” blobs, respectively. Figure adapted from [1].



Alpha-Synuclein
 $H^* = 0.4$
 $L_{\min} = 4$

Lysozyme
 $H^* = 0.5$
 $L_{\min} = 8$

Figure 2: Structural representation of blobs from three different protein types: membrane (*Erwinia* ligand-gated ion channel, ELIC), intrinsically disordered (alpha-synuclein), and soluble enzyme (lysozyme). The blobs shown here were detected using parameters aimed at detecting different types of residue clusters

Hydrophobic Blobs Simplify Analysis of Intrinsically Disordered Protein Simulations

- Residue-residue interactions from intrinsically disordered protein simulations were too noisy [2]
- Blob-level contacts are less noisy and reveal patterns of tertiary contacts

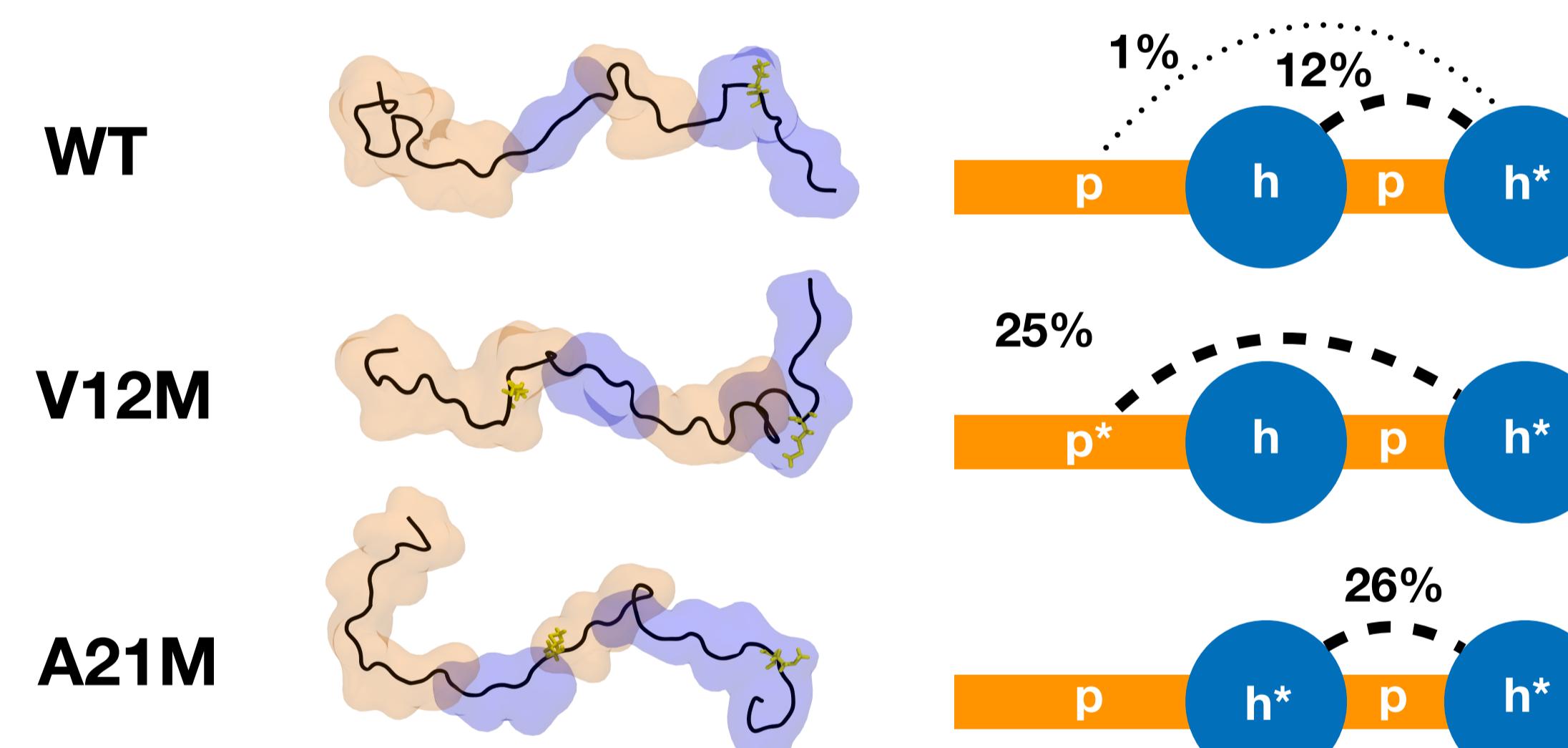
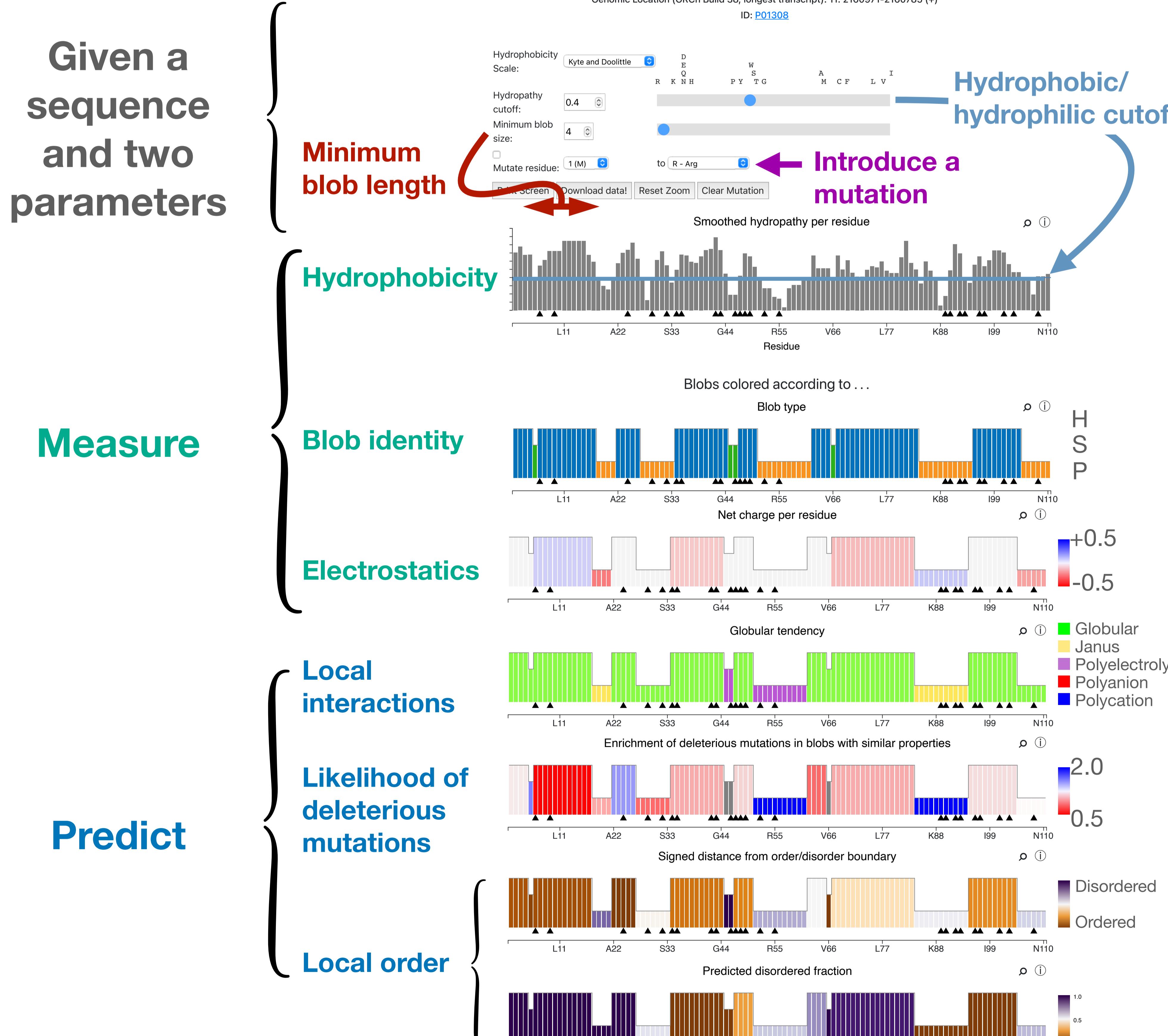


Figure 3: Contacts between blobs in amyloid beta. Dashed lines represent the percentage of frames where blobs are in contact. An asterisk (*) indicates that there is a methionine in the blob

Graphical User Interface



Blobulate your own protein!

blobulator.branniganlab.org

References

Acknowledgements

- Lohia, R., Hansen, M. E., & Brannigan, G. (2022). Contiguously hydrophobic sequences are functionally significant throughout the human exome. *Proceedings of the National Academy of Sciences*, 119(12). <https://doi.org/10.1073/pnas.2116267119>
- Lohia, R., Salari, R., Brannigan, G. Sequence specificity despite intrinsic disorder: How a disease-associated Val/Met polymorphism rearranges tertiary interactions in a long disordered protein. *PLoS Comput Biol*. 2019 Oct 18;15(10):e1007390. doi: 10.1371/journal.pcbi.1007390. PMID: 31626641; PMCID: PMC6821141.



- Busch Biomedical Foundation
- NRT, NSF DGE 2152059
- NIH 1R35GM134957 & R01AR076241