

Investigating the role of contiguous hydrophobicity and non-aliphatic hydrophobic residues in coevolution

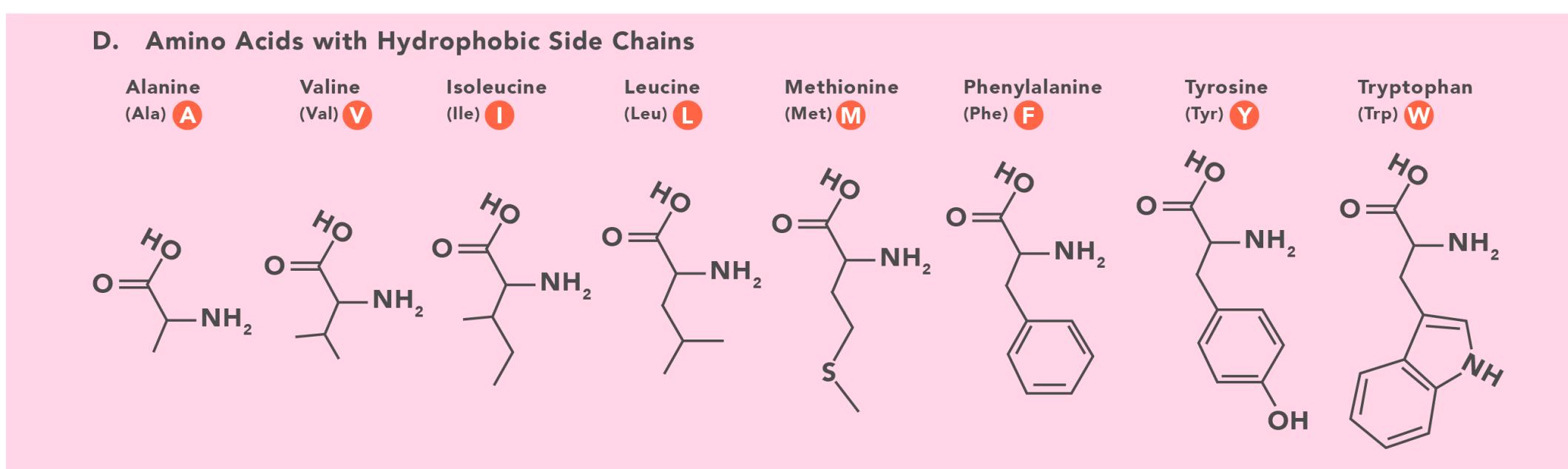
CCIB Spring Seminar

Connor Pitman, March 5th 2024



Water drives contact between hydrophobic molecules

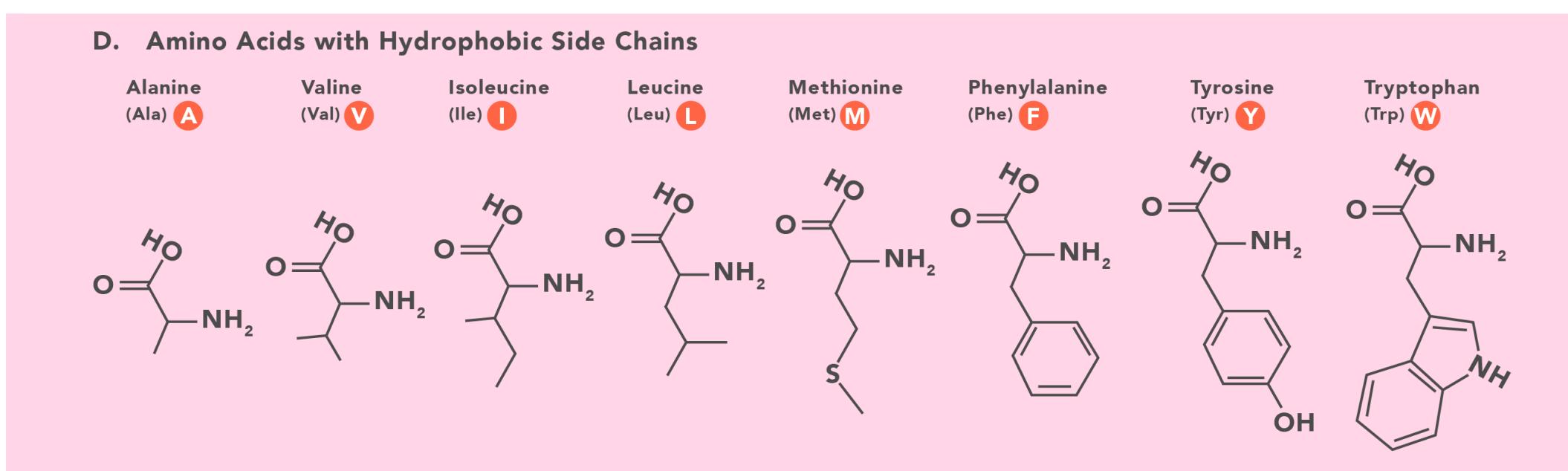
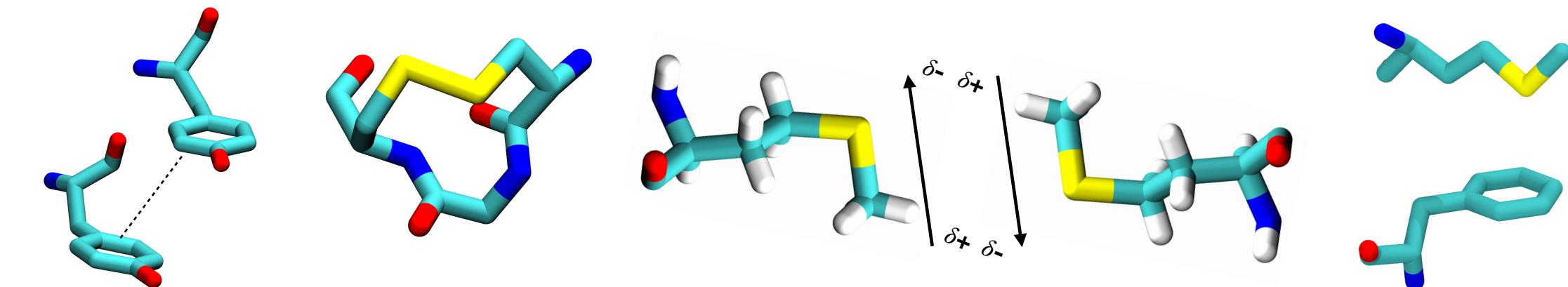
Not all hydrophobic amino acids are the same



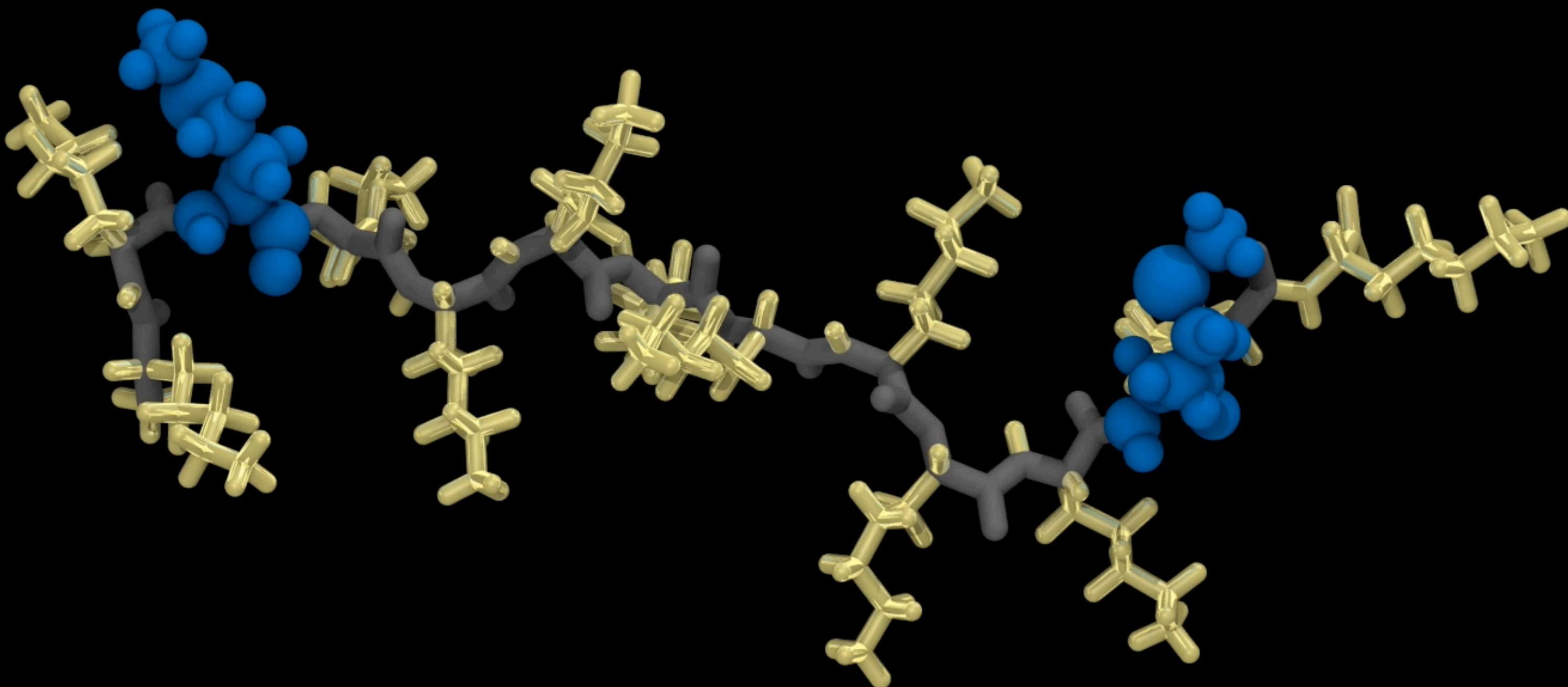
Credit: Technology Networks

Not all hydrophobic amino acids are the same

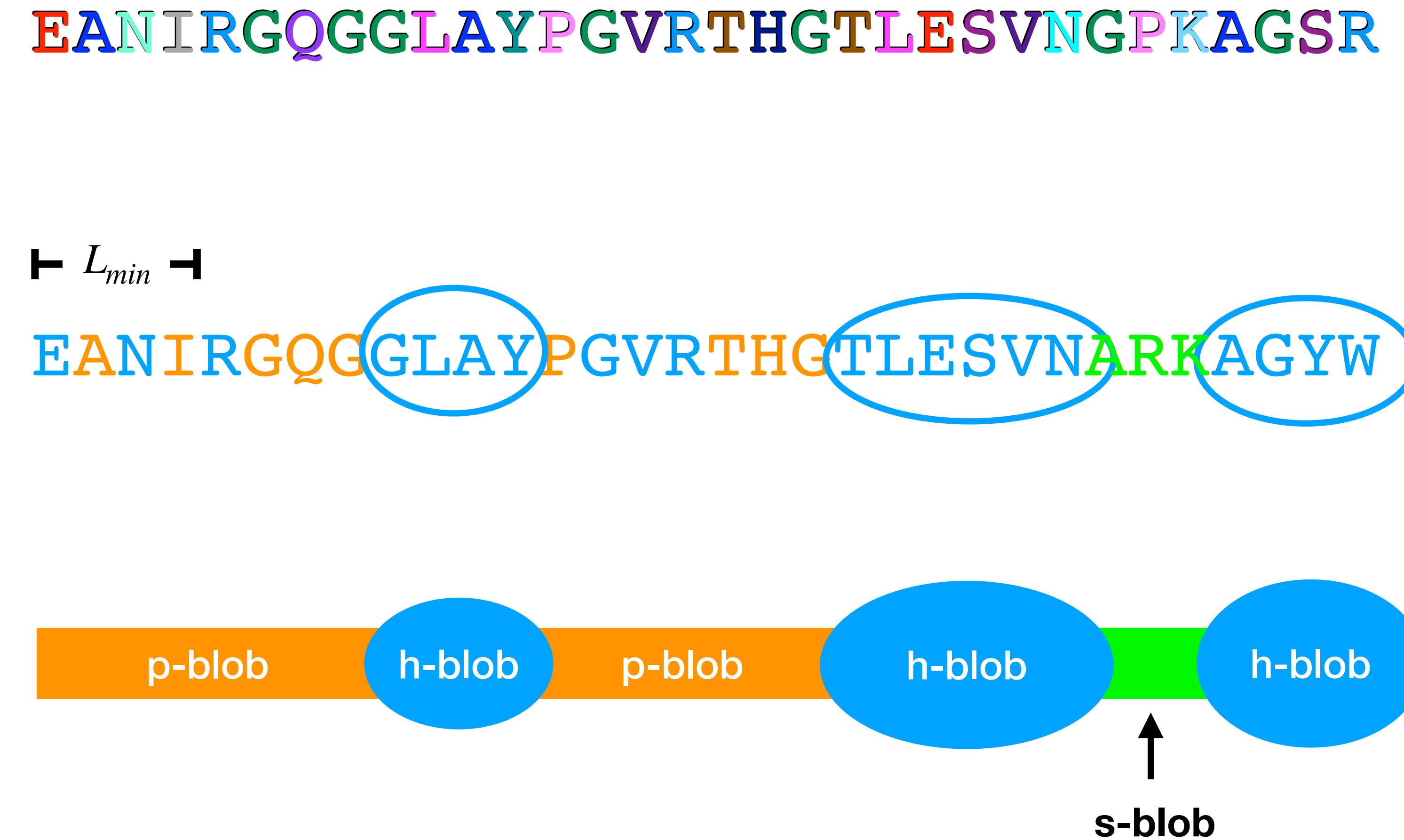
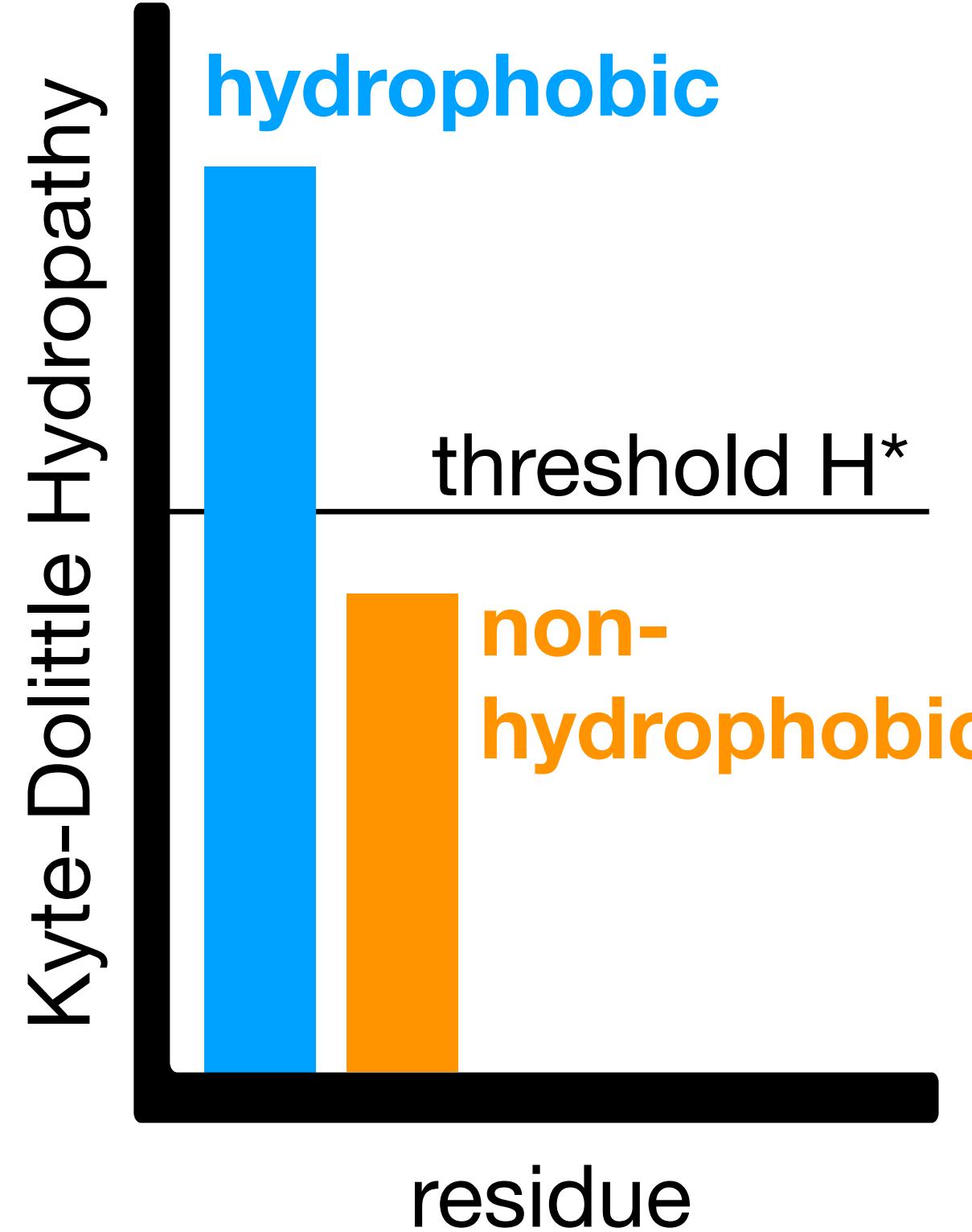
Aliphatic “oily” residues



...but context also matters

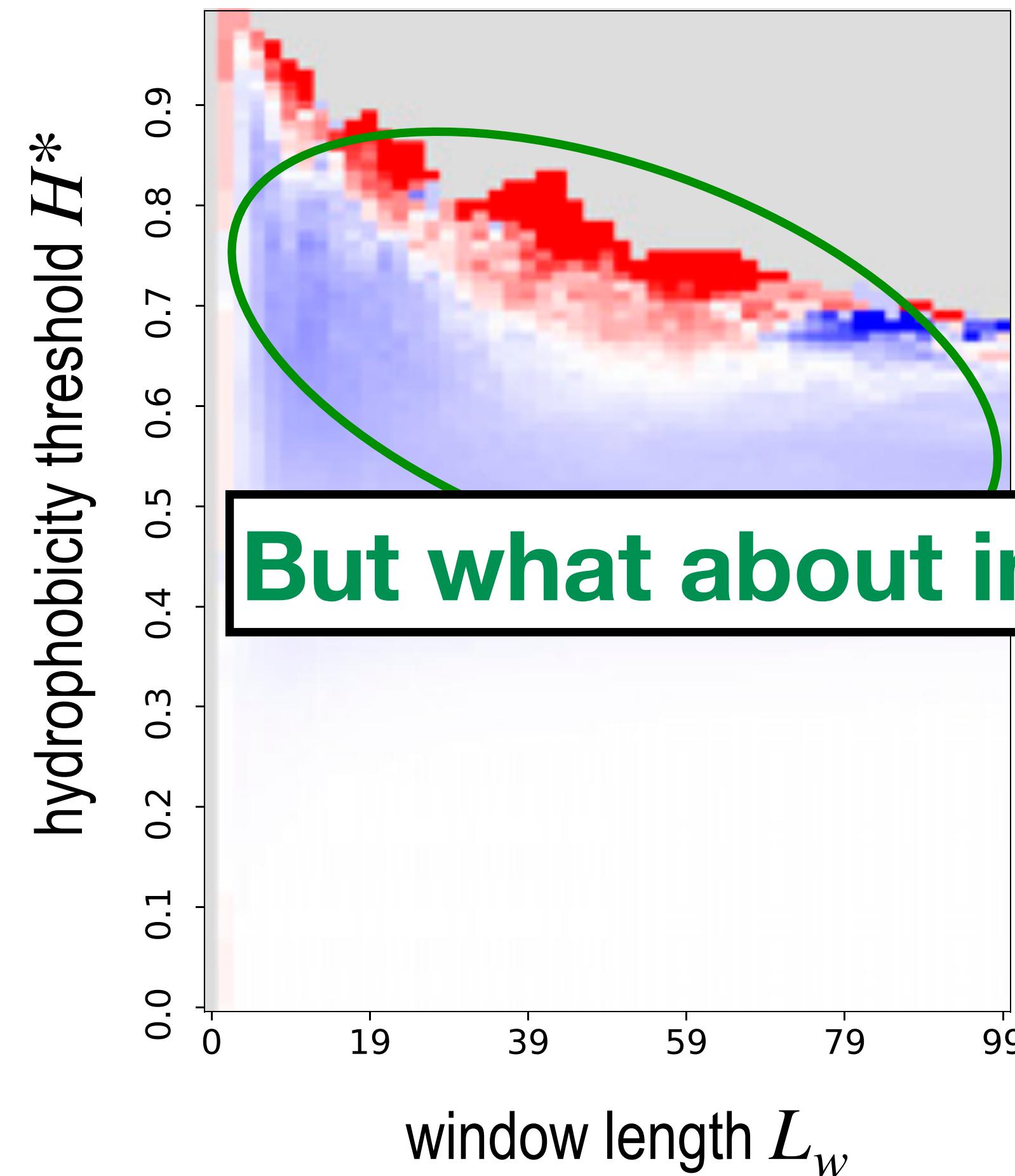


Blobulation: A tool for detecting hydrophobic modularity in protein sequences



Blobulation meaningfully reveals context

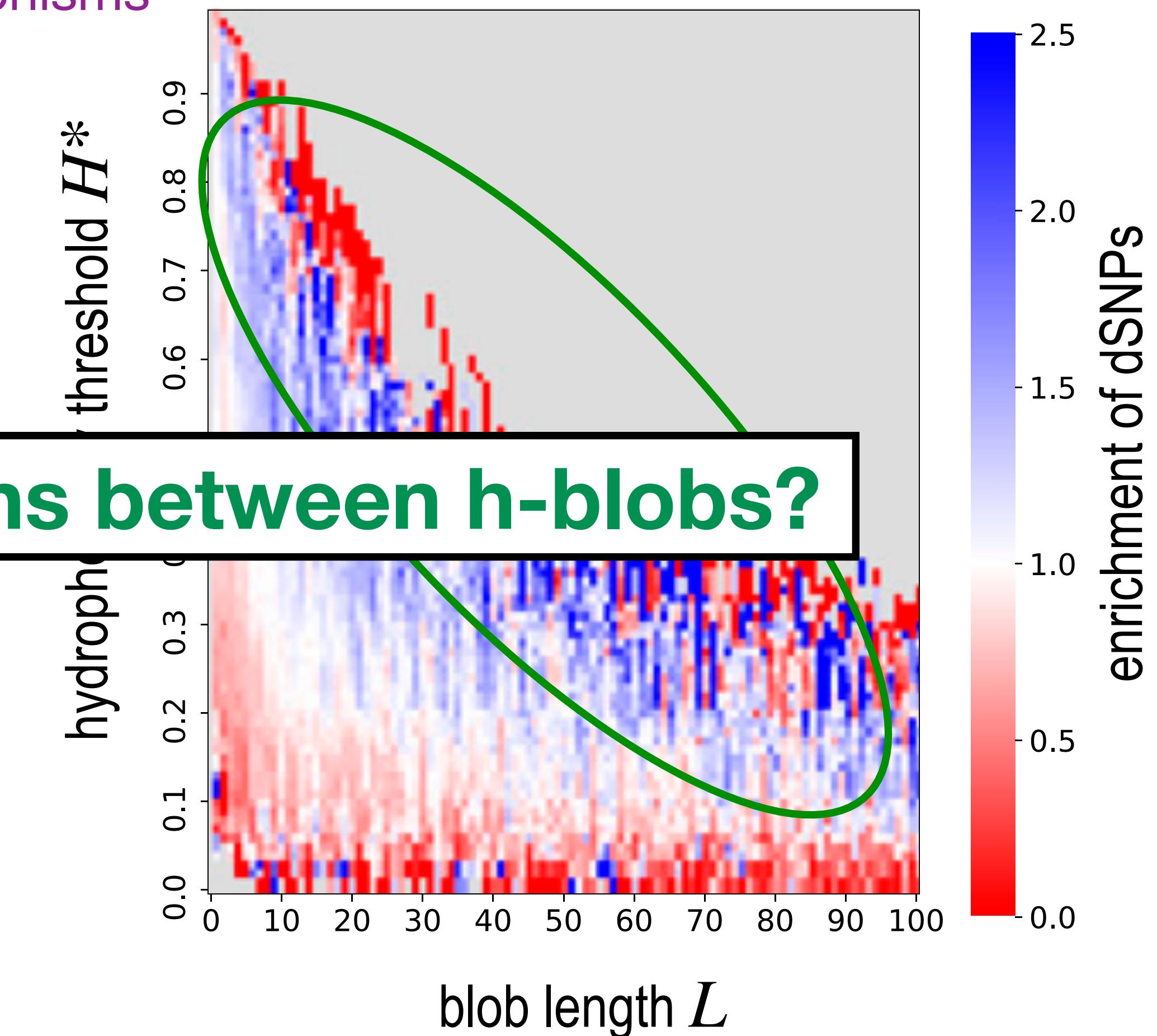
Moving Window



Disease-associated
Single Nucleotide
Polymorphisms

of dSNPs

Blobulation



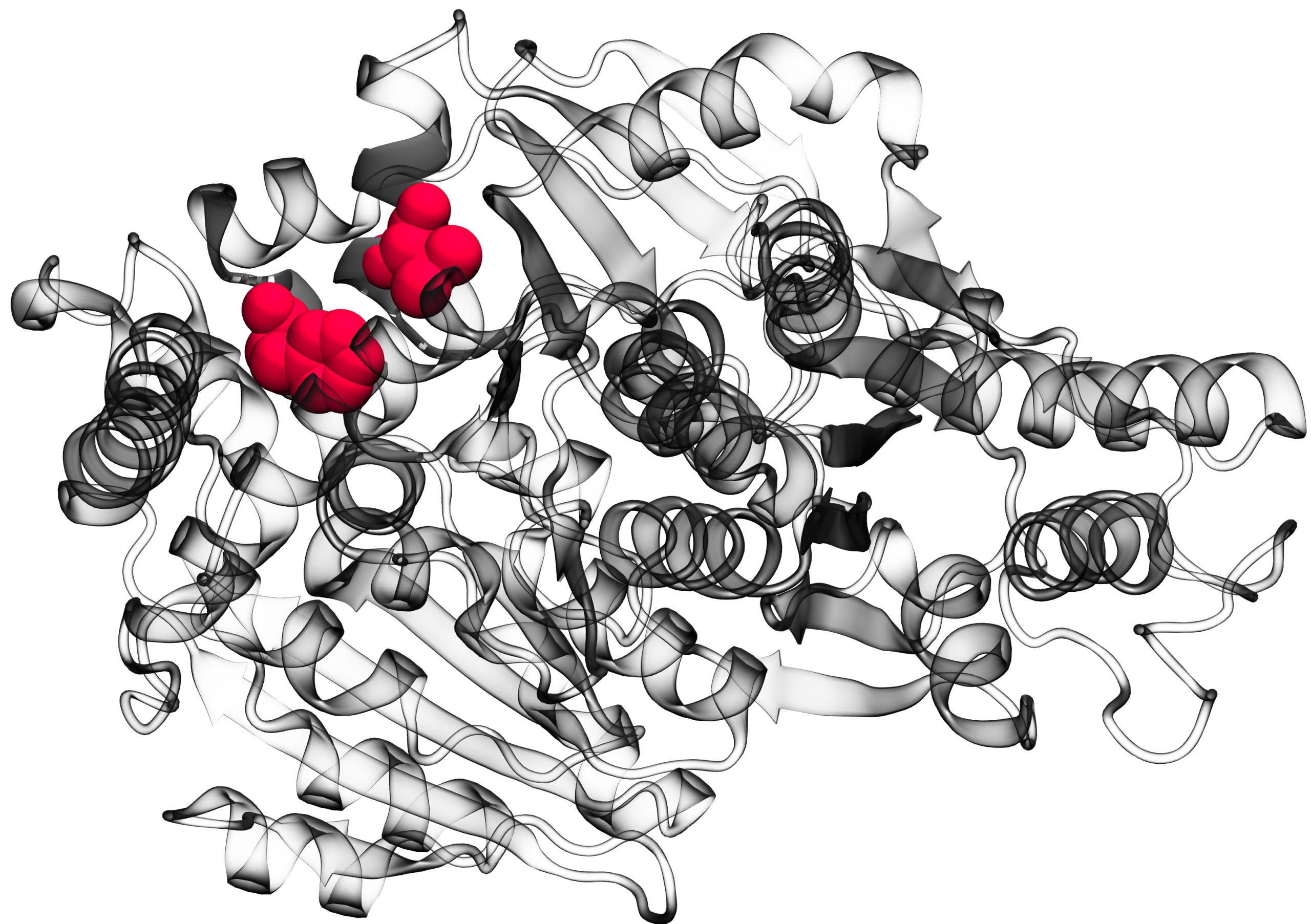
But what about interactions between h-blobs?

Research Questions:

- 1. Are residues in certain blob types more likely to interact with residues in other blob types?**
- 2. Are “specialty” hydrophobic residue pairs more likely to interact than non-specialty interaction residue pairs?**

Approach: Coevolving residues

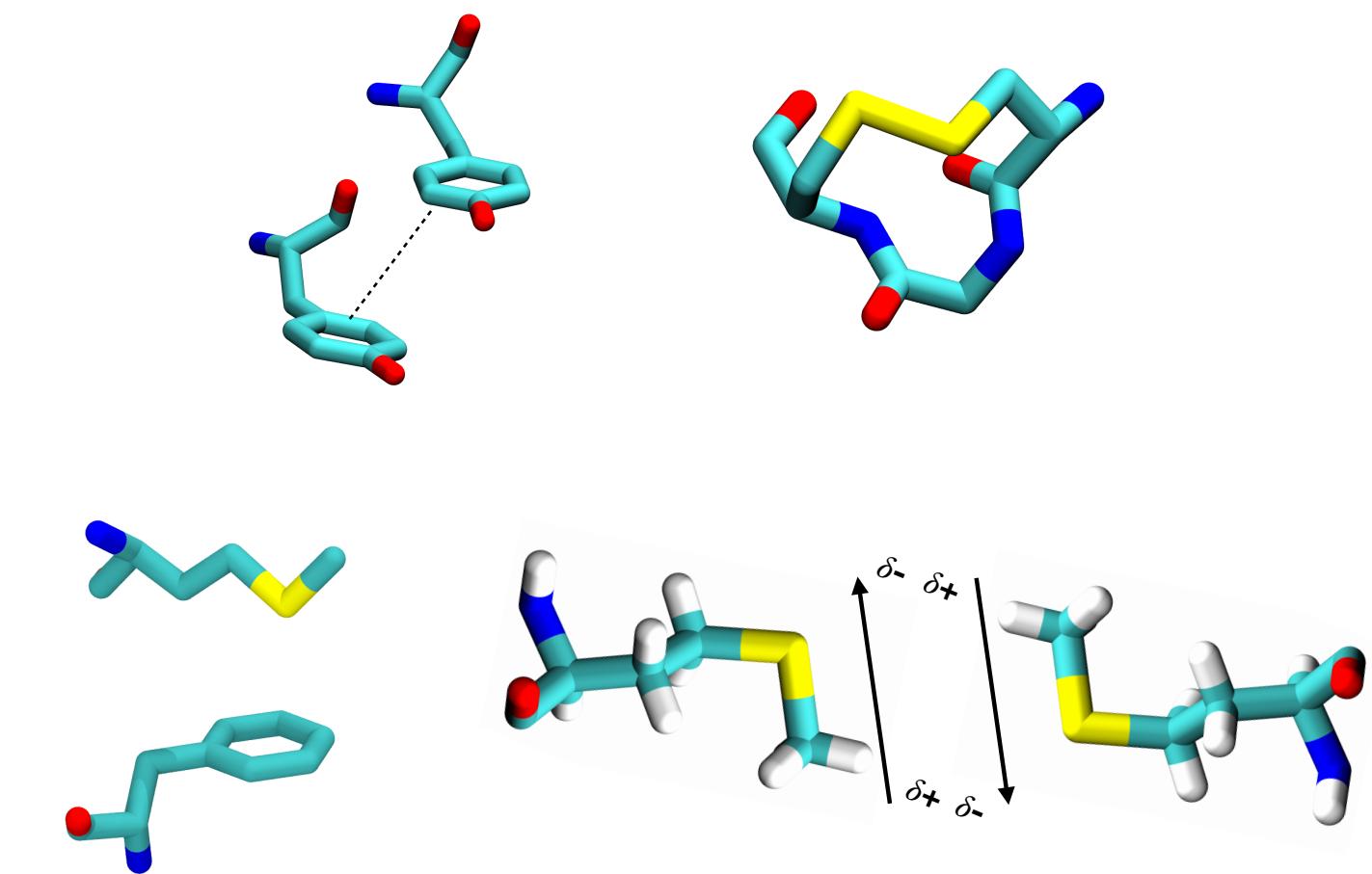
- Represent residue-residue contacts
- Sequence-based method
- For this study: A set of ~250,000 orthologous sequences among ~1,600 protein families in a bacterial proteome
- Software: CoMap



Hypothesis: Residues representing hydrophobic interactions will be enriched for coevolving mutations



Coevolving residue pairs (ex. a, b) tend to be found in h-blobs



Coevolving residues are enriched for specialty interaction pairs

Coevolving residues tend to be found in blobs of the same type

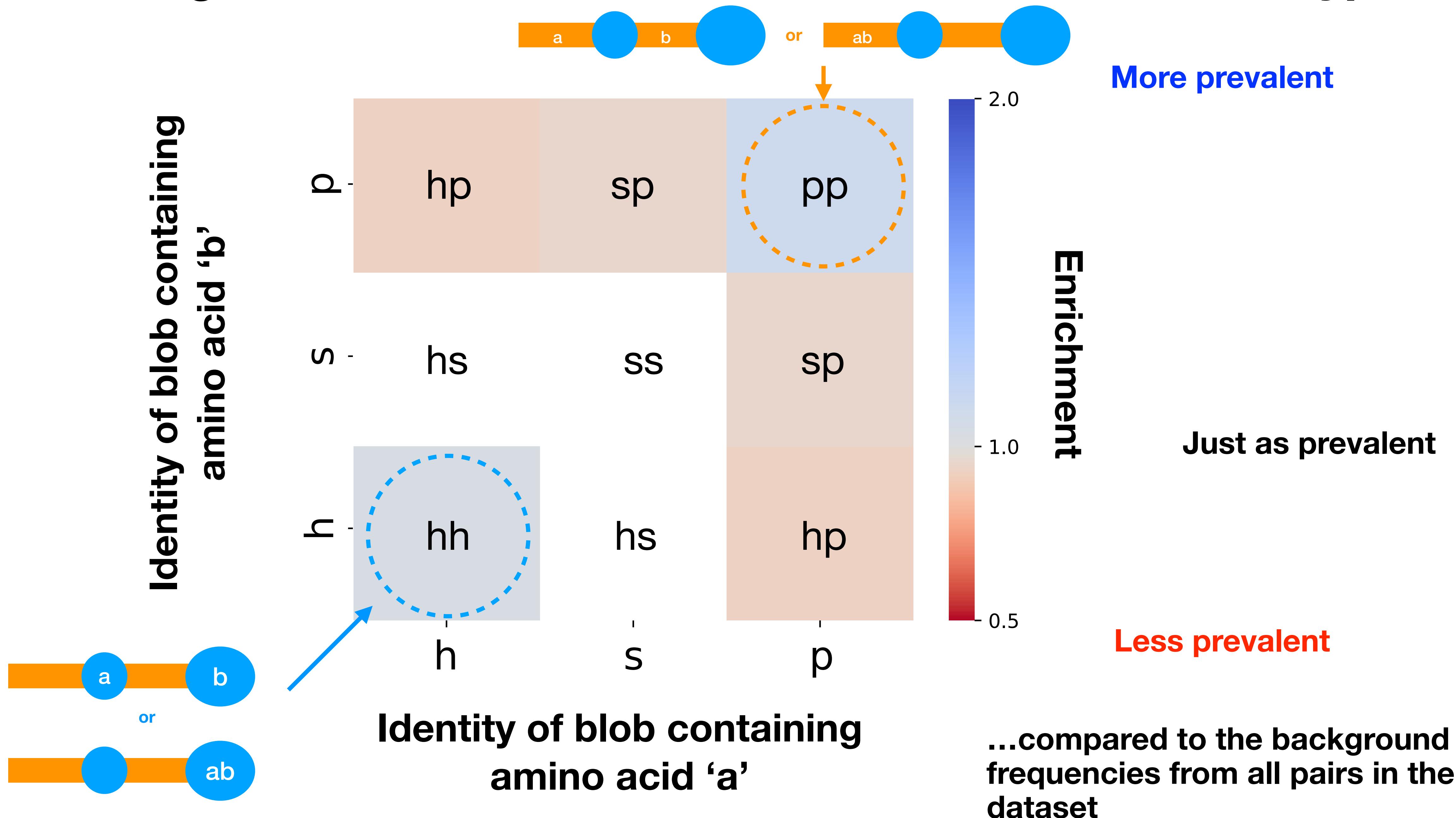
More prevalent

Just as prevalent

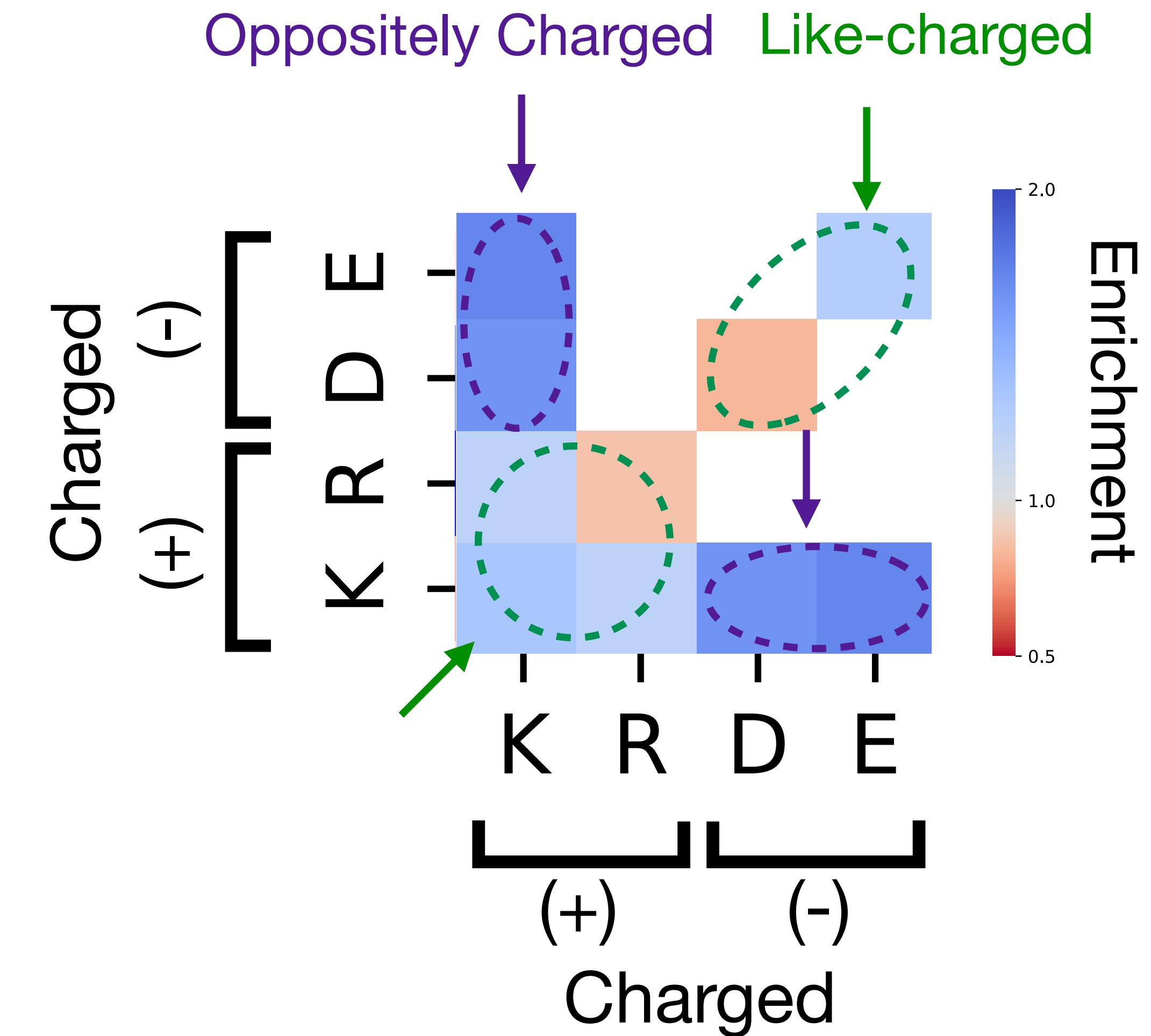
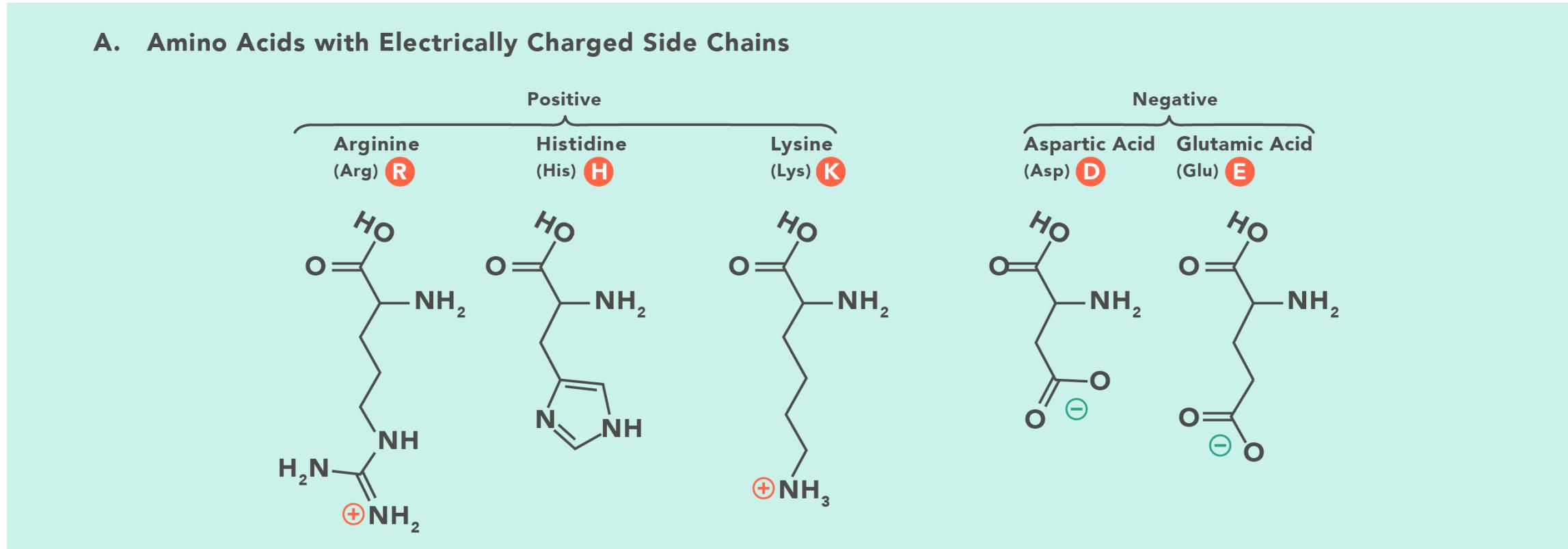
Less prevalent

...compared to the background frequencies from all pairs in the dataset

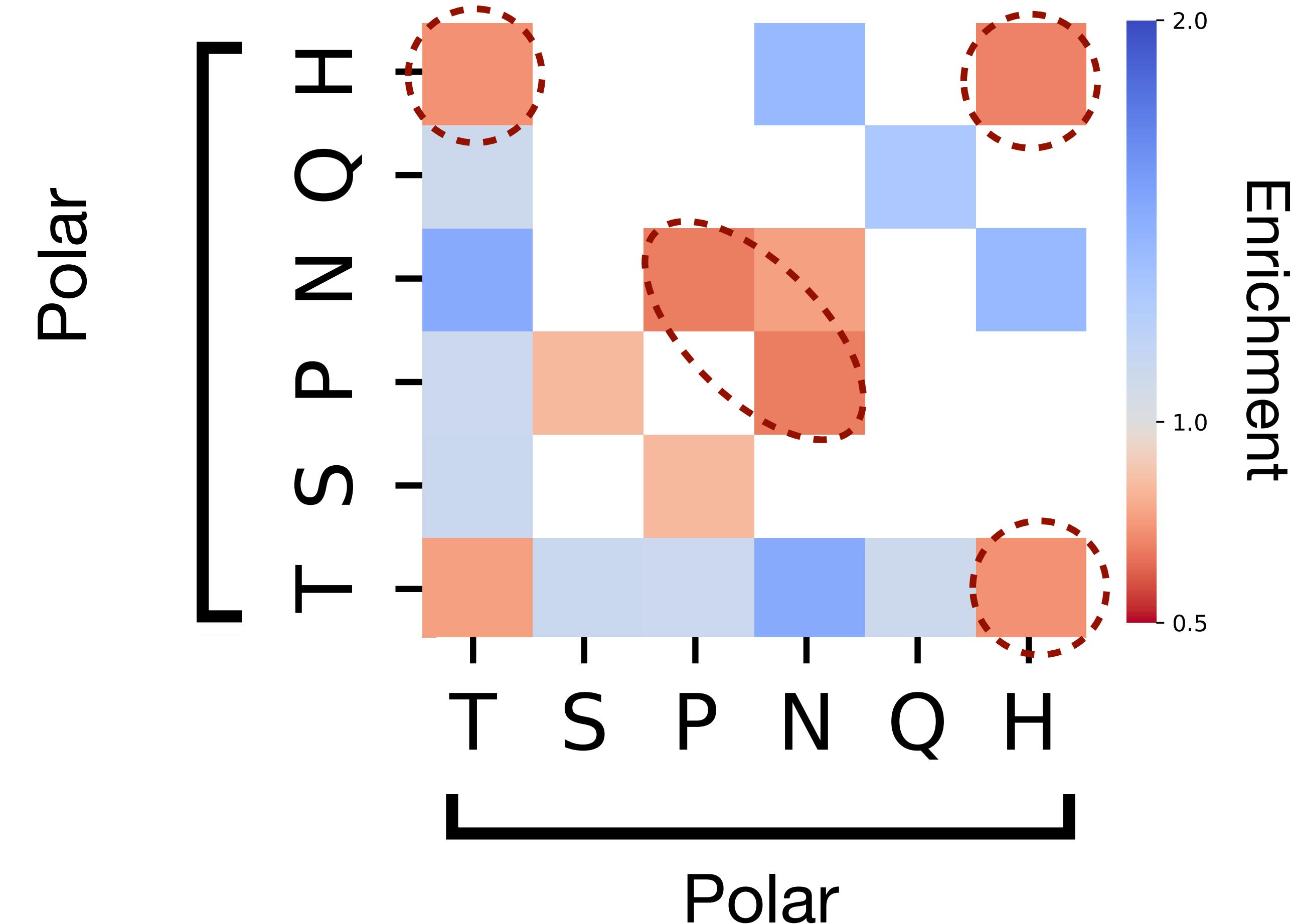
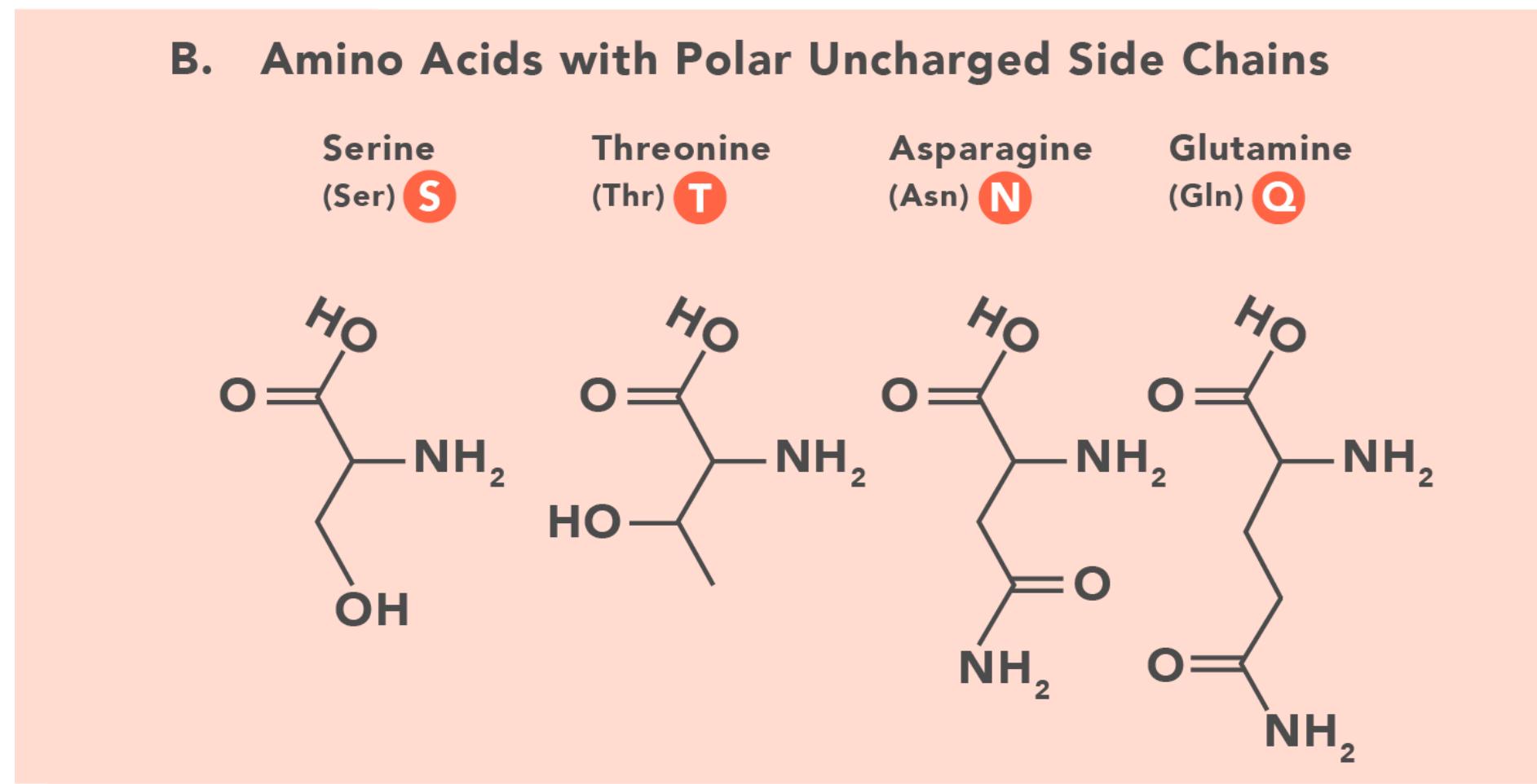
Coevolving residues tend to be found in blobs of the same type



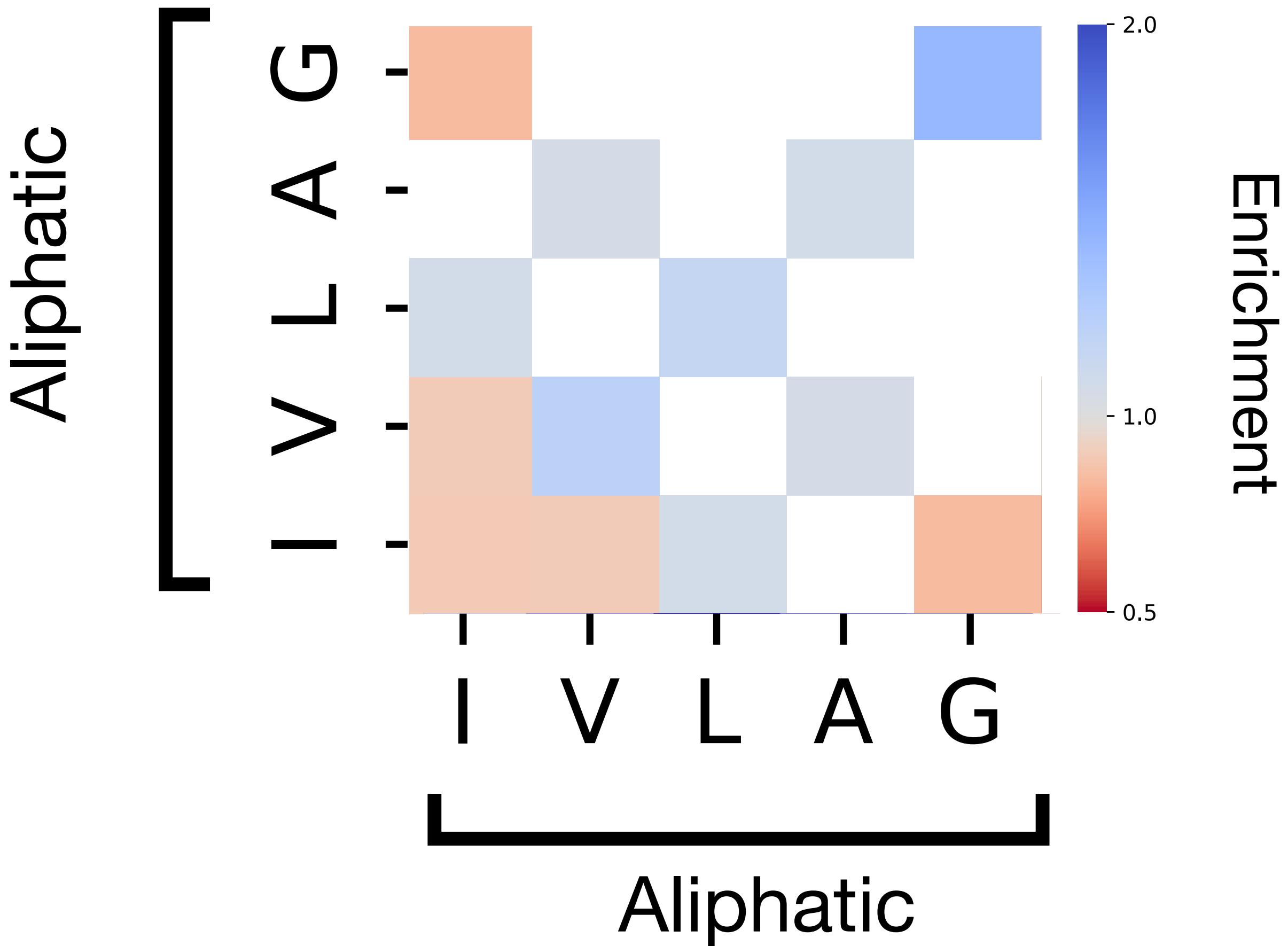
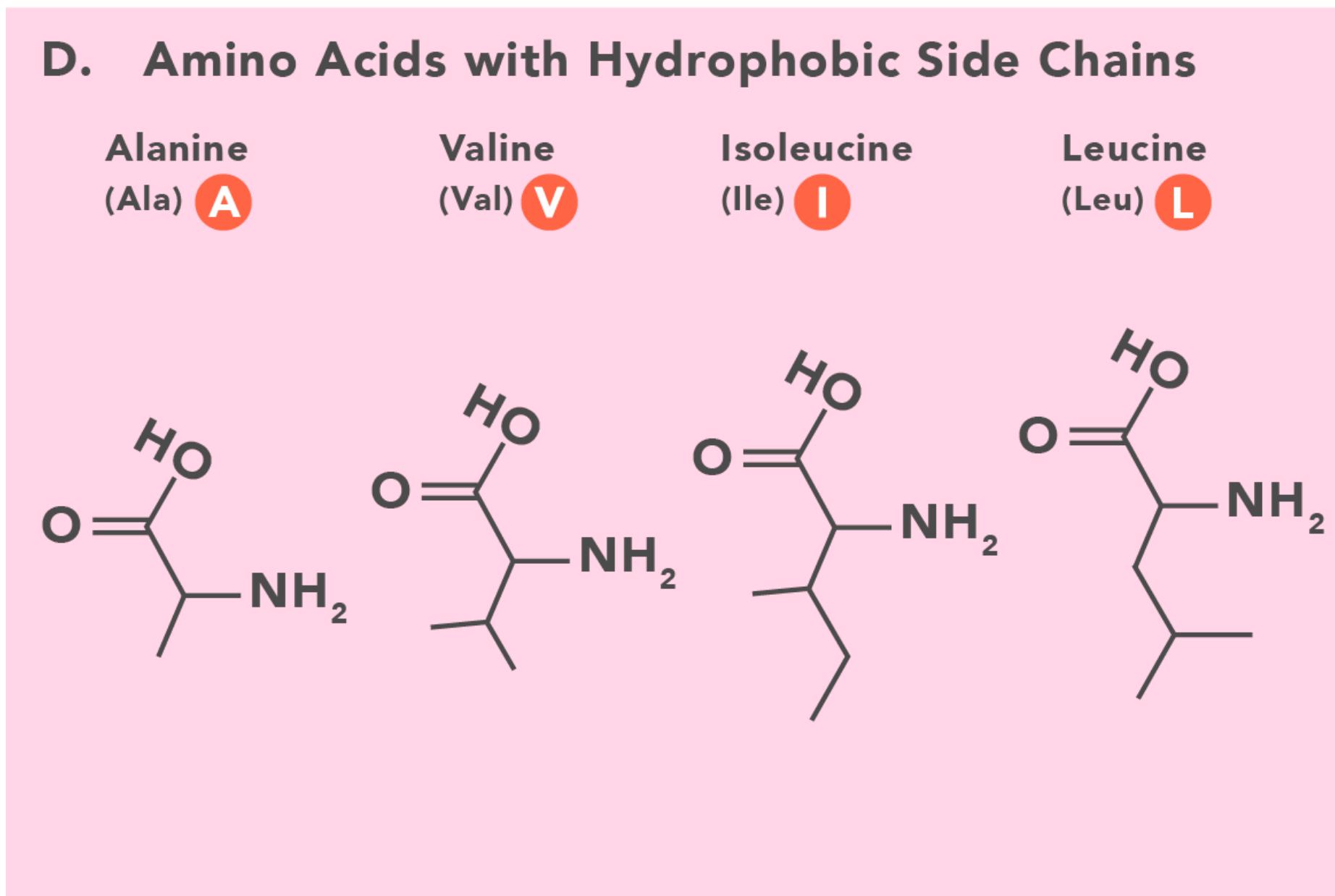
Coevolving residues are enriched for oppositely charged residue pairs



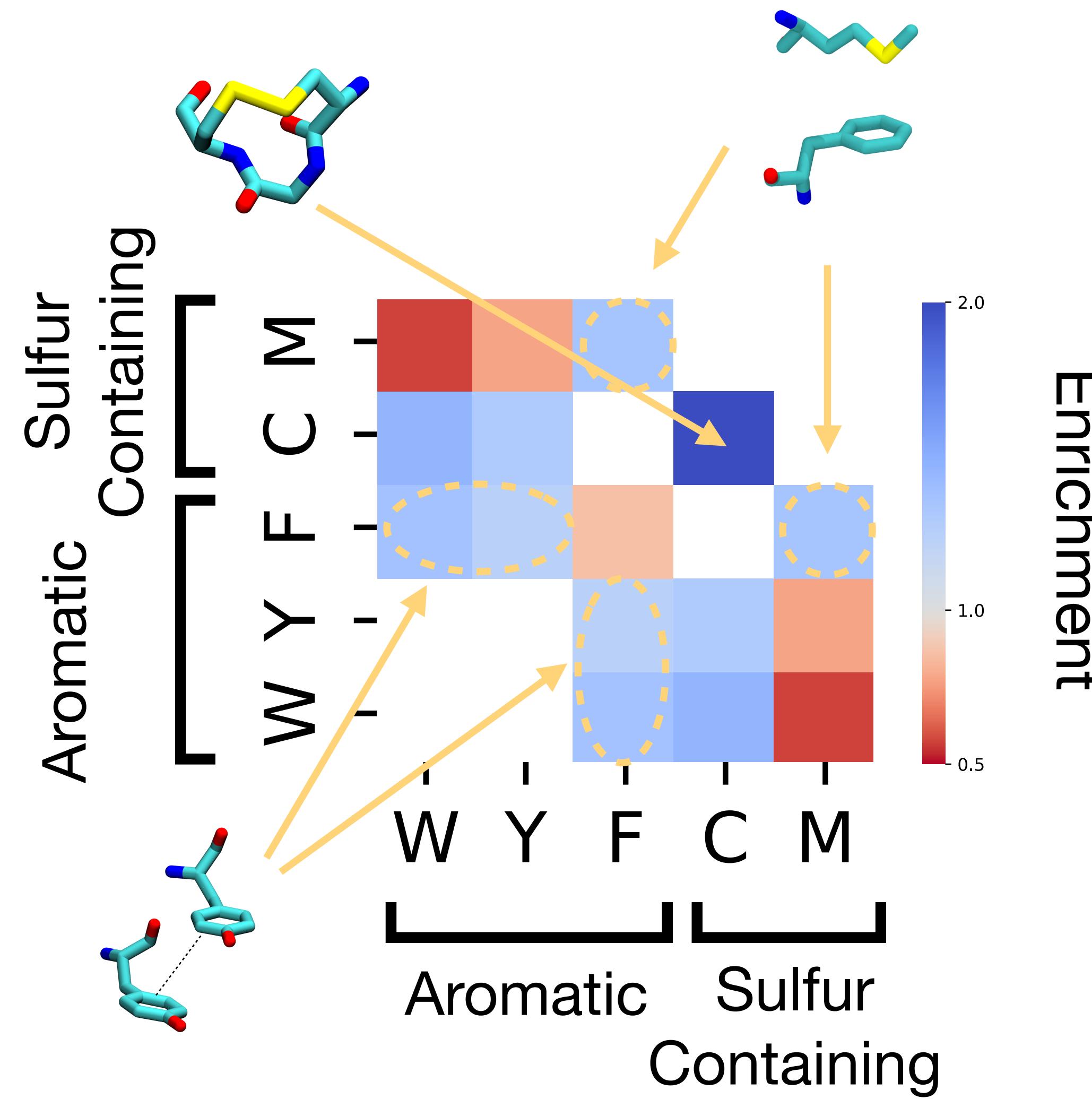
Enrichment of coevolving polar-polar pairs



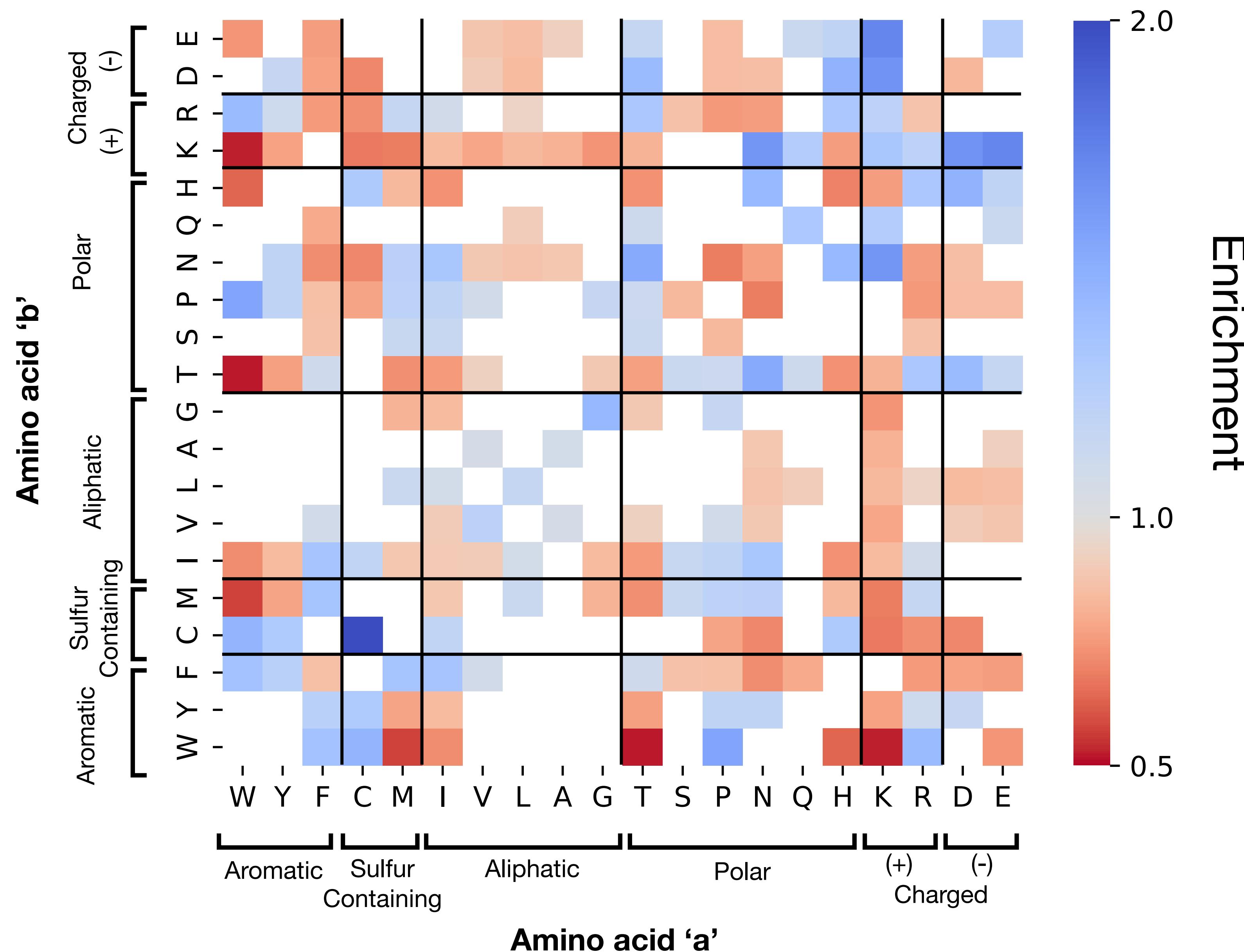
Coevolving pairs are weakly enriched for aliphatic-aliphatic residues



Coevolving residues are enriched for specialty hydrophobic pairs



Other interactions to pursue



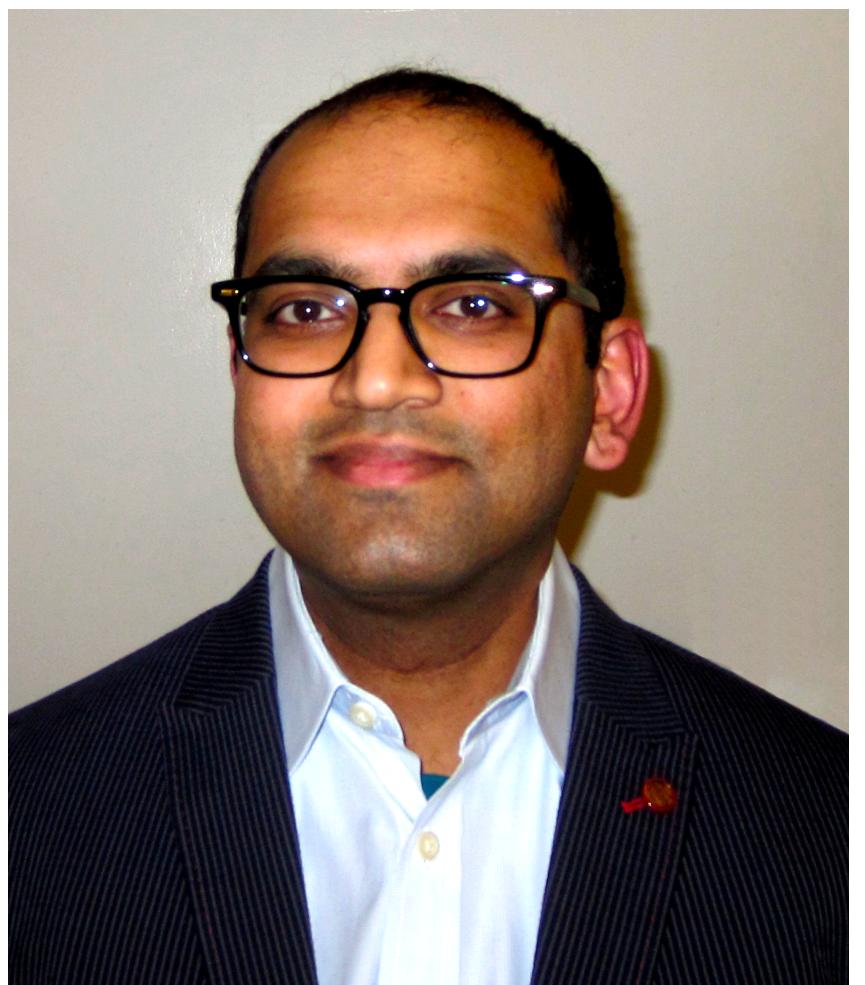
Summary

- Coevolving residues in this dataset are enriched for:
 - Residue pairs found in blobs of the same type
 - Some specialty interaction pairs
- Suggesting that both context and hydrophobic “specialty” residues play a role in intraprotein interactions

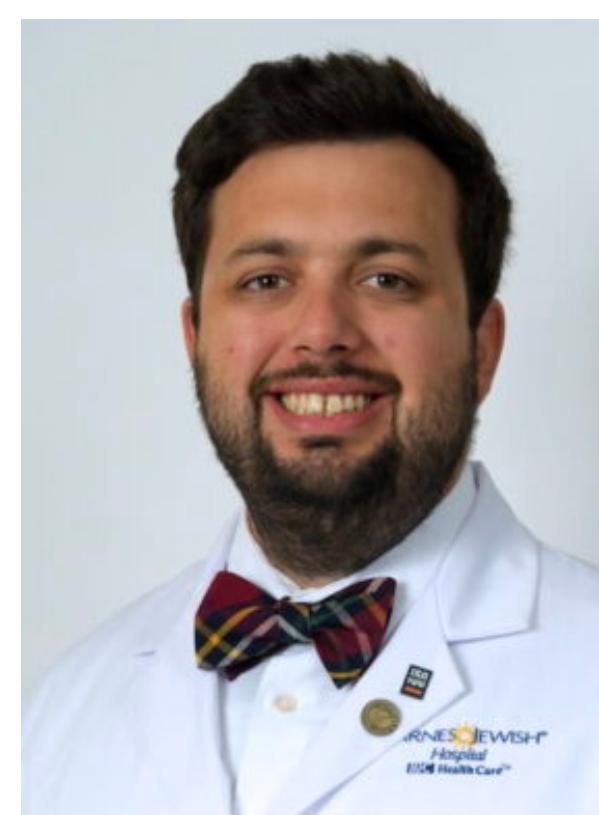
Future Directions:

- Investigate the same coevolving residue patterns in:
 - Membrane proteins
 - Intrinsically disordered proteins

Acknowledgements



Office of Advanced Research
Computing



Questions?