

# **Structural Determinants of Protein Evolution**

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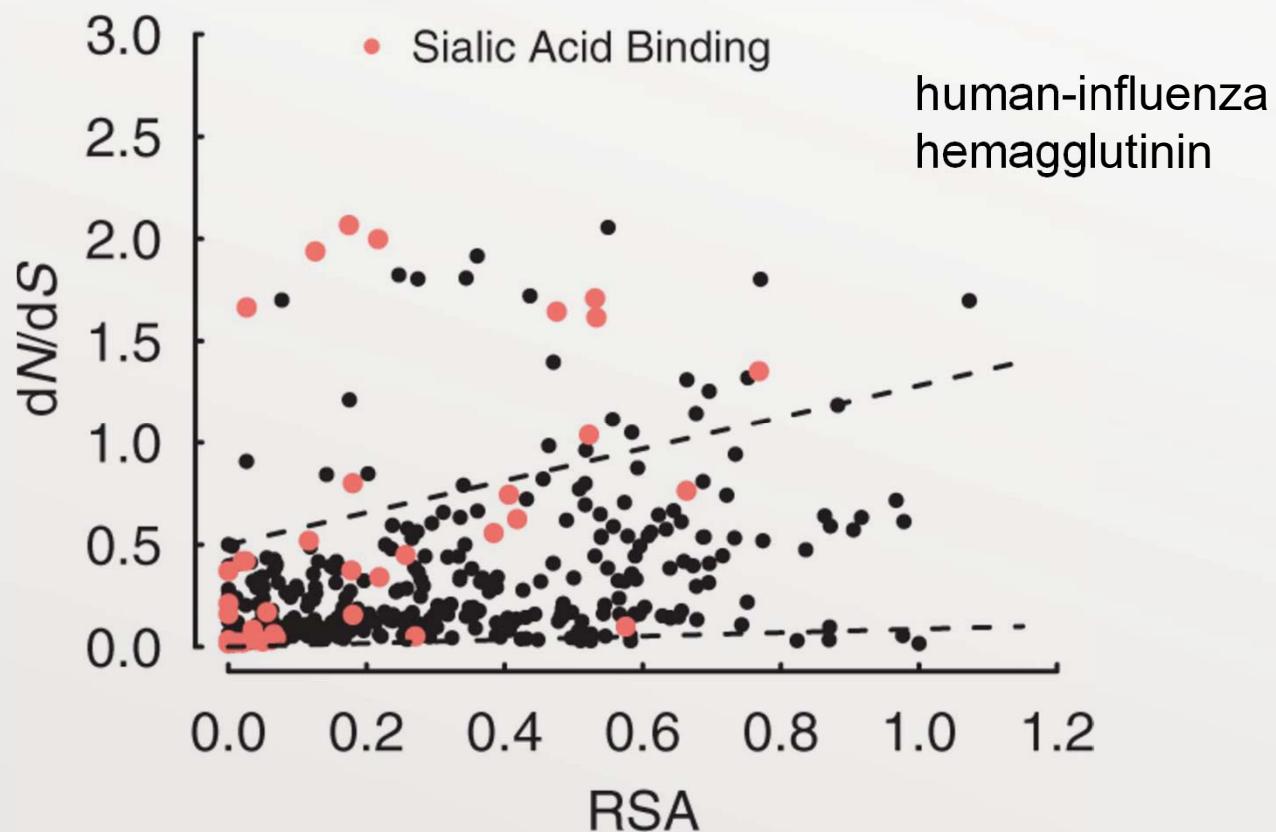
BEACON Congress, Aug 19 2014

# Why are some sites in viral proteins more variable than others?

Influenza virus hemagglutinin

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... GTIKSWDESYIELKVEVP ...  
... GTIKSWDESYTELKVDVP ...  
... GTIKSWDENYTELKVDVP ...  
... GTIKSWDENYAELKVDVP ...  
... GTIKSWDESYTELKVEVP ...  
... GTIKSWDESYTELKVDVP ...  
... GTIKSWDESYTELKVDVP ...
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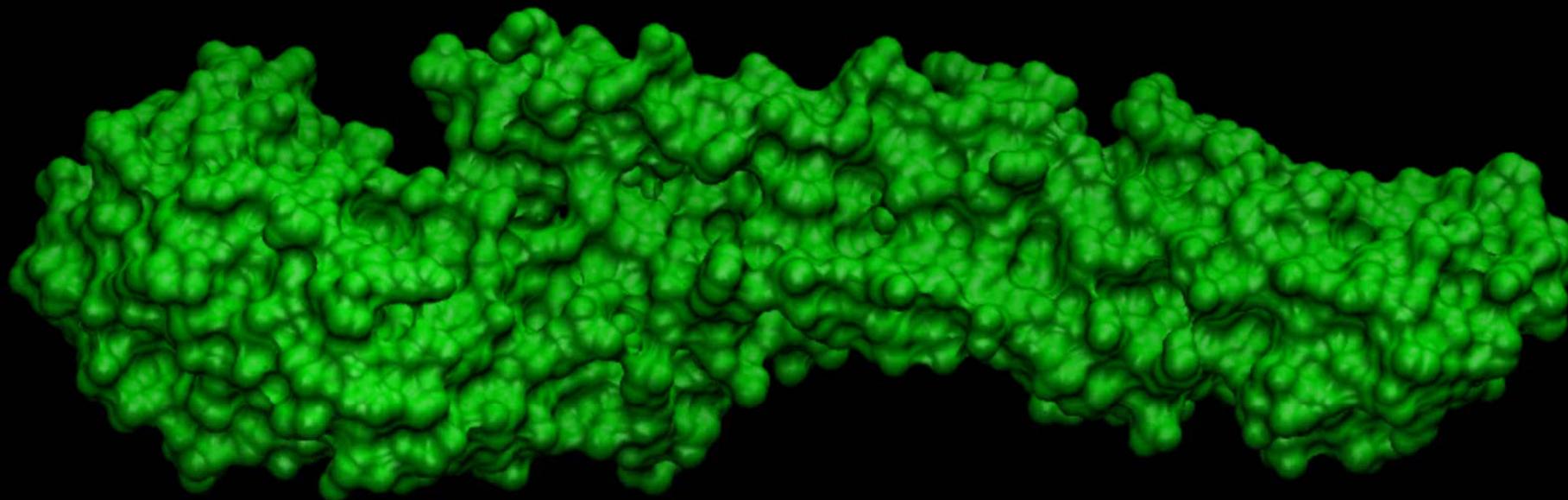
# Buried residues (sites) evolve more slowly than exposed residues



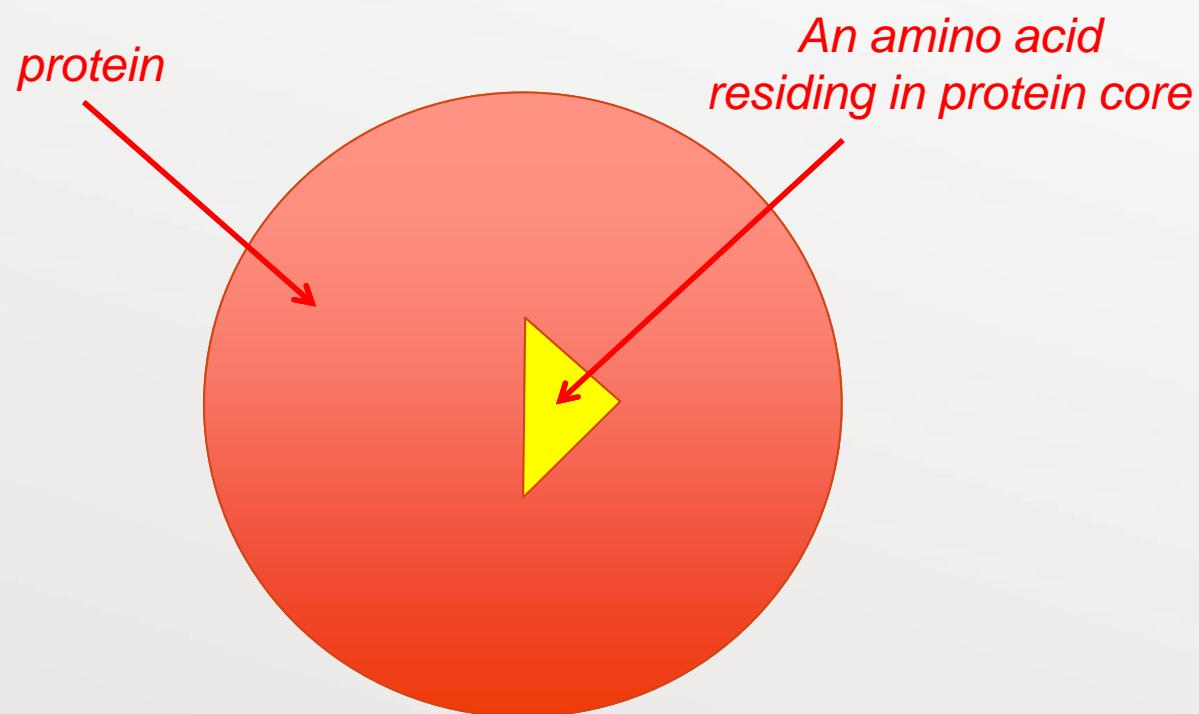
Meyer & Wilke, 2013, MBE, **30**, 36-44

Amino acid sites in the core of proteins have lower solvent accessible surface area

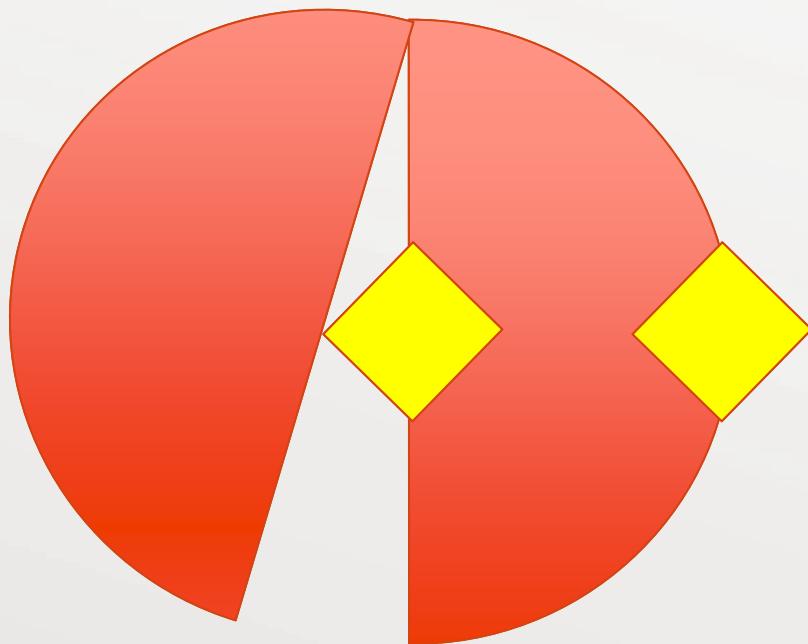
Influenza virus hemagglutinin



Amino acid substitutions in the core are disruptive

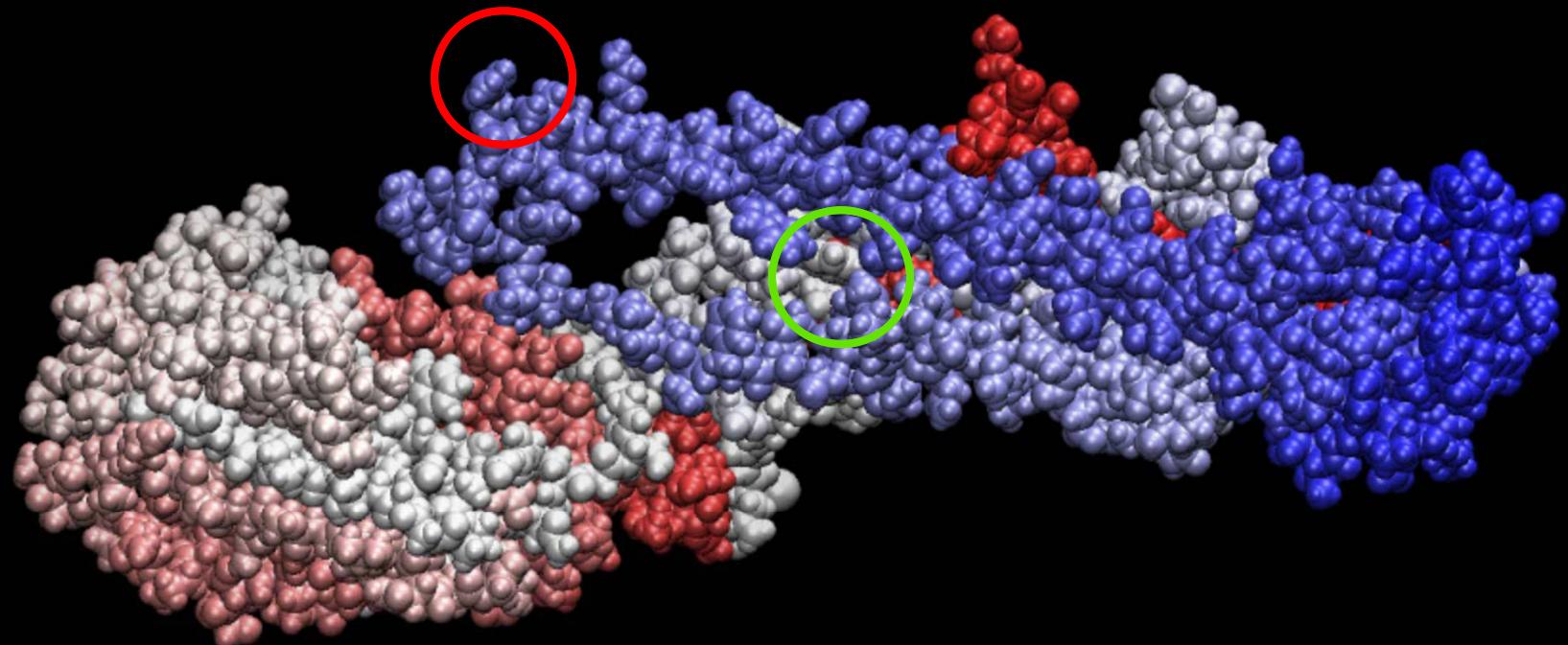


Amino acid substitutions in the core are disruptive

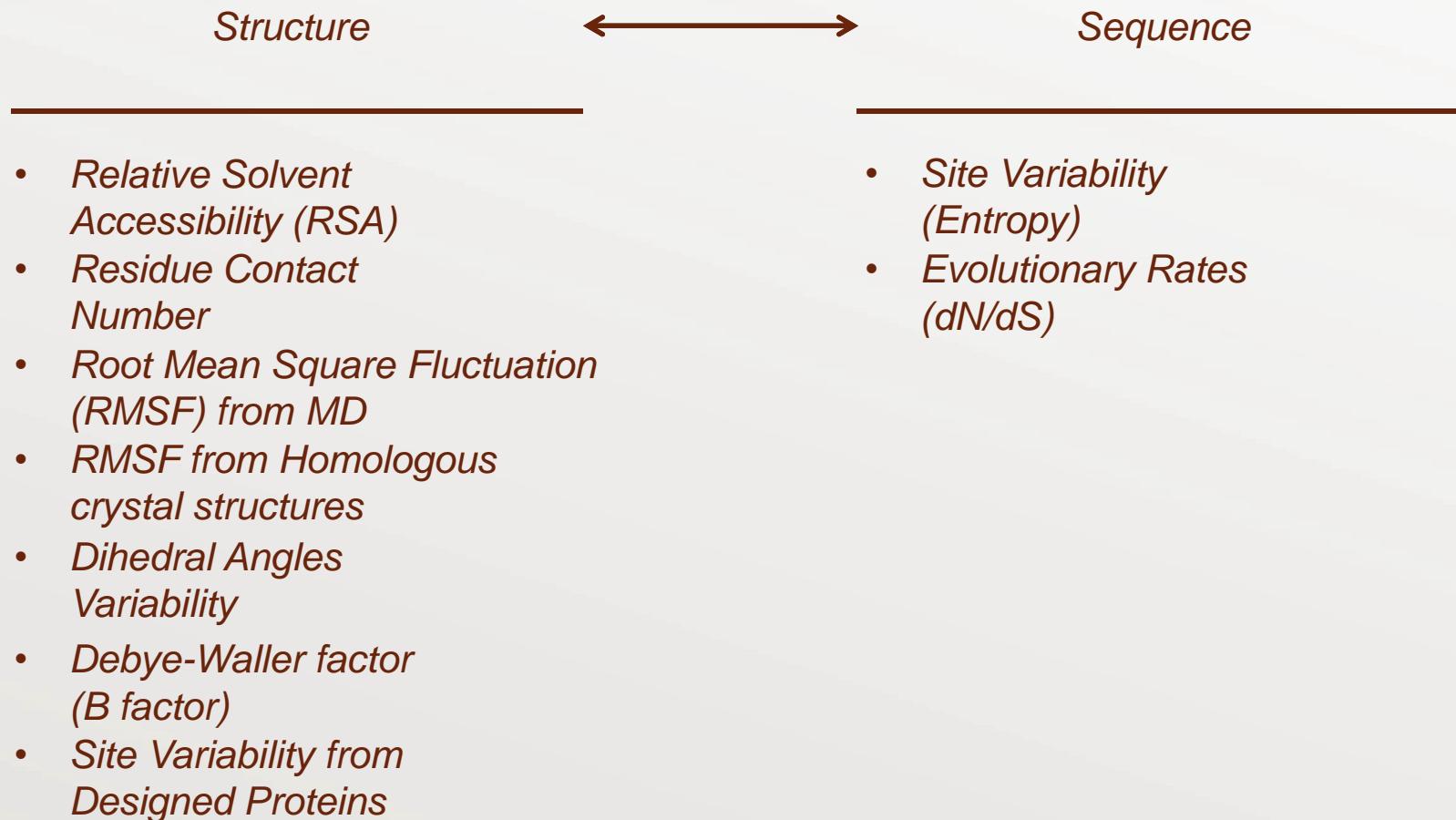


# Proteins are dynamic 3D entities

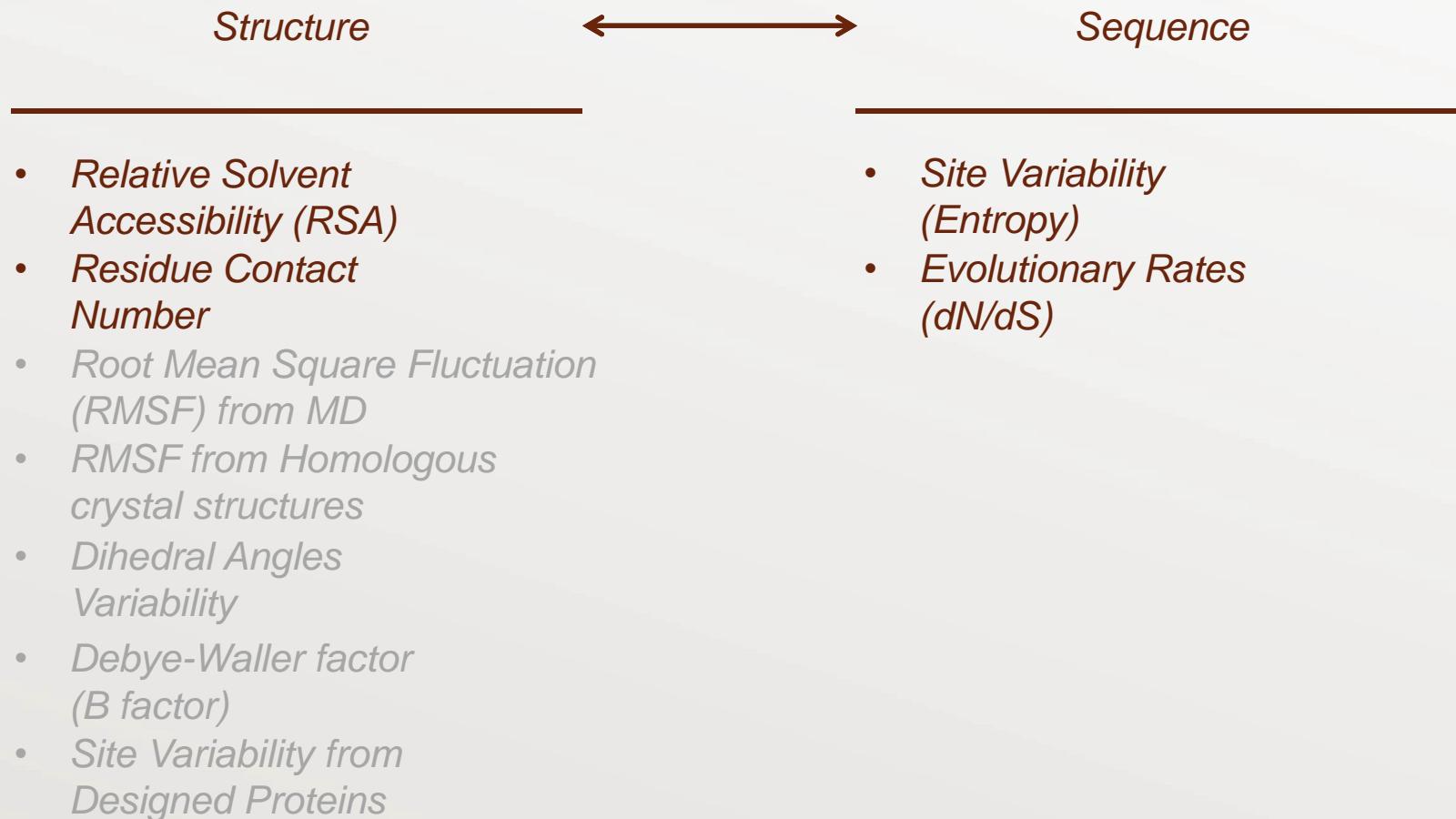
Influenza virus hemagglutinin



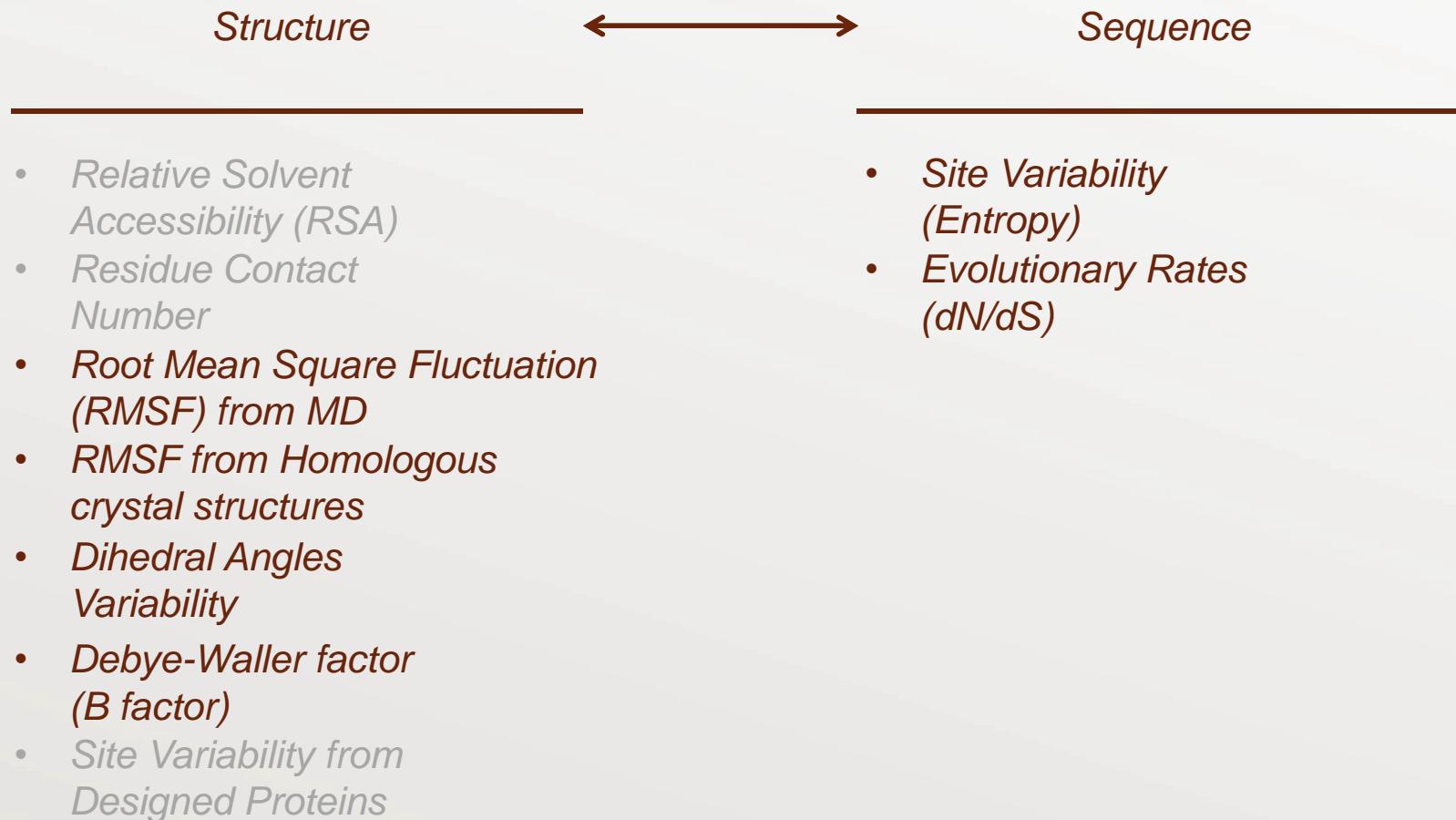
# Does structural variation have any prediction power for the sequence evolution of the protein?



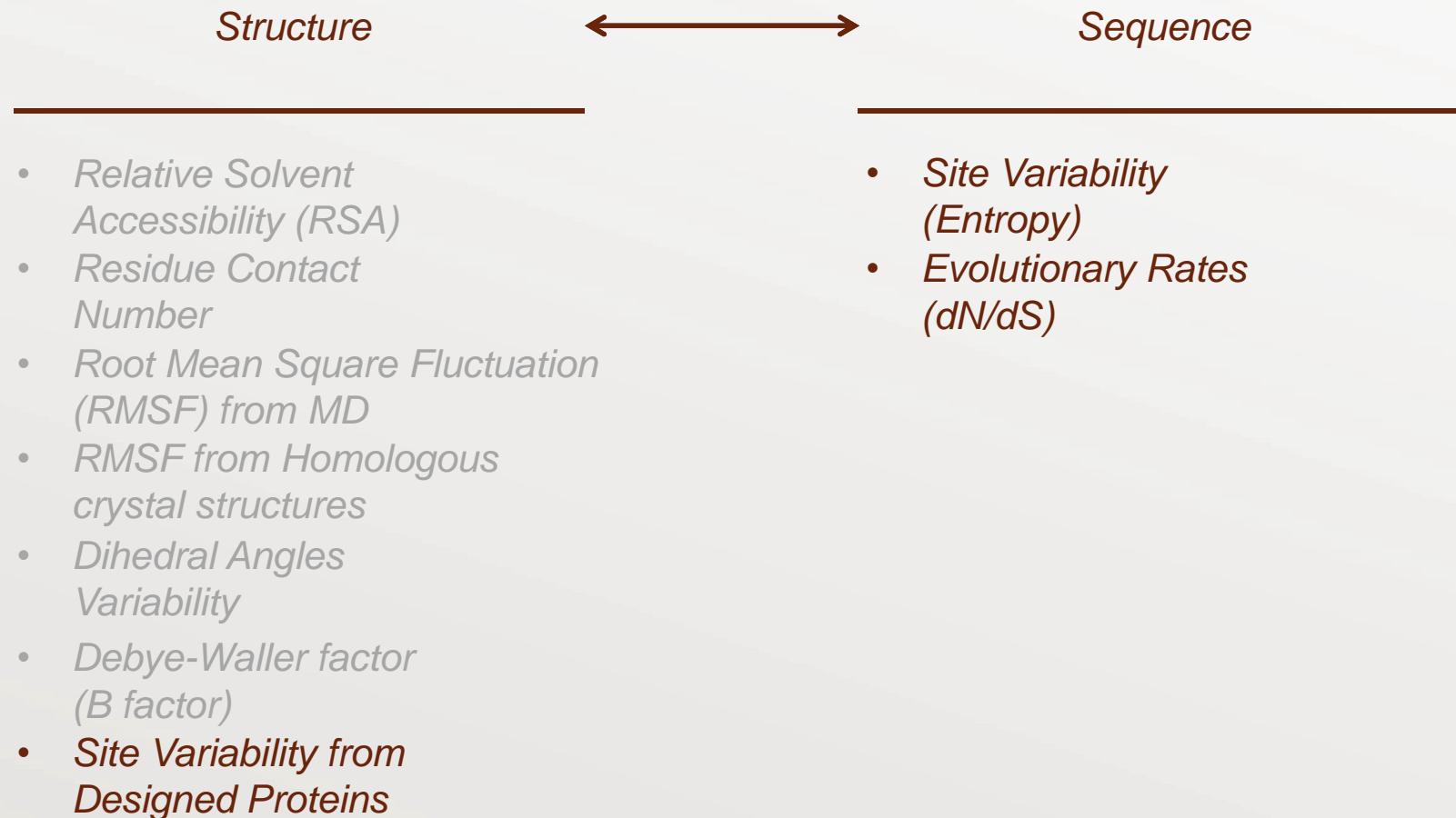
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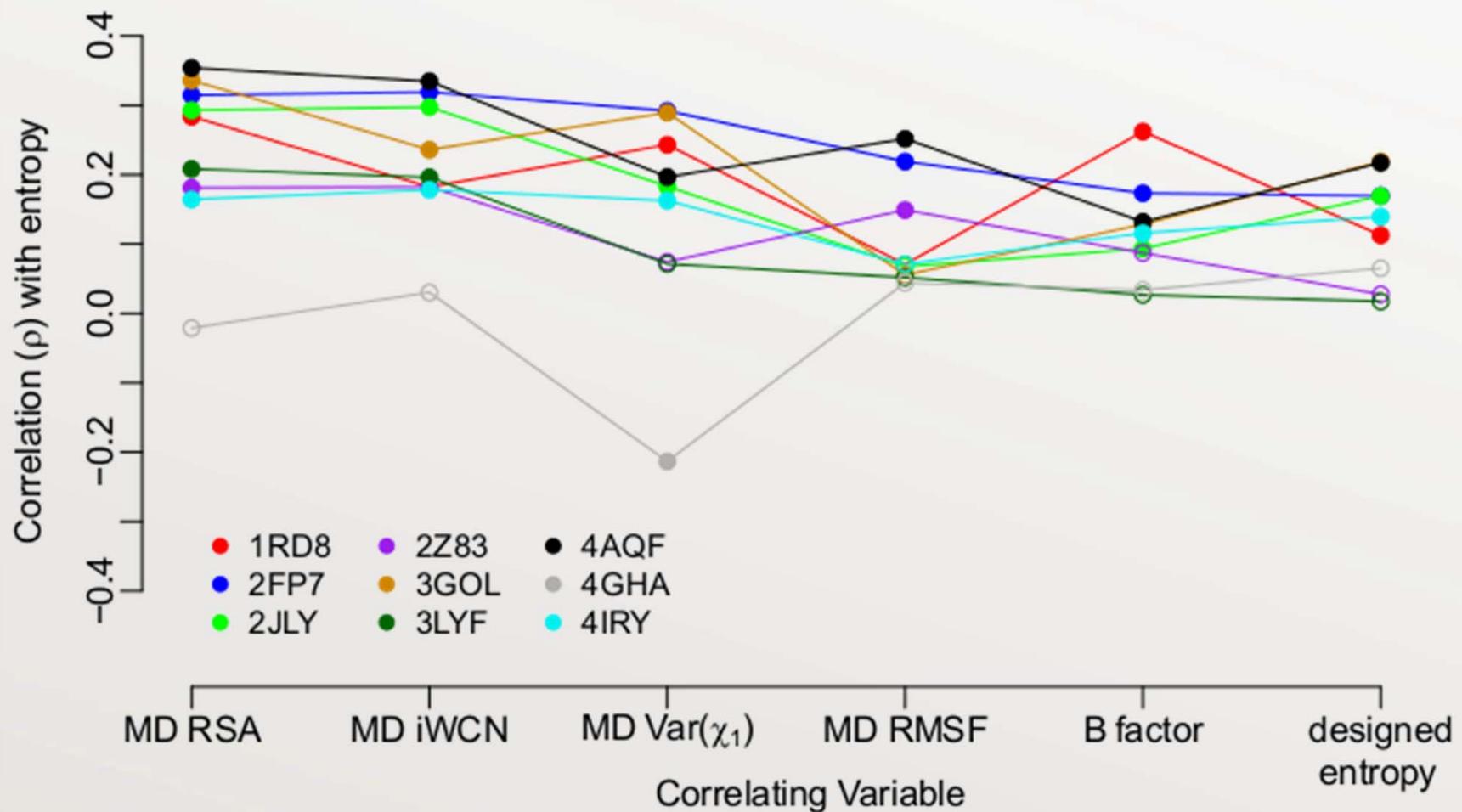
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# 9 viral proteins were analyzed

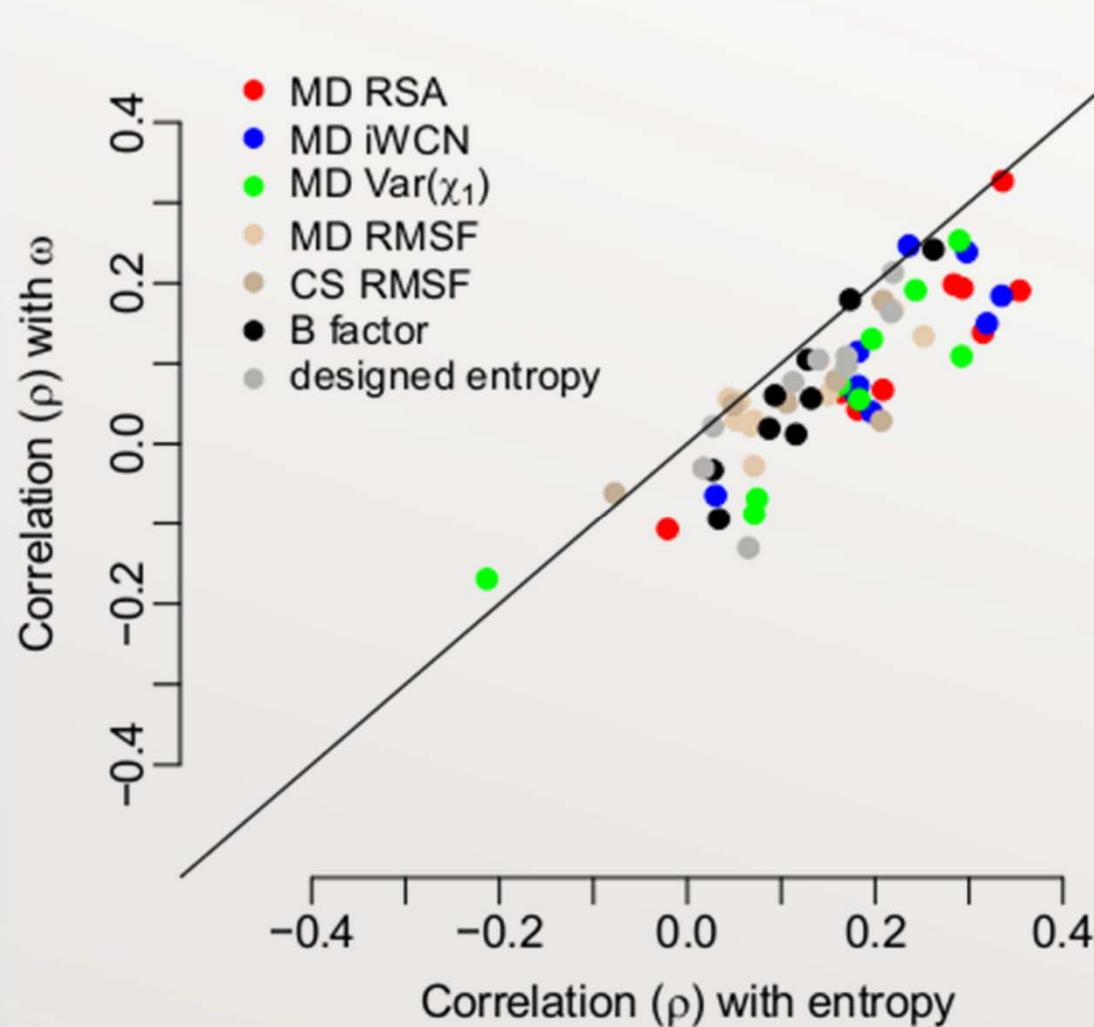
- Crimean-Congo Hemorrhagic Fever Virus Nucleocapsid
- Dengue Protease – Helicase
- West Nile Protease
- Influenza Nucleoprotein
- Marburg Virus RNA Binding Domain
- Hepatitis C Protease
- Japanese Encephalitis Helicase/Nucleoside
- Hemagglutinin Precursor
- Rift Valley Fever Virus Nucleoprotein

# Buriedness measures outperform flexibility measures

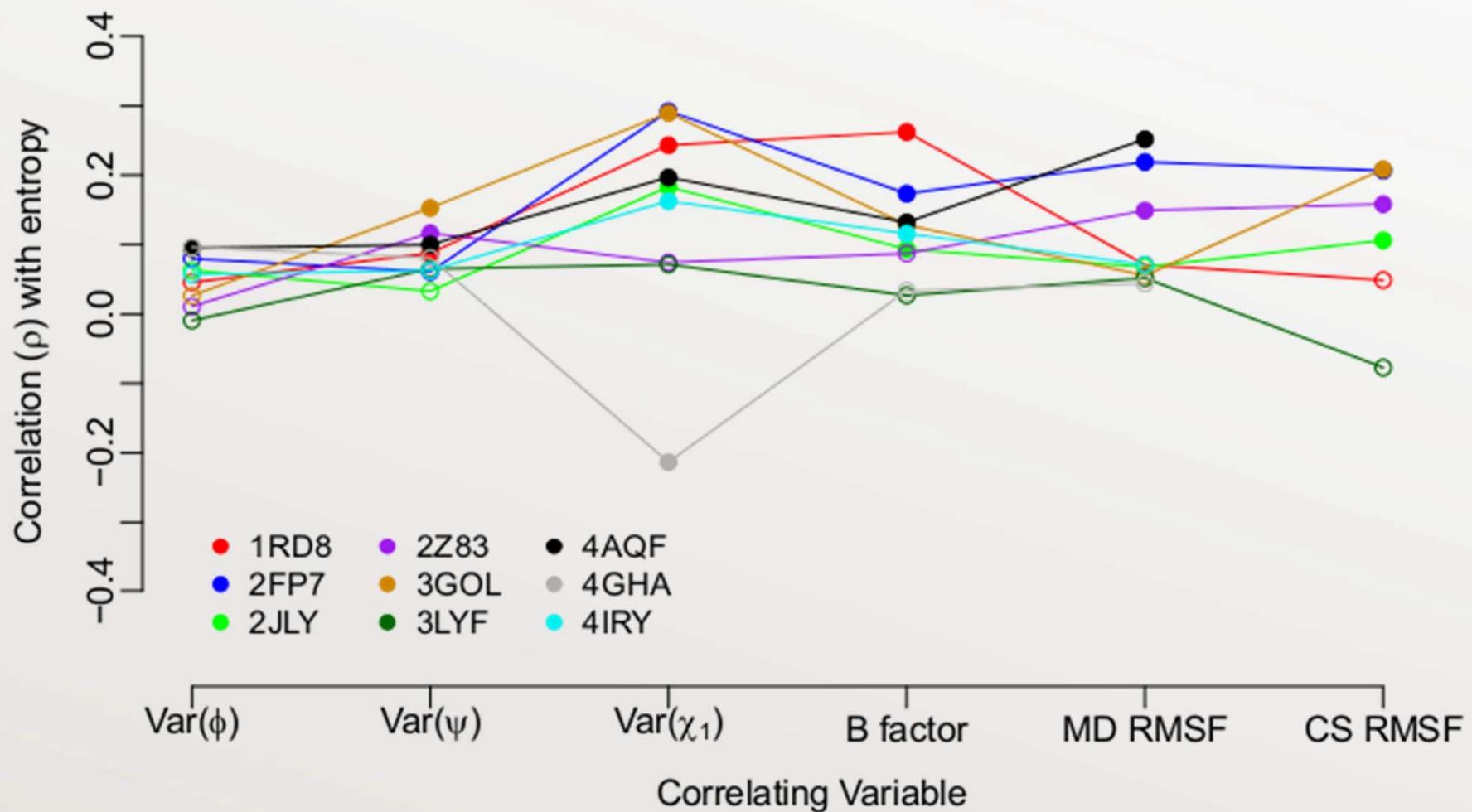


# Sequence Entropy vs. Evolutionary Rates

## Which one is a better measure of sequence variability?

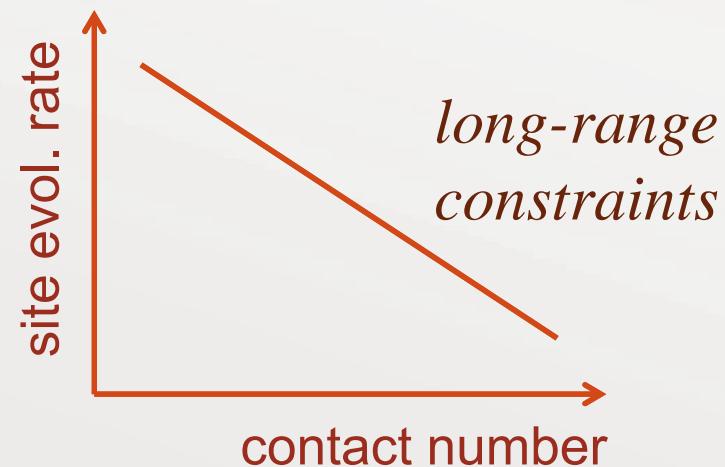
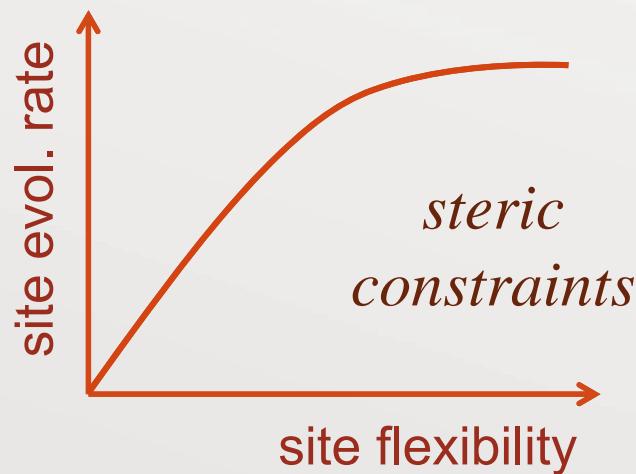


# Flexibility measures: Not strong indicators of sequence variability



# Summary

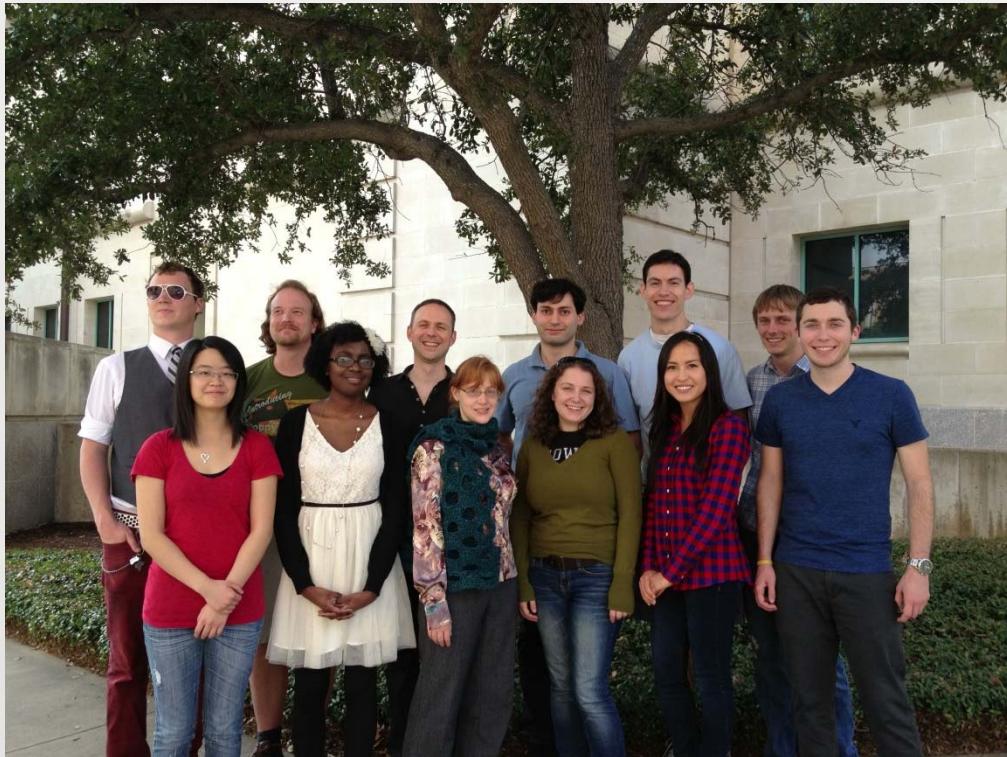
- Structural Measures of site flexibility correlate positively, but weakly in general, with sequence variability measures ( $\rho \sim 0.1$ ) .
- Local packing density and Relative Solvent Accessibility are moderately good indicators of the site variability in viral proteins ( $\rho \sim 0.2$  &  $\rho \sim 0.3$ ) .
- On a dataset of 213 proteins:  $\rho \sim 0.4$ ,  $\rho \sim 0.5$ ,  $\rho \sim 0.5$



- Shahmoradi et al. 2014, [arXiv:1404.7511](https://arxiv.org/abs/1404.7511), “ Predicting evolutionary site variability from structure in viral proteins: buriedness, flexibility, and design ”

# Acknowledgments

Claus Wilke (PI)



**Wilke Lab members**

Daria Sydkova

Eleisha Jackson

Stephanie Spielman

Austin Meyer

Art Covert

Dakota DerryBerry

Viswanadham Sridhara

# References

1. Predicting evolutionary site variability from structure in viral proteins: buriedness, packing, flexibility, and design, Shahmoradi, Amir and Sydykova, Dariya K and Spielman, Stephanie J and Jackson, Eleisha L and Dawson, Eric T and Meyer, Austin G and Wilke, Claus O, *Journal of Molecular Evolution (JME)* 79, 3-4, 130–142, 2014.
2. Intermediate divergence levels maximize the strength of structure--sequence correlations in enzymes and viral proteins, Jackson, Eleisha L and Shahmoradi, Amir and Spielman, Stephanie J and Jack, Benjamin R and Wilke, Claus O, *Protein Science*, 25, 7, 1341-1353, 2016.
3. Dissecting the roles of local packing density and longer-range effects in protein sequence evolution, Shahmoradi, Amir and Wilke, Claus O, *Proteins: Structure, Function, and Bioinformatics*, 84, 6, 841-854, 2016.

# References

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@article{shahmoradi2014predicting,  
  title={Predicting evolutionary site variability from structure in viral proteins:  
buriedness, packing, flexibility, and design},  
  author={Shahmoradi, Amir and Sydykova, Dariya K and Spielman, Stephanie J  
and Jackson, Eleisha L and Dawson, Eric T and Meyer, Austin G and Wilke, Claus  
O},  
  journal={Journal of molecular evolution},  
  volume={79},  
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  pages={130--142},  
  year={2014},  
  publisher={Springer US}  
}
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@article{jackson2016intermediate,  
  title={Intermediate divergence levels maximize the strength of structure--  
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  journal={Protein Science},  
  volume={25},  
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  year={2016}  
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