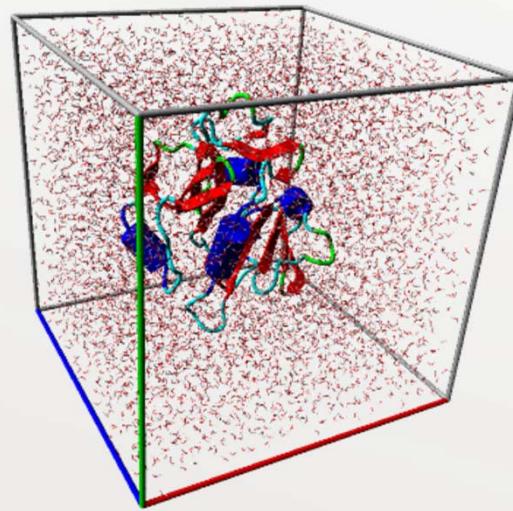


Insights into Protein Evolution via Molecular Dynamics Simulations



Amir Shahmoradi, Wilke Lab, UT Austin
BEACON Congress, Aug 12-15, 2013

Acknowledgments



Claus Wilke (PI)



Austin Meyer
(MD analysis)



Daria Sydkova
(structural analysis)

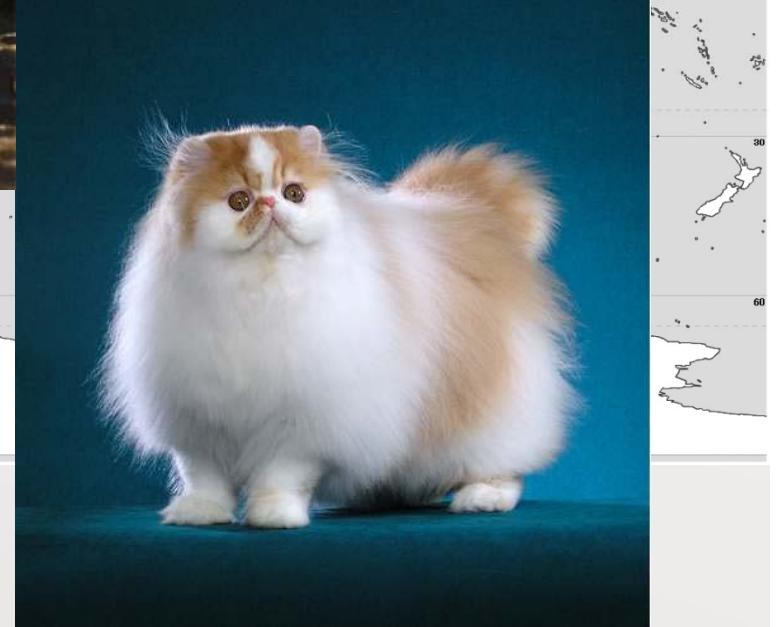
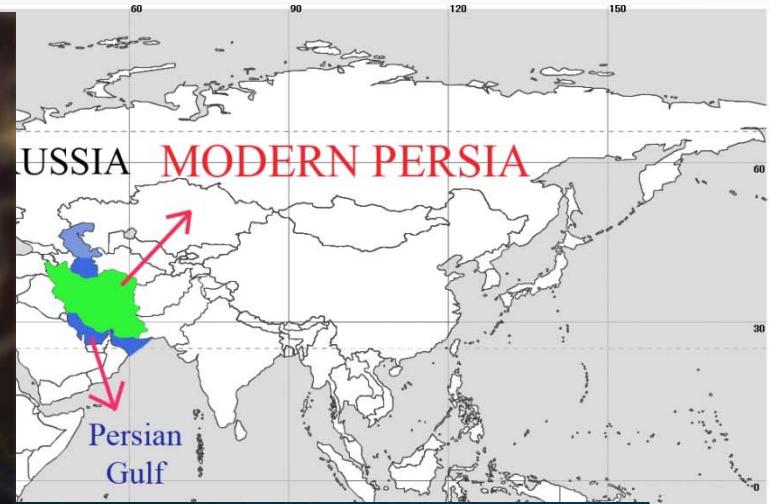
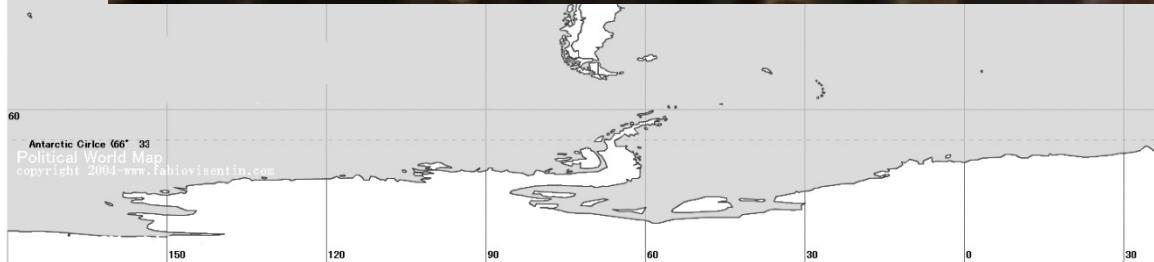


Eleisha Jackson
(protein design)

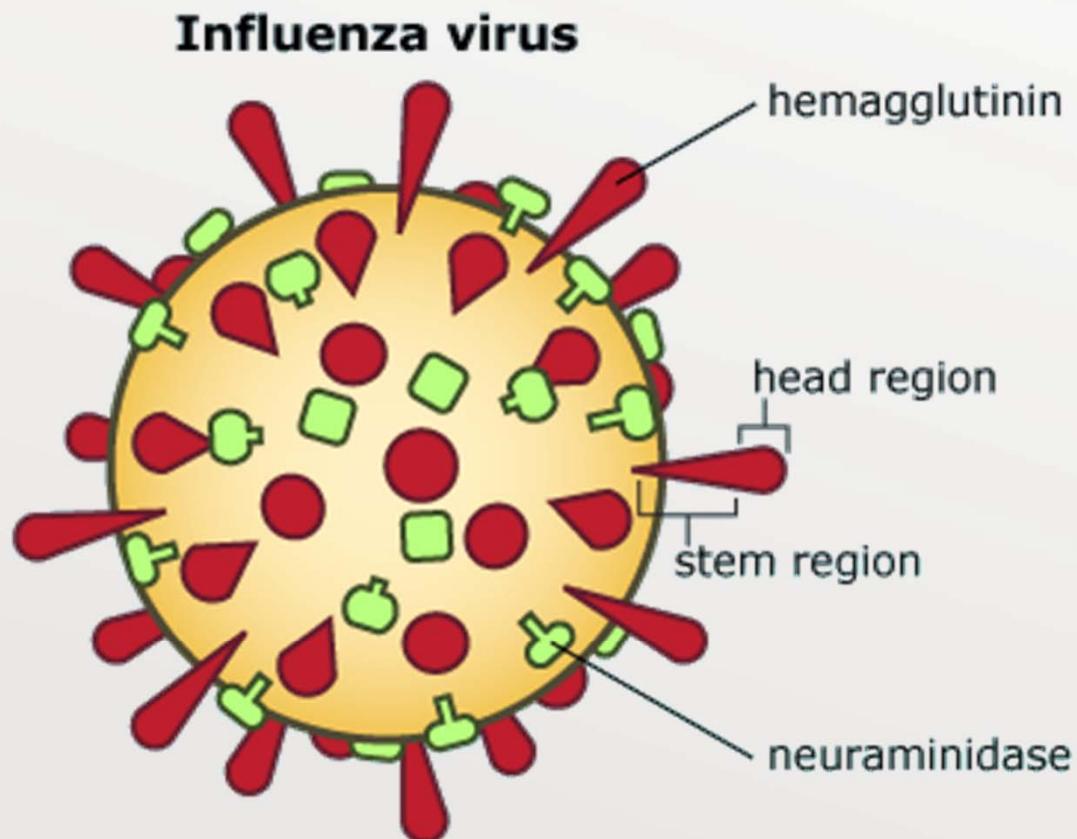


Stephanie Spielman
(sequence evolution)

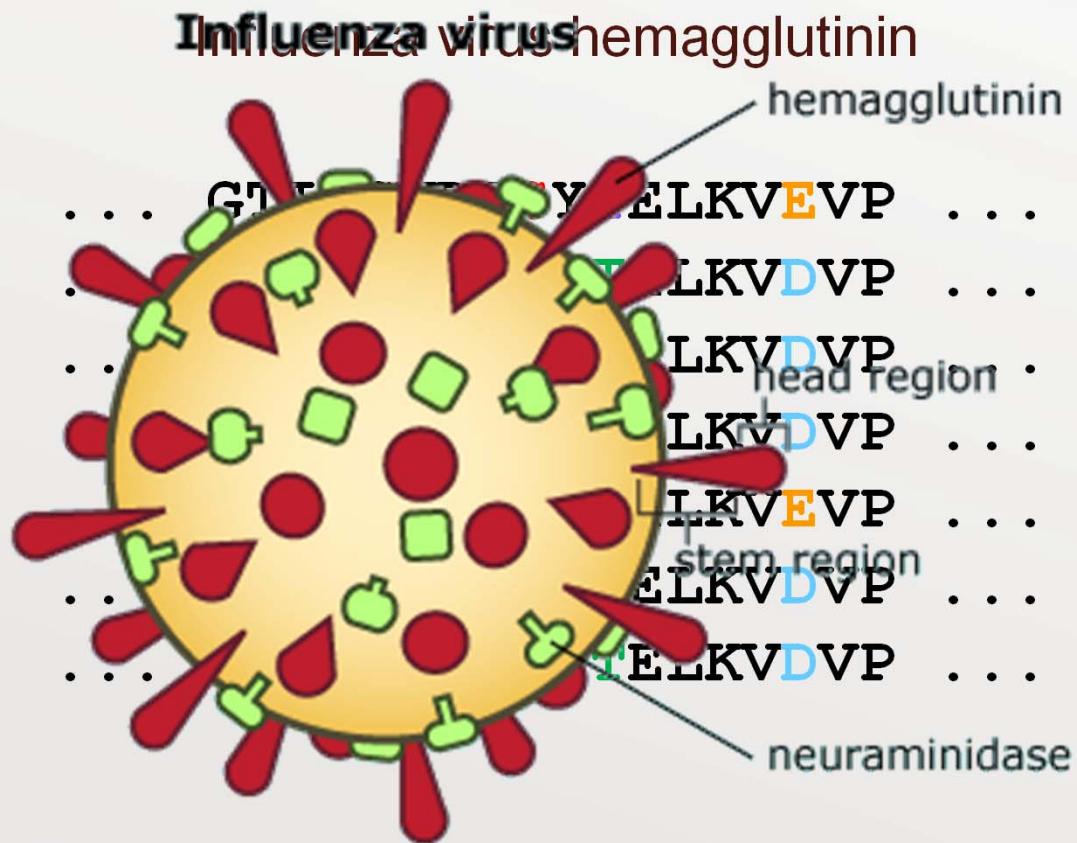
Where am I from originally?



Why do some viruses evolve so much in a short time?

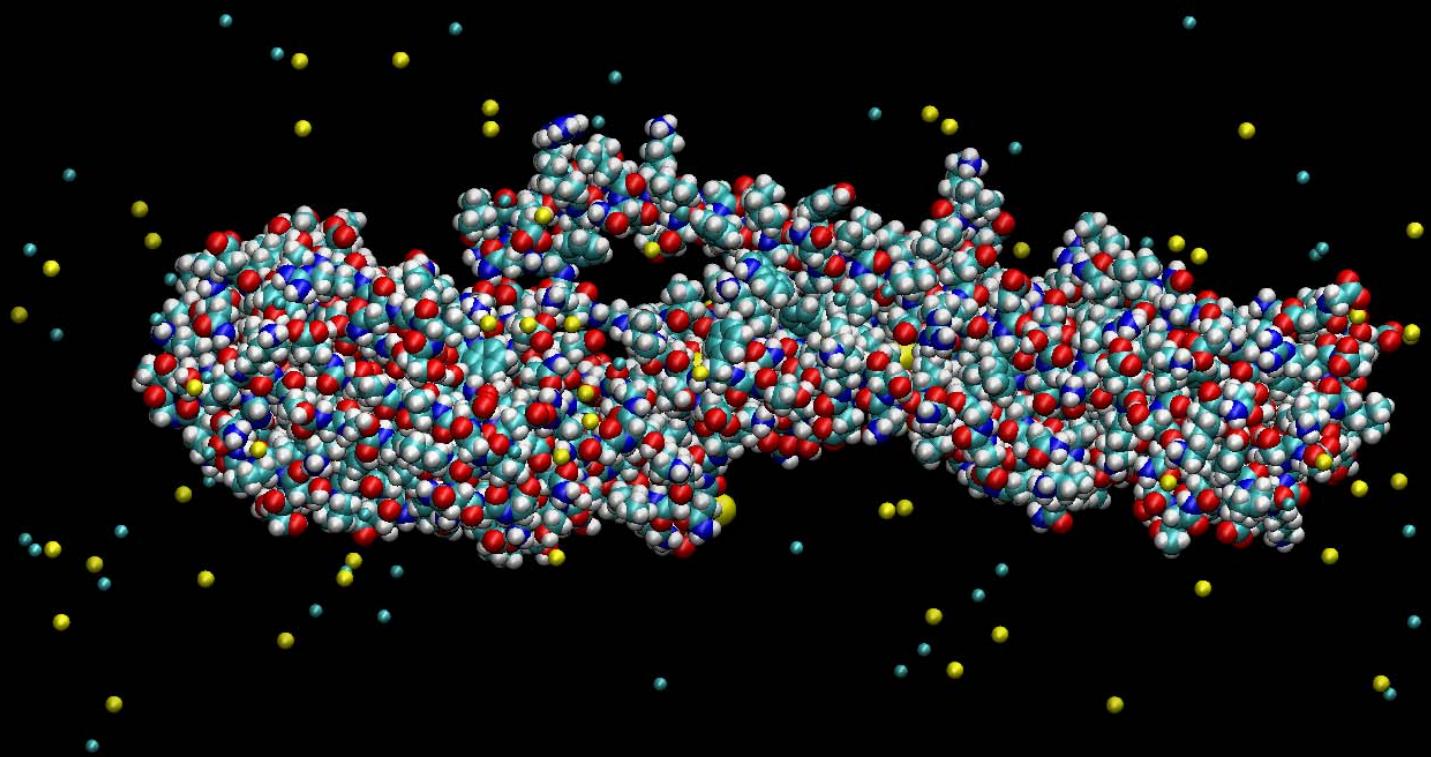


Why are some sites in viral proteins more variable than others?



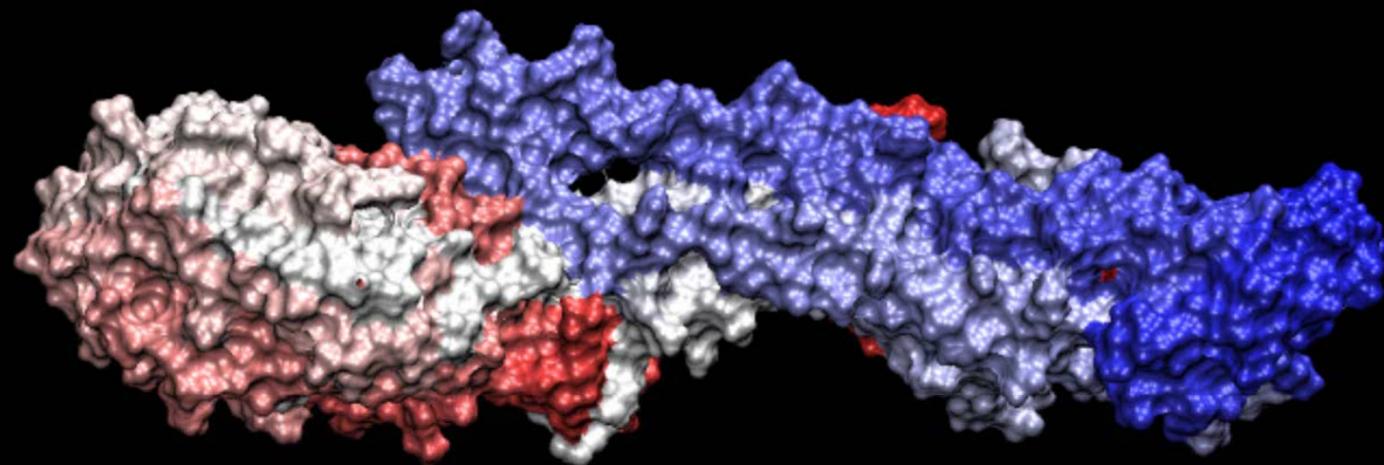
Proteins are large biological molecules consisting of one or more chains of amino acids.

Influenza virus hemagglutinin

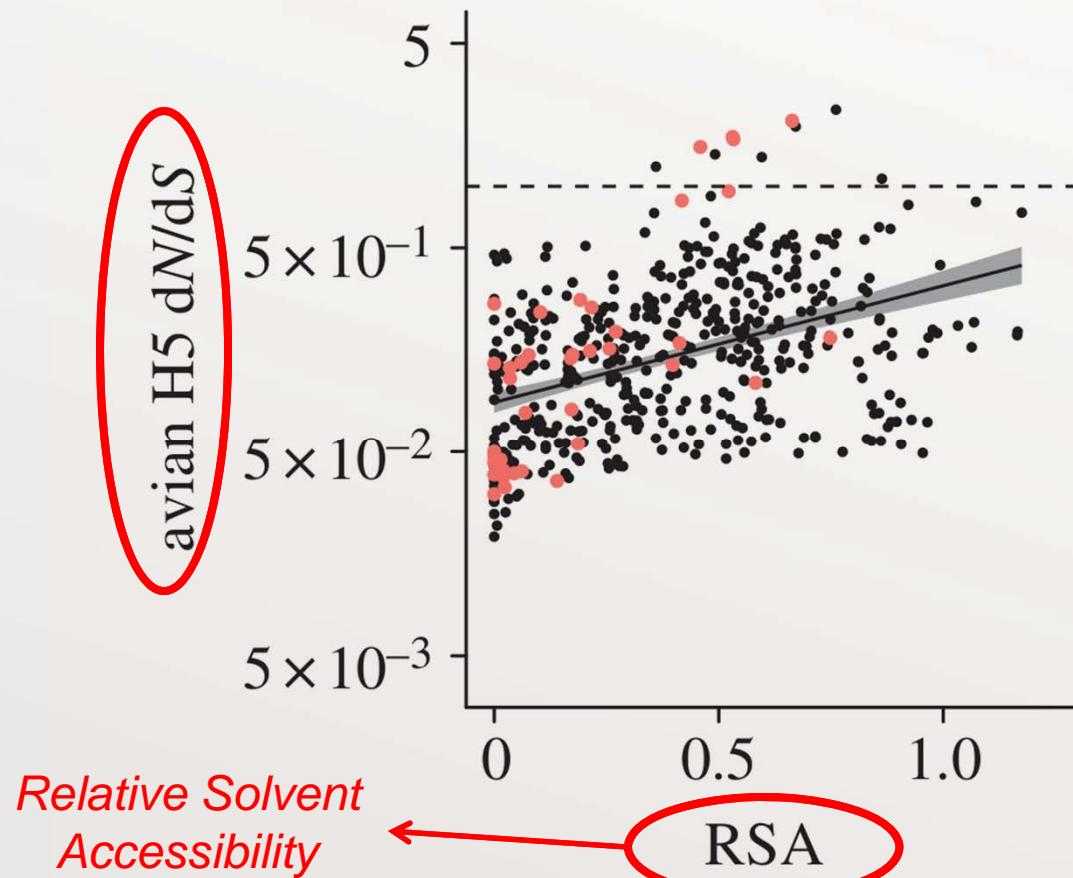


Amino acid sites in the core of proteins have lower solvent accessible surface areas

Influenza virus hemagglutinin

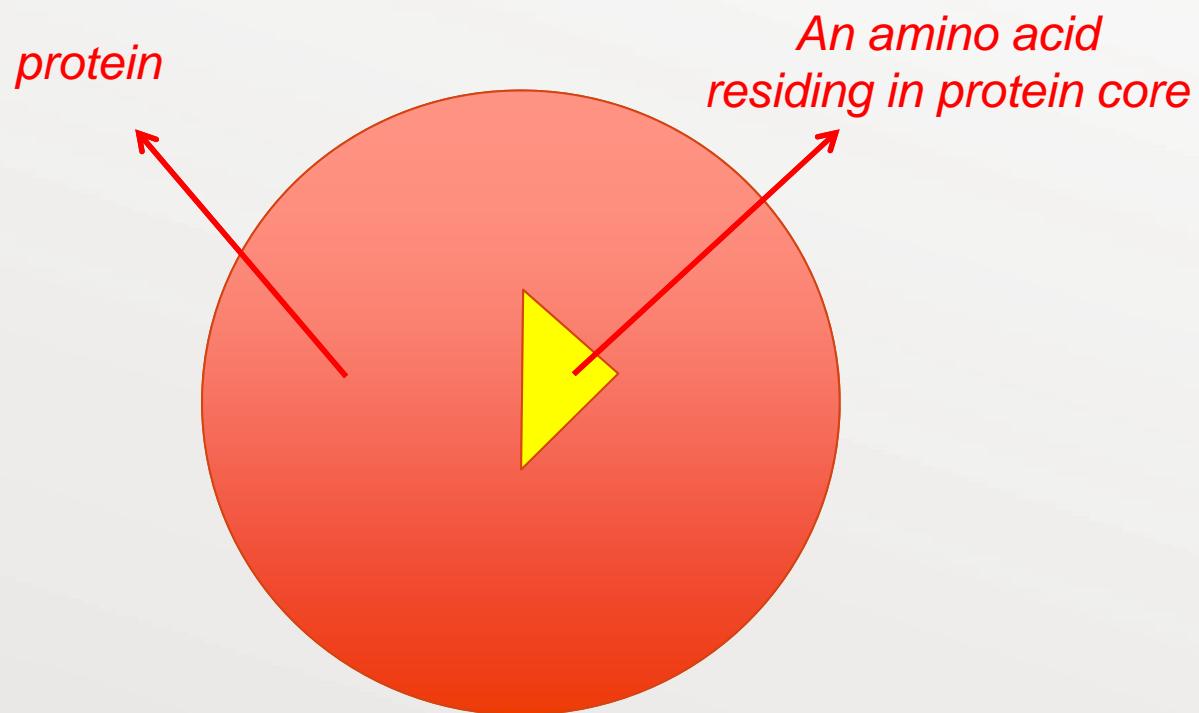


Buried residues (sites) evolve more slowly than exposed residues

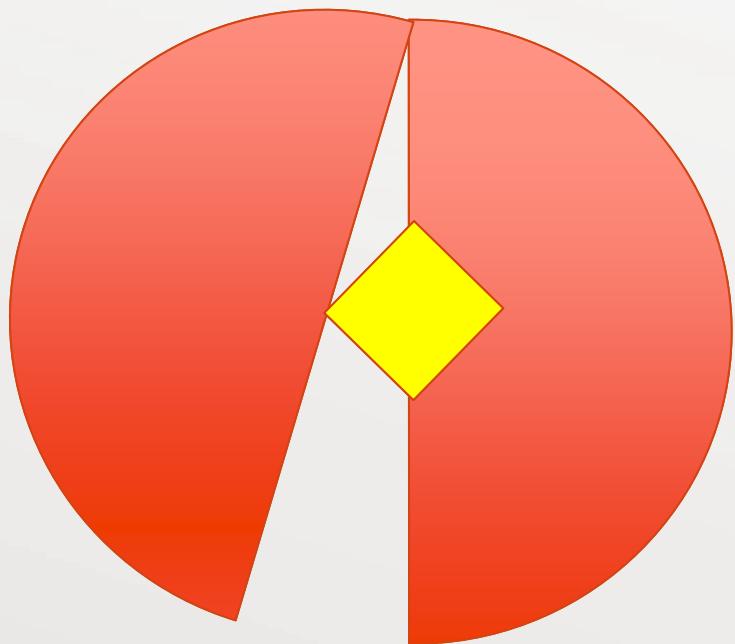


Meyer, Dawson, Wilke, 2013, Phil Trans R Soc B 368: 20120334

Buried residues (sites) evolve more slowly than exposed residues

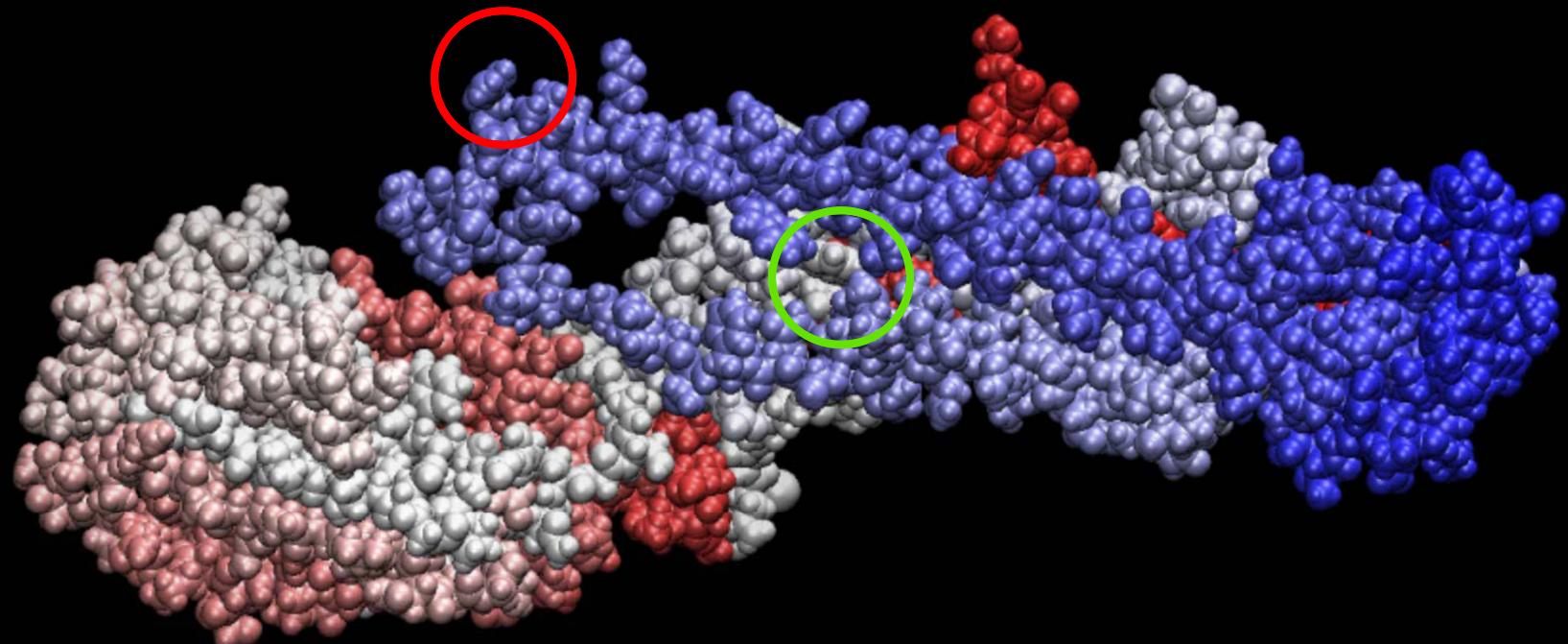


Buried residues (sites) evolve more slowly than exposed residues

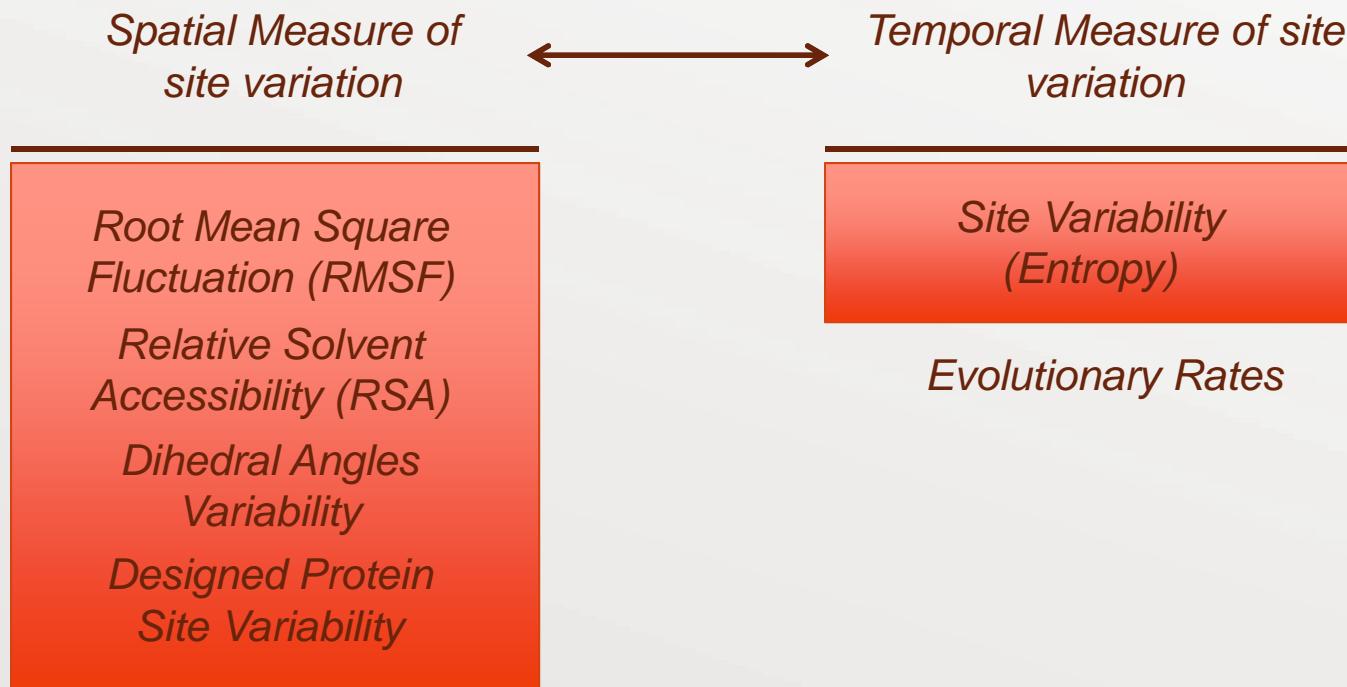


Proteins are dynamic, 3D entities

Influenza virus hemagglutinin



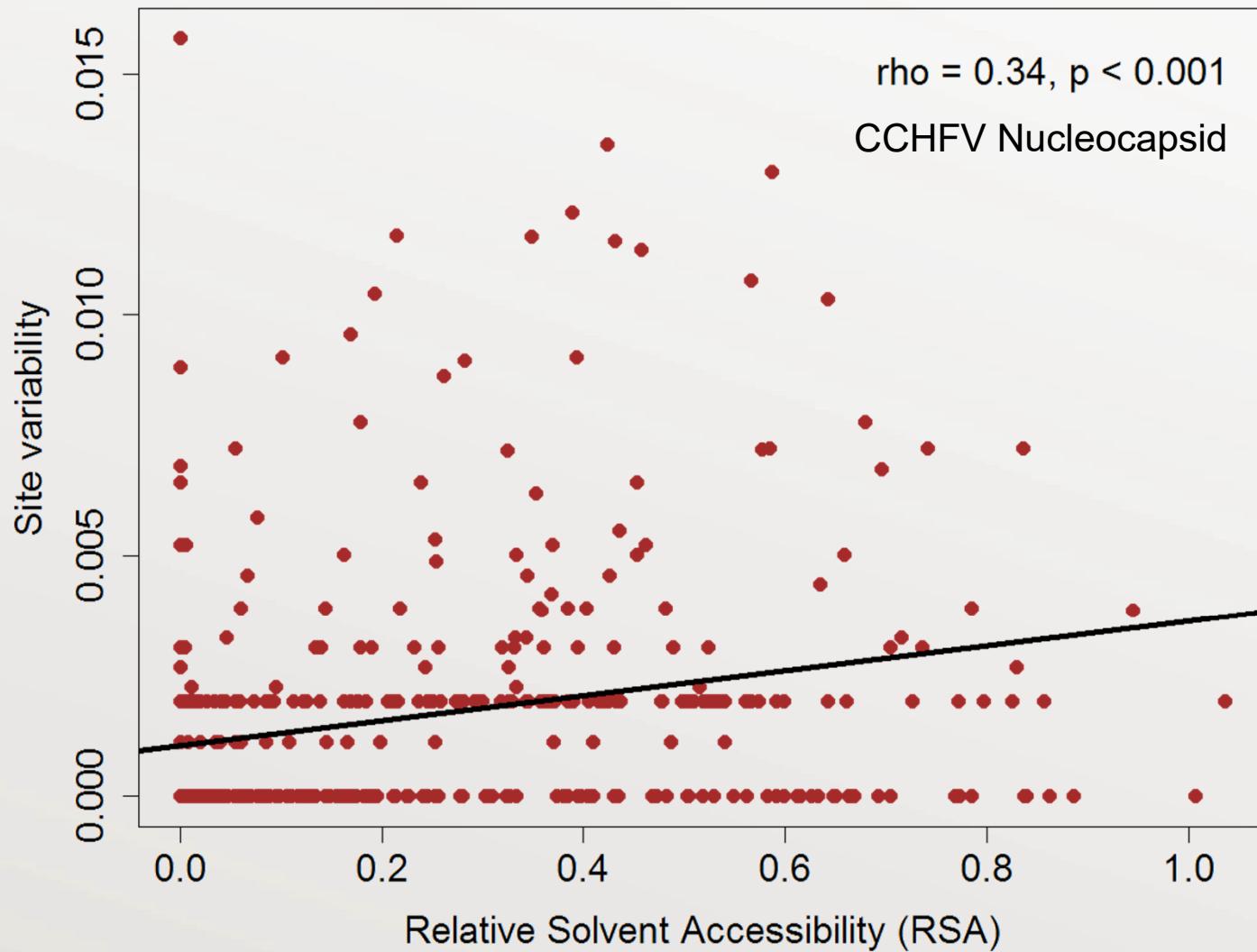
Does structural variation have any prediction power for the sequence evolution of the protein?



10 structures from 8 viral proteins were analyzed

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

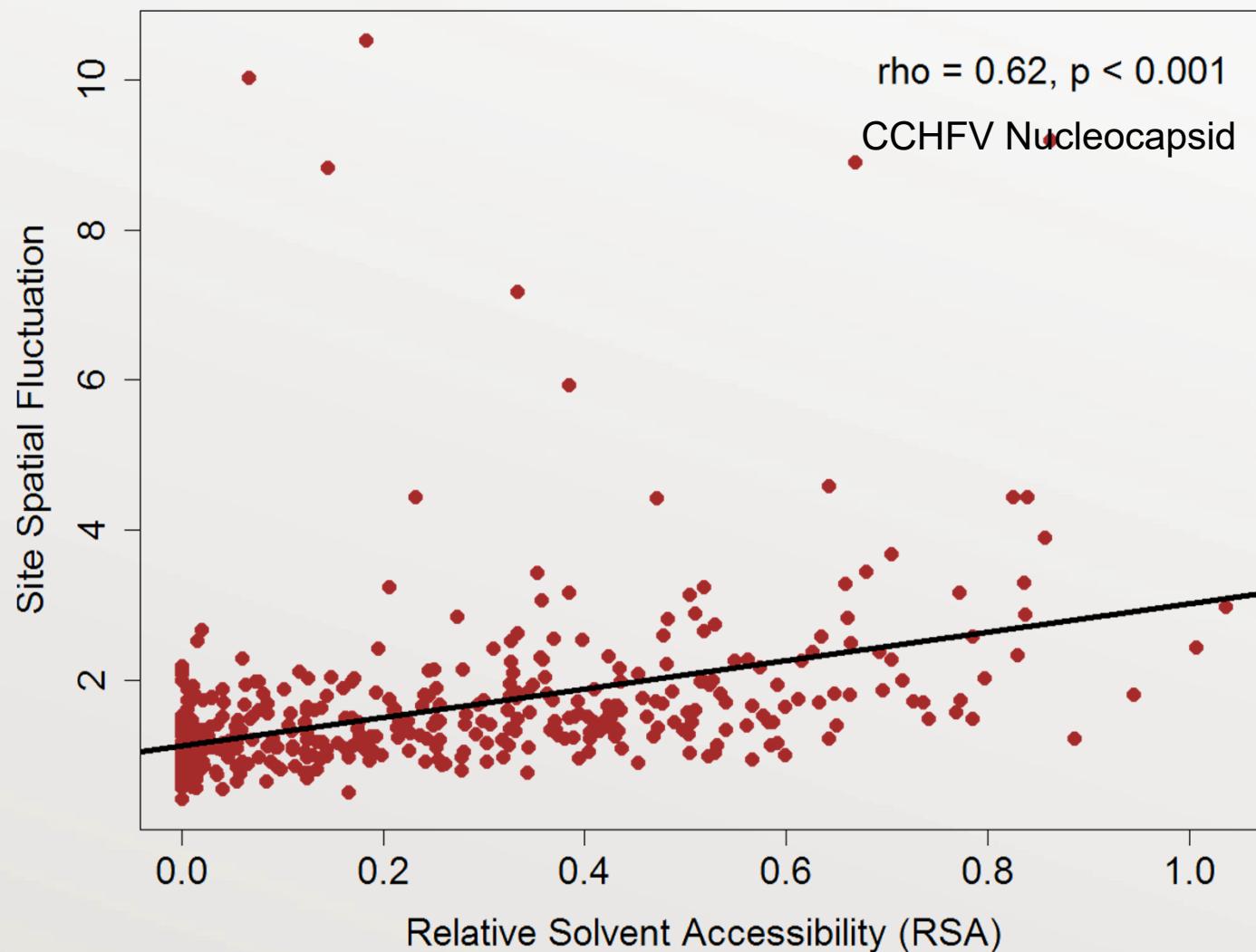
Relative Solvent Accessibility (RSA) correlates positively with site variability



Relative Solvent Accessibility (RSA) correlates positively with site variability

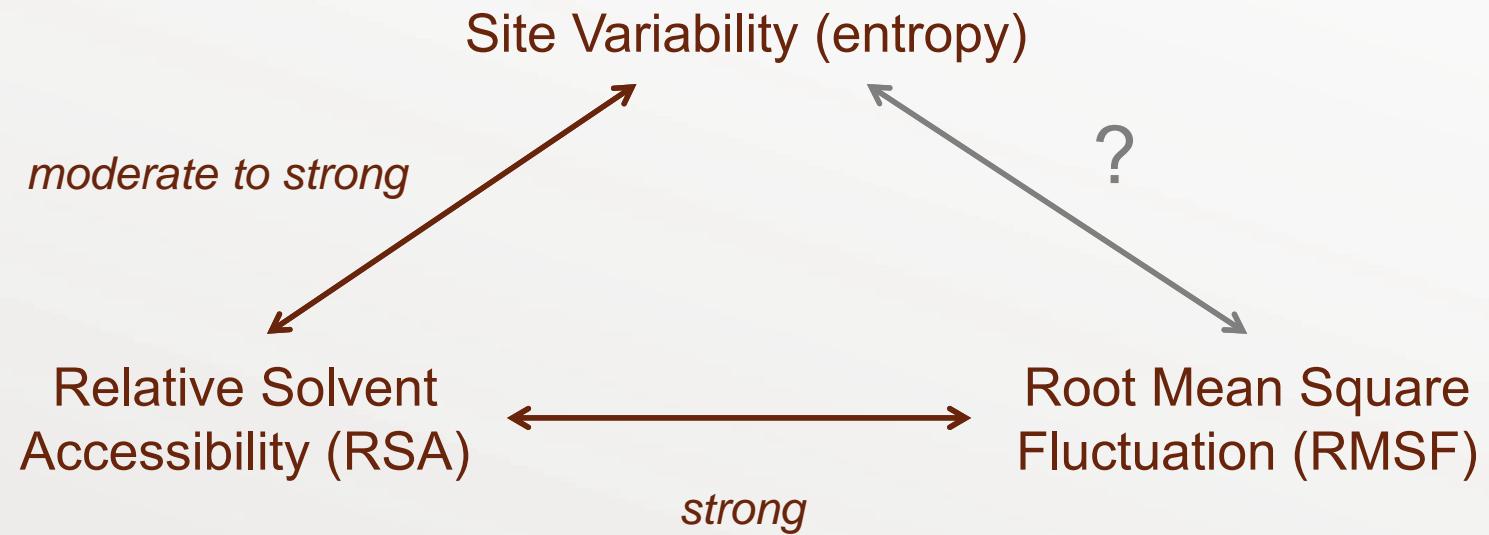
Protein	Spearman correlation	P value
CCHFV Nucleocapsid	0.34	1.6×10^{-14}
Influenza Hemagglutinin	0.30	3.4×10^{-12}
Dengue Protease	0.29	1.8×10^{-10}
Hepatitis C Protease	0.37	2.2×10^{-16}
Influenza Nucleoprotein	0.15	2.0×10^{-3}
JEV Helicase	0.18	2.4×10^{-4}
MARV RNA Binding Domain	0.00	0.94

Relative Solvent Accessibility (RSA) correlates positively with residue spatial fluctuations

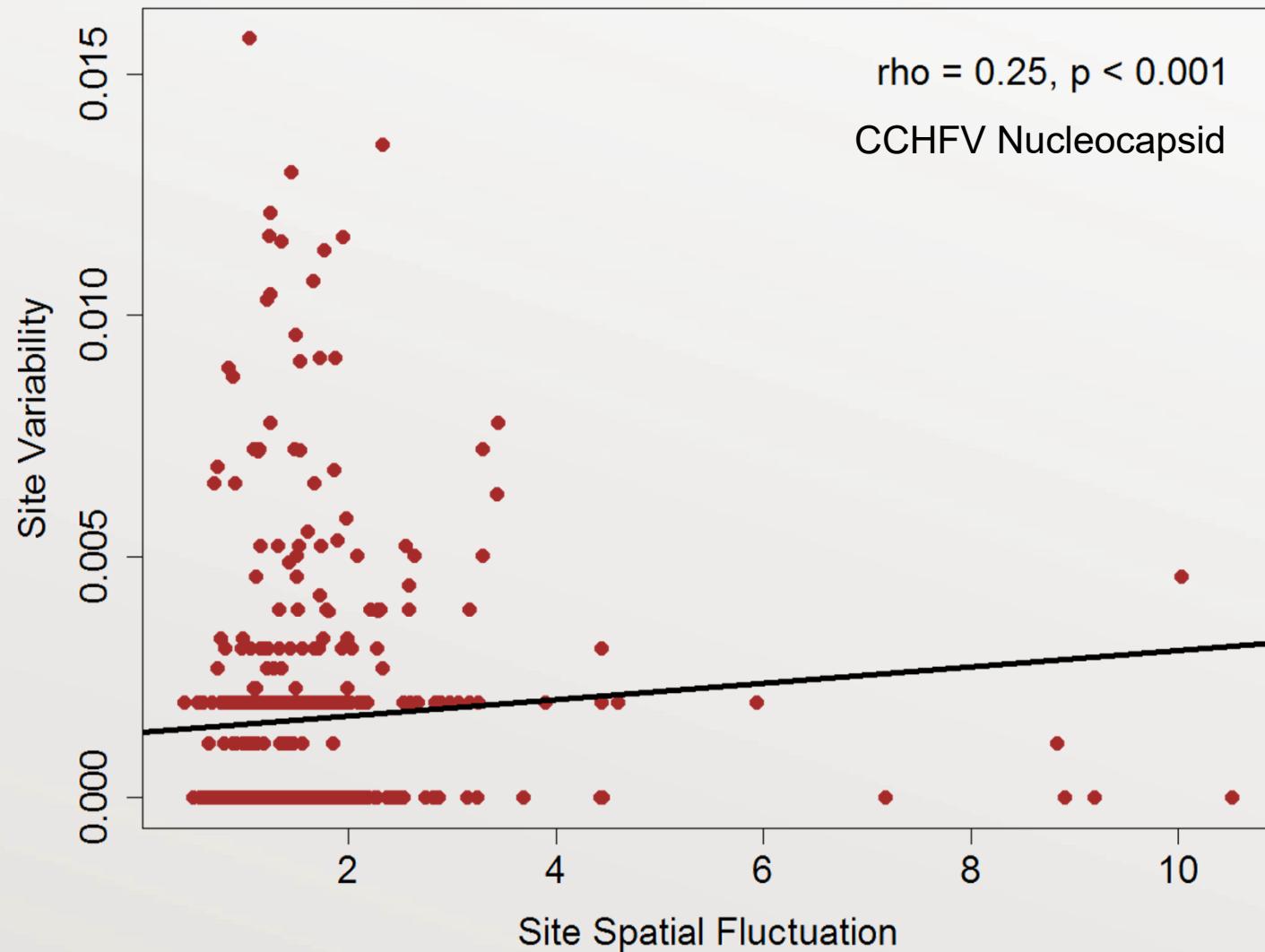


Relative Solvent Accessibility (RSA) correlates positively with residue spatial fluctuation

Protein	Spearman correlation	P value
CCHFV Nucleocapsid	0.62	2.2×10^{-16}
Influenza Hemagglutinin	0.49	2.2×10^{-16}
Dengue Protease	0.37	7.4×10^{-16}
Hepatitis C Protease	0.33	5.6×10^{-16}
Influenza Nucleoprotein	0.53	2.2×10^{-16}
JEV Helicase	0.53	2.2×10^{-16}
MARV RNA Binding Domain	0.54	1.2×10^{-10}

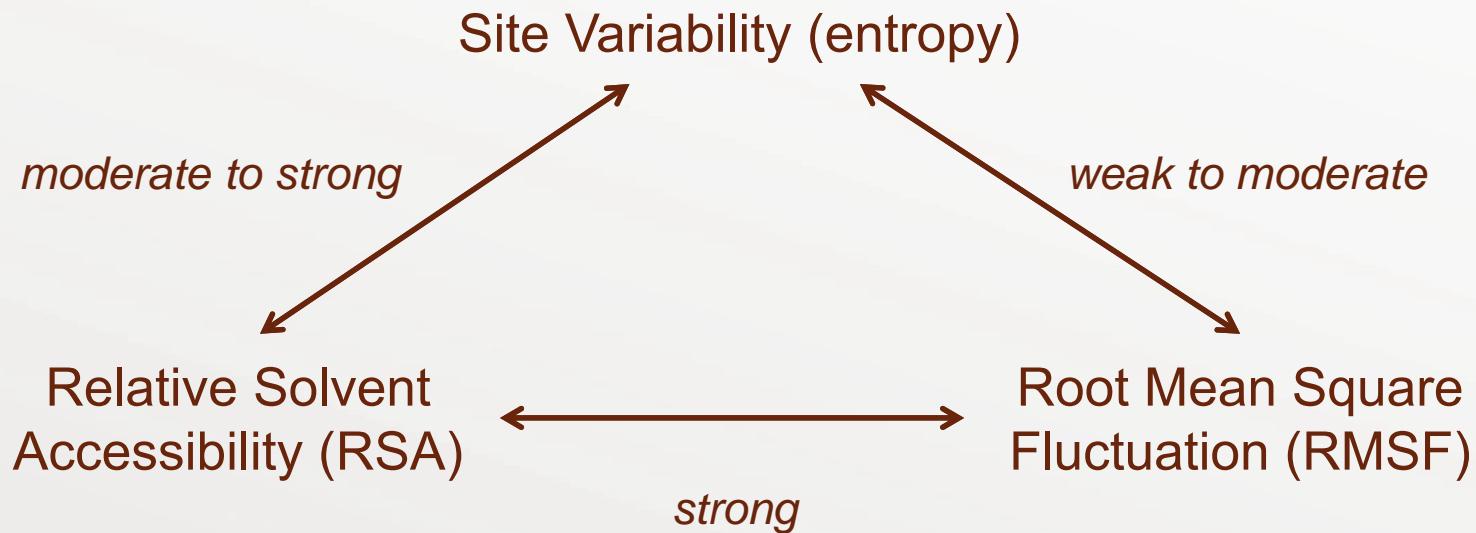


Site variability correlates positively with residue spatial fluctuations in some proteins



Site variability correlates positively with residue spatial fluctuations in some proteins

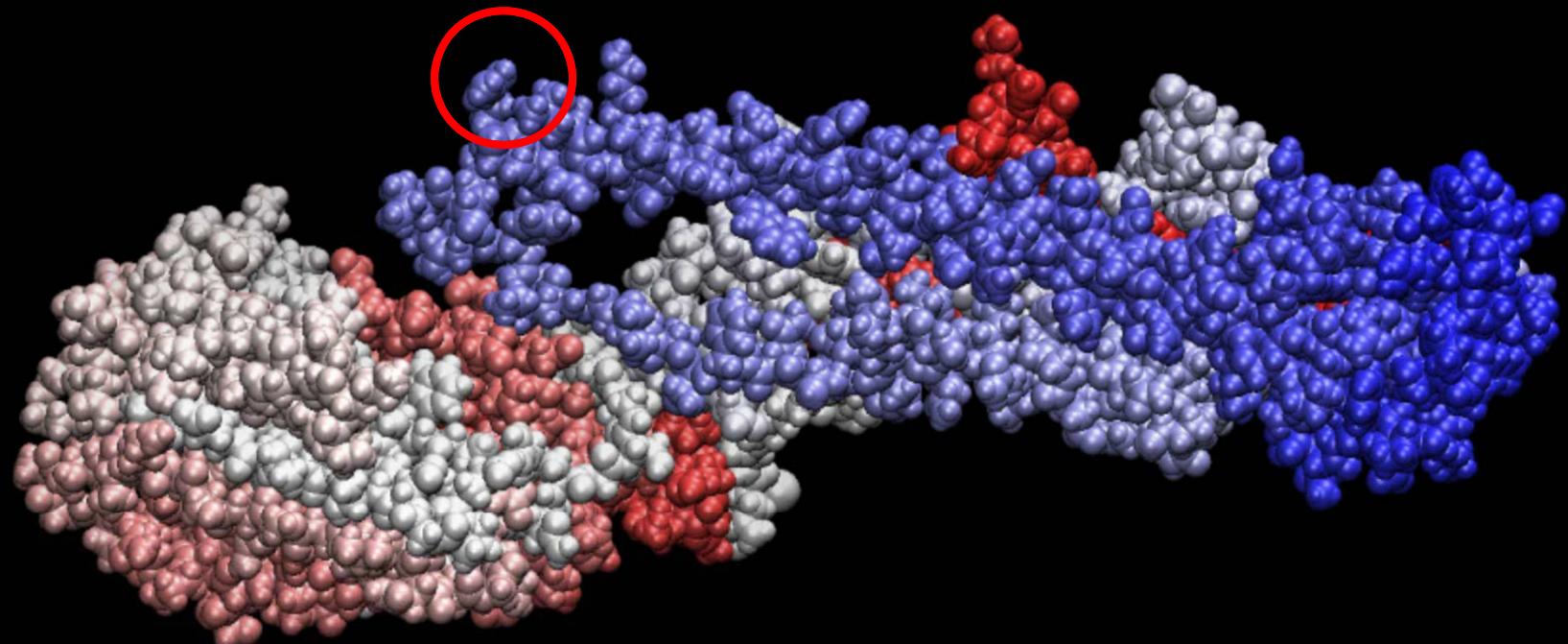
Protein	Spearman correlation	P value
CCHFV Nucleocapsid	0.25	2.8×10^{-8}
Influenza Hemagglutinin	0.06	0.19
Dengue Protease	0.07	0.14
Hepatitis C Protease	0.08	0.06
Influenza Nucleoprotein	0.07	0.15
JEV Helicase	0.15	0.002
MARV RNA Binding Domain	0.04	0.62

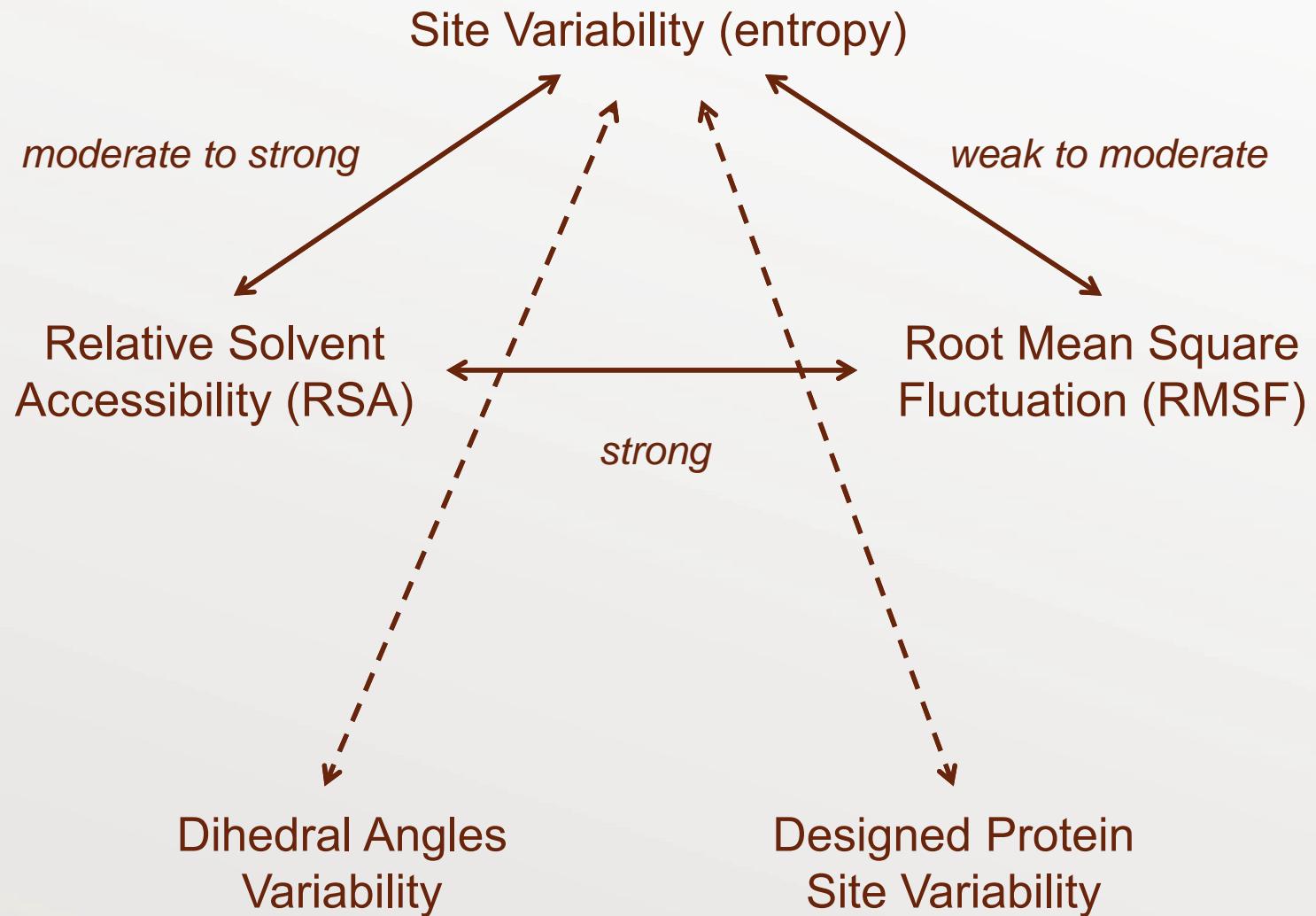


- RMSF inherently does not influence sequence variability to a large degree
 - or
- RMSF from short MD simulations is a biased measure of site-specific mobility and fluctuation

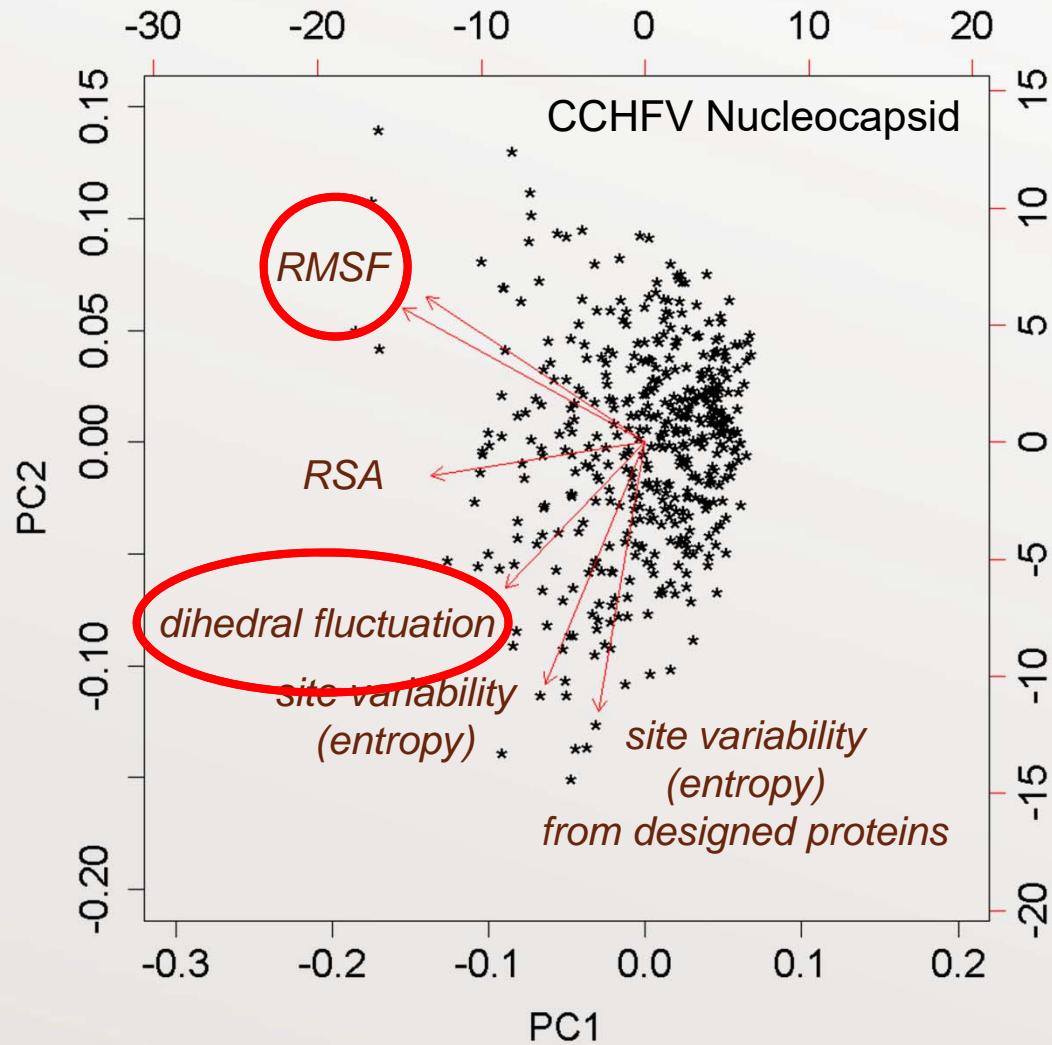
Proteins are dynamic, 3D entities

Influenza virus hemagglutinin





RMSF from short MD simulations is likely a biased measure of site-specific mobility and fluctuation



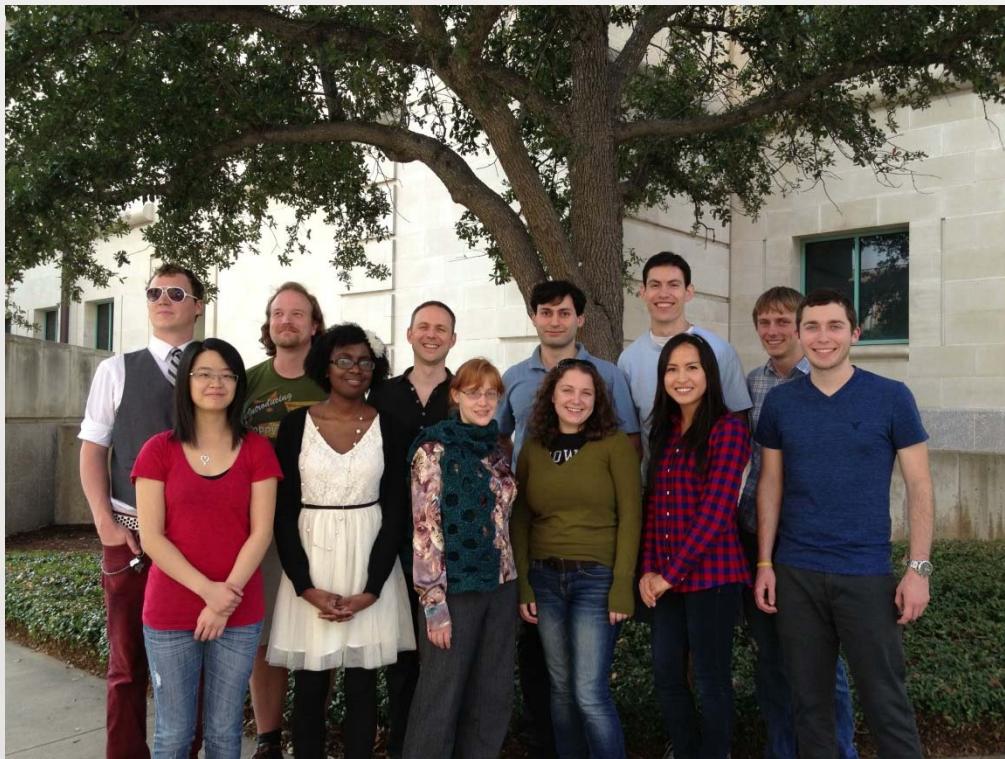
Summary

- Protein's 3D structure and dynamics has significant influence on the sequence evolution and site variability.
- Root-Mean-Square-Fluctuation (RMSF) from MD simulations seems to be a biased measure of site-specific structural fluctuation.
 Possible remedy: run Accelerated MD simulations.
- Solvent accessible area can serve as a good indicator of site-specific evolutionary rates in viral proteins.

Acknowledgments



Claus Wilke (PI)



Wilke Lab members

Austin Meyer

Daria Sydkova

Stephanie Spielman

Eleisha Jackson

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

```
@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},  
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```

References

```
@article{shahmoradi2014predicting,  
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References

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@article{jackson2016intermediate,  
  title={Intermediate divergence levels maximize the strength of structure--  
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```
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  protein sequence evolution},  
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