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**Grenoble
Alpes**



RICE

Studying Protein Structure through Hydrogen Exchange and Coarse- grained Conformational Sampling

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Rice University

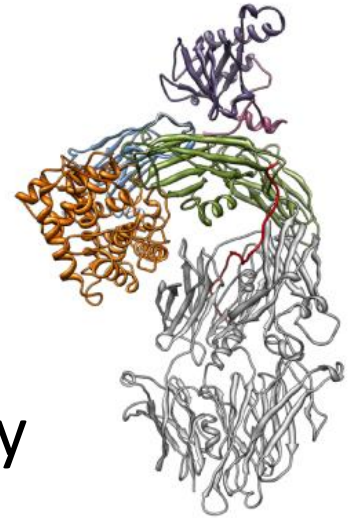
M. Papanastasiou, D. Ricklin, J. Lambris

University of Pennsylvania

Experimental techniques in structural biology

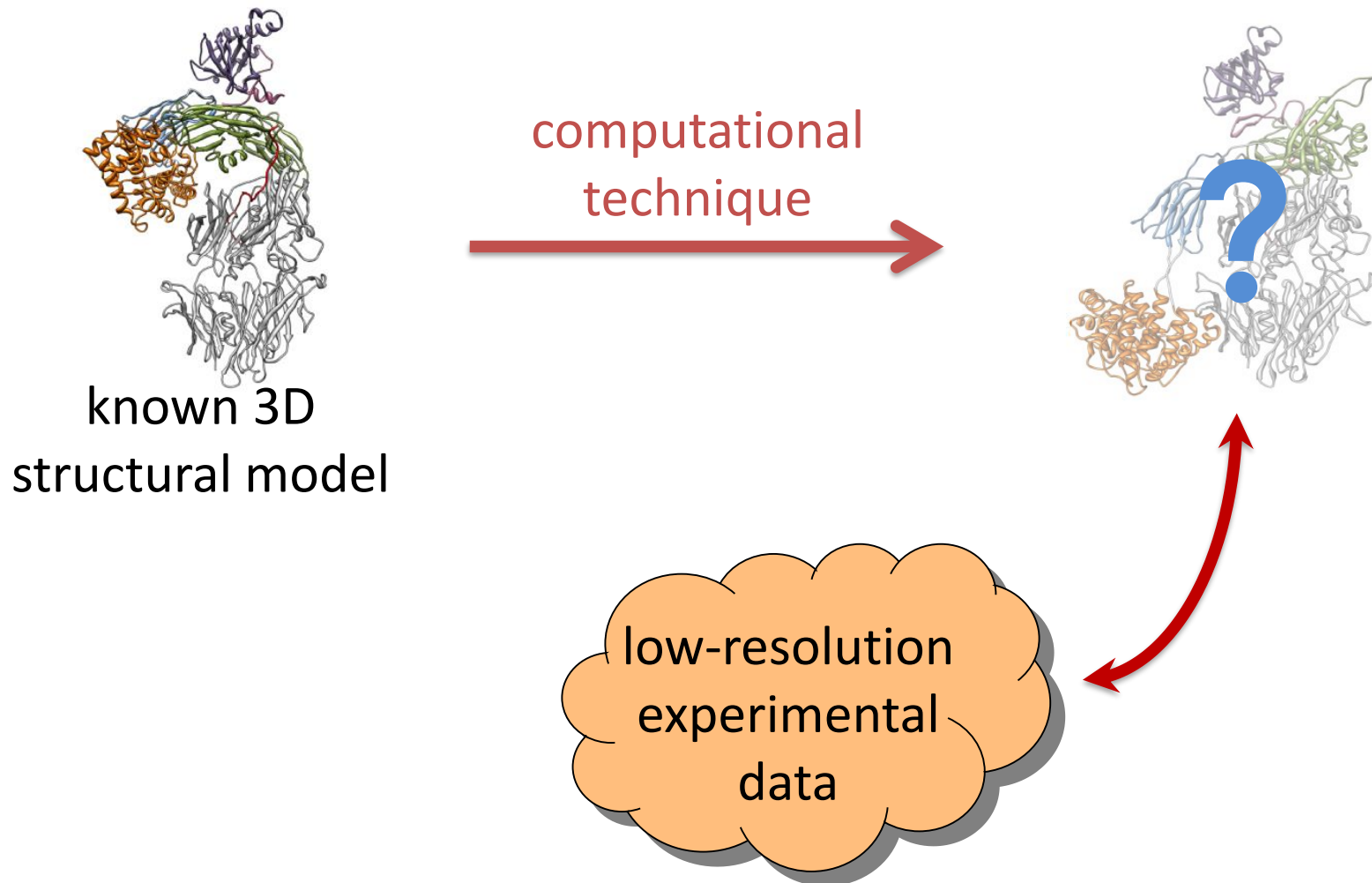
highest resolution → structural model

- X-ray crystallography
 - most structures in protein data bank (PDB)
- nuclear magnetic resonance spectroscopy
- cryo-electron microscopy
- ...
- hydrogen exchange / mass spectrometry



lowest resolution

Objective: study a protein state described by low-resolution experimental data



Hydrogen exchange detected by mass spectrometry (HX-MS)

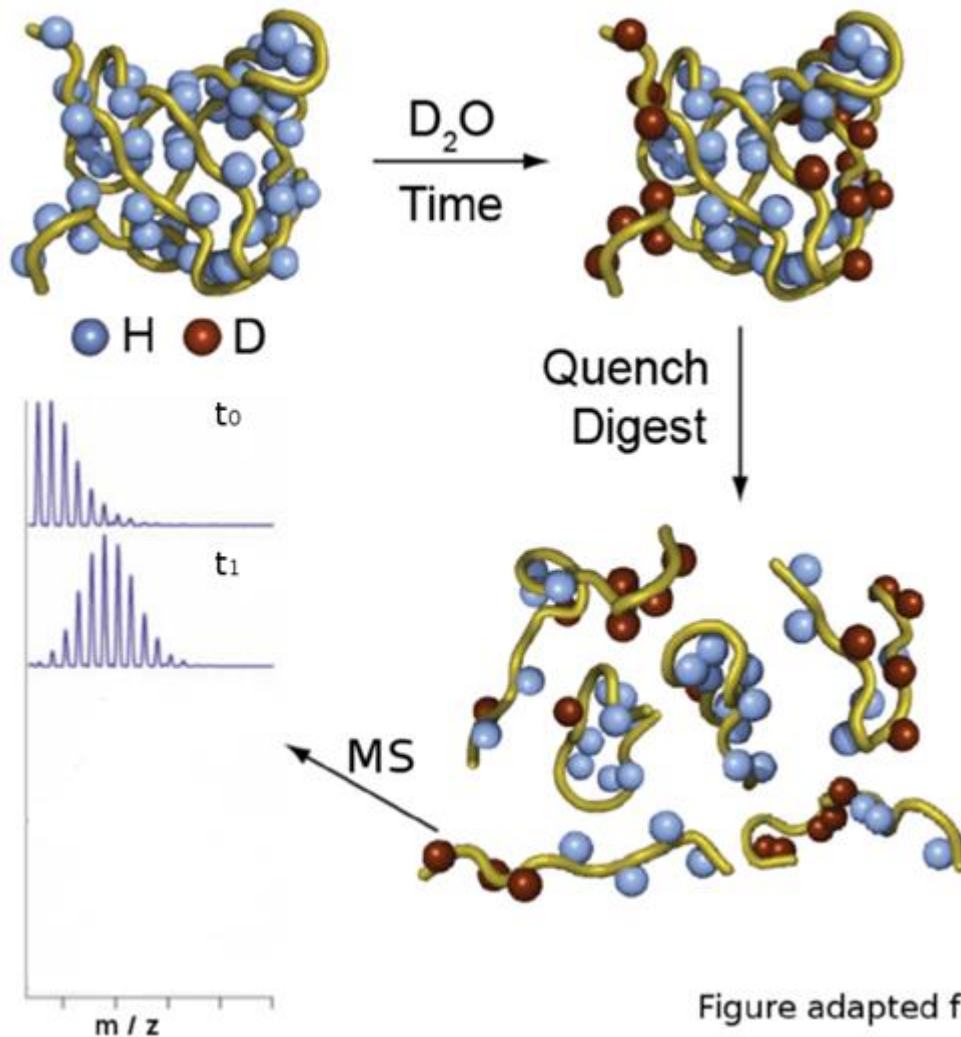
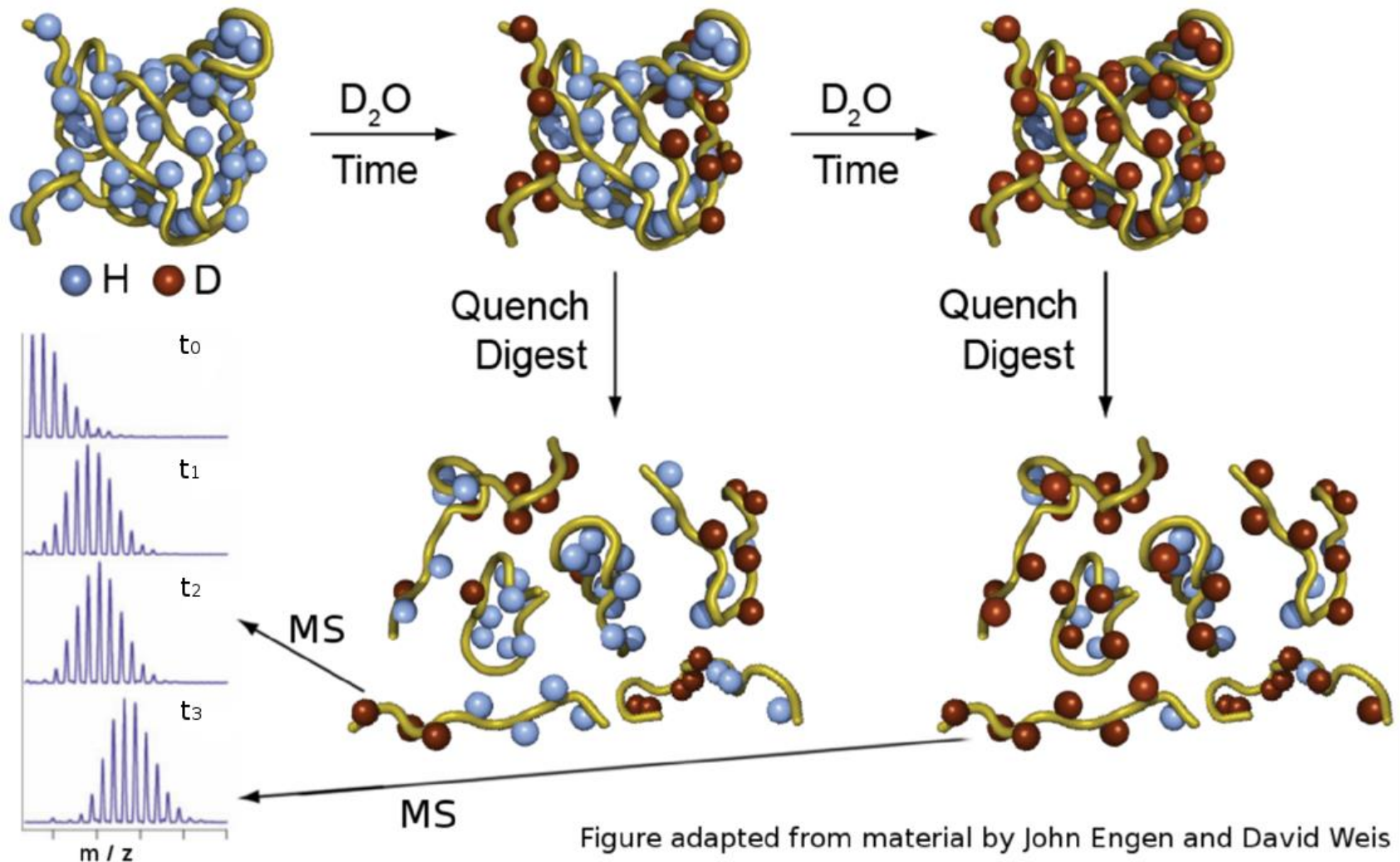


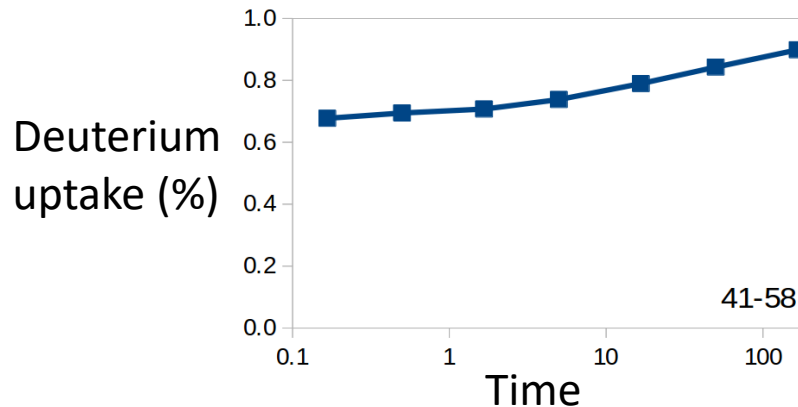
Figure adapted from material by John Engen and David Weis

Hydrogen exchange detected by mass spectrometry (HX-MS)



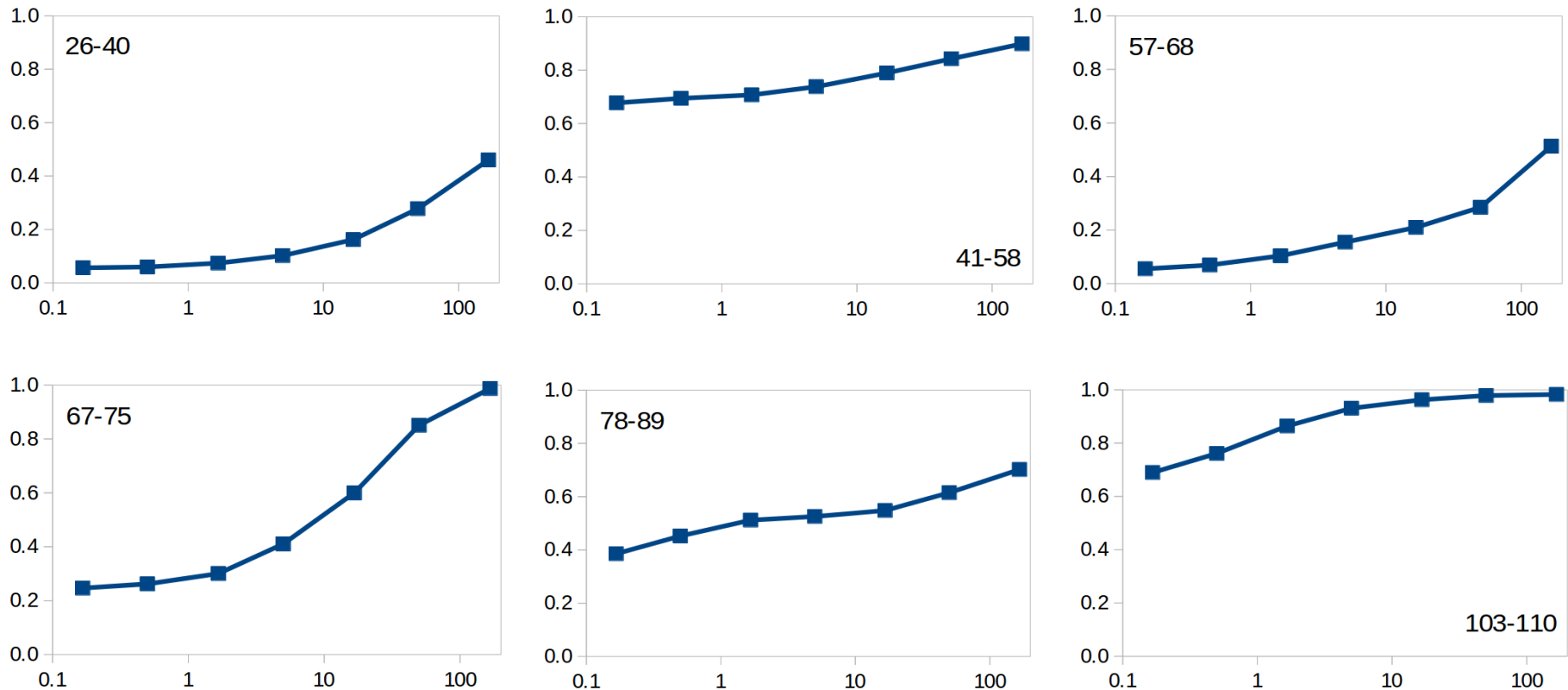
Hydrogen exchange detected by mass spectrometry (HX-MS)

Output: deuterium-uptake curves of peptides

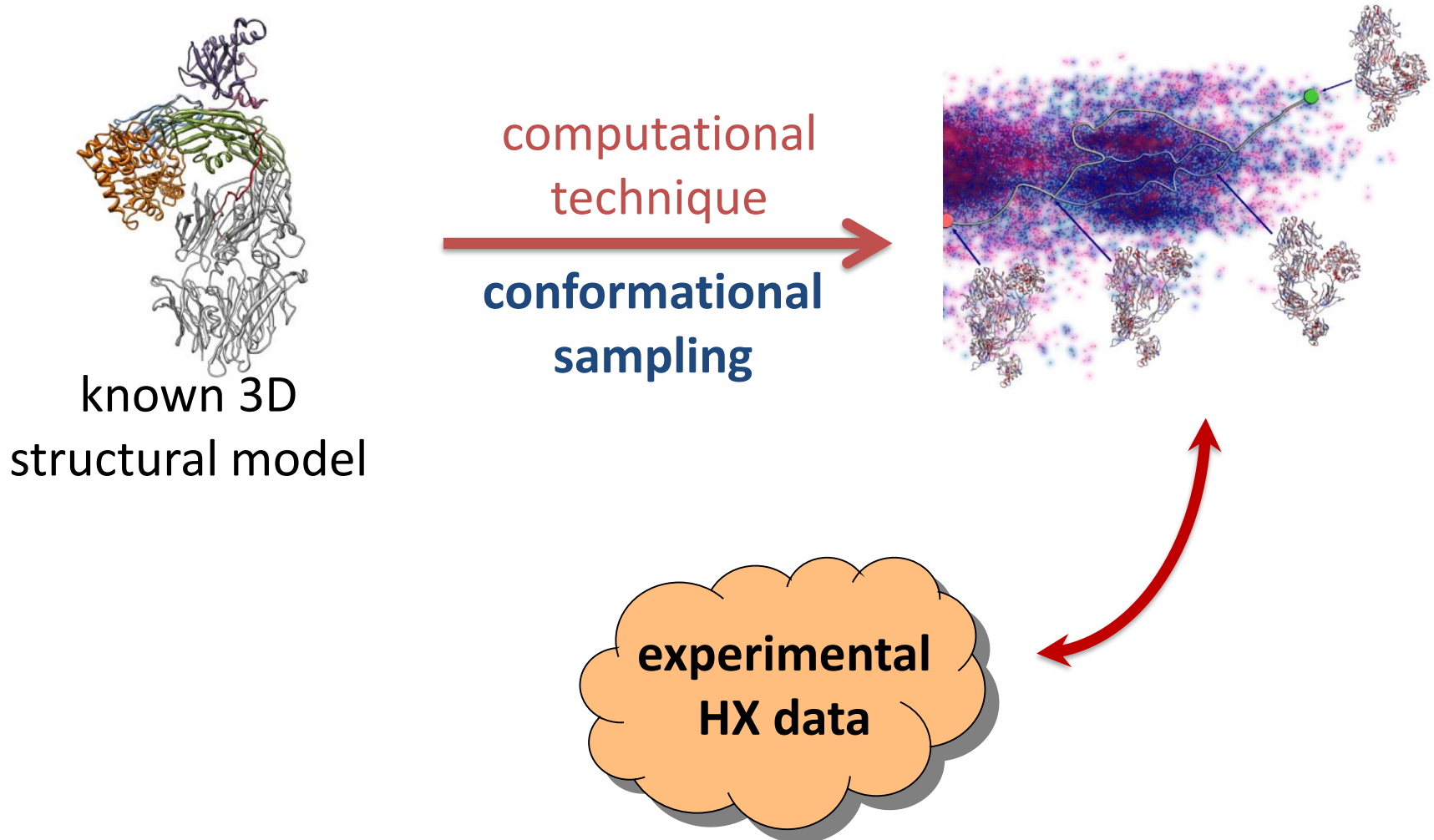


Hydrogen exchange detected by mass spectrometry (HX-MS)

Output: deuterium-uptake curves of peptides



Studying a protein state described by experimental HX data



Computational techniques for protein conformational sampling

Molecular dynamics

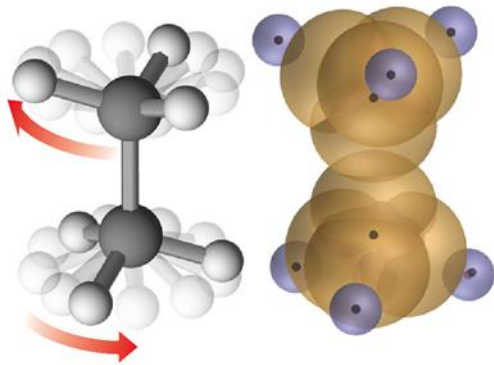
Markov-chain Monte Carlo

Coarse-grained conformational sampling

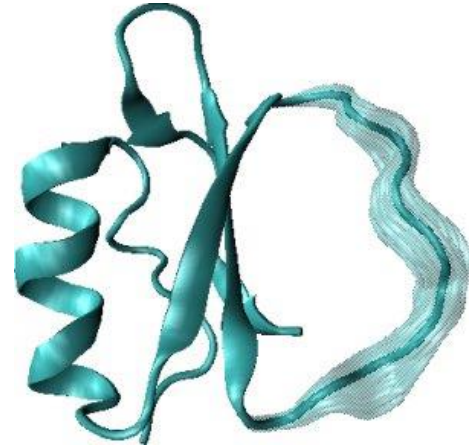
sampling-based planning algorithms (from robotics)

→ **SIMS** (structured intuitive move selector)

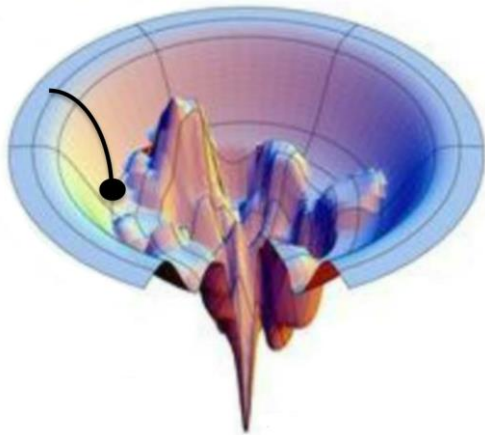
Structured intuitive move selector (SIMS)



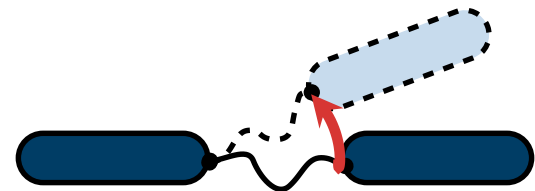
dihedral angle perturbation



closed loop sampling

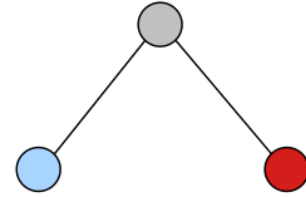
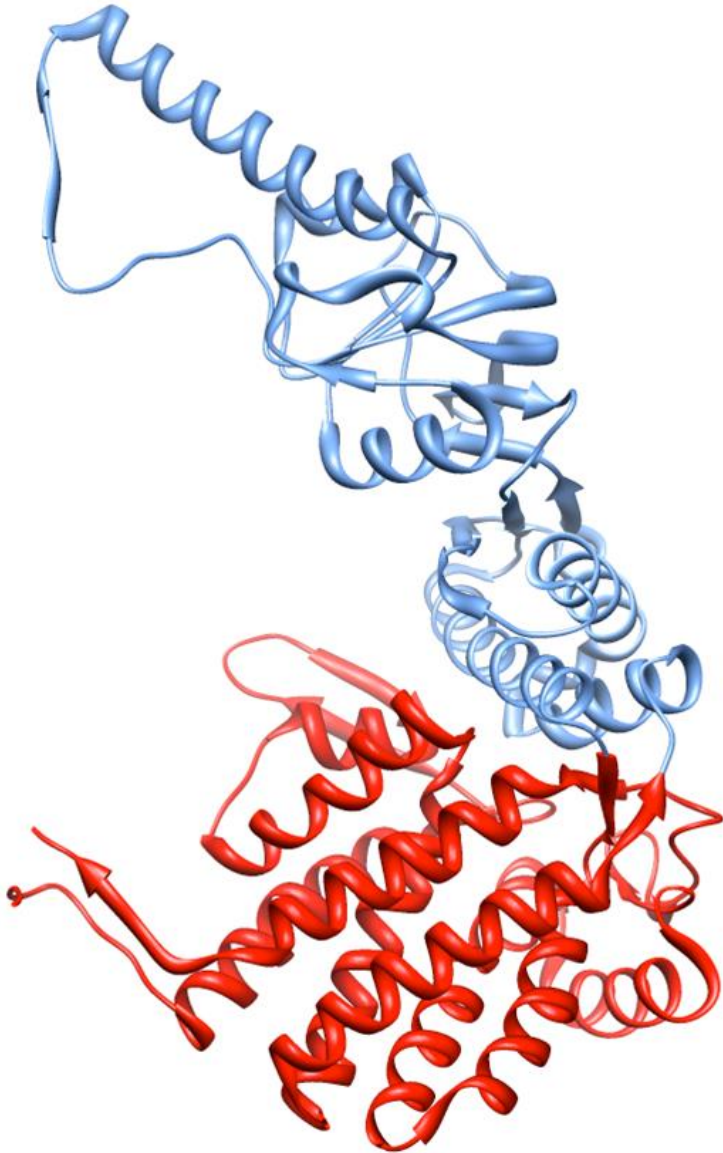


energy minimization

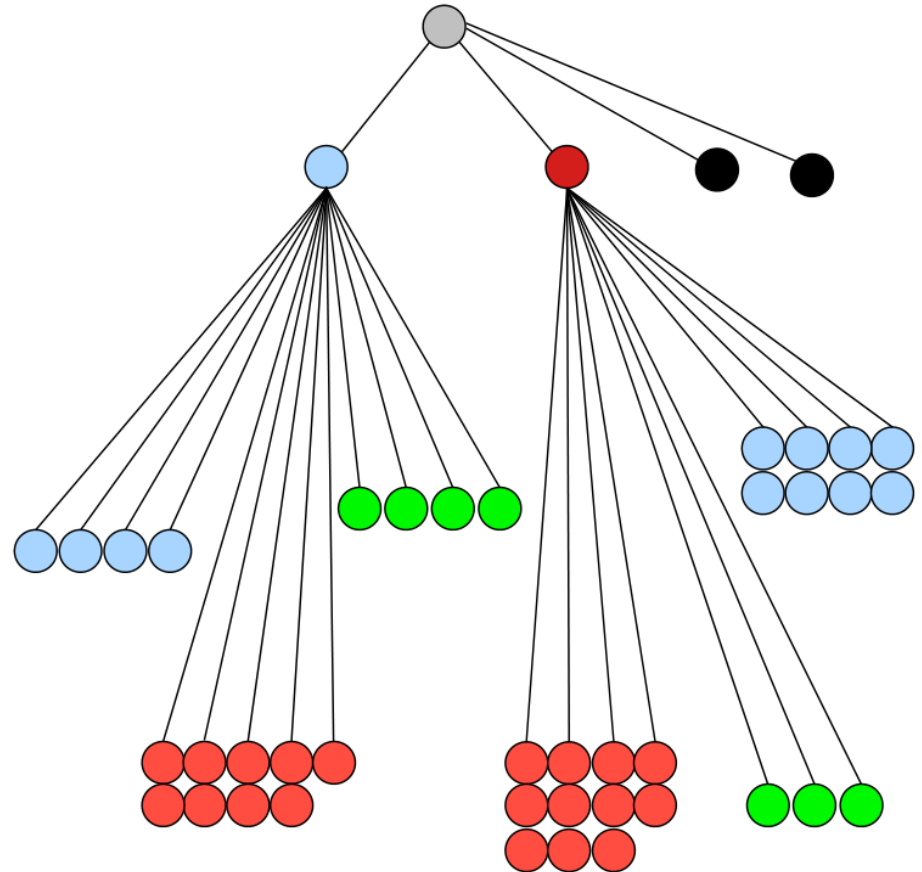
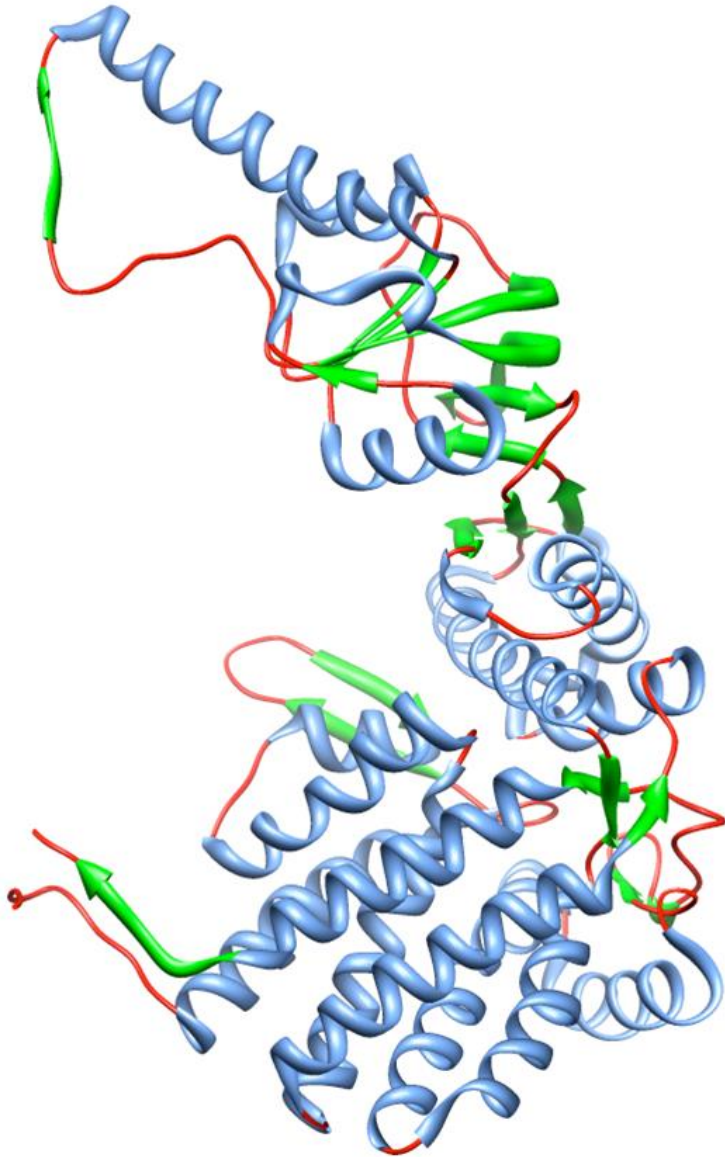


rigid-body transformation

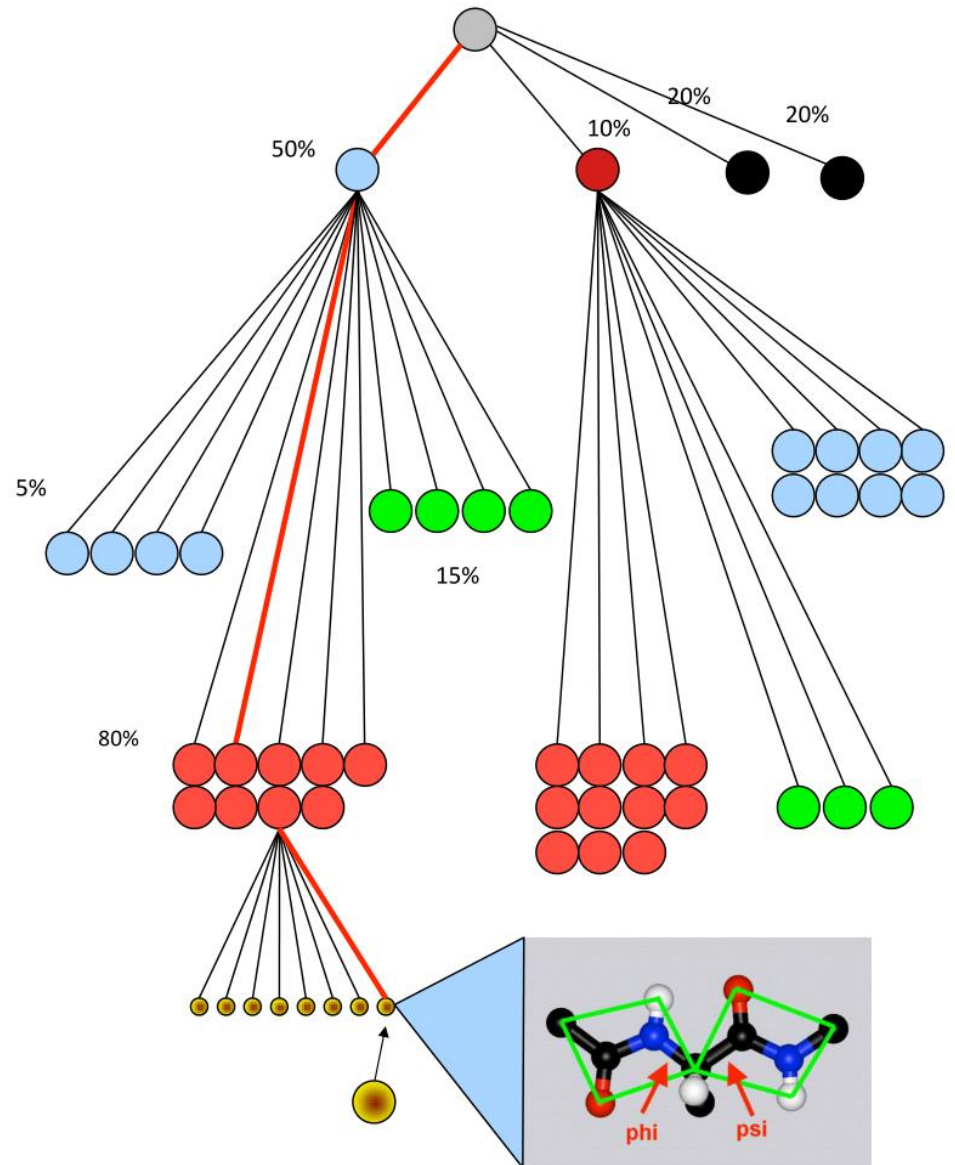
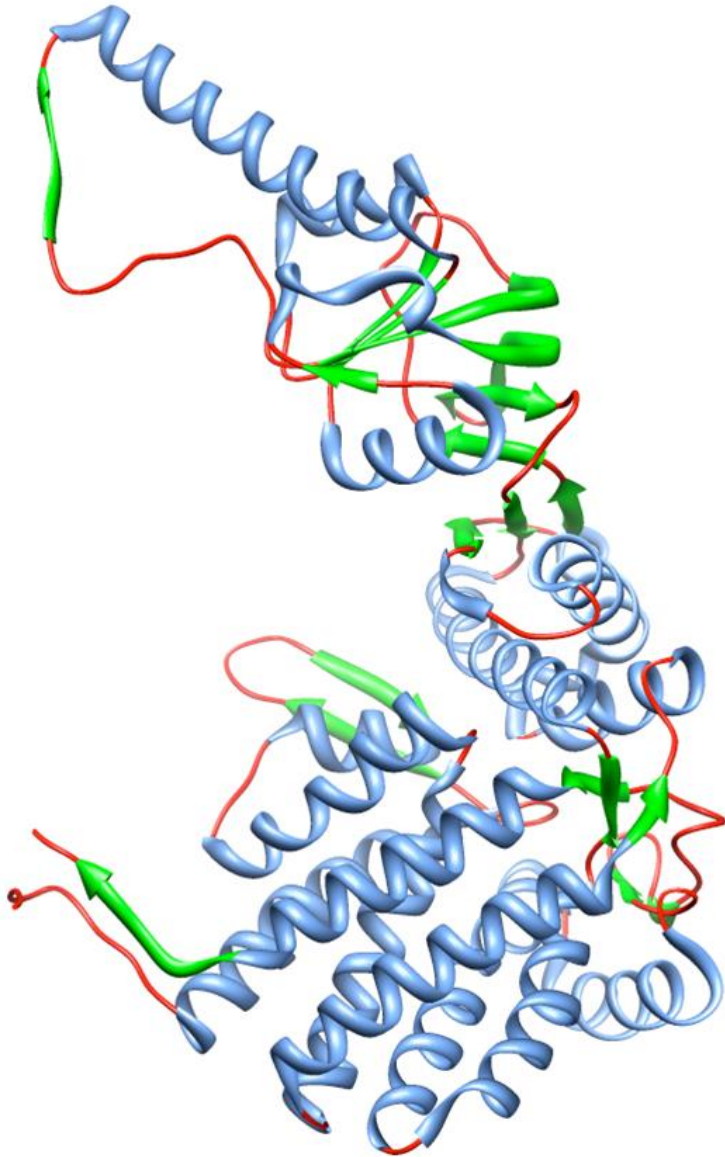
Multi-resolution conformational sampling



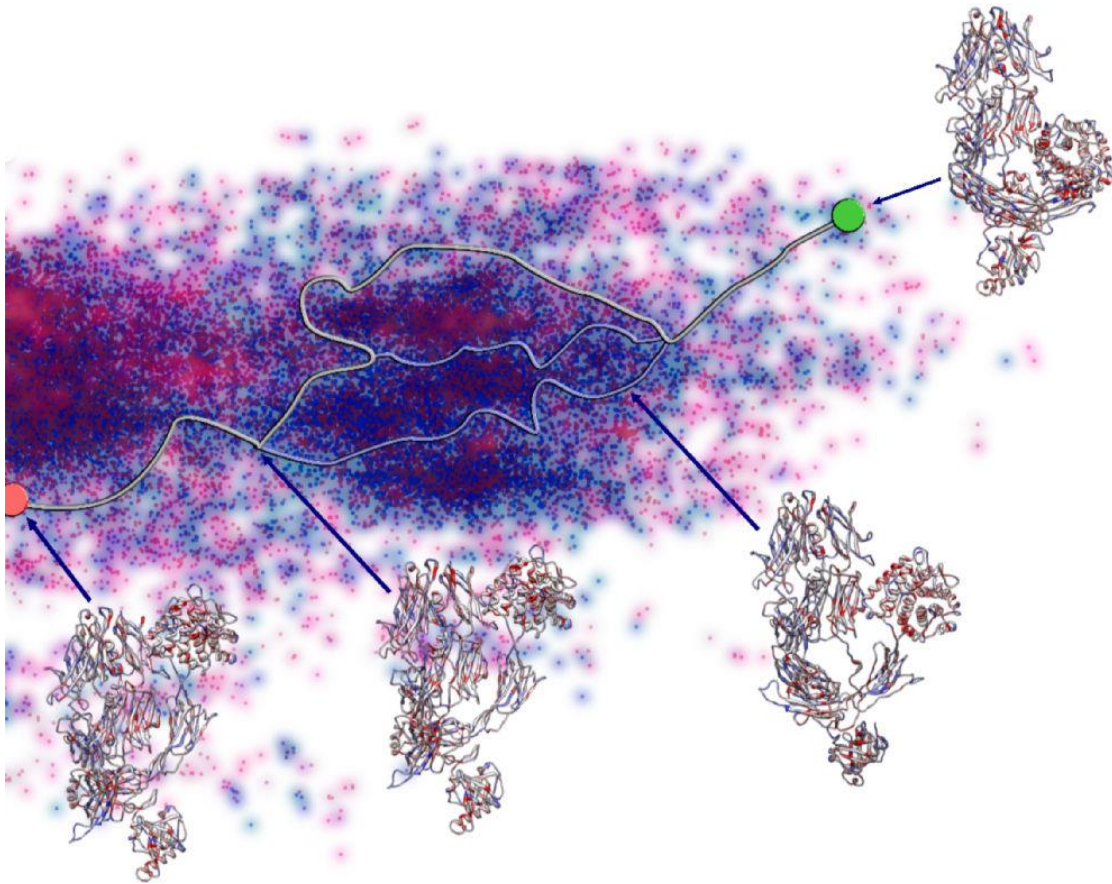
Multi-resolution conformational sampling



Multi-resolution conformational sampling



How to assess the conformations generated by the sampling method?



HX prediction model: conformation → HX data

Hydrogen-exchange prediction model

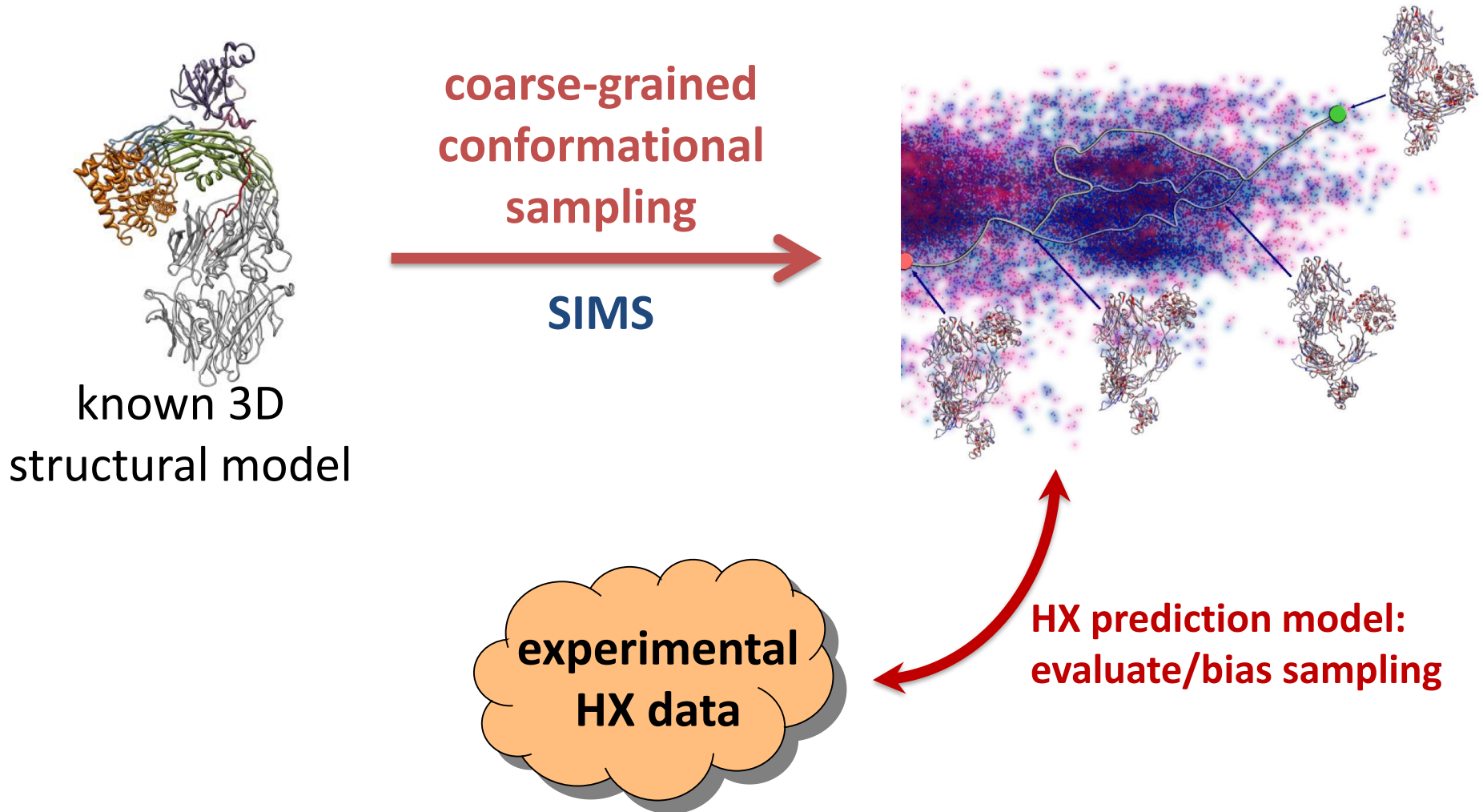
Phenomenological approximation of
protection from hydrogen exchange

[Vendruscolo, Paci, Karplus]

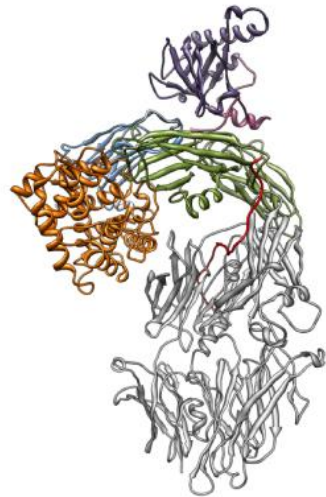
Idea: hydrogen exchange is influenced by
residue—residue interactions

- hydrogen bonds
- packing density

Studying a protein state using HX data and conformational sampling

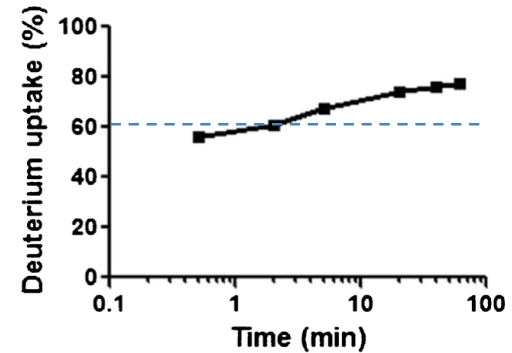


App. 1: Improve the fit to experimental hydrogen-exchange data

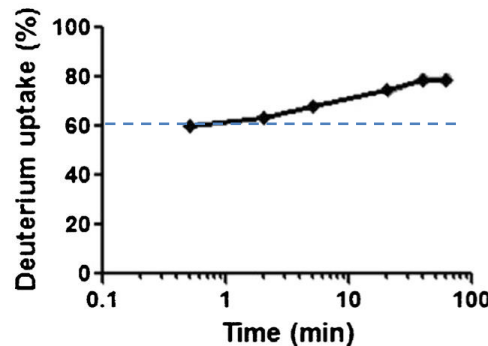


crystal structure

phenomenological
equation

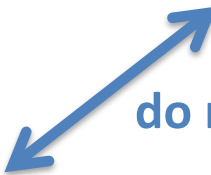


**structurally-derived
HX data**



**experimentally-observed
HX data**

do not usually match



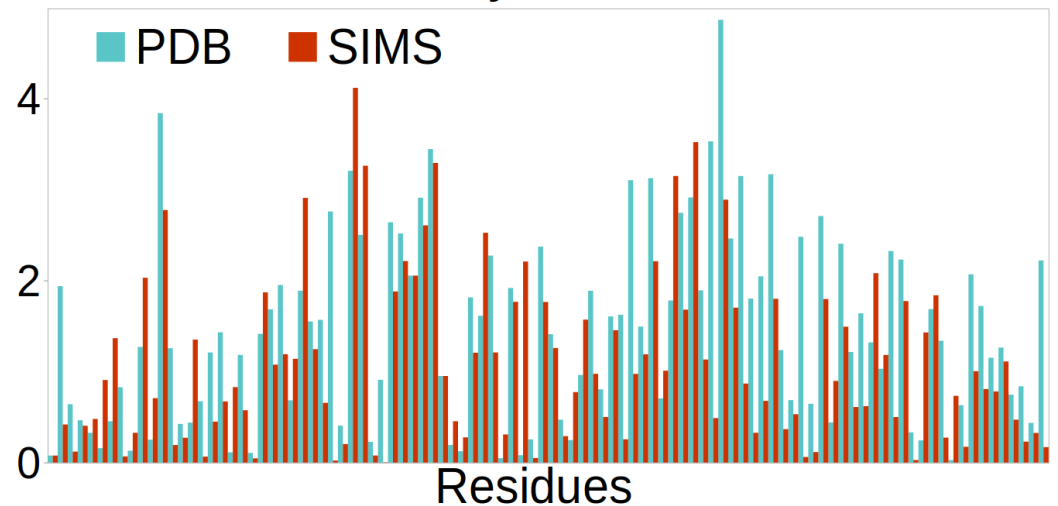
[Devaurs, Antunes,
Papanastasiou, Moll, Ricklin,
Lambris, Kavraki; Frontiers in
Molecular Biosciences, 2017]

Staphylococcal Nuclease (SN)

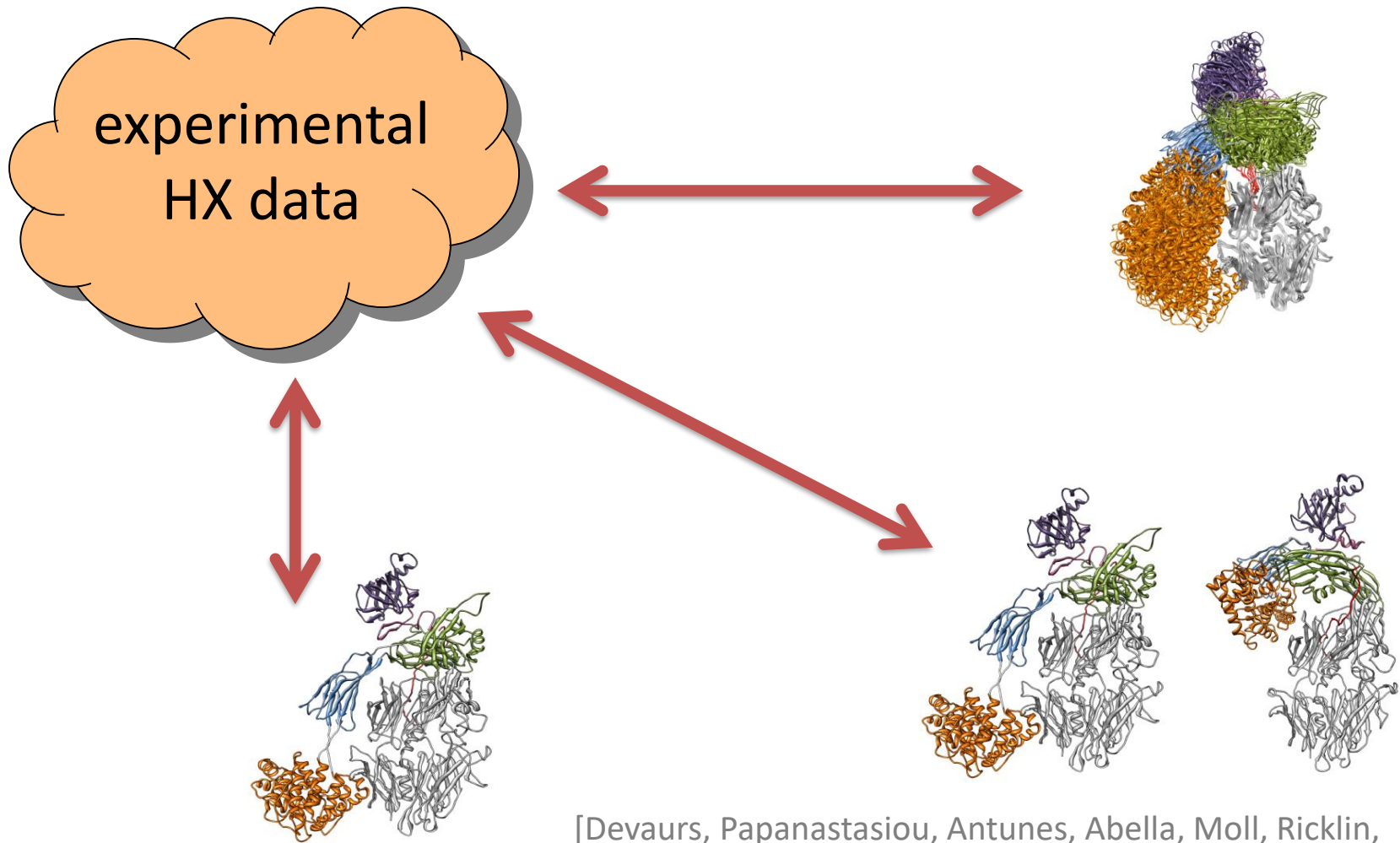


- Structure reported in the PDB
- Structure generated by SIMS

Difference between experimentally-obtained and structurally-derived HX data



App. 2: Analyze the variability of a protein's native state

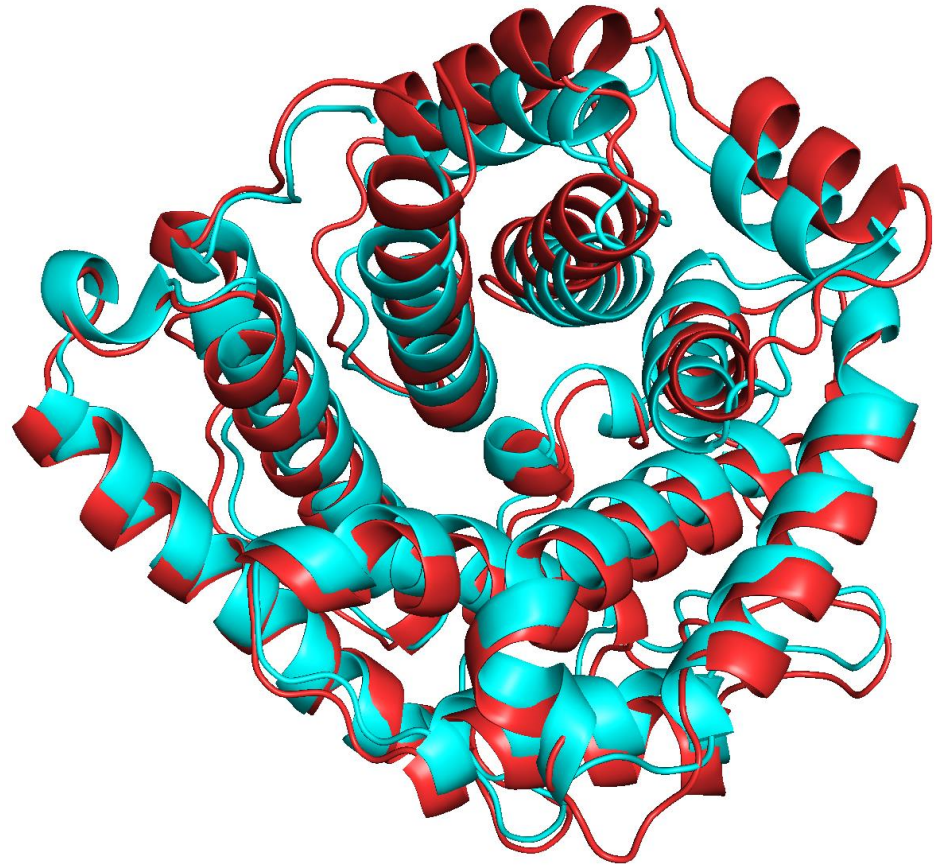
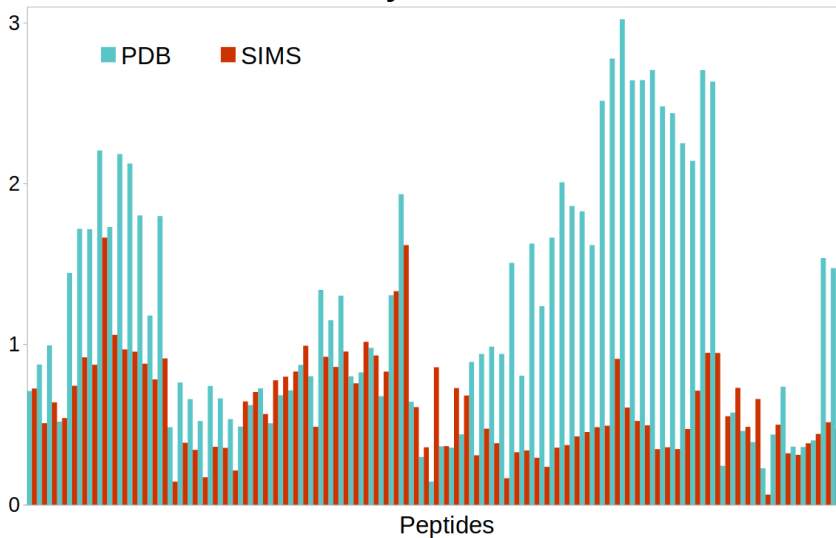


[Devaurs, Papanastasiou, Antunes, Abella, Moll, Ricklin, Lambris, Kavraki; Int J Comp Bio Drug Design, 2018]

Complement protein C3d

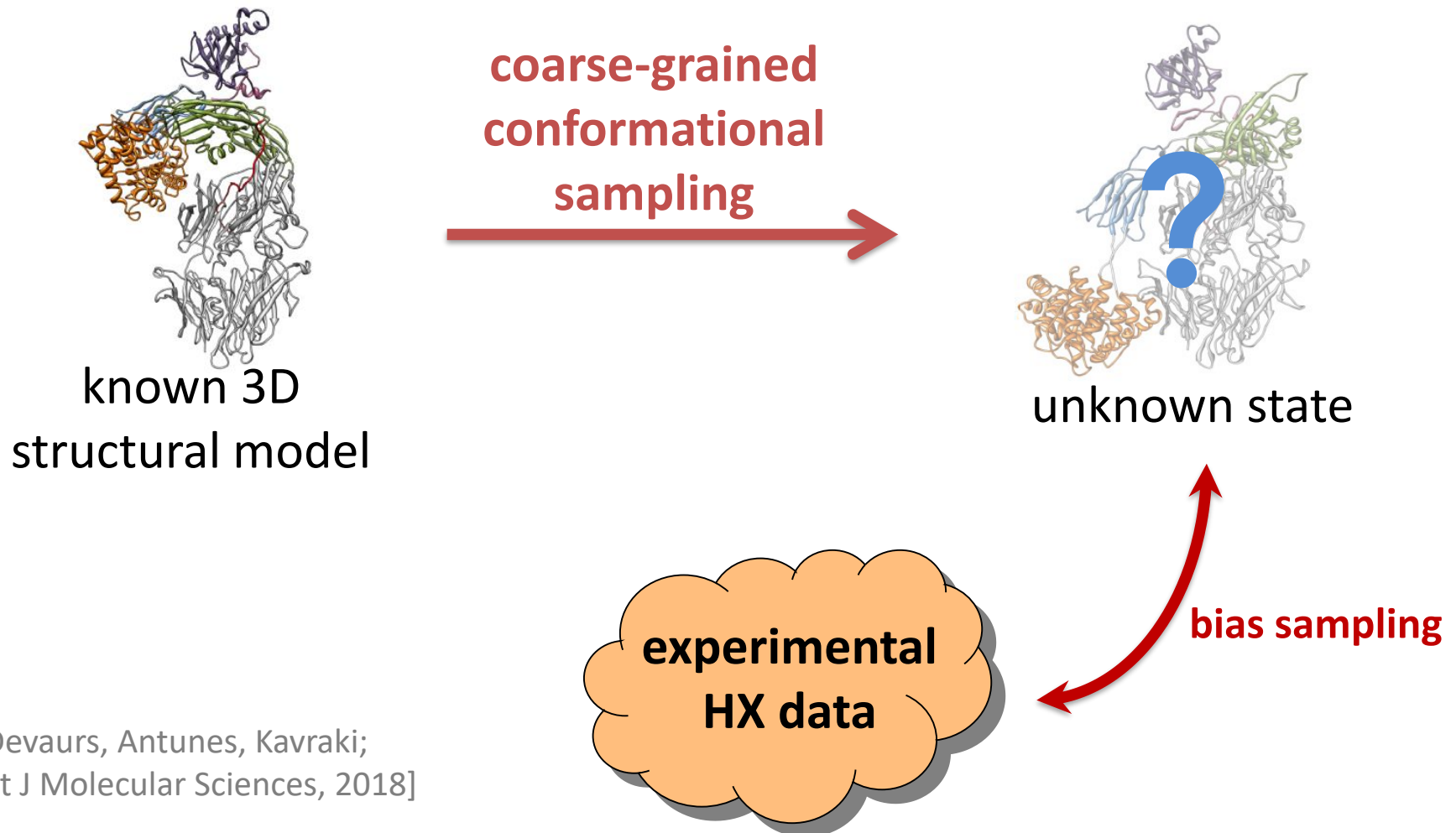
Differences between the PDB and SIMS conformations characterize the variability of C3d's native state

Difference between experimentally-obtained and structurally-derived HX data



Structure reported in the PDB
Structure generated by SIMS

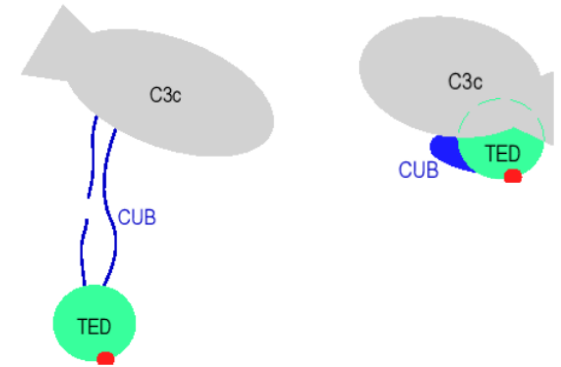
App. 3: Generate a structural model for an unknown protein state



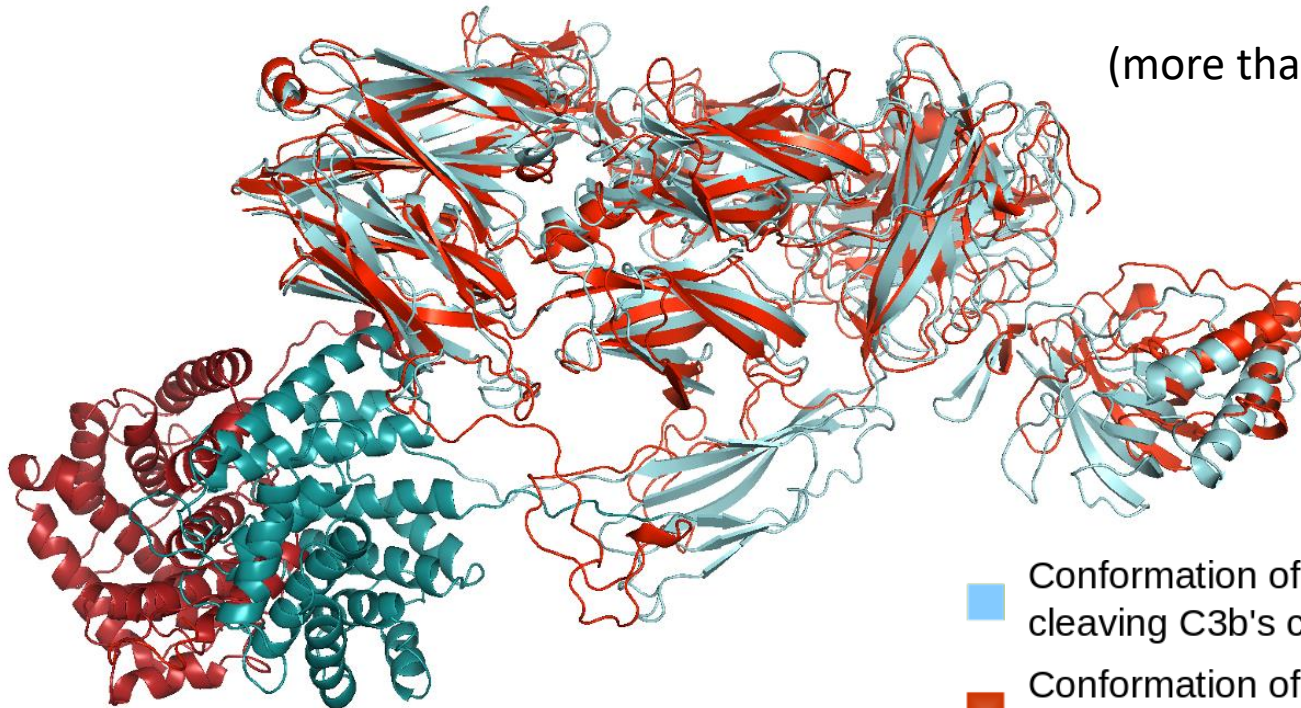
Complement protein iC3b

Problem: no high-resolution structural model
(but two competing low-resolution models)

Solution: SIMS yields a conformation
that helps validate one model



(more than 1500 amino acids)



- Conformation of iC3b obtained by cleaving C3b's crystal structure
- Conformation of iC3b produced by SIMS guided by the HX-MS data

Conclusion

Hydrogen exchange (HX) combined with **coarse-grained conformational sampling** is useful to study protein structure

Current applications

- 1) improve the fit to experimental HX data
- 2) analyze the variability of a protein's native state
- 3) generate a structural model for an unknown state



Thank you!

Prof. Lydia Kavraki



Prof. John Lambris

