

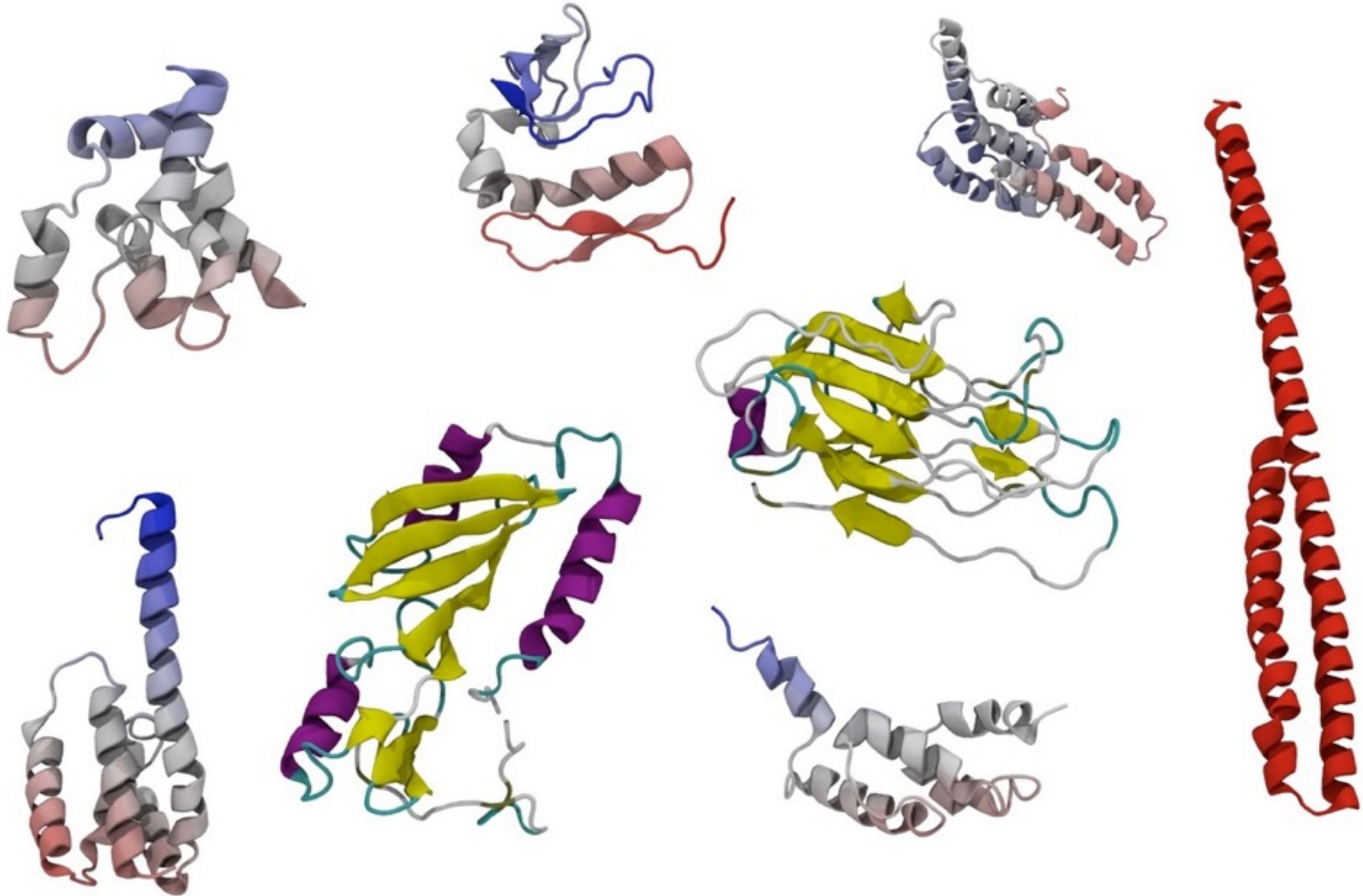
# From sequence to structure to binding using physics and GPUs

Alberto Perez

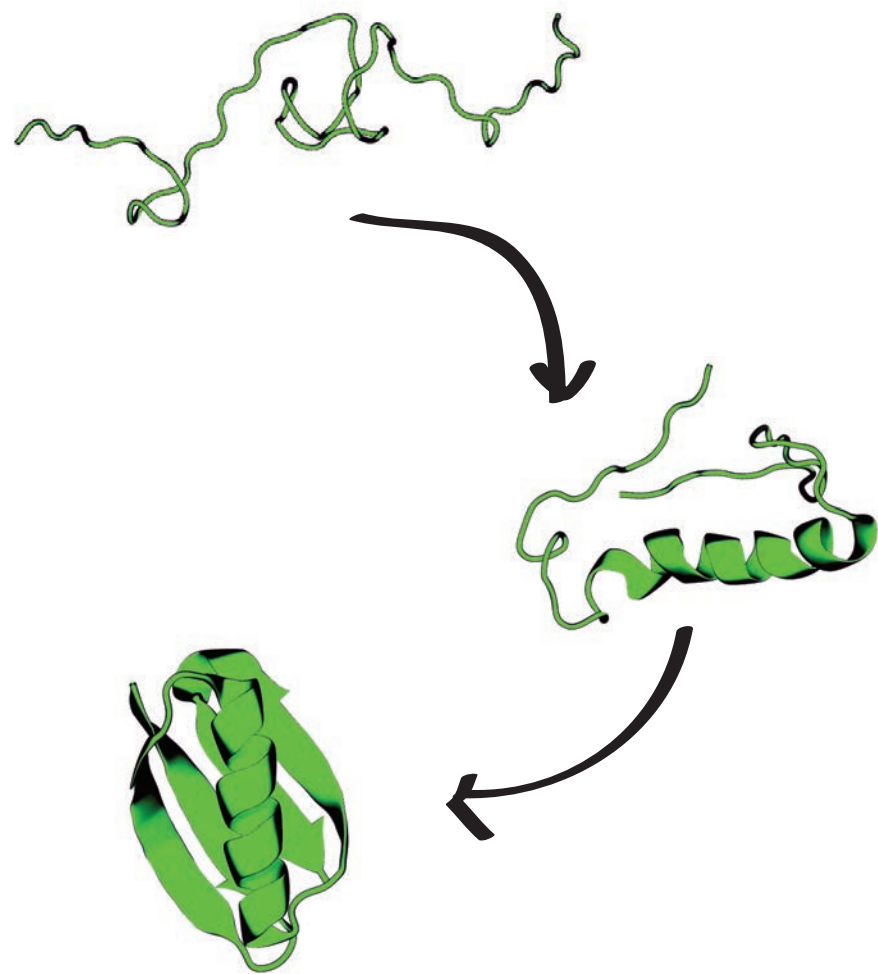
Dill group

Proteins fold and have hydrophobic  
cores

# Proteins are diverse



# The protein folding problem



Can we use computers to predict the structure of proteins from their sequence?

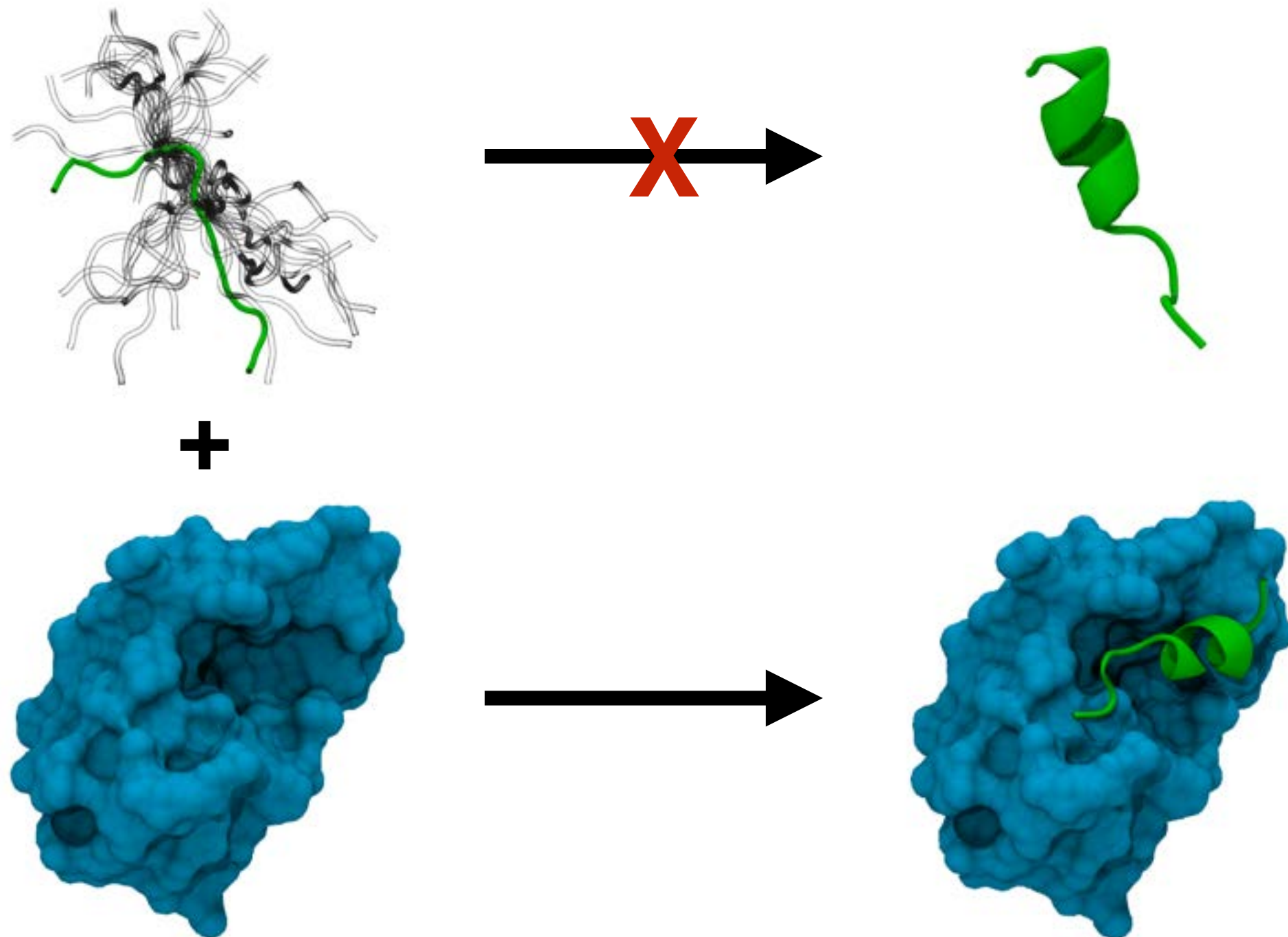
Protein Folding/  
Structure prediction



# Protein structure is key to rational drug design



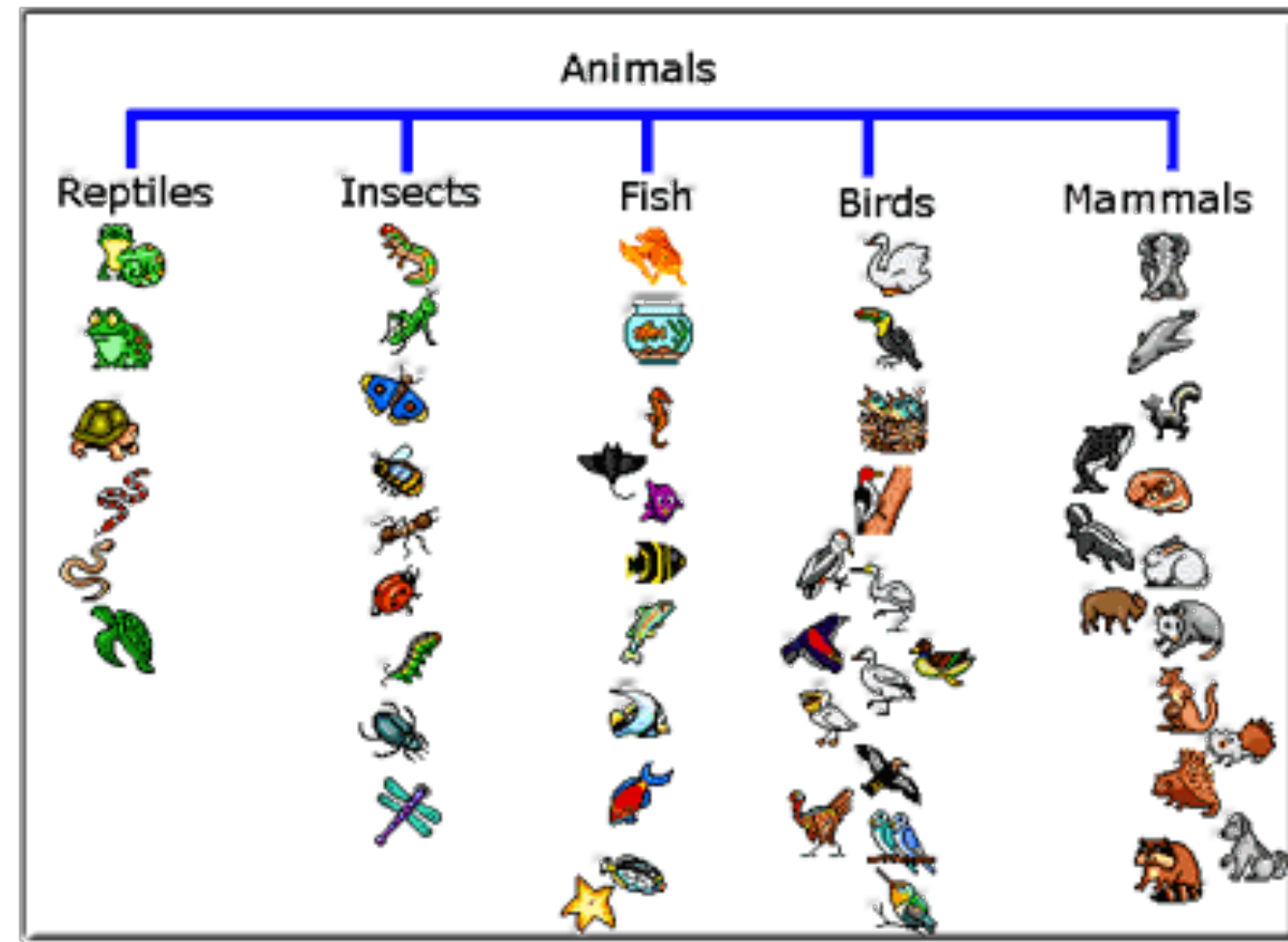
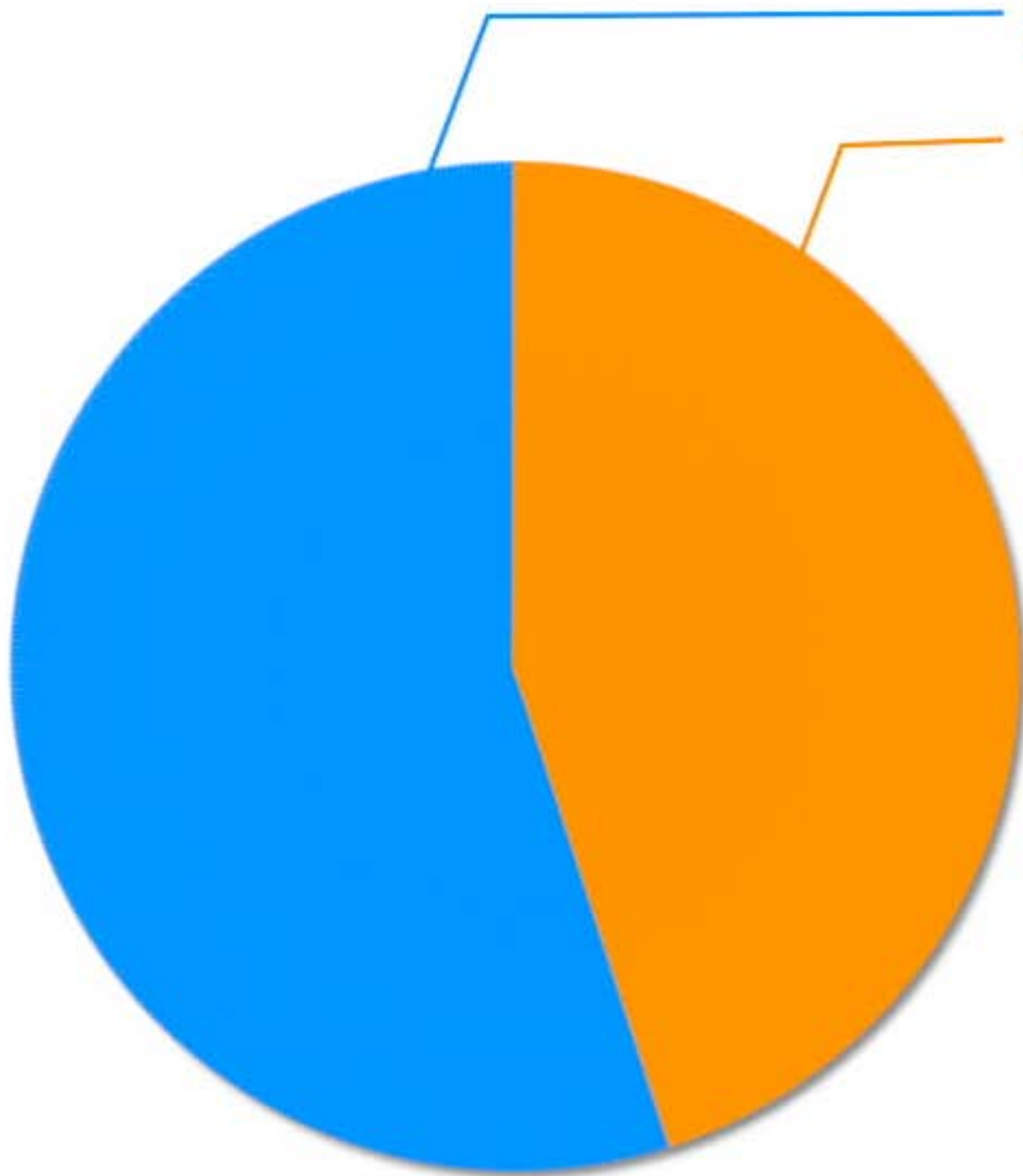
# Peptide interactions in cancer



# We don't know what half of the protein families look like

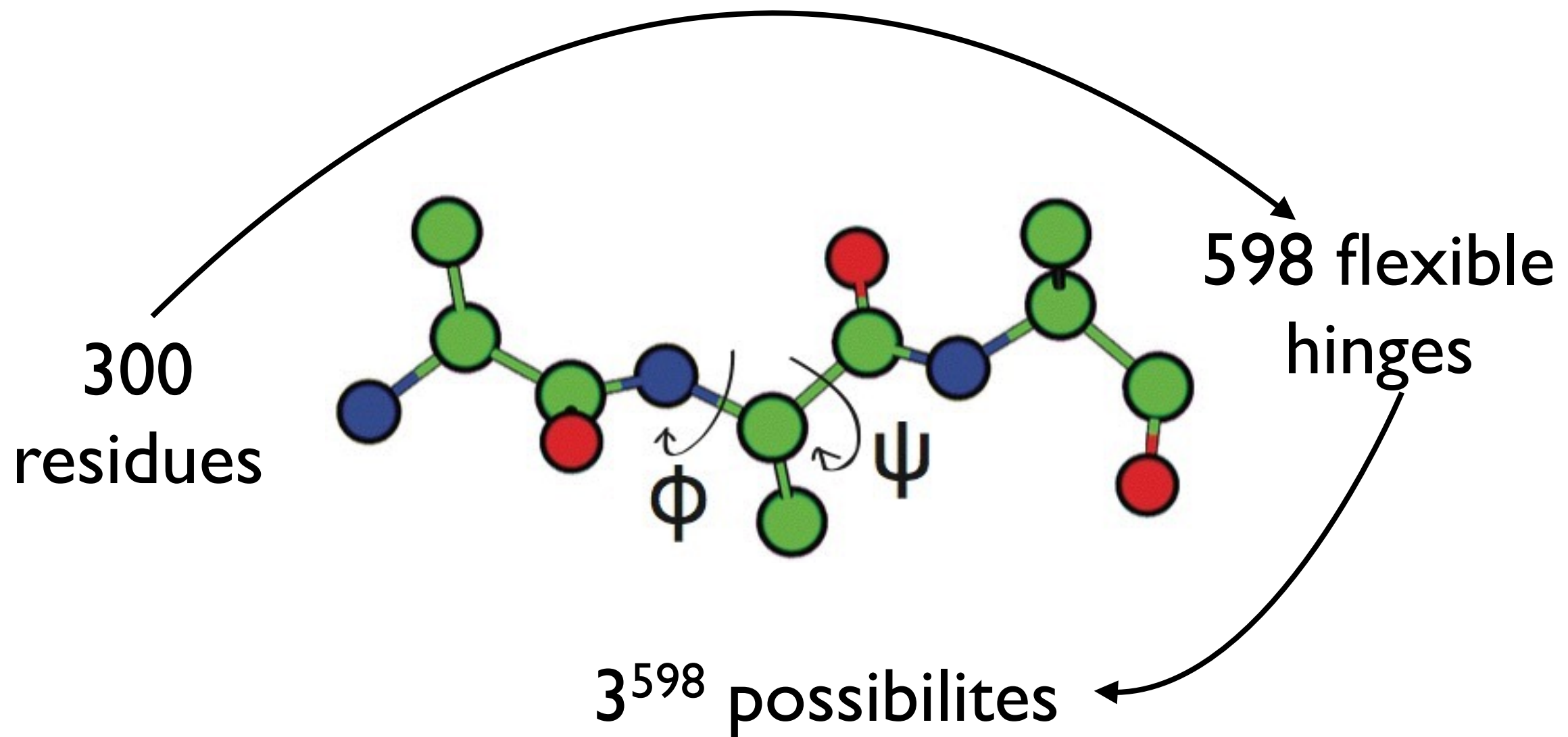
55% No Structure

45% One Structure





# Why BlueWaters? Huge conformational surface to sample



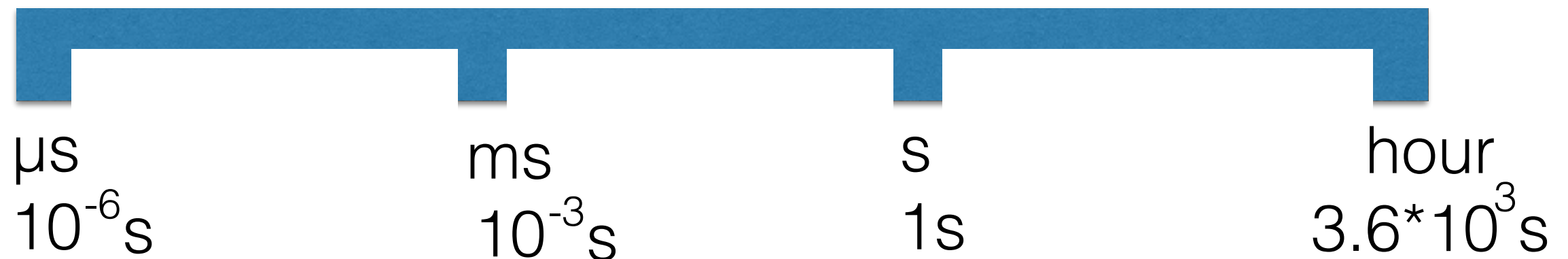




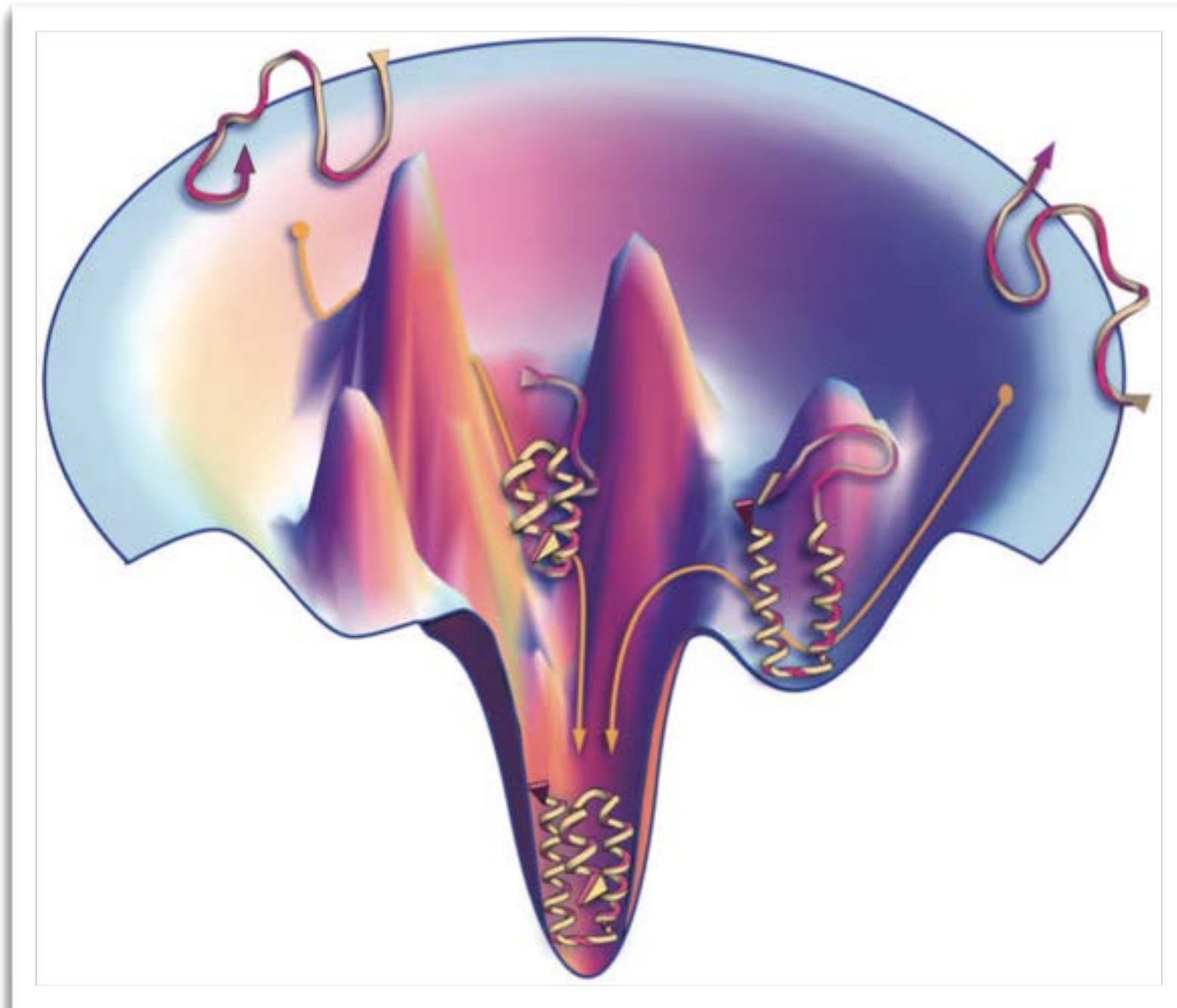


# Proteins find the native state fast

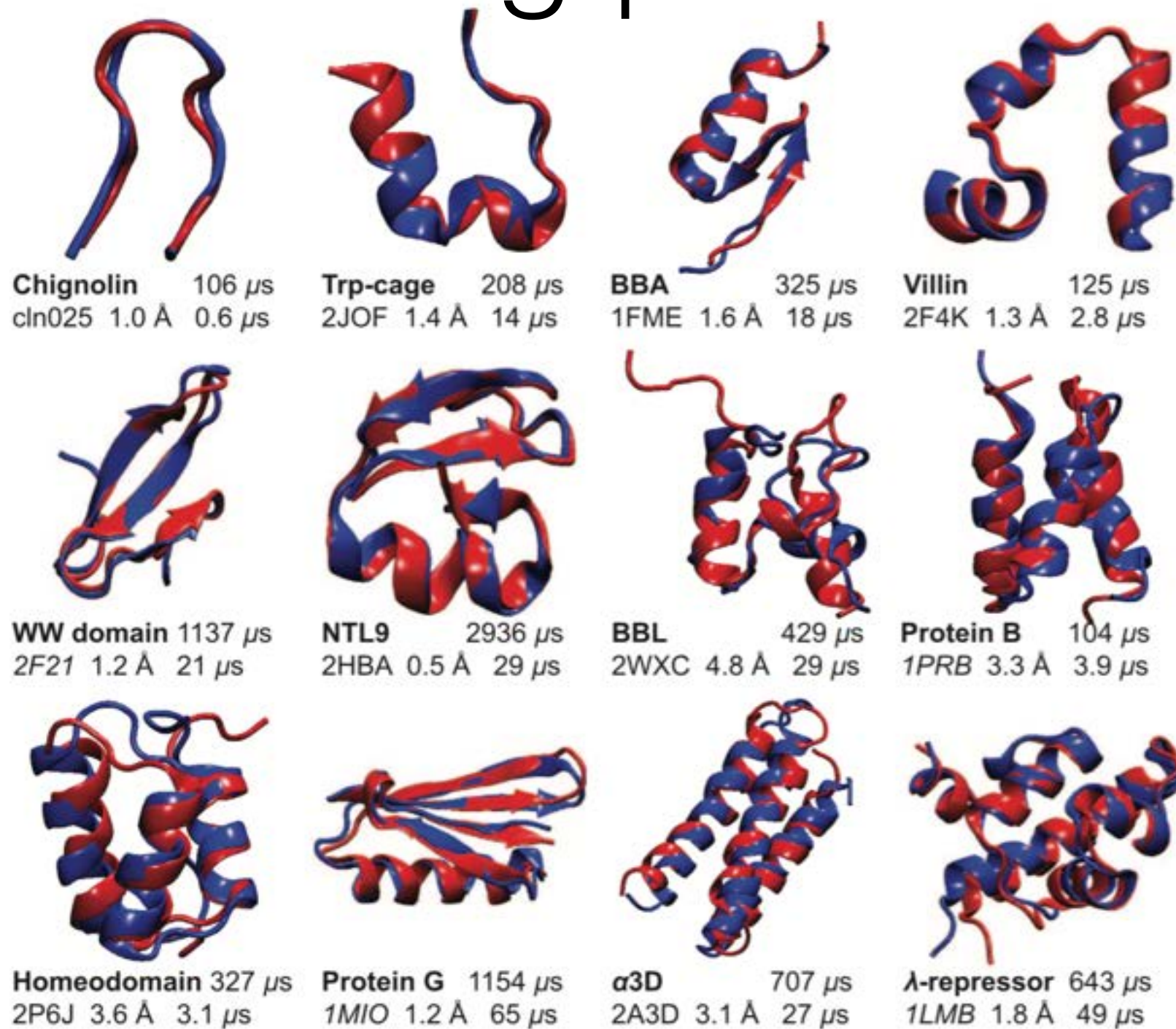
## Protein Folding Time



# Proteins have funneled landscapes

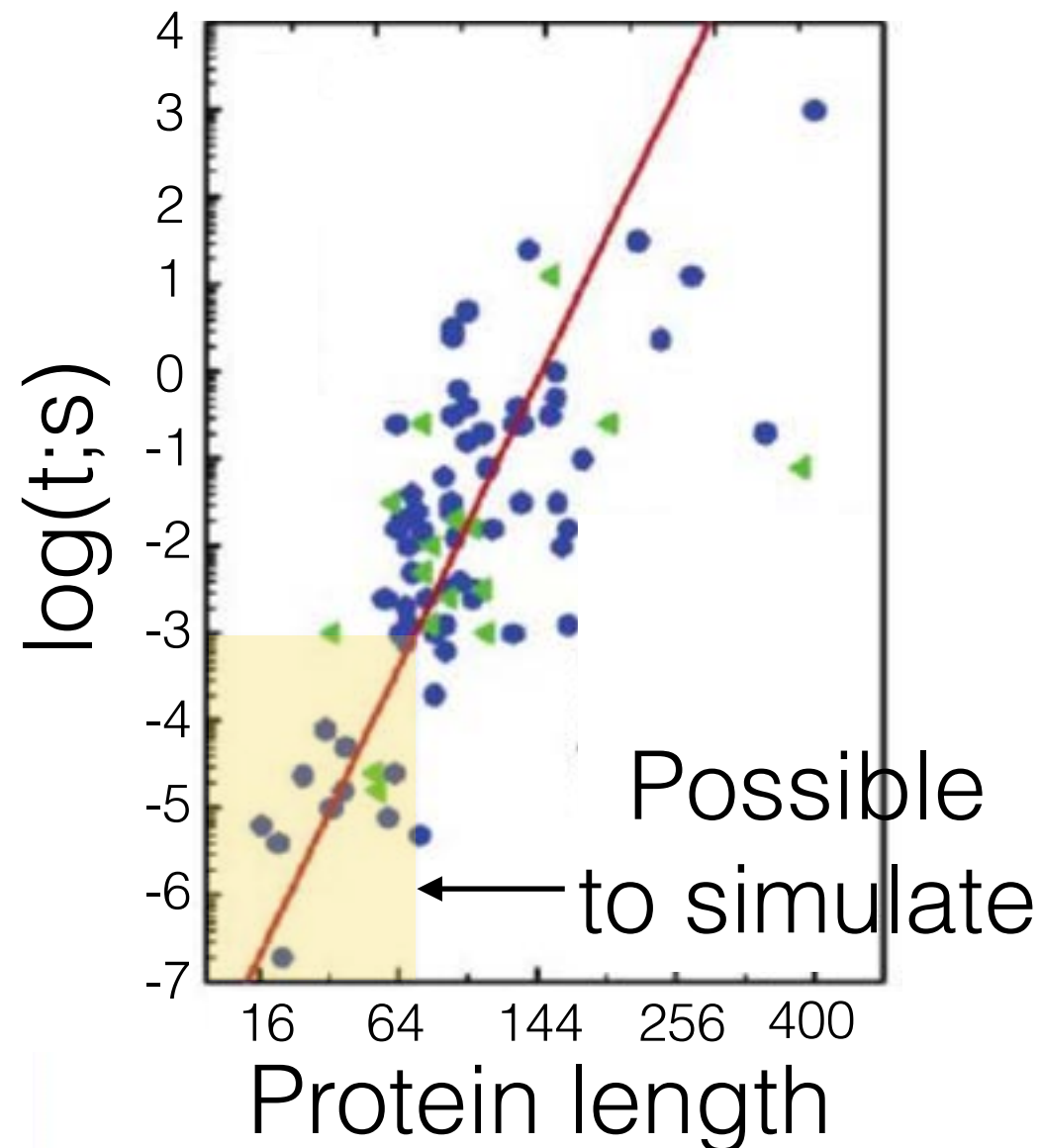


# Anton can fold the fastest folding proteins

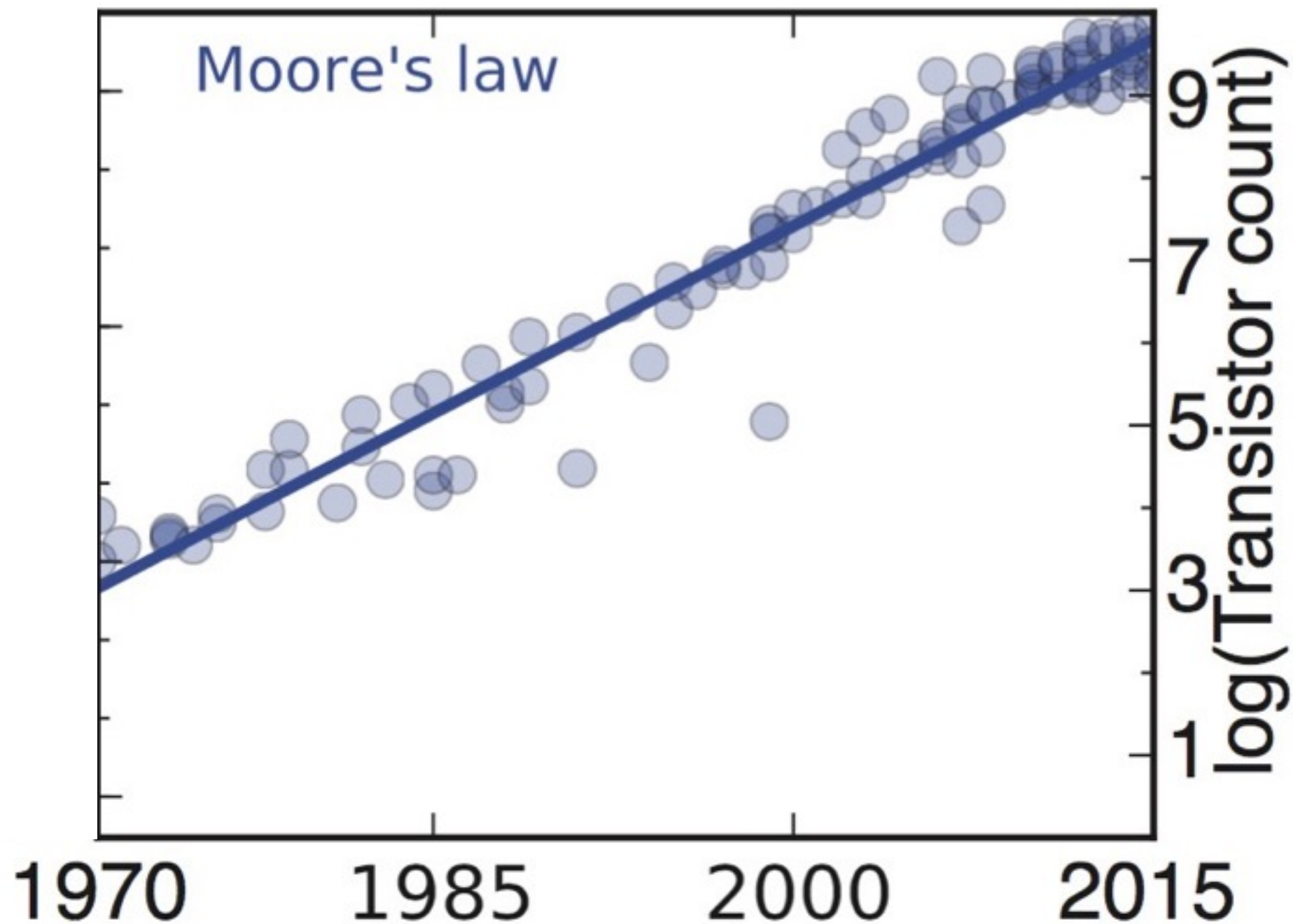




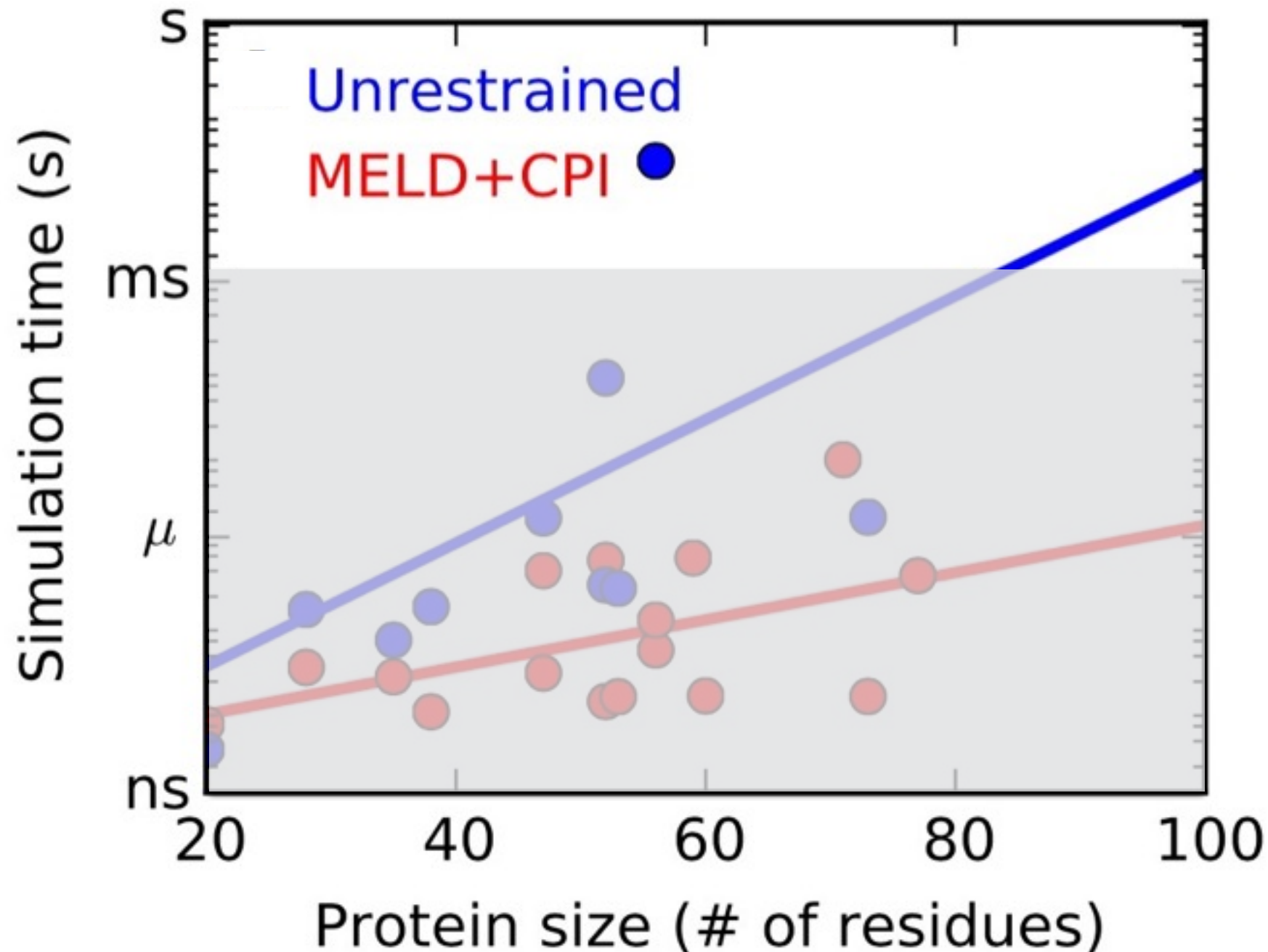
# Folding time scales exponentially with protein size



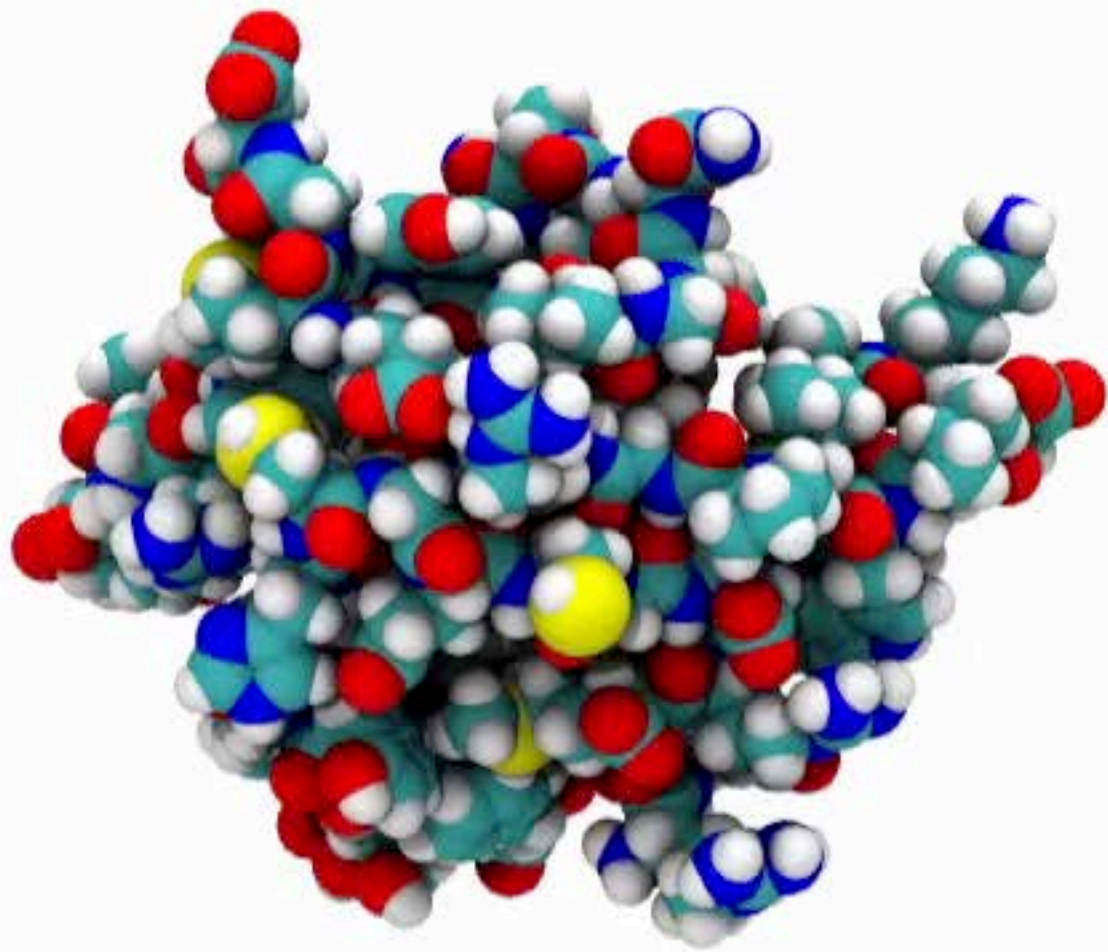
# Computers are getting faster, and so are MD techniques



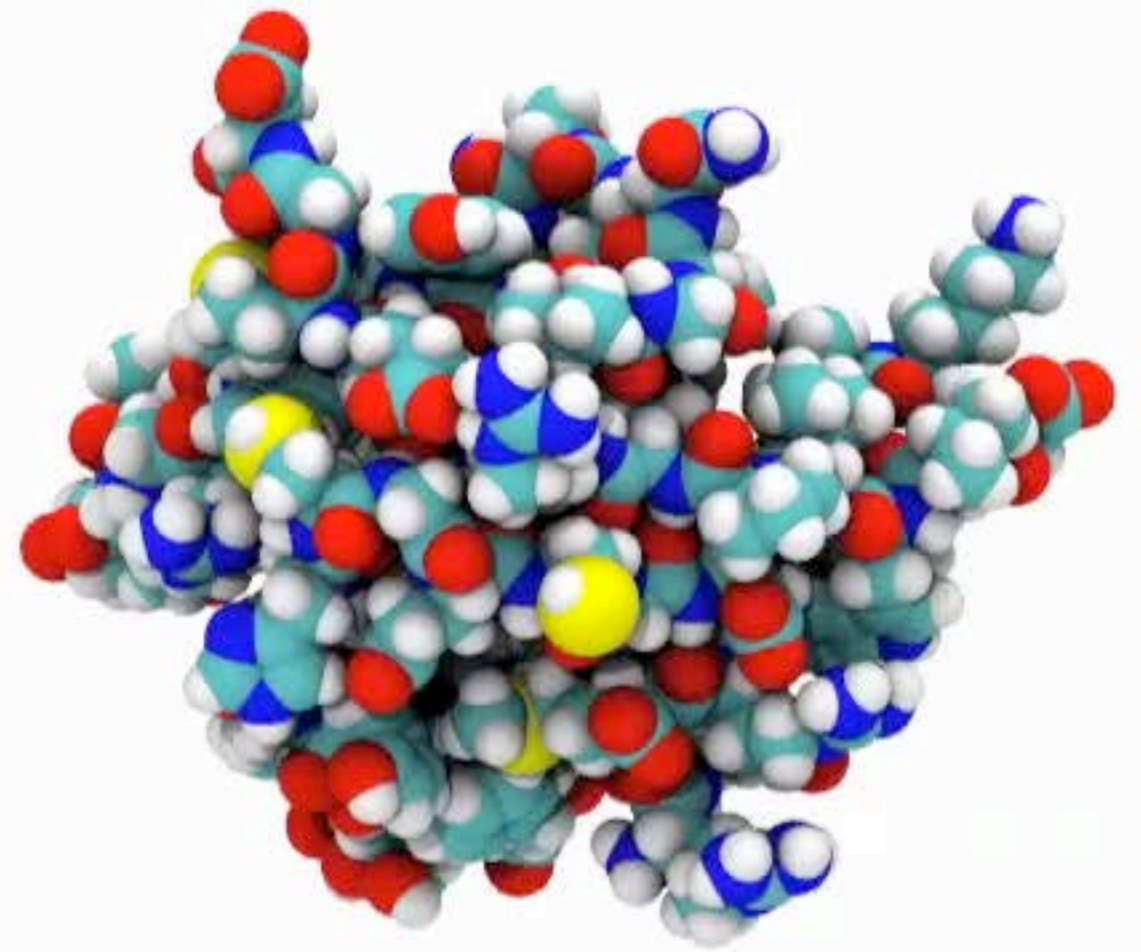
MELD rescales the exponential sampling problem; BW powers the search



MD is the basis of our method



CPU



GPU



We impose heuristics based on general knowledge of globular proteins

- Polar
- Hydrophobic

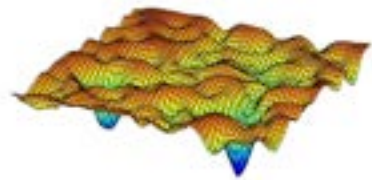


- Contacts present in native structure
- Possible contacts

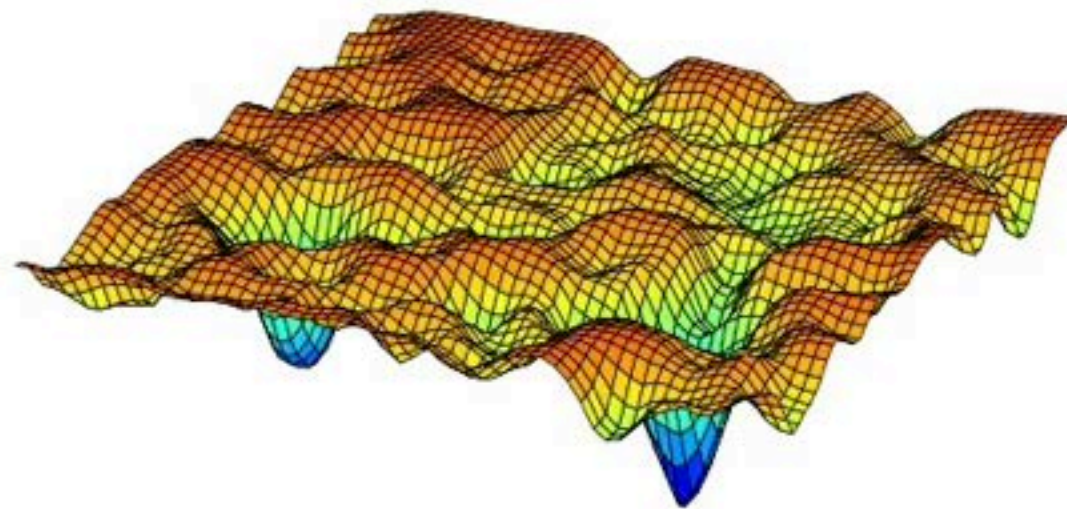
**Heuristic:**

**hydrophobic pairing**

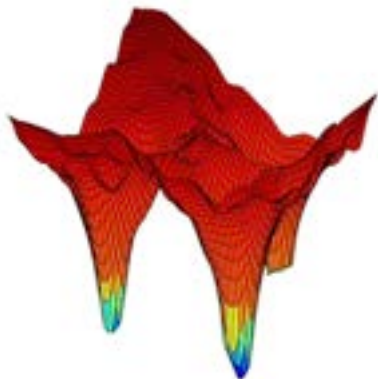
We use Hamiltonian Replica Exchange to enhance sampling



● High Temperature / Weak Restraints



● Low Temperature / **Strong Restraints**



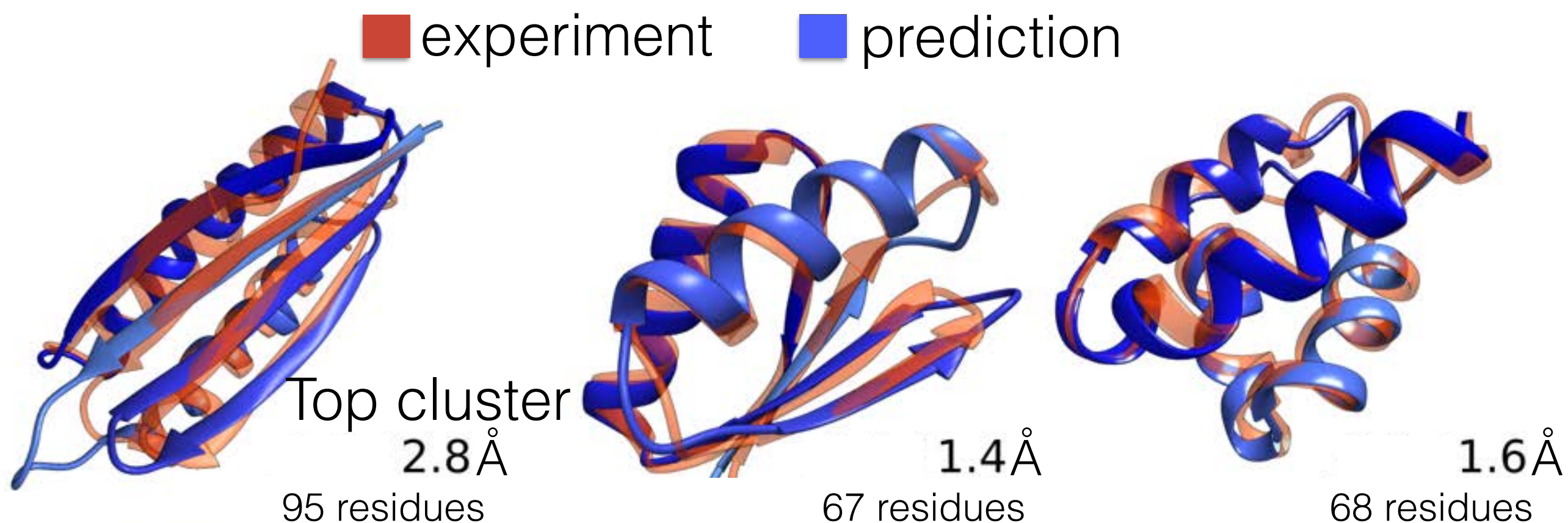
# Results

# CASP: a protein folding blind competition

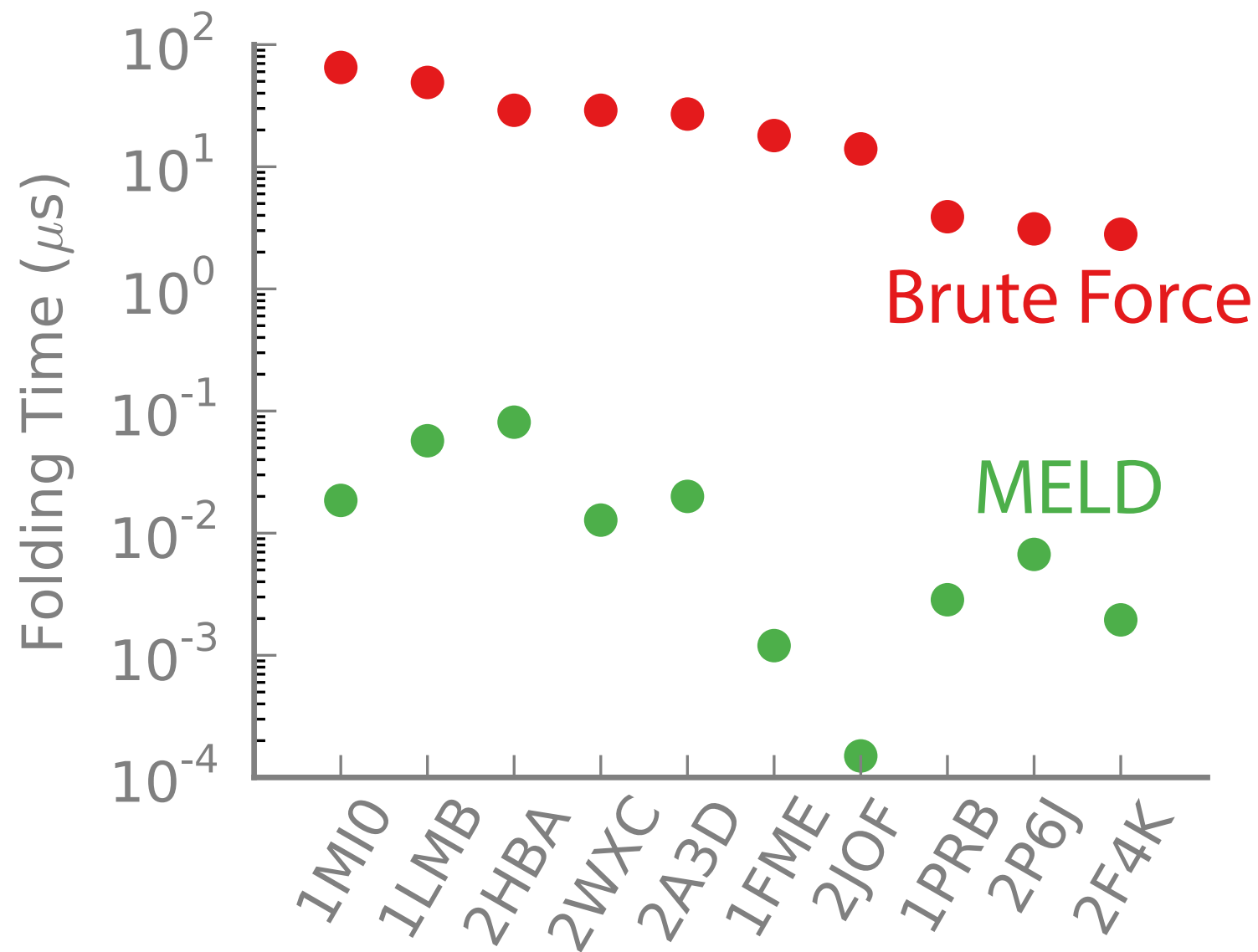
- May-August
- ~2 new target per day
- 1-3 weeks to predict structure
- 27 predictions in 2014
- Over 50 predictions since may (BW)
- Quick turnaround/more sampling/analysis



# First free-energy based method to predict structures ab initio in blind competition



Heuristics sample native states  
10,000x faster than the folding time



# Blue Waters Team Contributions

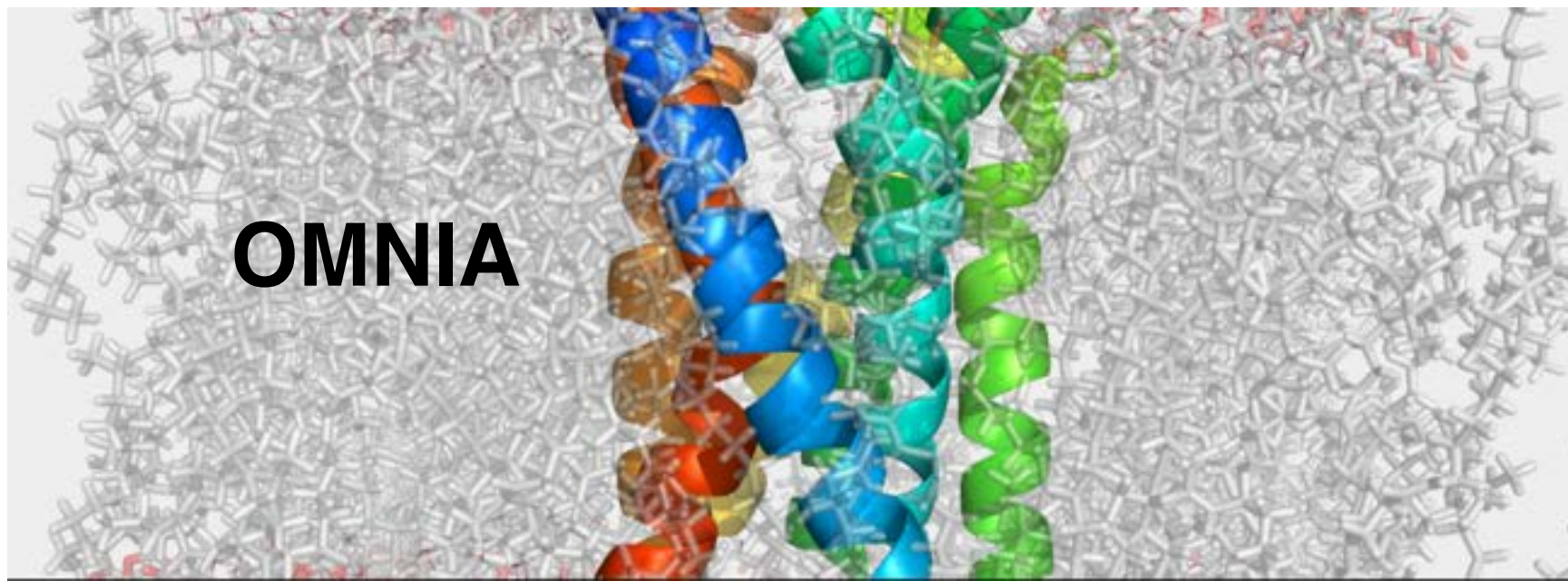
- Compilation openmm/meld (Victor Anisimov)
- BWPy / Conda

# Broader Impact



MELD plugin

MELD front end





# Thanks!

