To the ExaScale and Beyond: *Statistically Motivated Linear Scaling for Protein Dynamics*

T. J. Lane

Pande Group (the Folding@home guys)
Department of Chemistry
Stanford University

Dynamics is often critical to function

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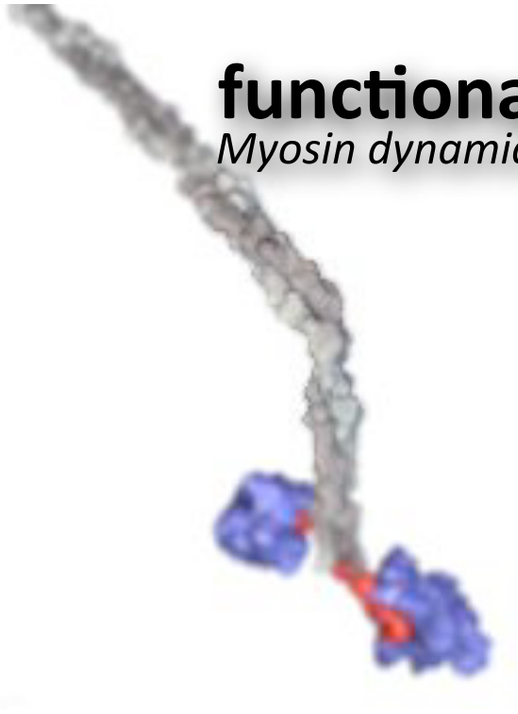
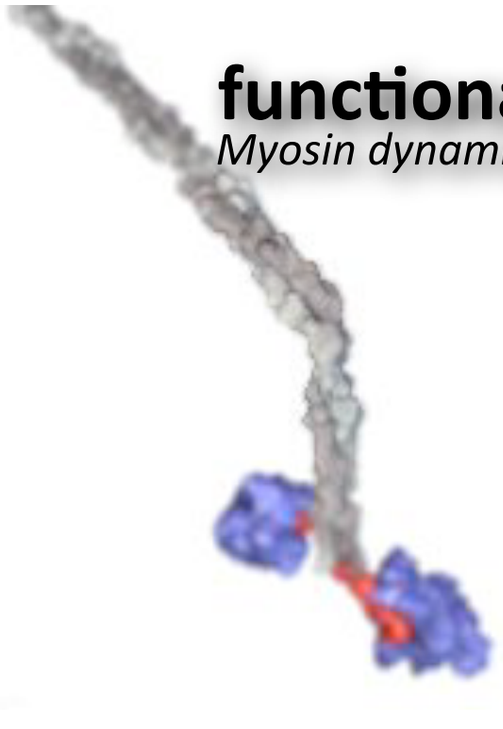


functional motion

Myosin dynamics from Vale lab

Dynamics is often critical to function



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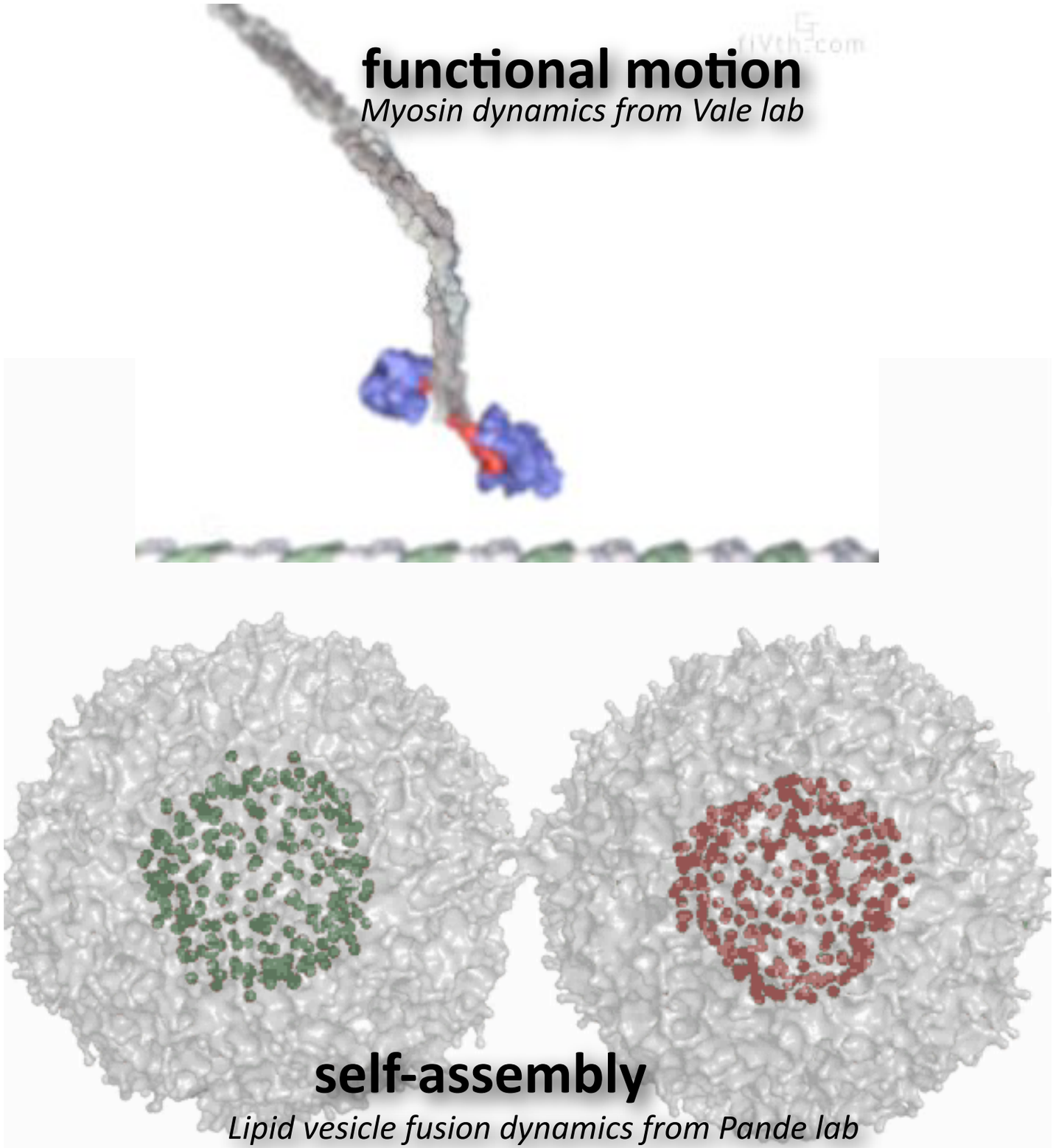

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Lipid vesicle fusion dynamics from Pande lab

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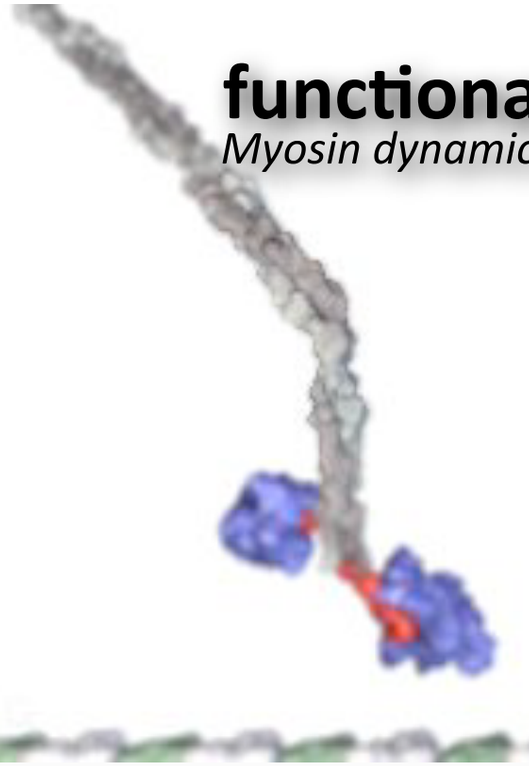

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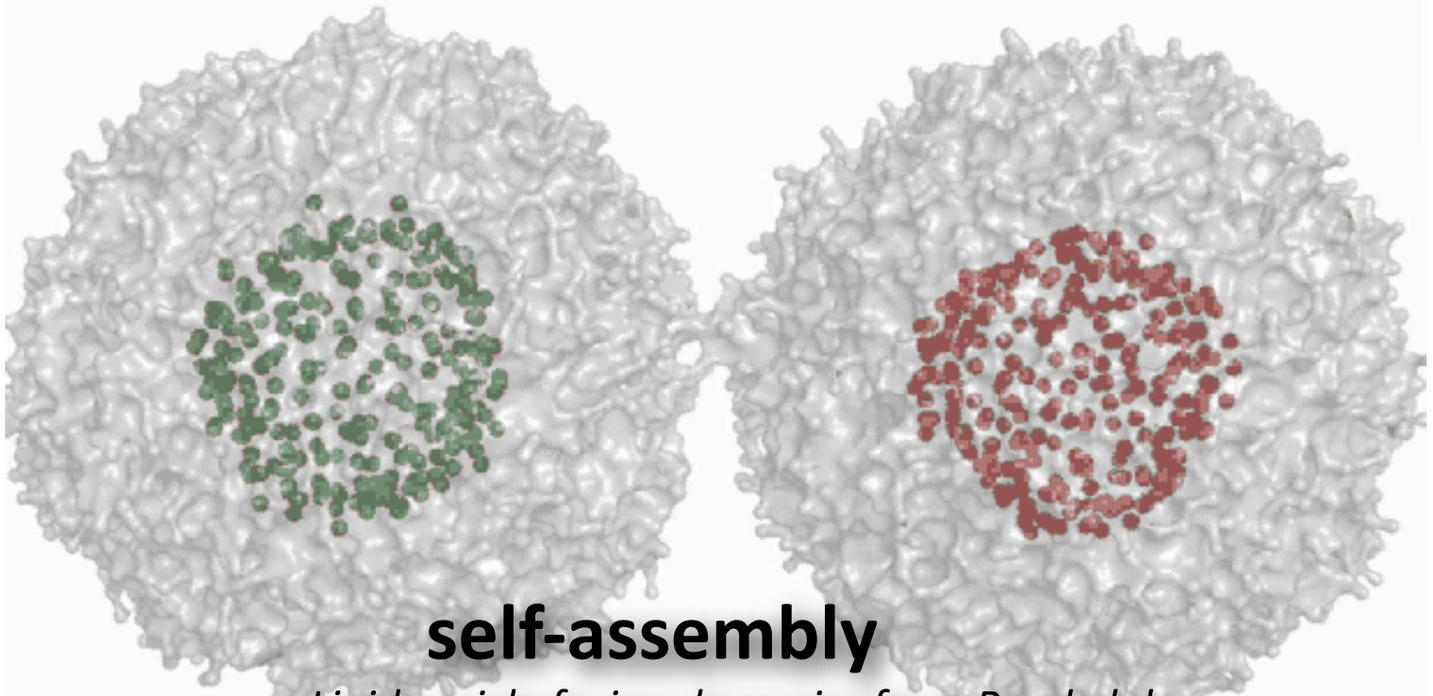

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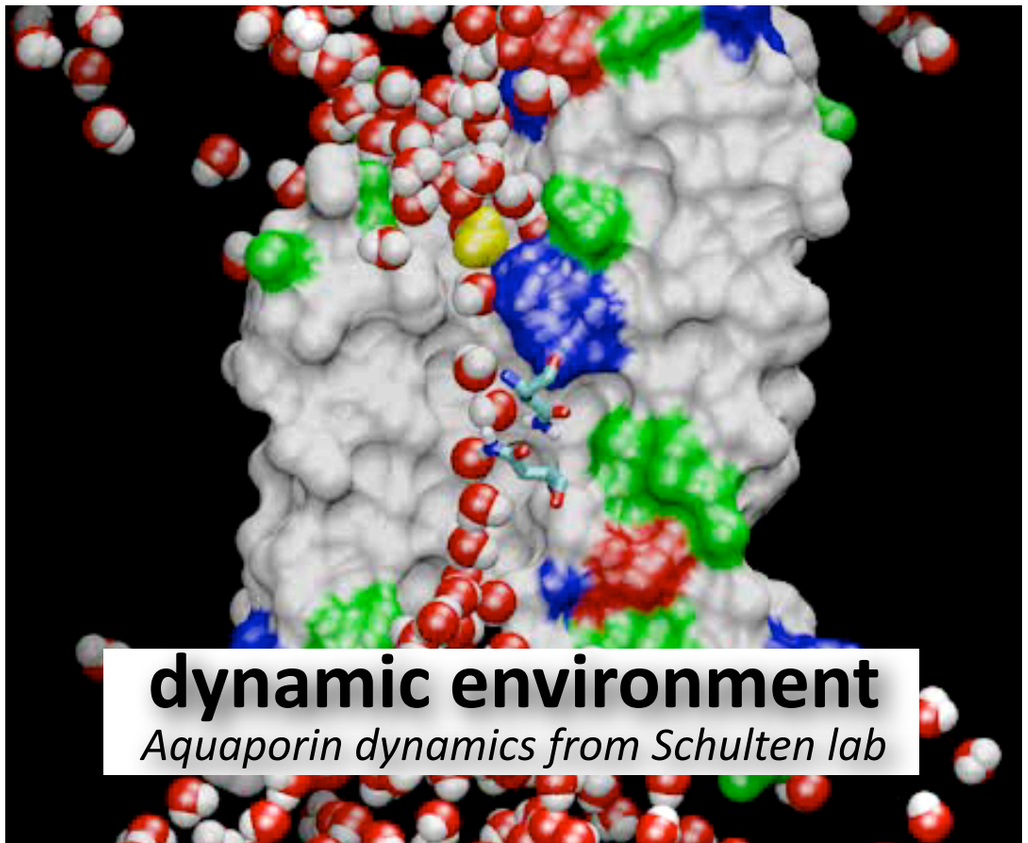


dynamic environment
Aquaporin dynamics from Schulten lab

What is protein folding?

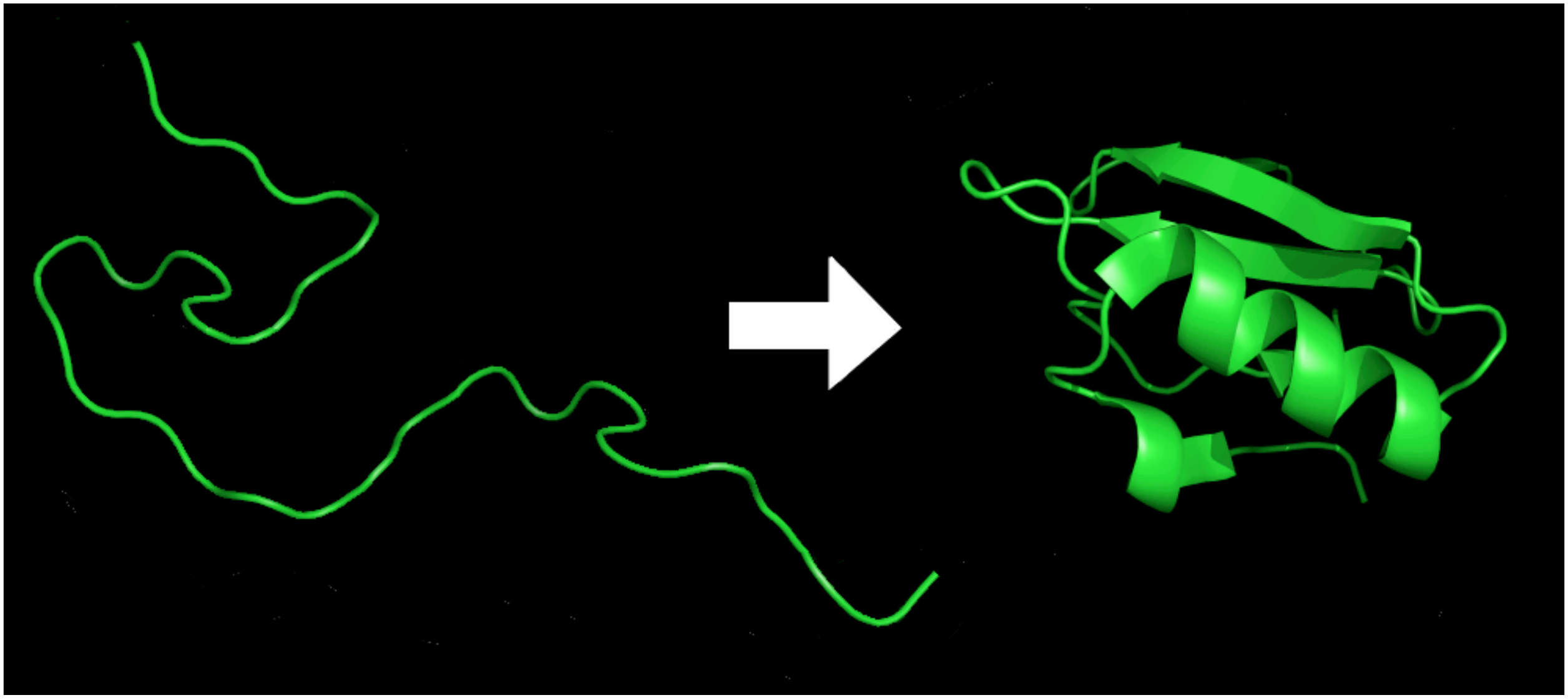
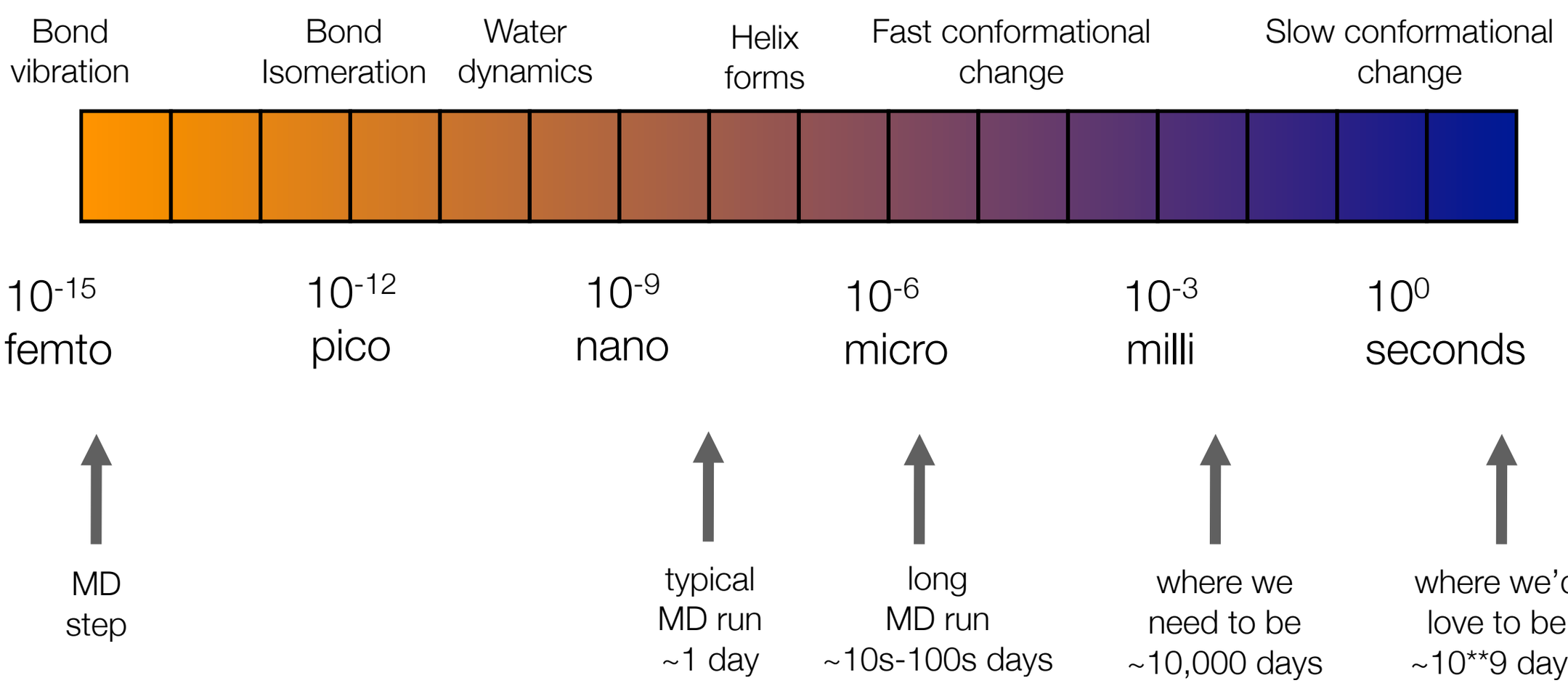


image: wikipedia

The nightmare of simulating long time scales



How do you break a billion-fold impasse?

Combine multiple, powerful, complementary technologies

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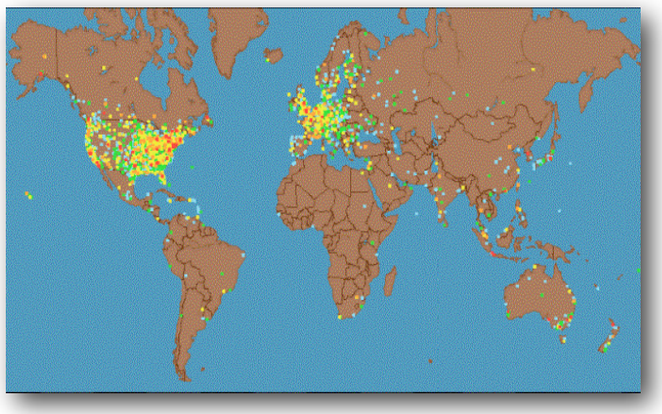
very large-scale
distributed computing



Most powerful computer cluster in the world (~8 petaflops)

10^4x to 10^5x

http://folding.stanford.edu

Voelz, *et al*, *JACS* (2010)
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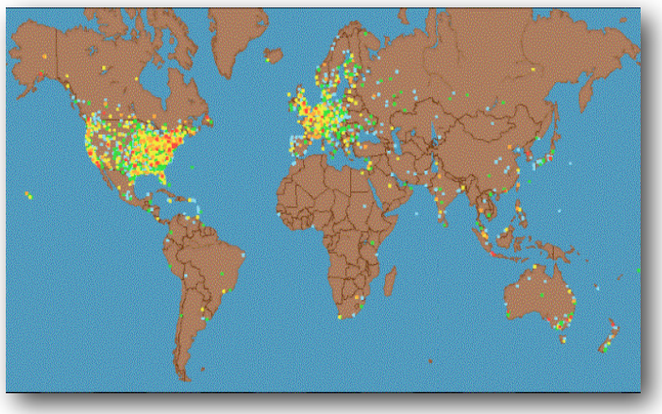

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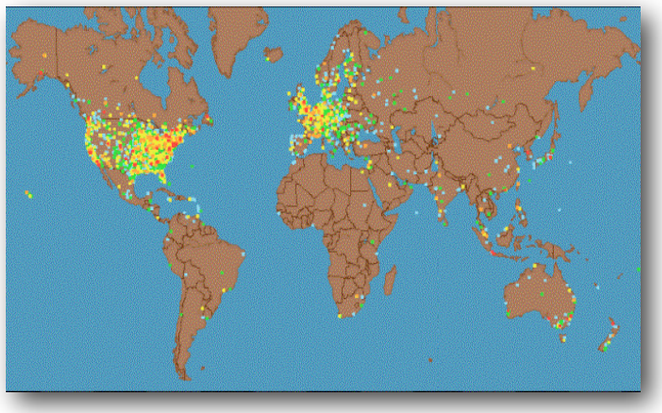

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2) OpenMM: Very
fast MD (~1µs/day)
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~1µs/day for implicit solvent simulaton of small proteins (~40aa)

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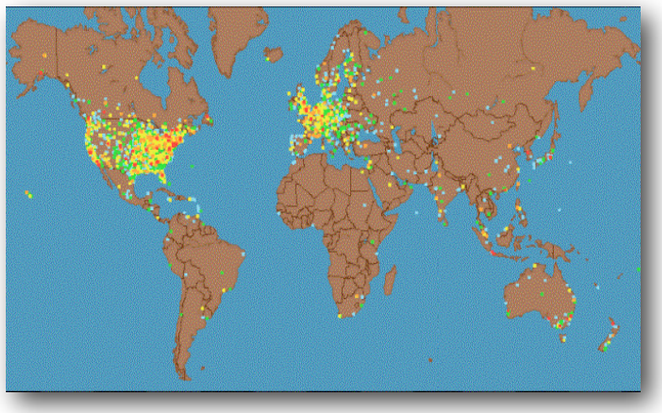

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very long timescale dynamics by combining many simulations

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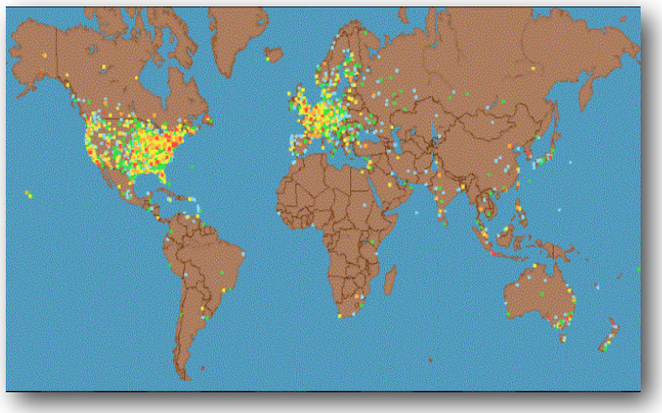

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“States and rates” is a familiar paradigm

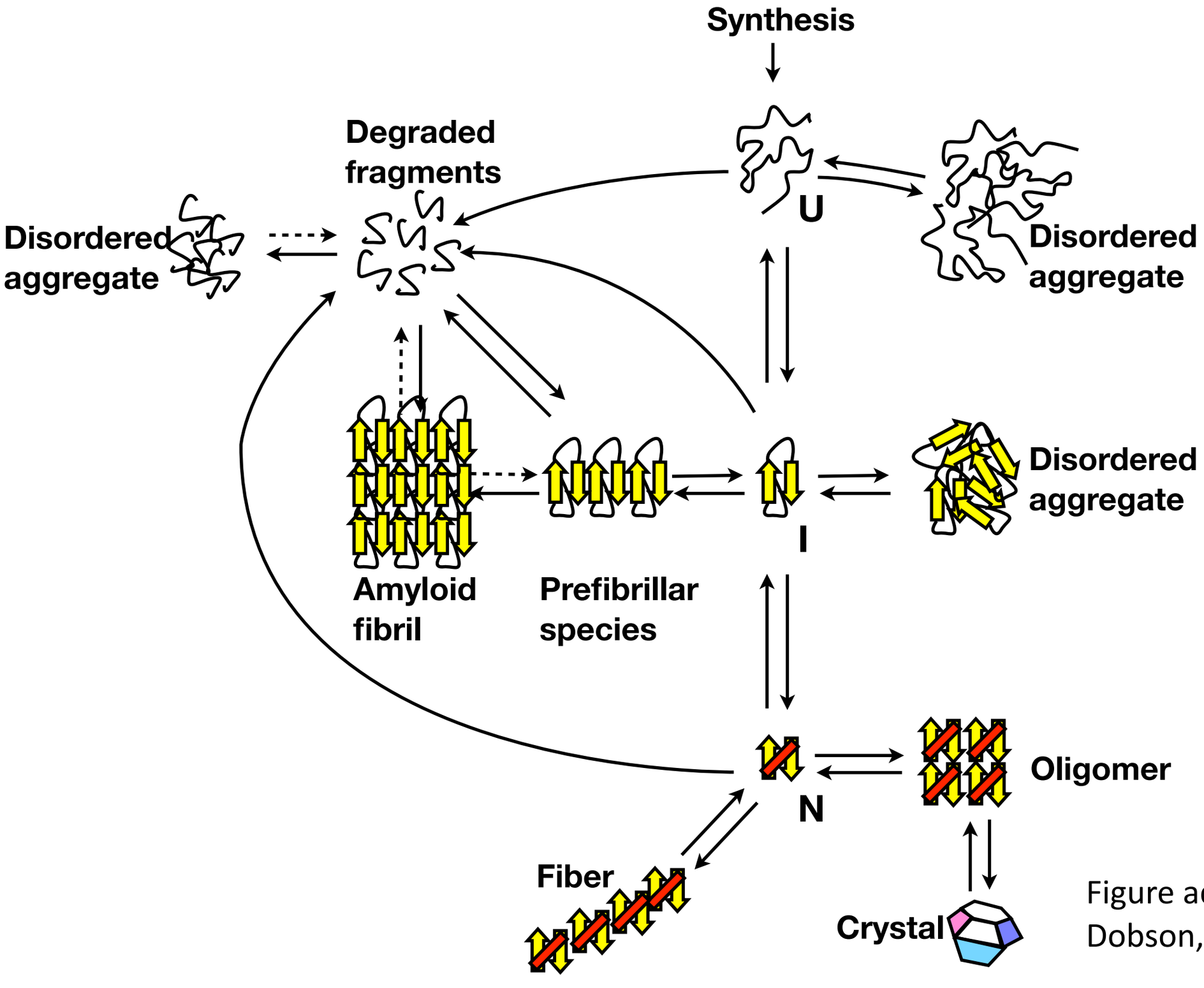


Figure adapted from Dobson, et al, *Nature*

MSMs coarse grain conformation space (to ~3Å) to build a Master equation

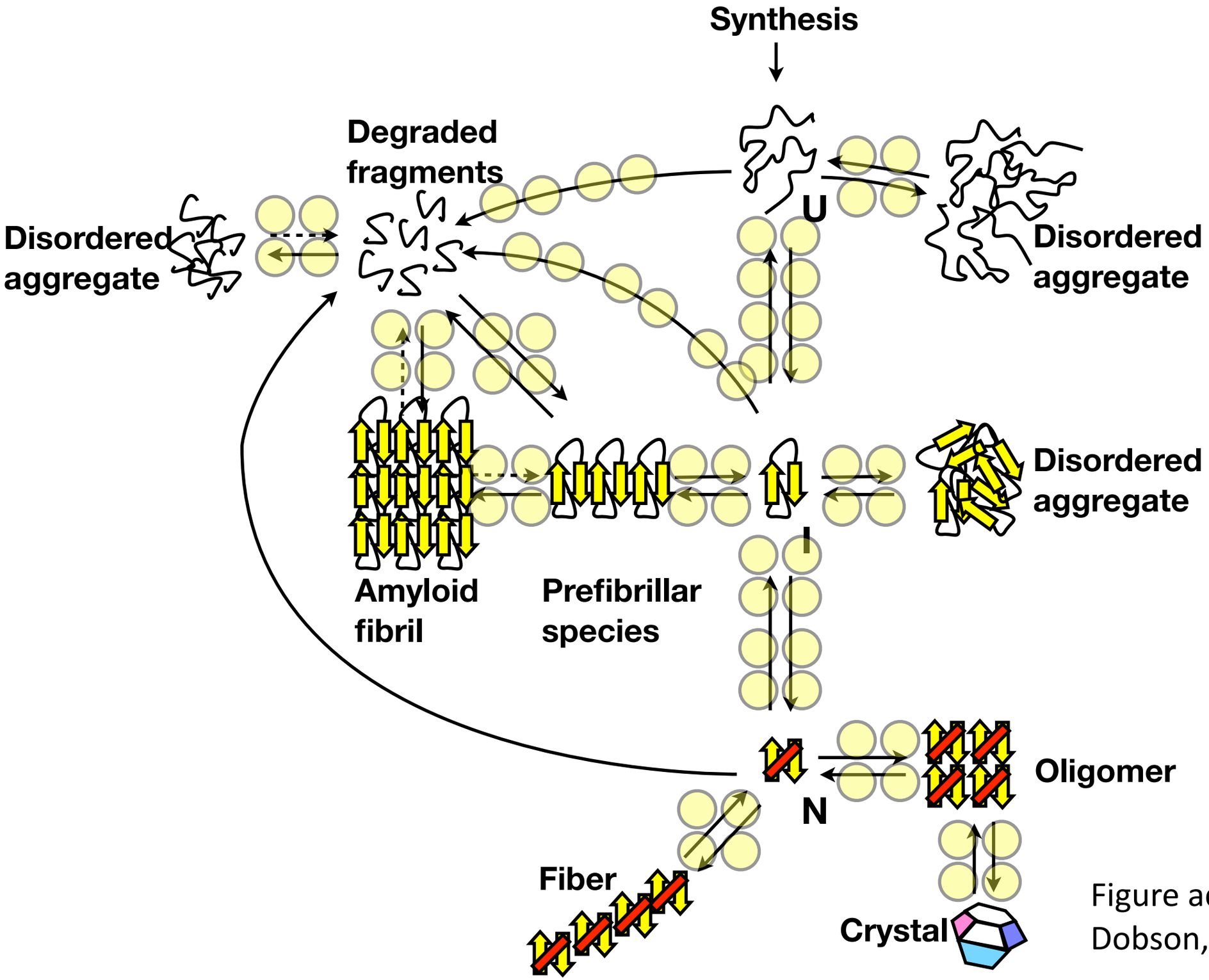
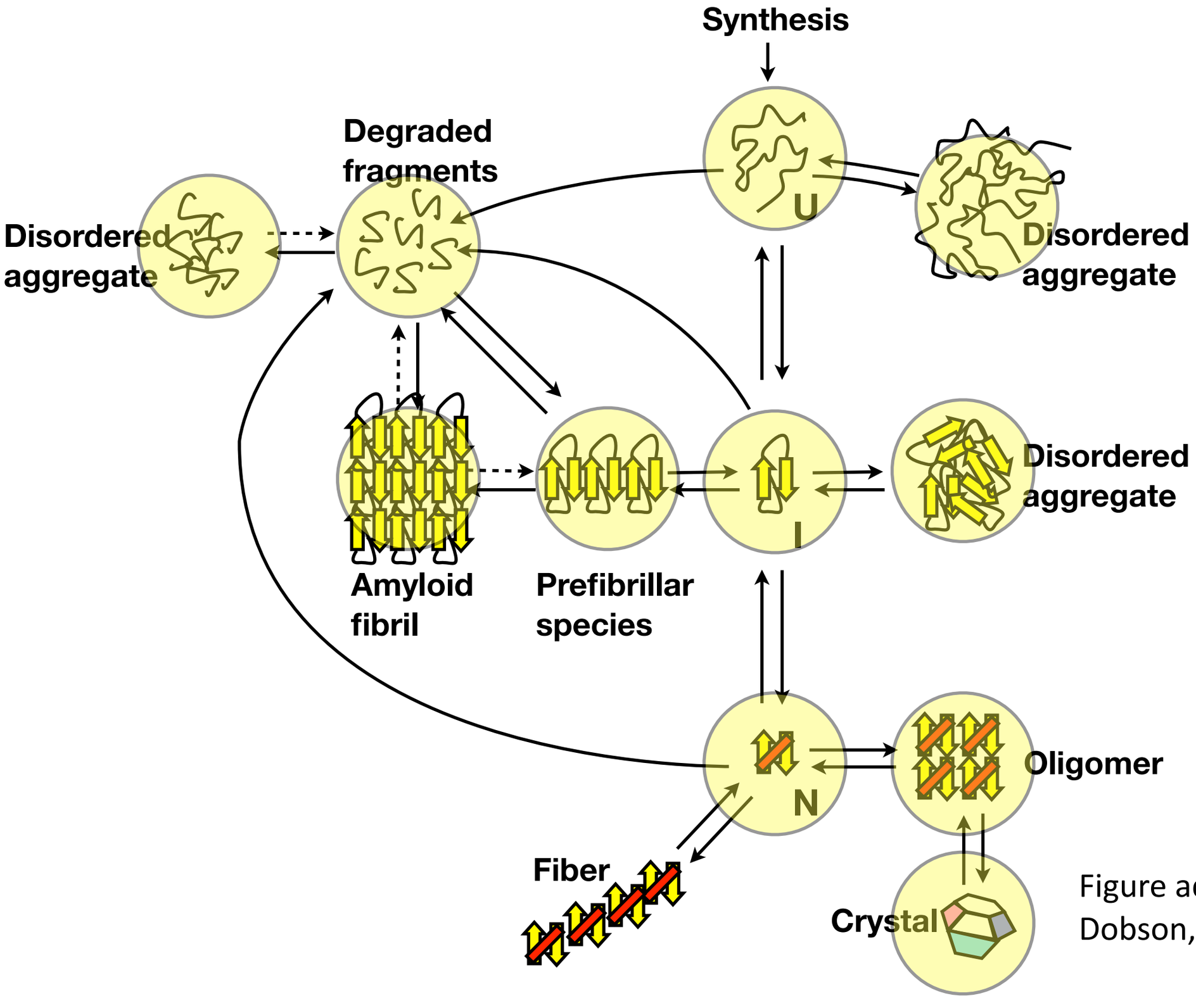


Figure adapted from Dobson, et al, *Nature*

but also derive a coarser view for human consumption



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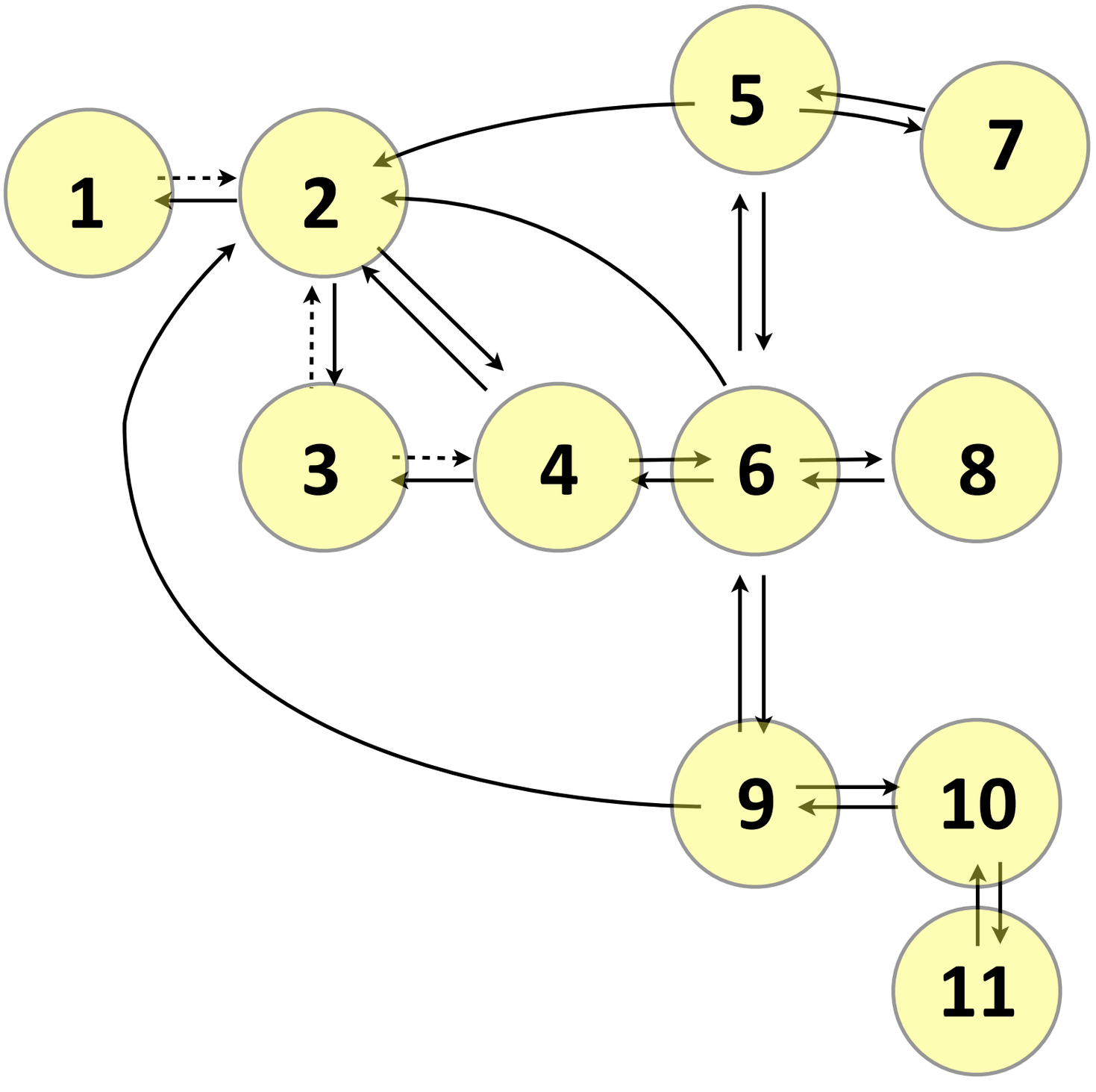
How does one build an MSM?



How does one build an MSM? MSMBuilder

Use Active Learning-like adaptive methods to infer p_{ij}

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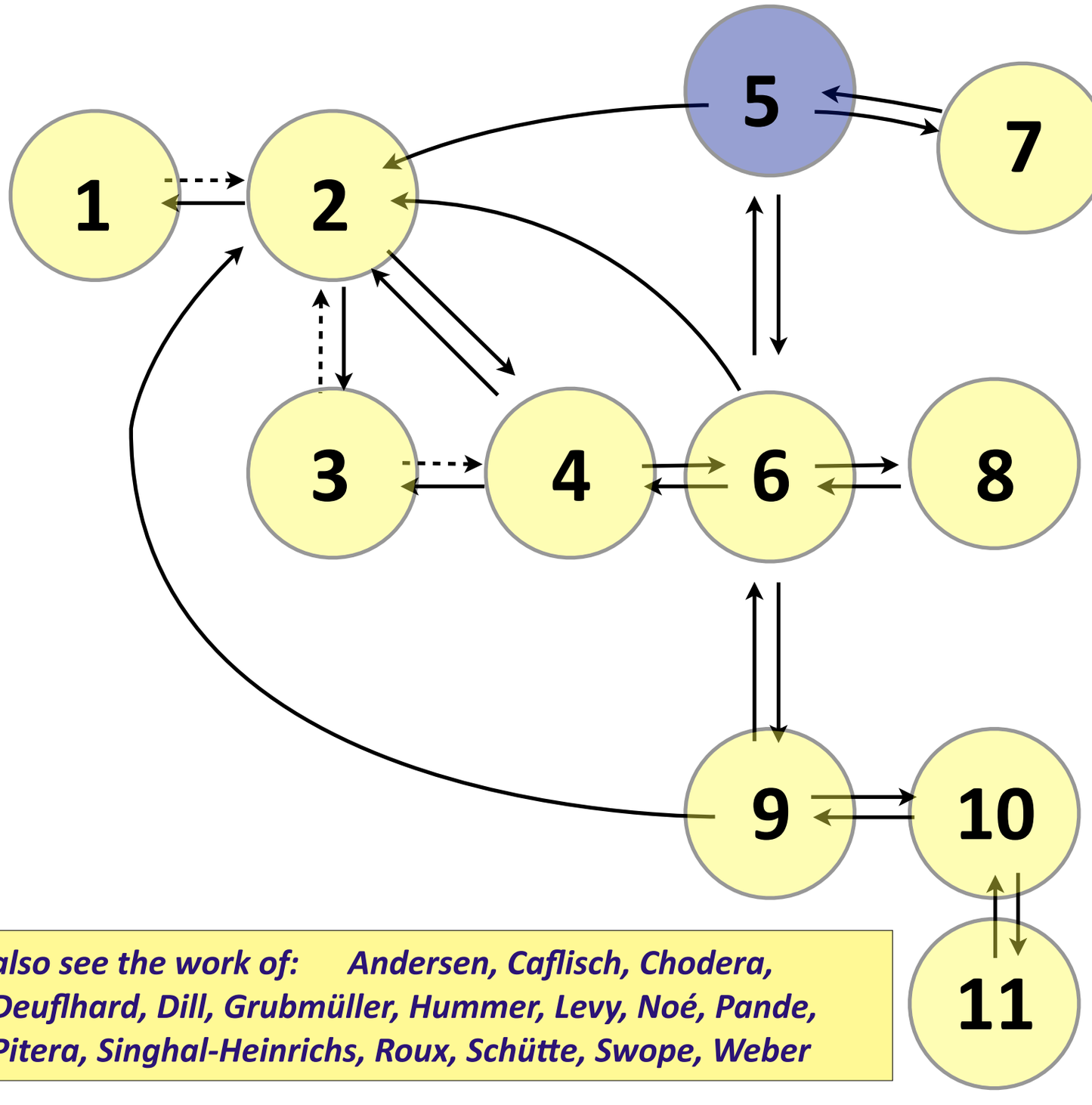

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1. **Kinetic clustering:** structures are combined into a state if they rapidly interconvert

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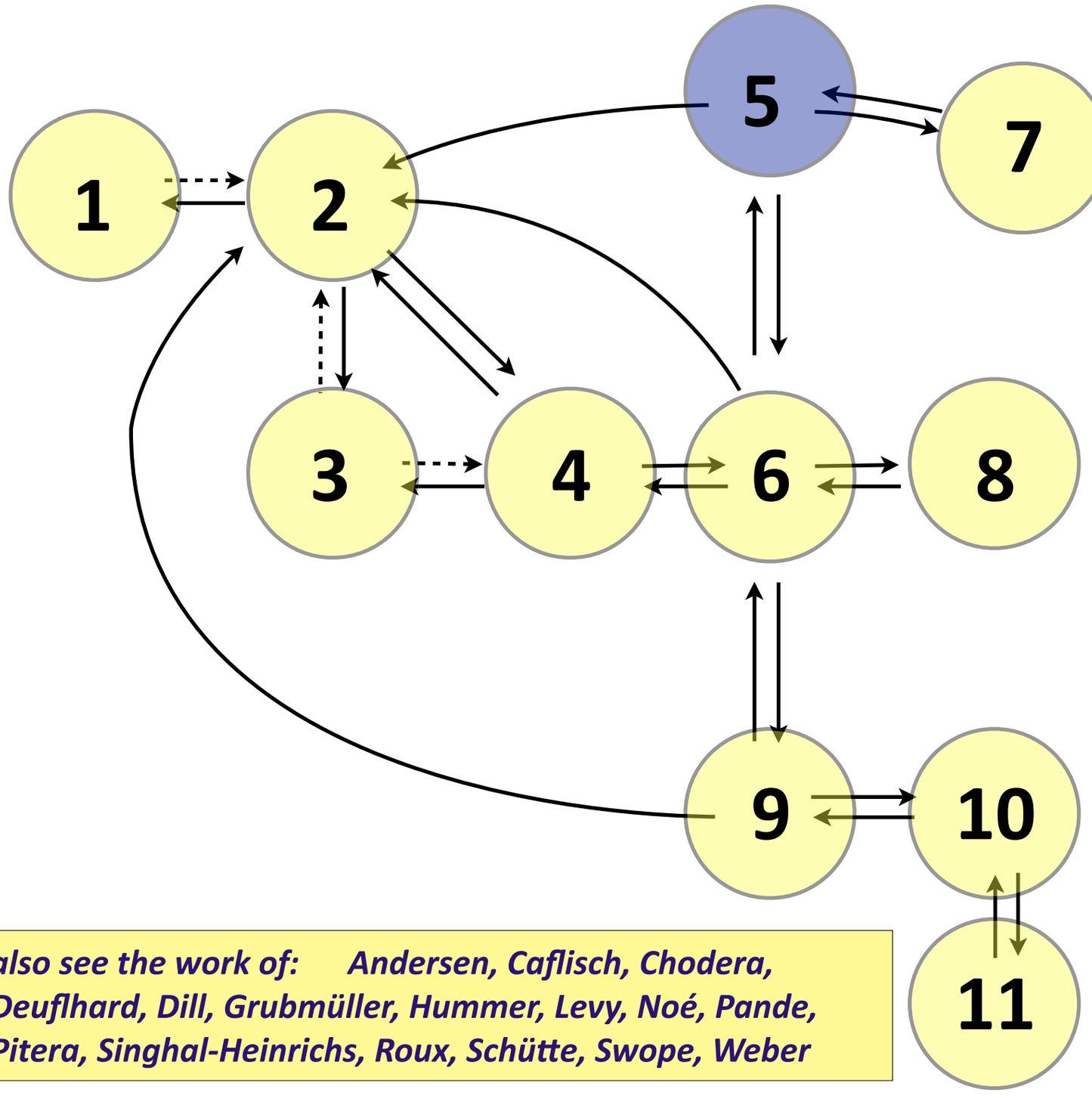

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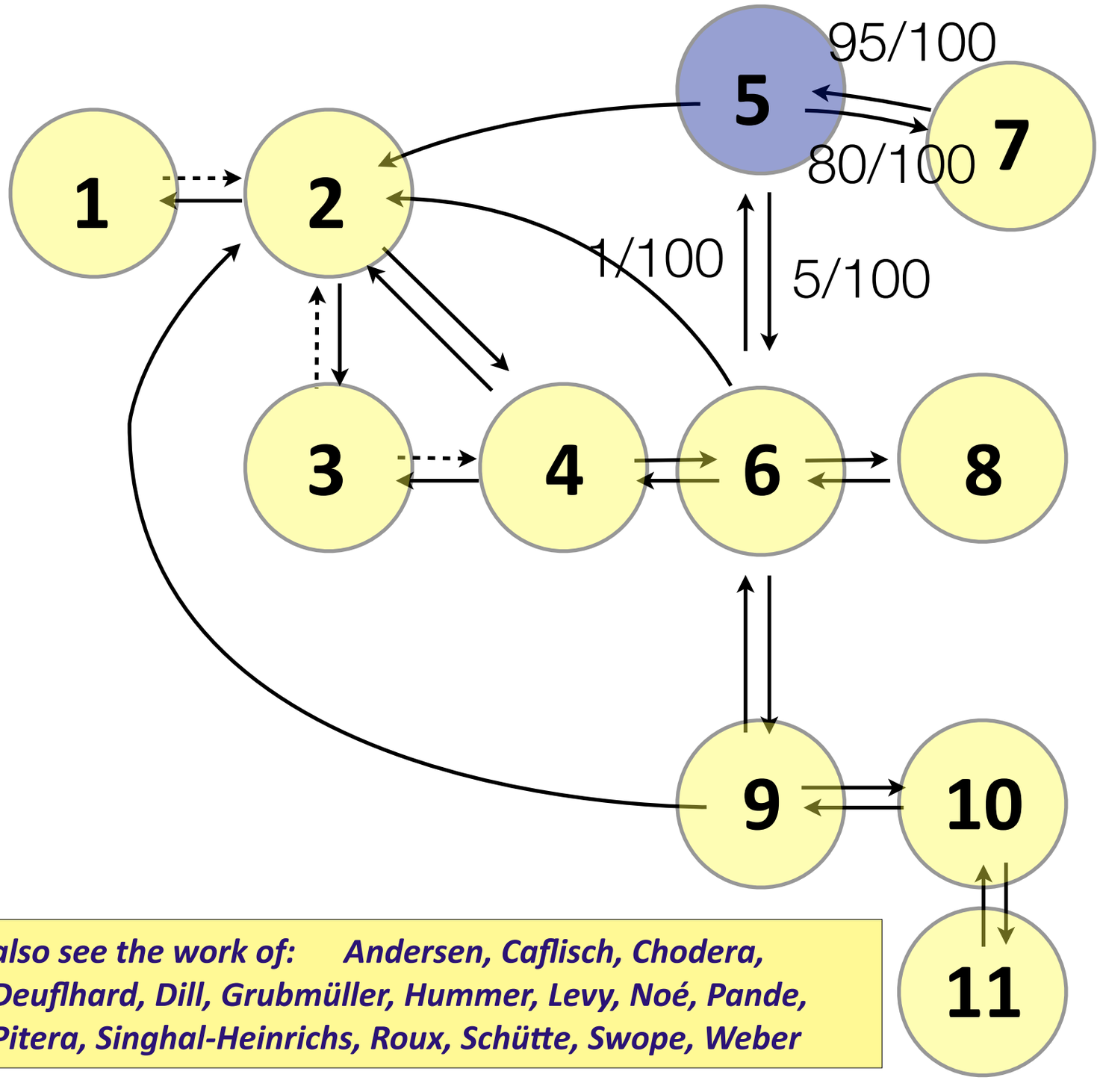

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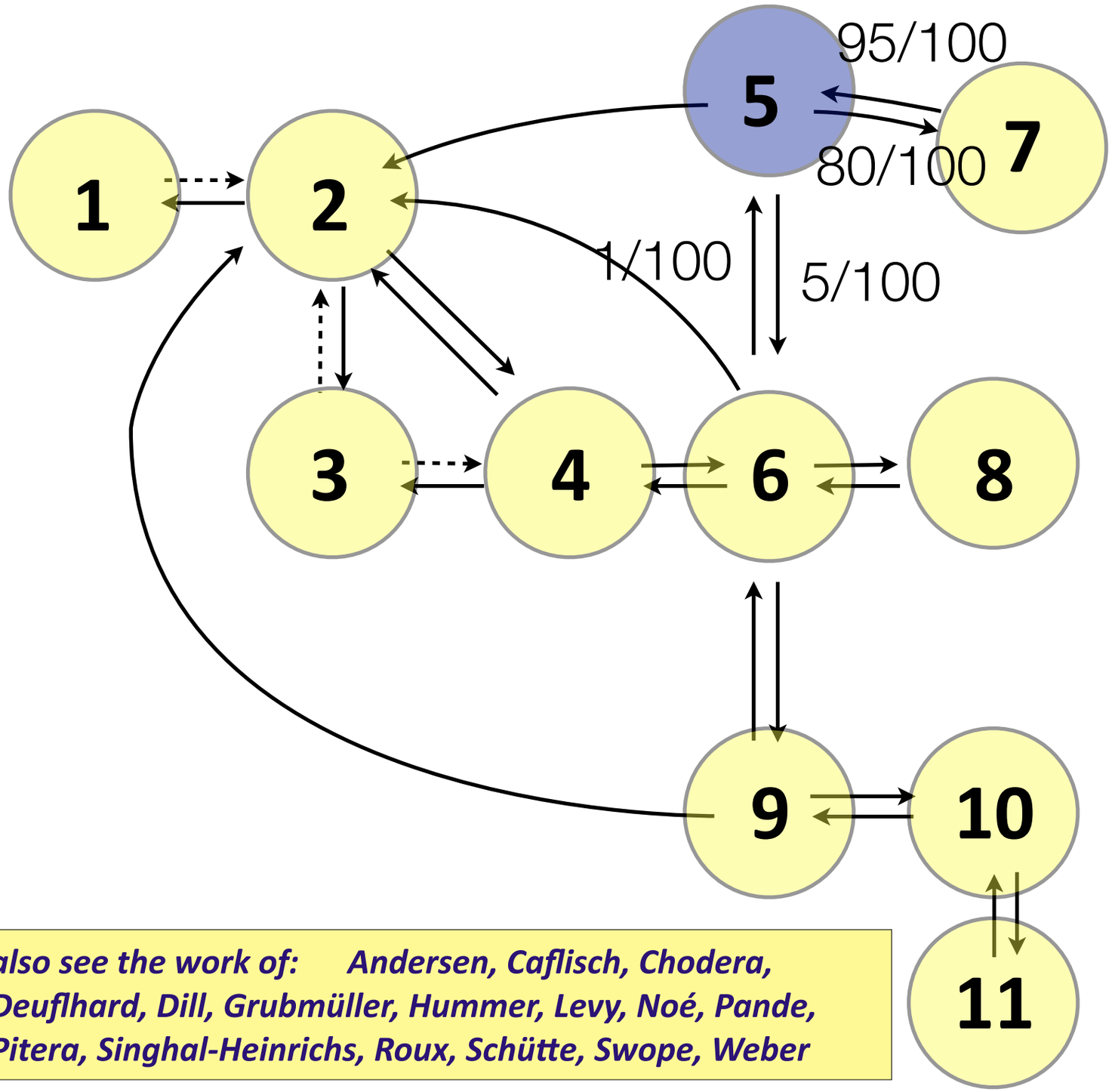

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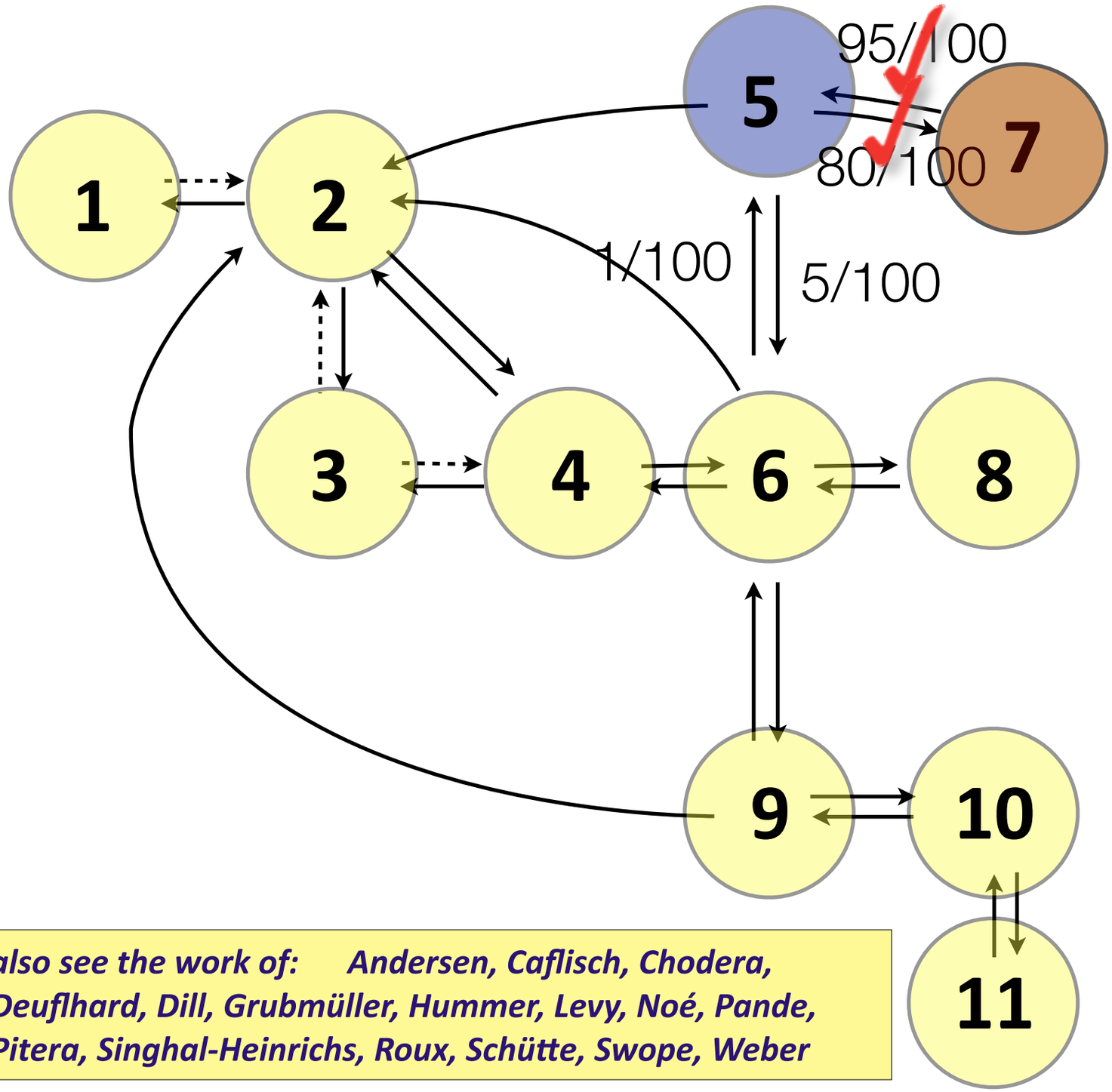

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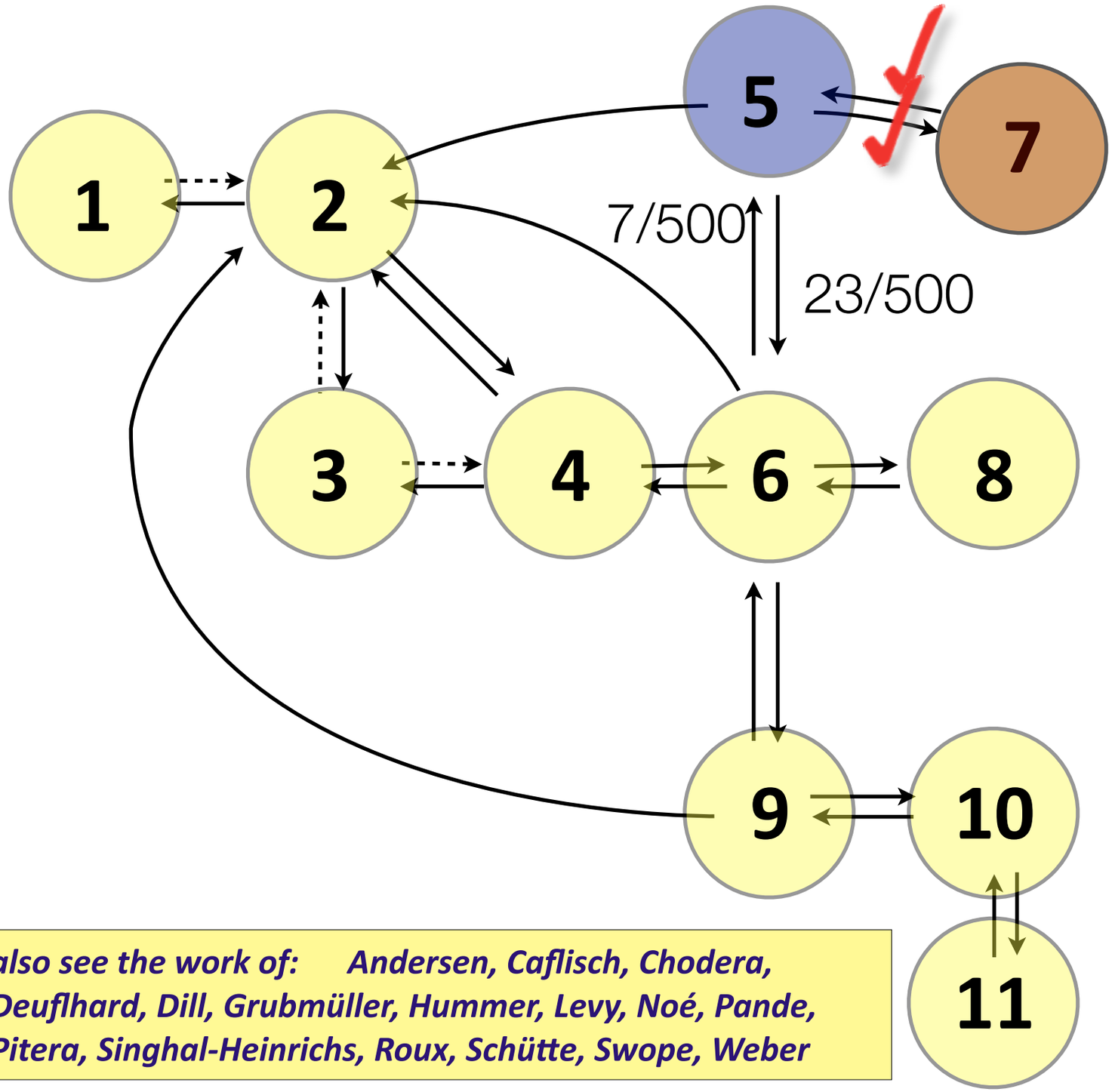

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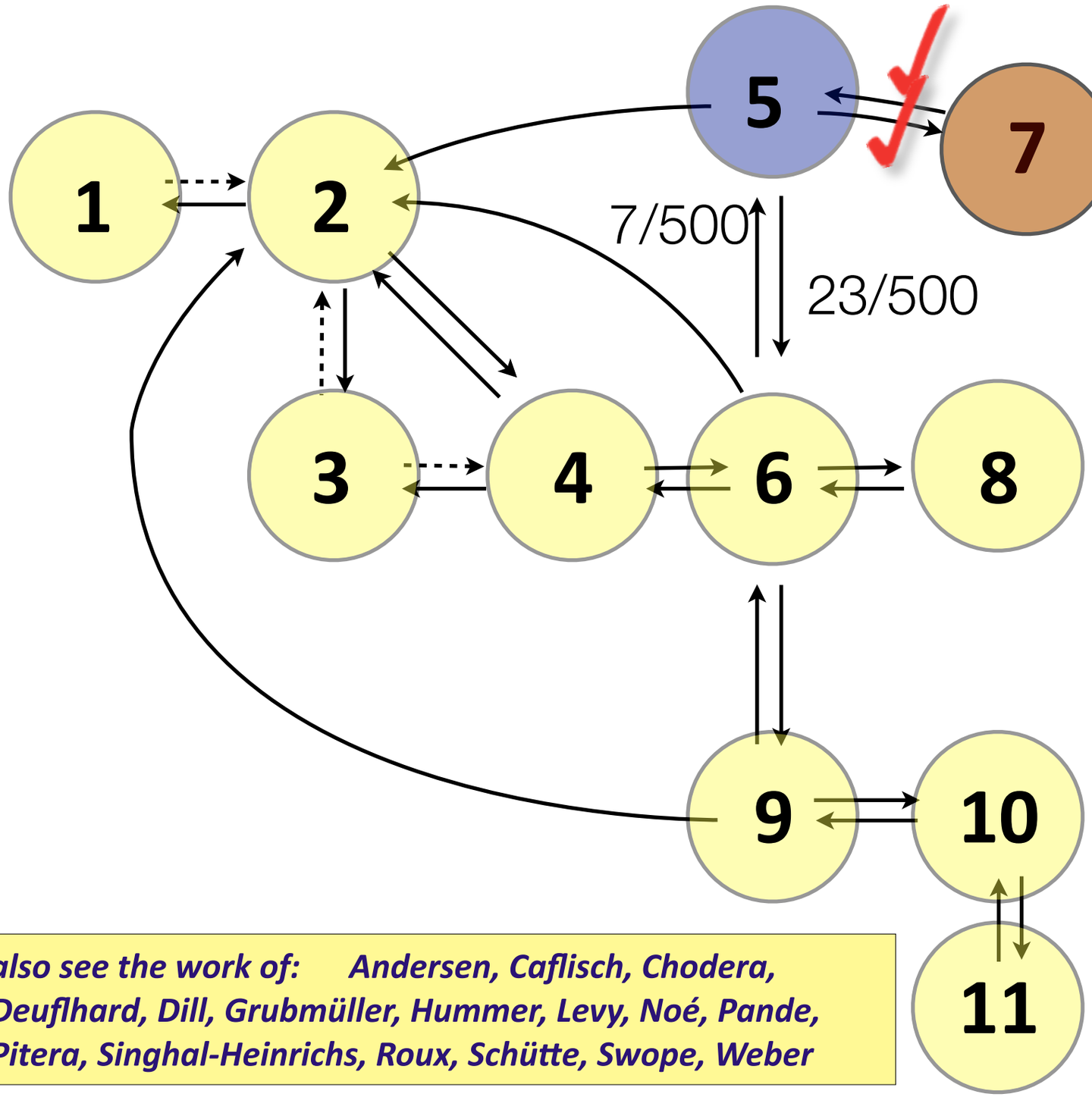

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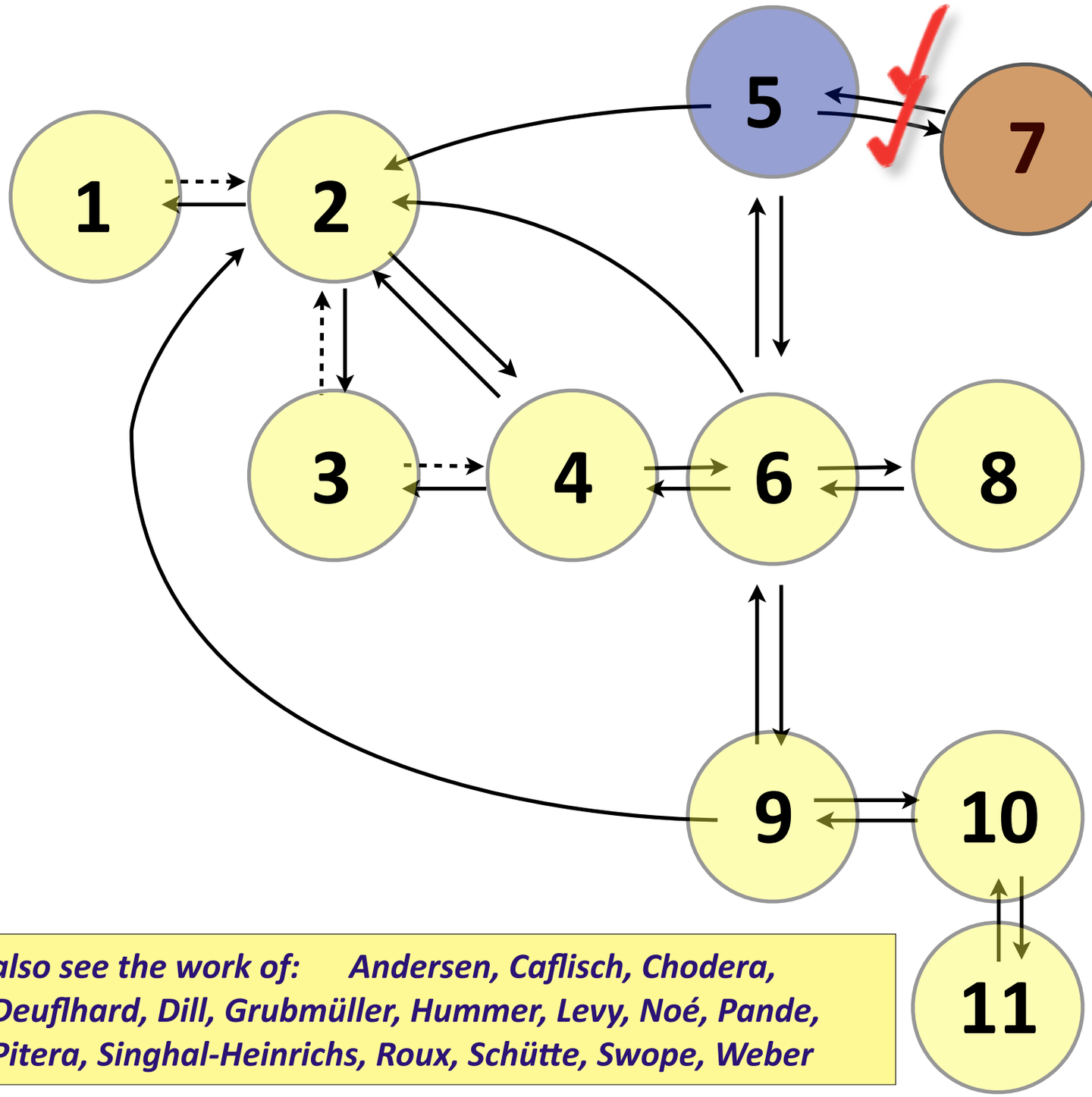

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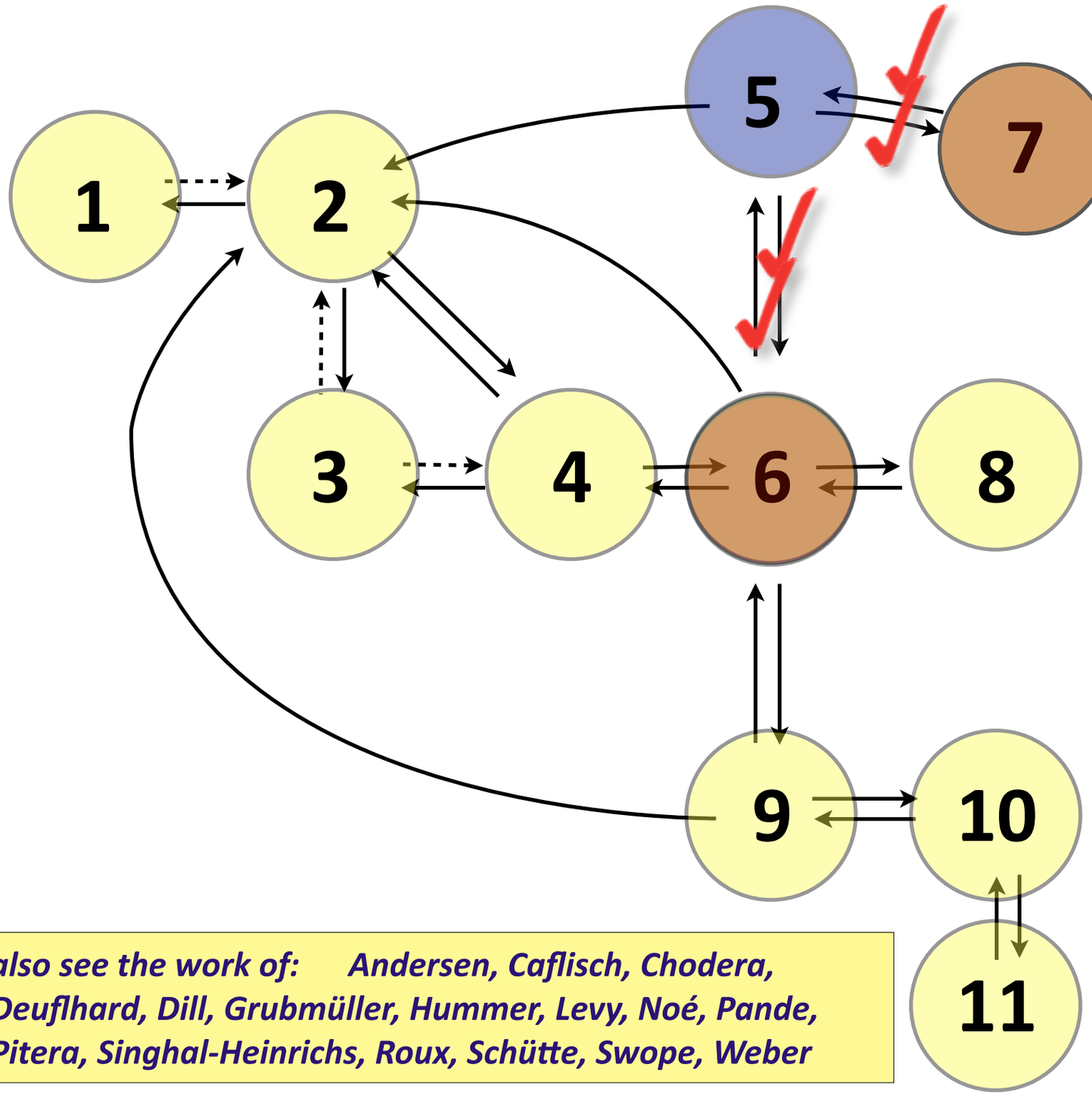

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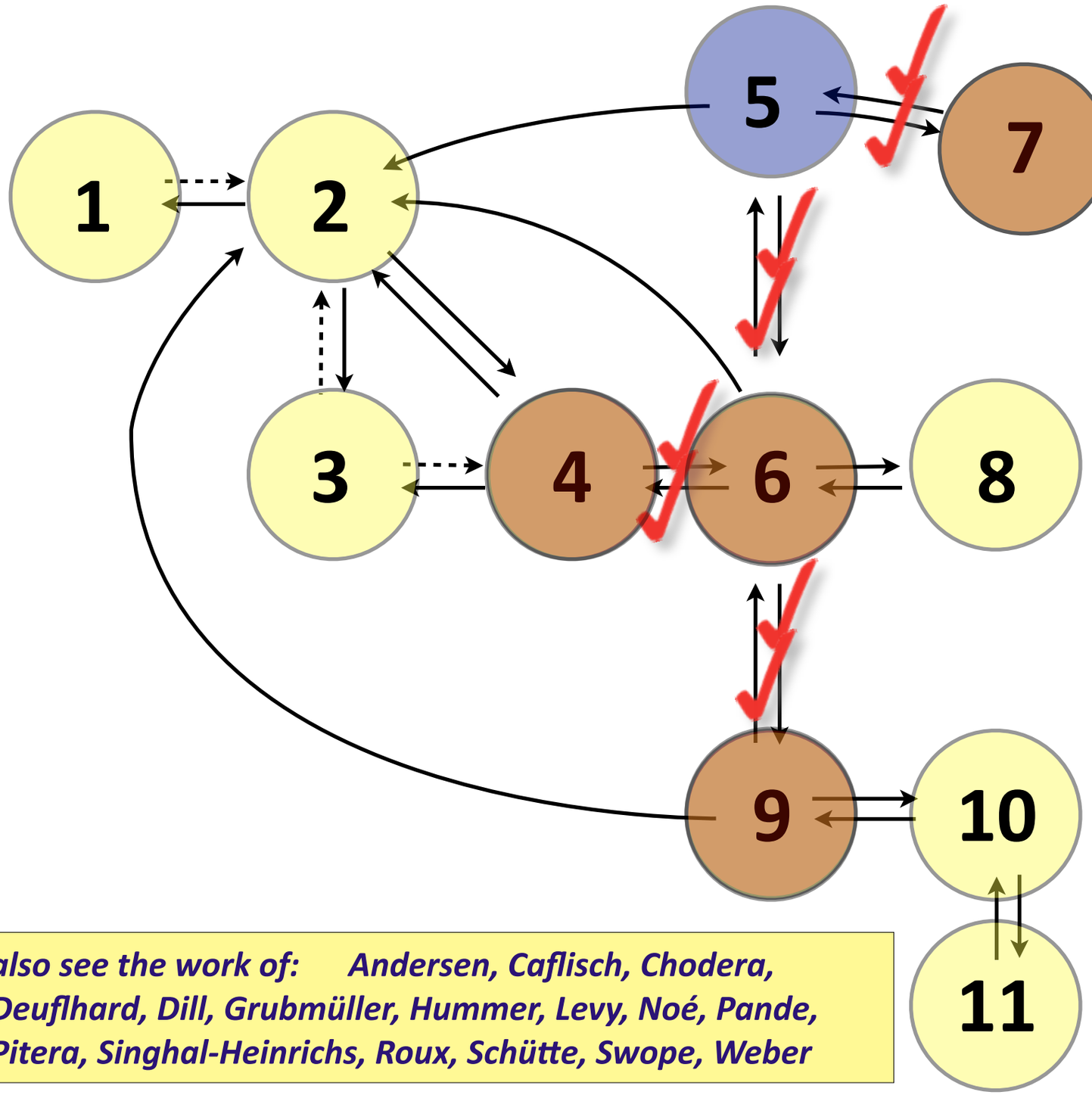

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4. **Repeat until tolerances are met**

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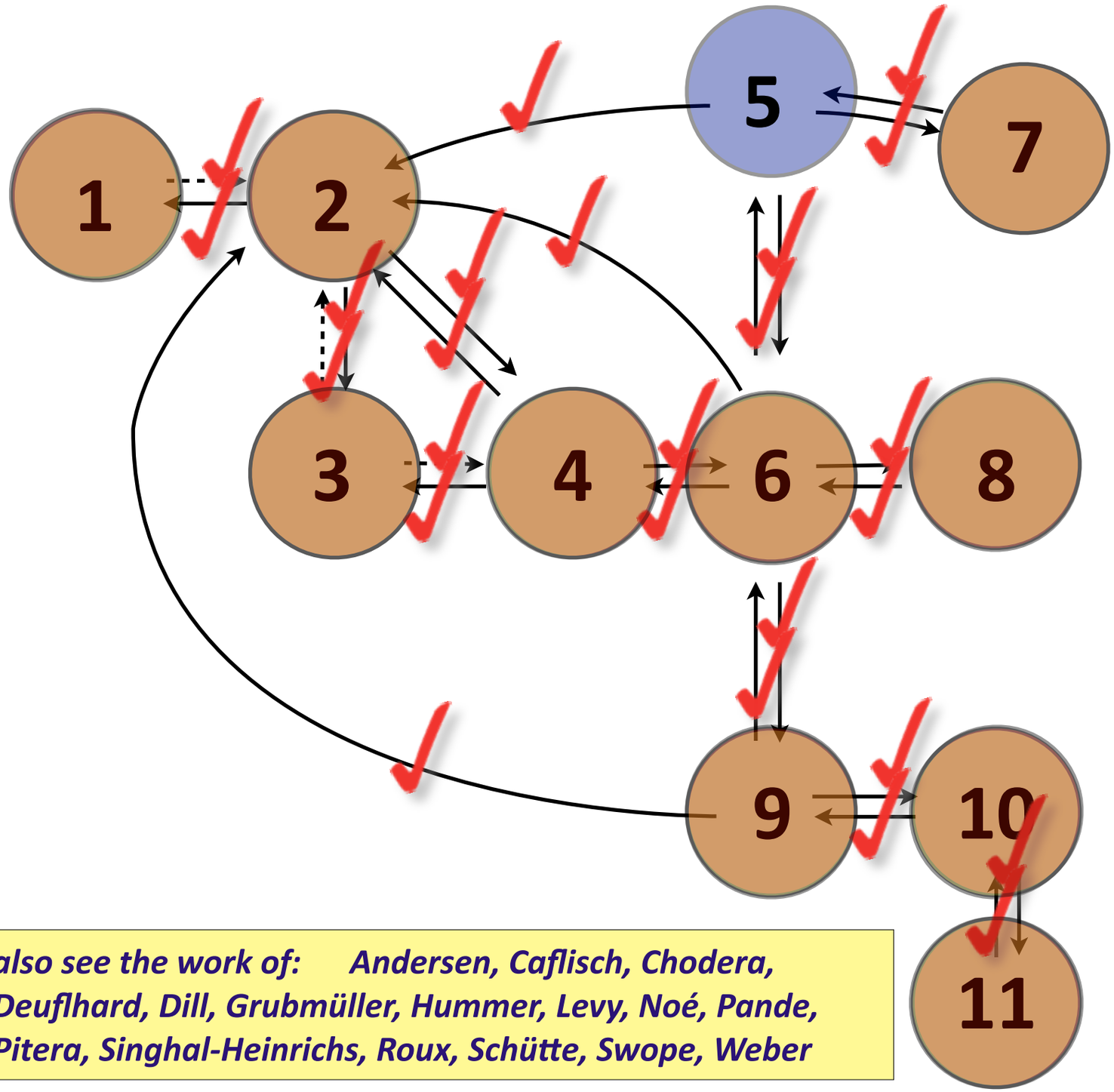

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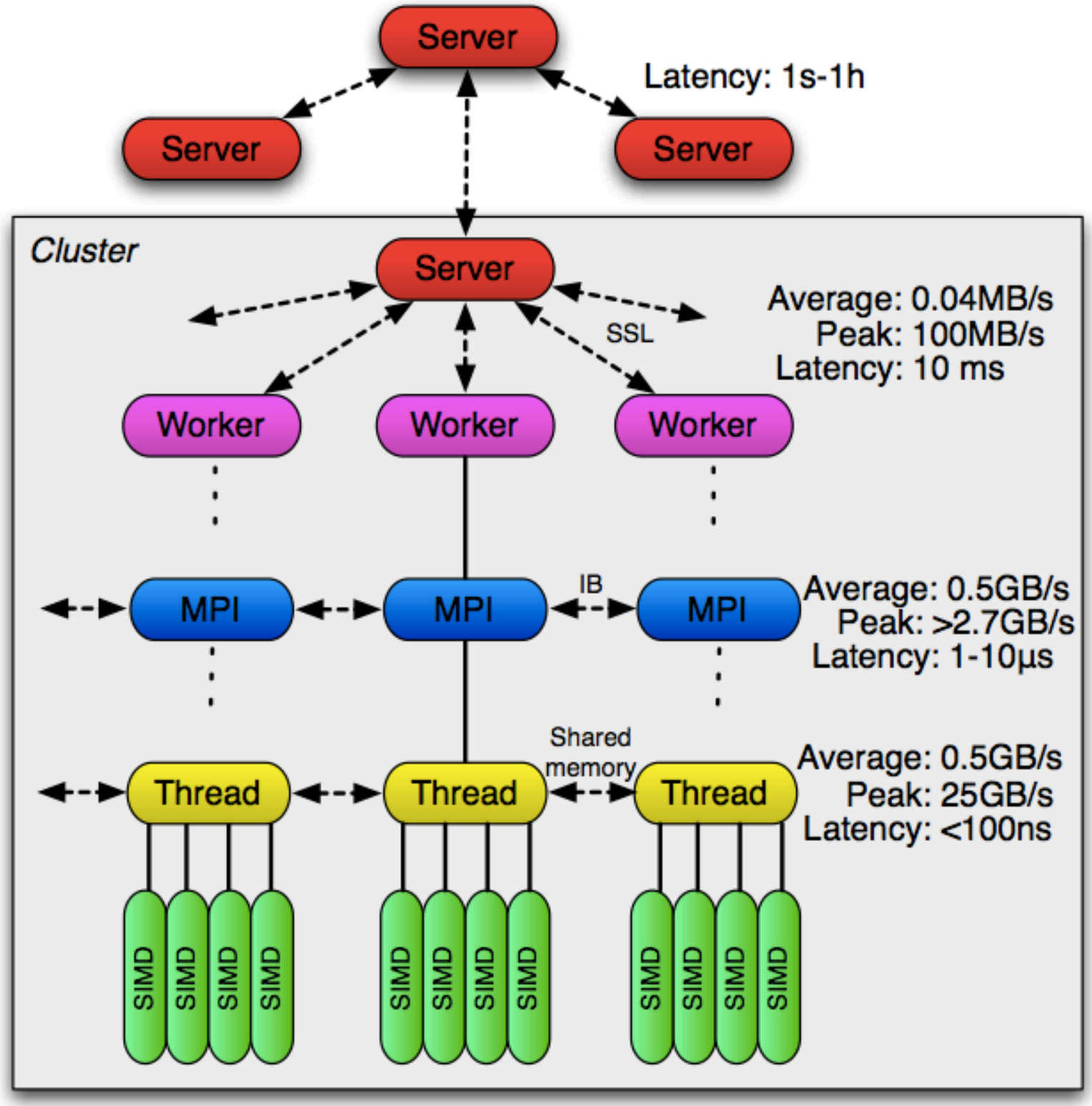
Linear scaling across multiple HPC machines

Copernicus

Copernicus: A Massively Parallel Engine for Simulation



Copernicus: A Massively Parallel Engine for Simulation

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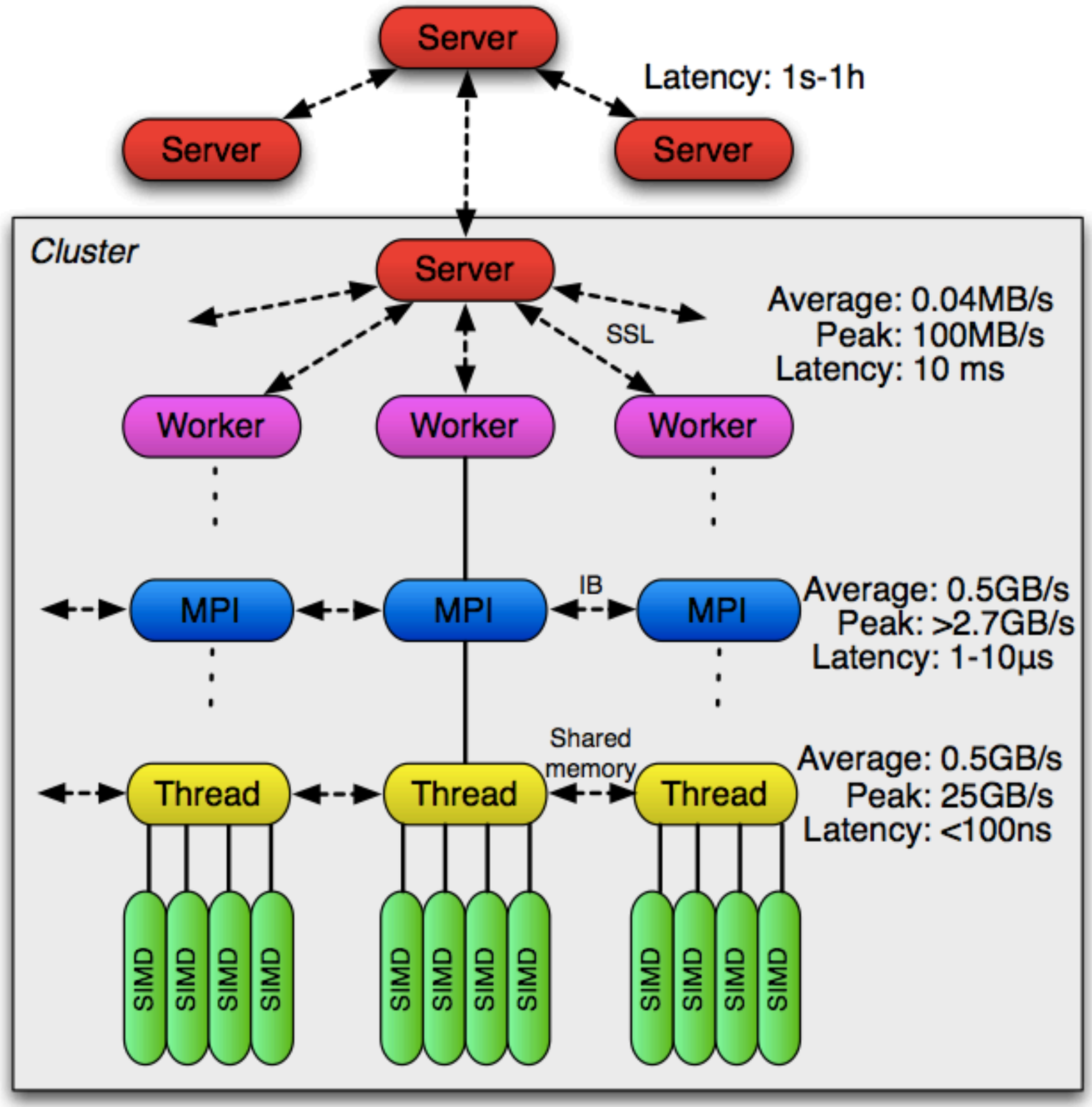

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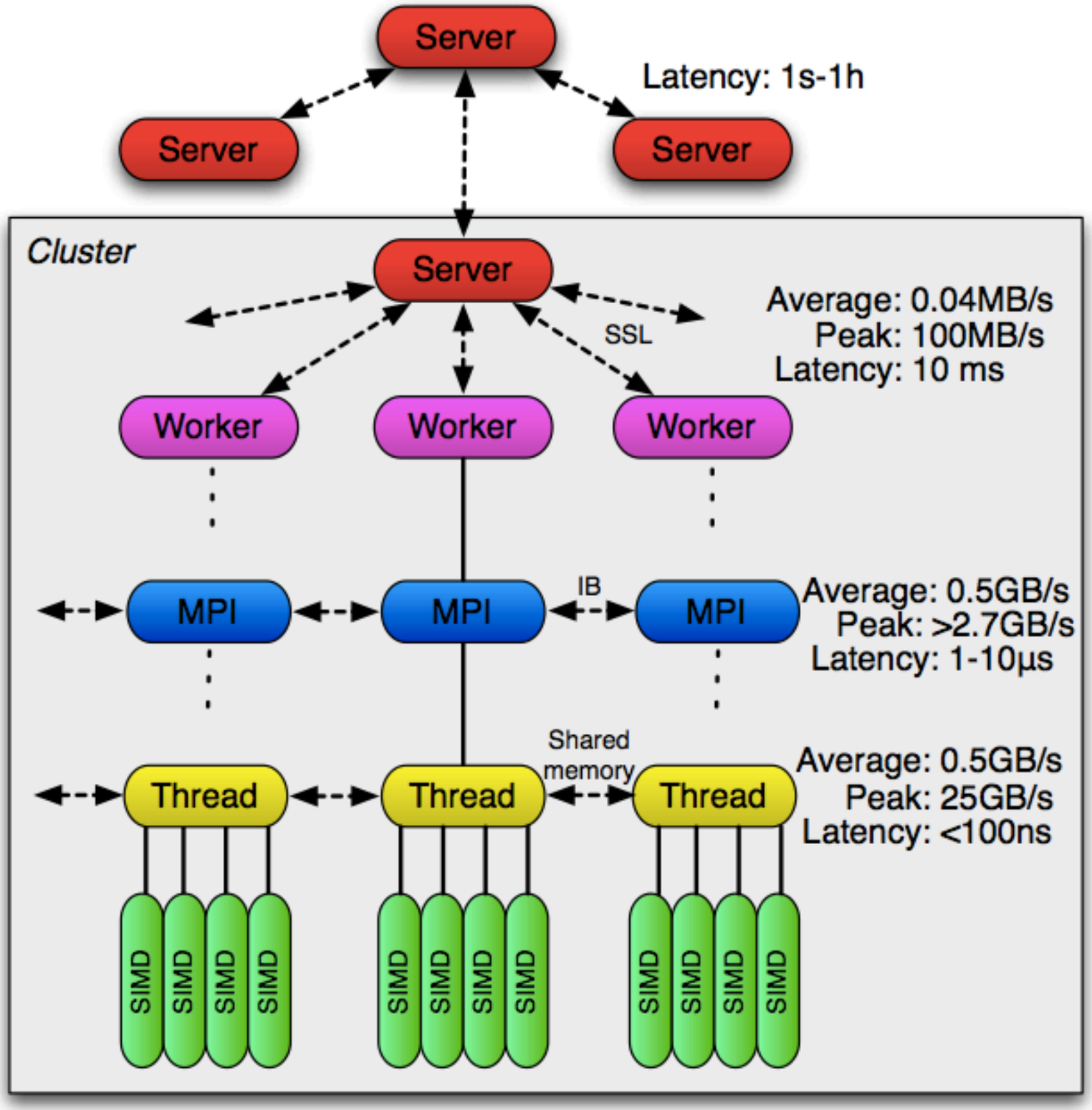

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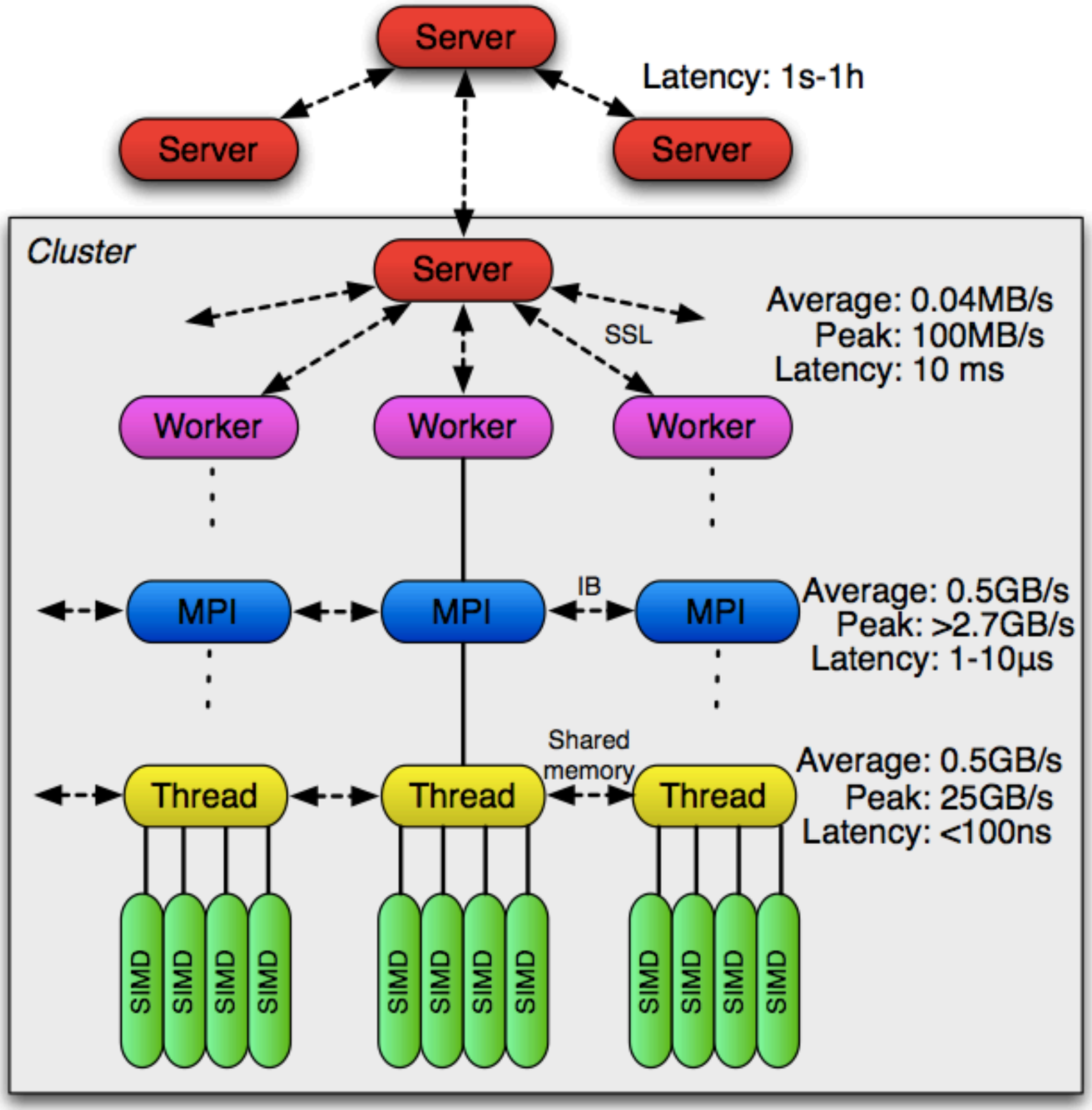
3. Uses real-time clustering to adaptively drive simulations to convergence



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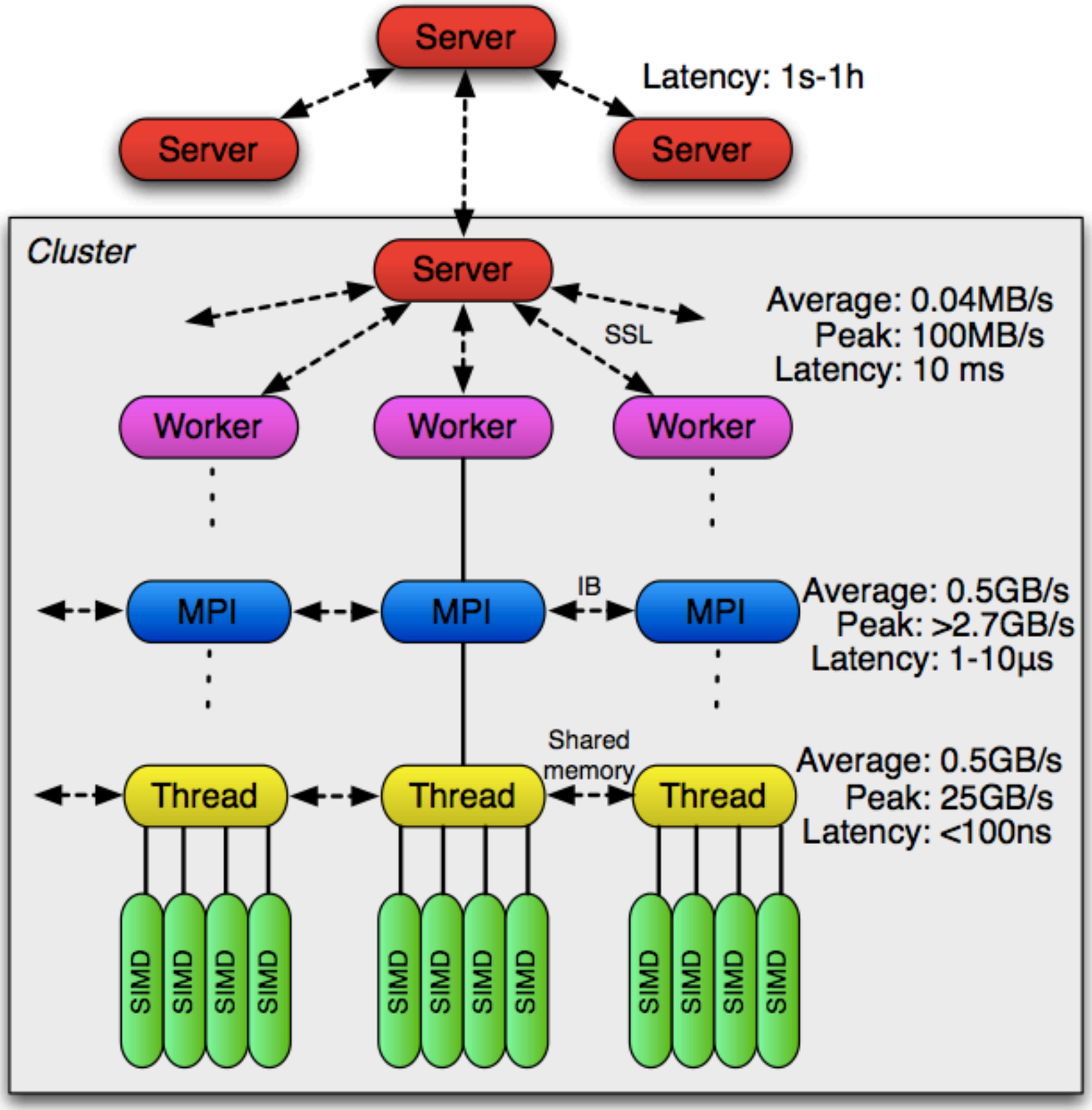

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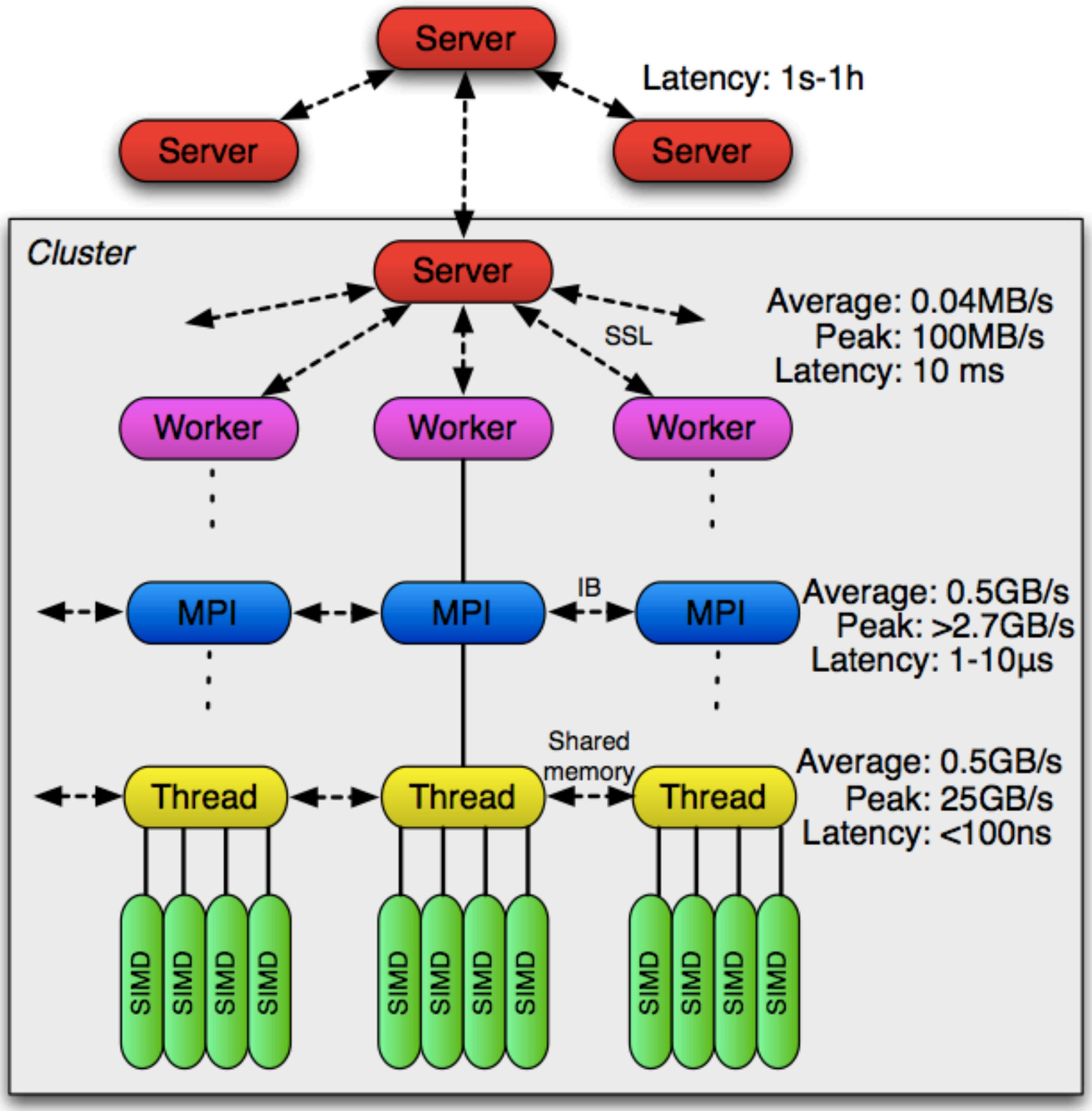
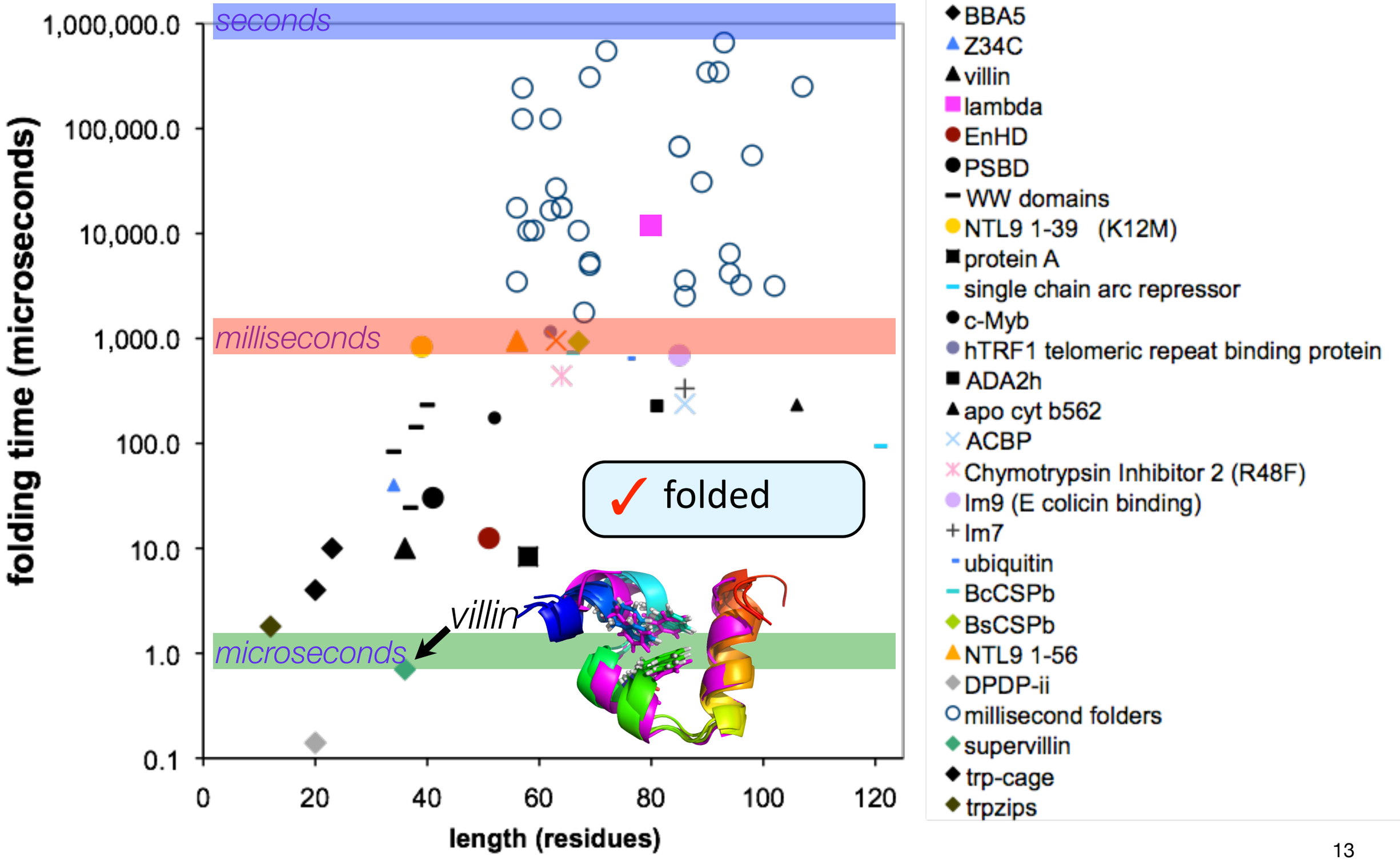
5. Near linear scaling in time-to-solution (folded protein)



Application: folding on the millisecond timescale



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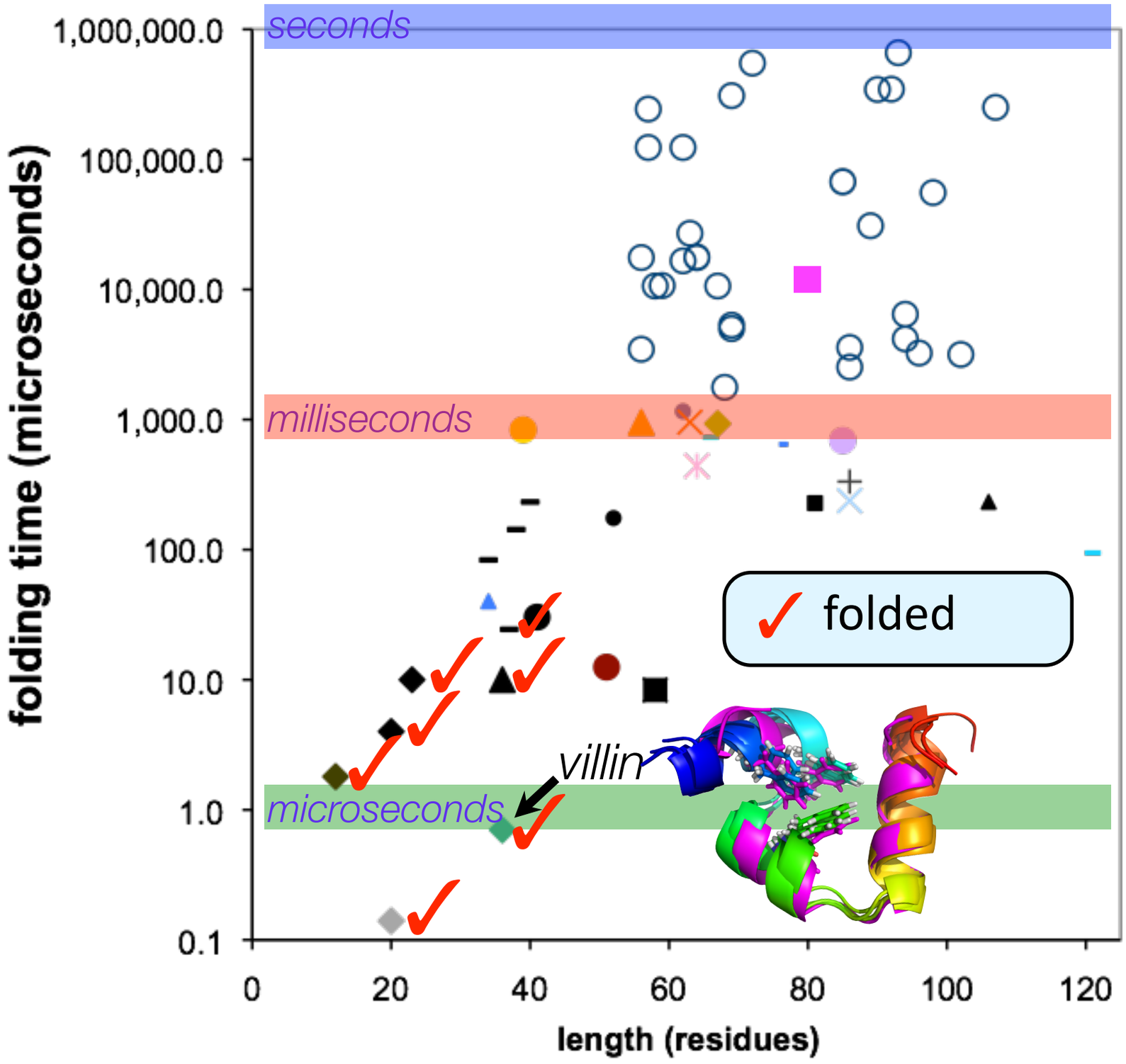

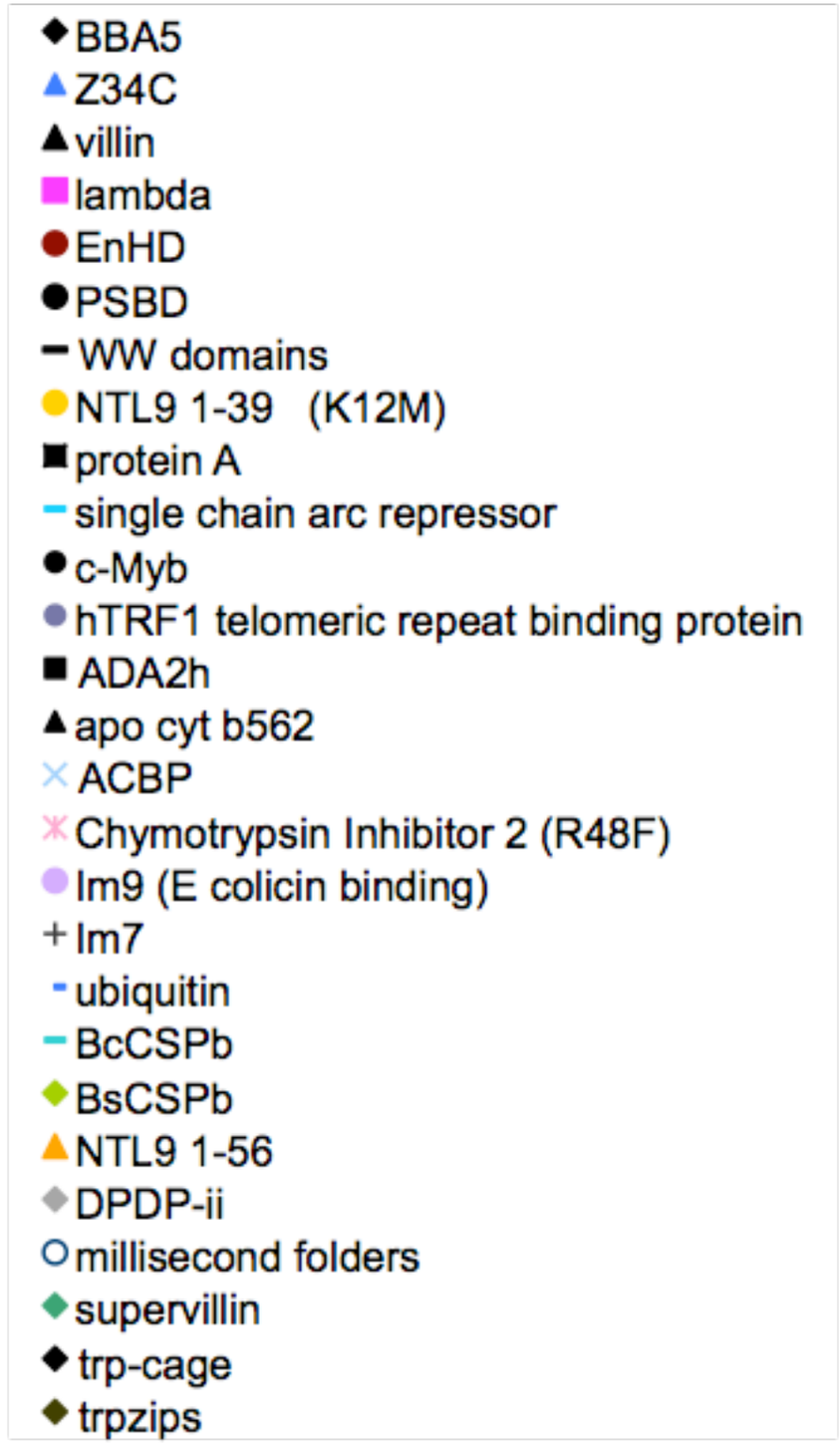

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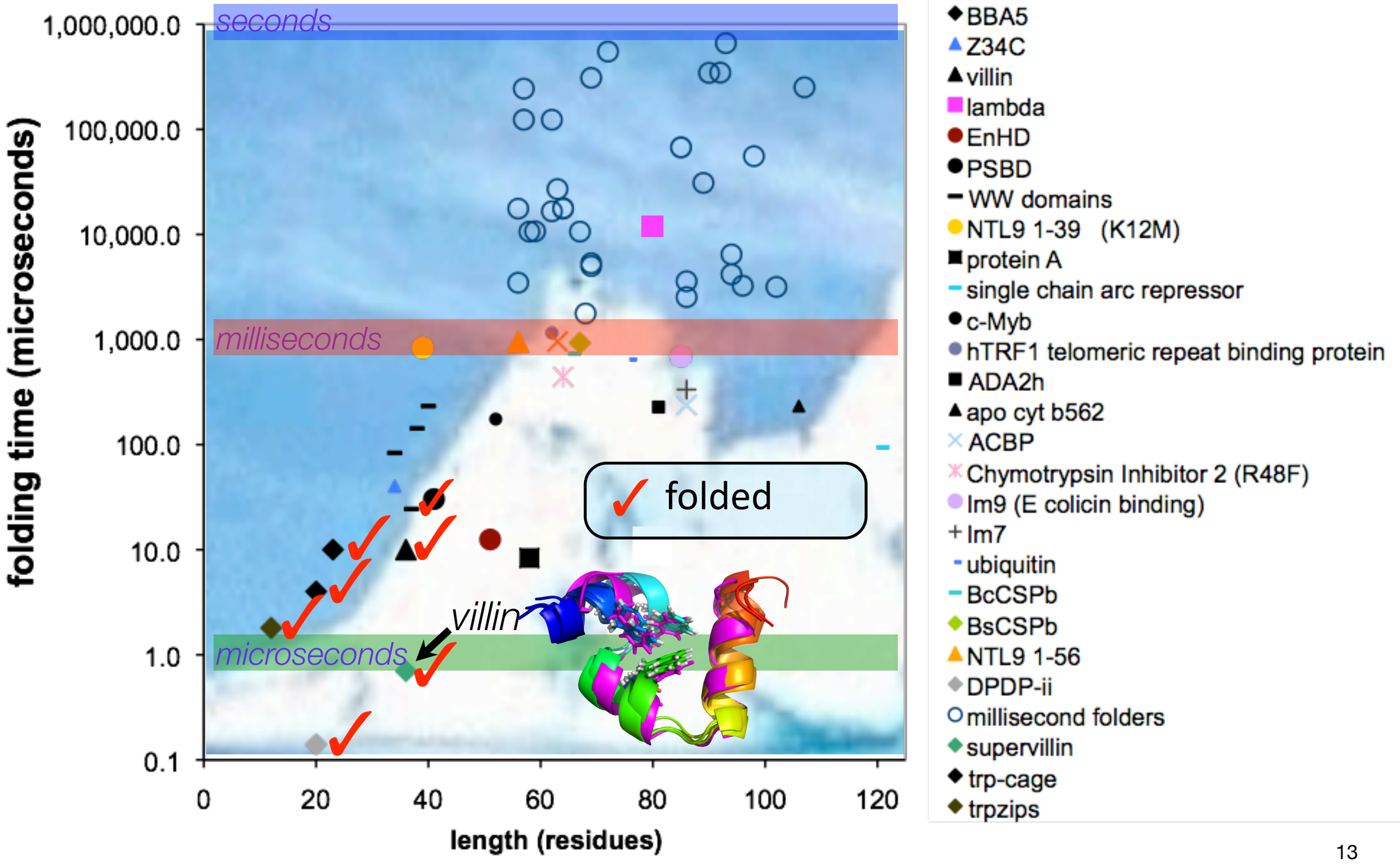

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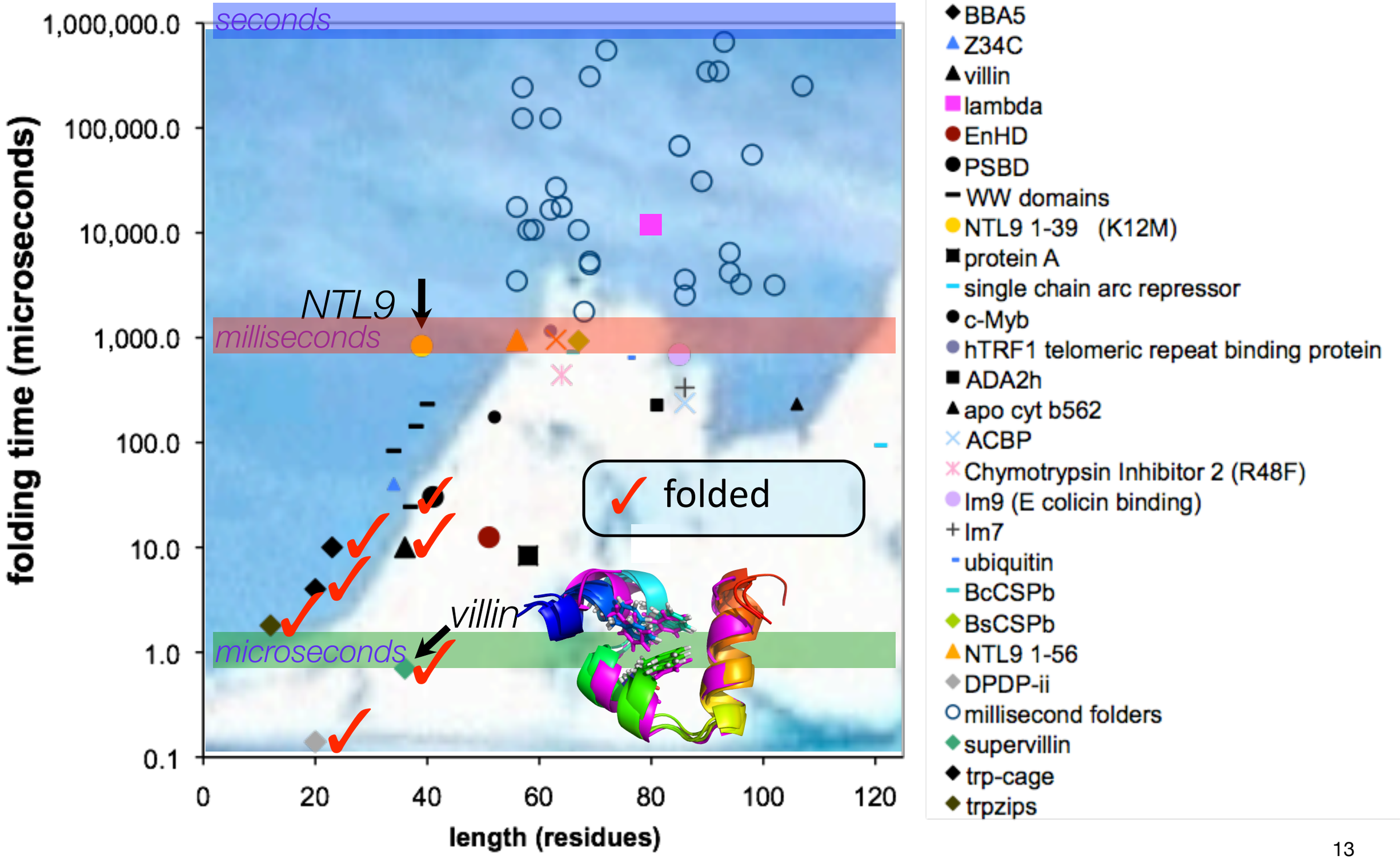

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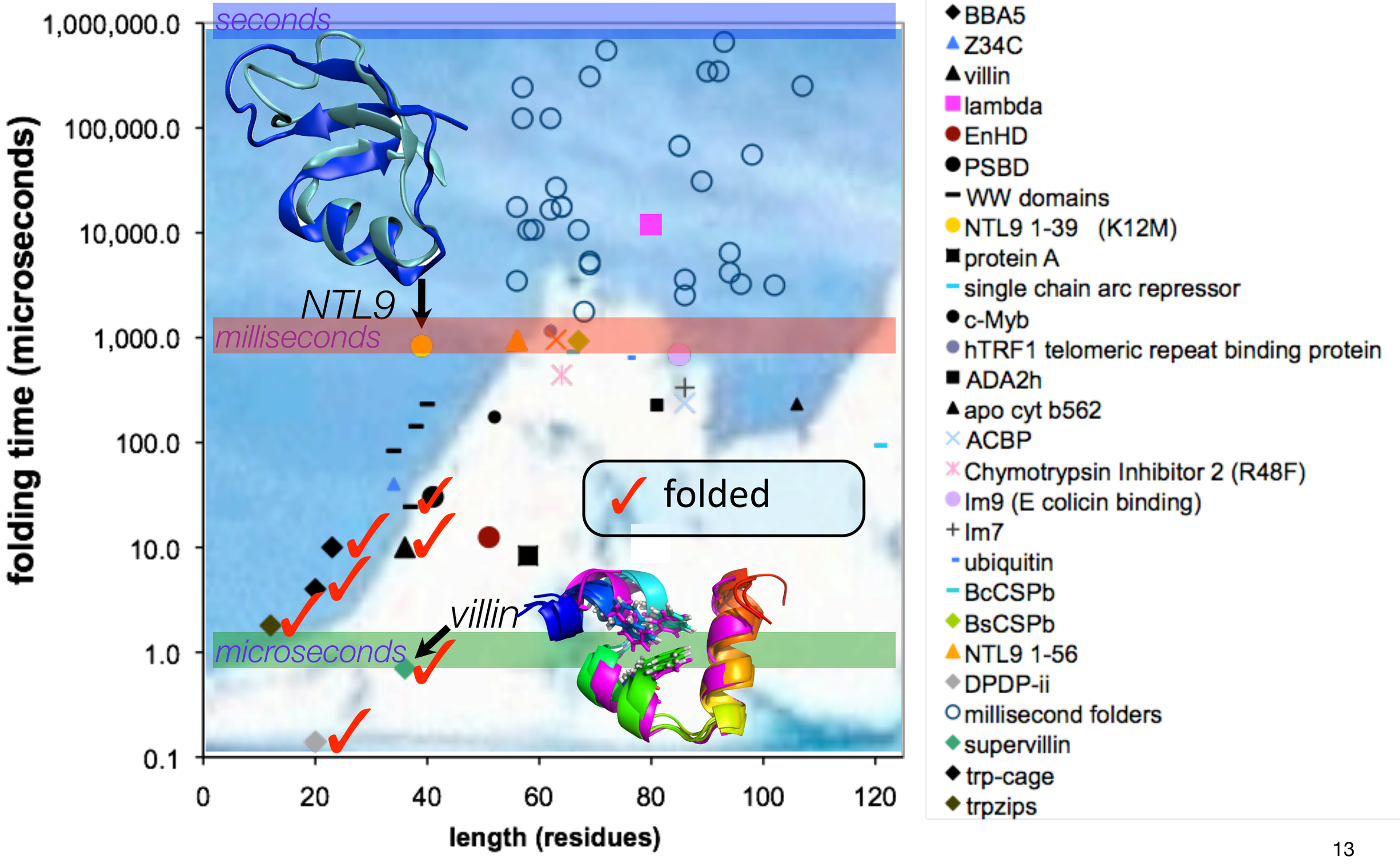
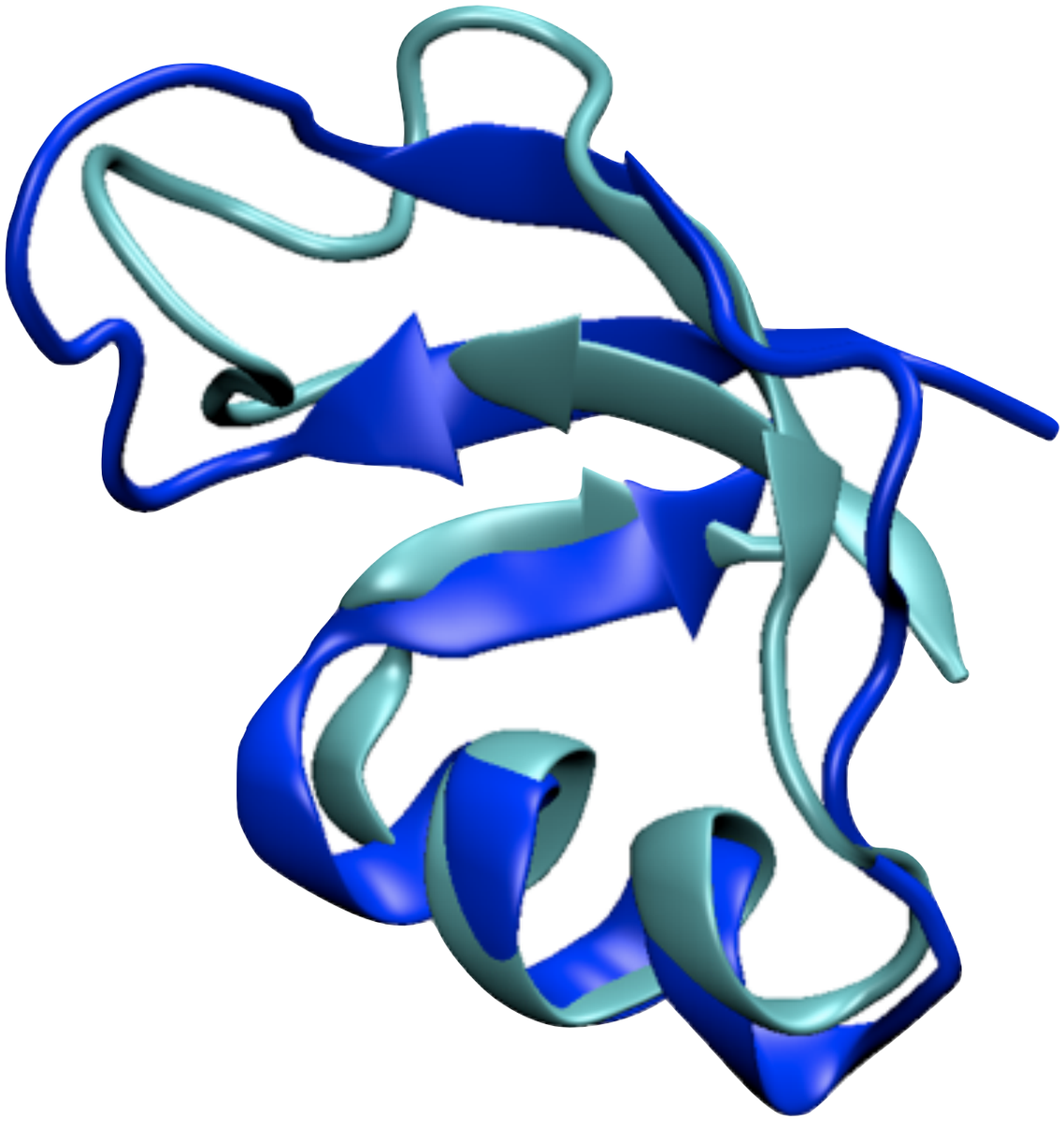
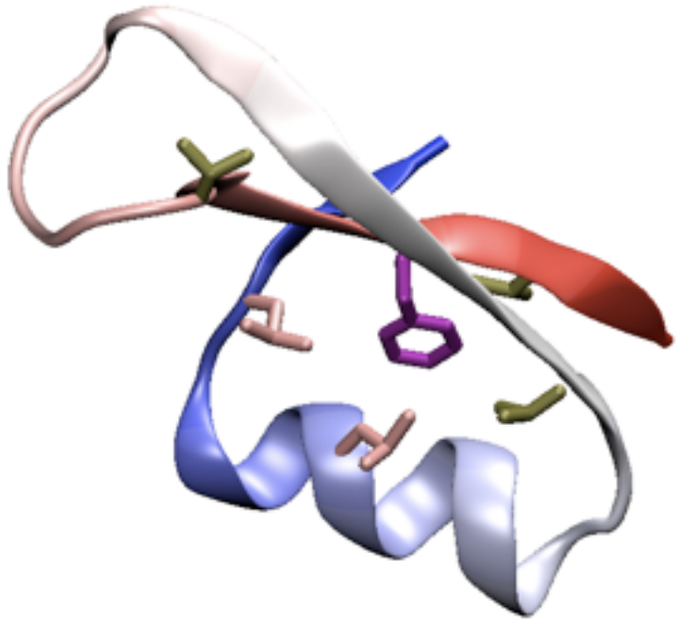


(Voelz, Bowman, Beauchamp, VSP)

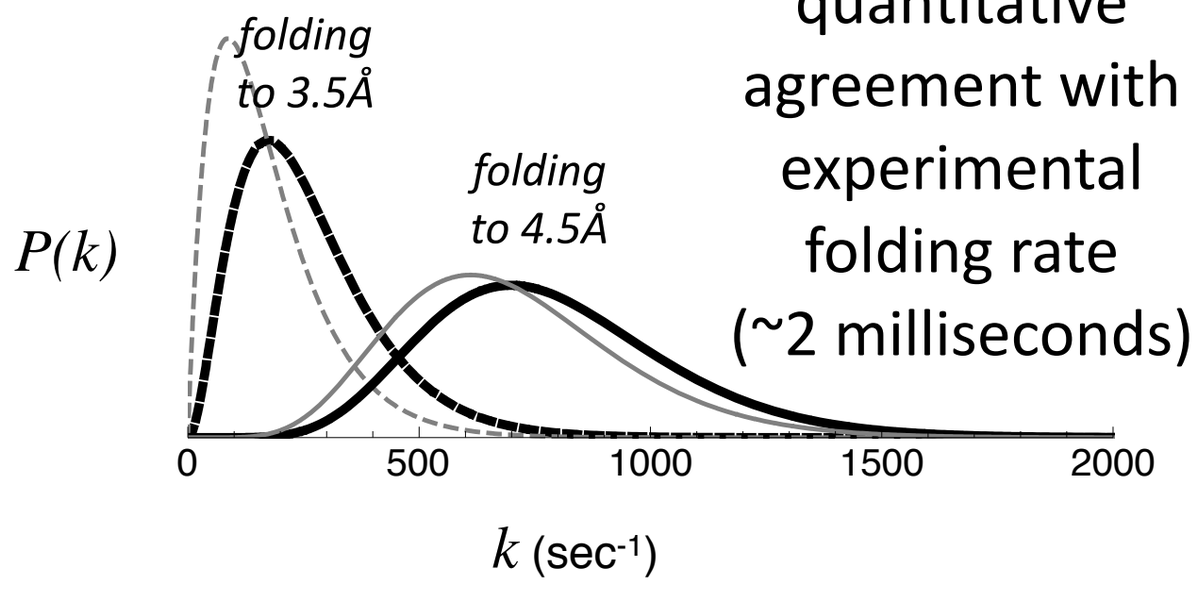
Successful millisecond protein folding: NTL9



crystal structure vs simulation
(3.17Å RMSD-Cα)



native-like packing, with PHE5 in the hydrophobic core



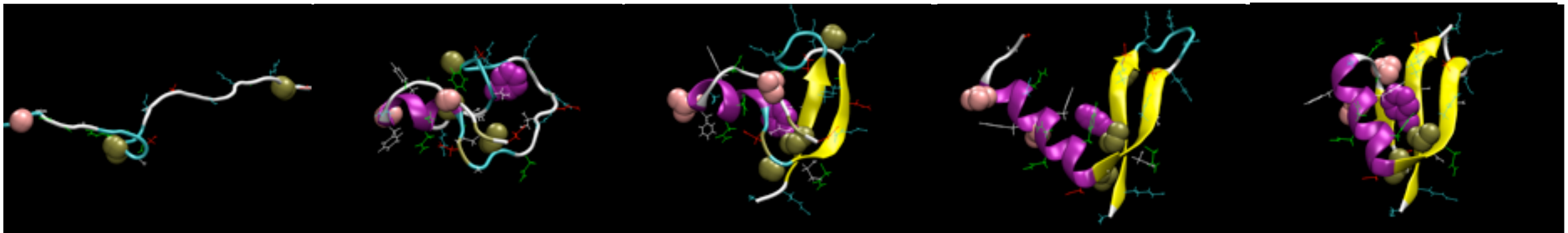
quantitative agreement with experimental folding rate (~2 milliseconds)

Pathway seen in the movie: *Series of **metastable states***

(Voelz, Bowman, Beauchamp, VSP)

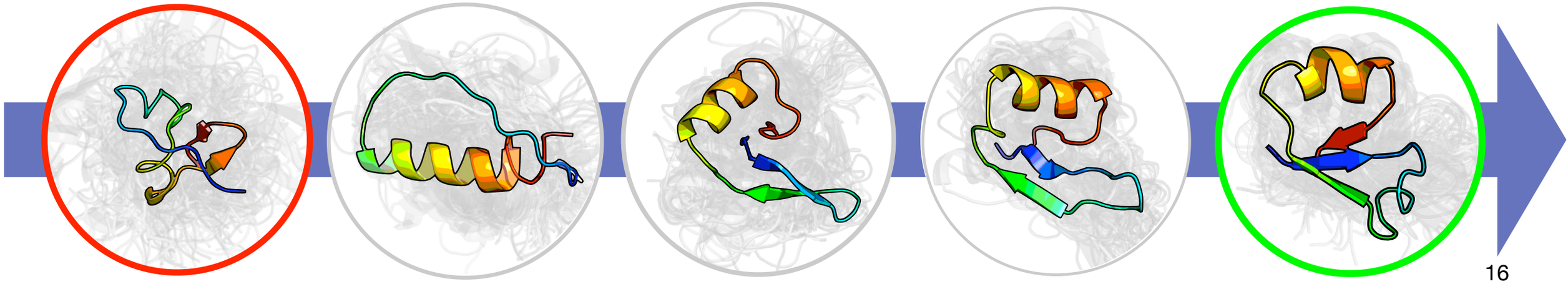
Voelz, Bowman, Beauchamp, Pande. *JACS* (2010)

snapshots from the movie:

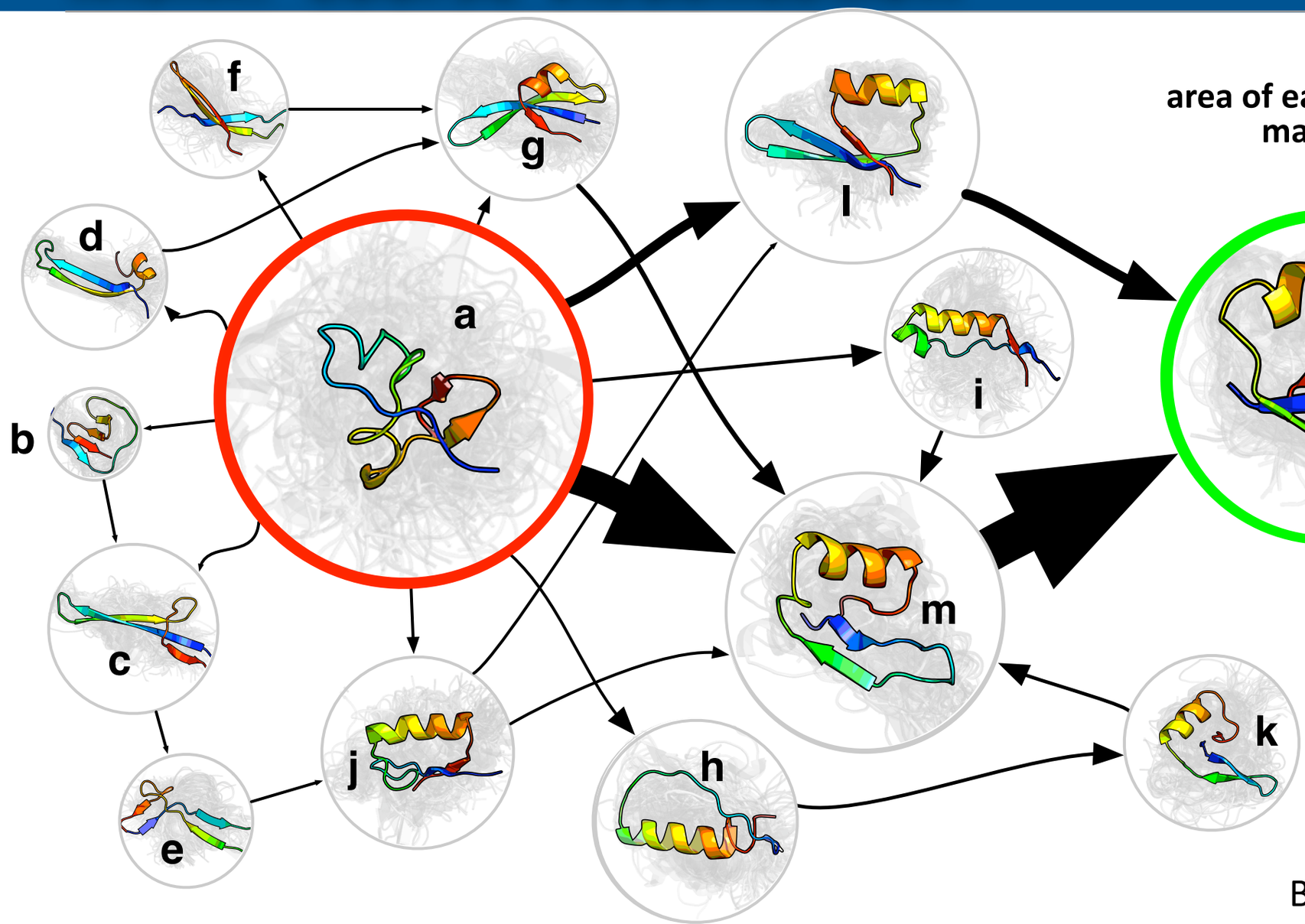


starts in unfolded state	helix forms early	collapse, then beta sheet forms	final part of beta ready to align	folded structure forms

correspond to states from our Markov State Model:



Repeating with many more trajectories yields an MSM: coarse visualization (Voelz, Bowman, Beauchamp, VSP)



area of each state is proportional to macrostate free energy

a→l→n and **a→m→n** comprise 10% of the total flux

width of each arrow is proportional to transition flux

Flux calculation method:

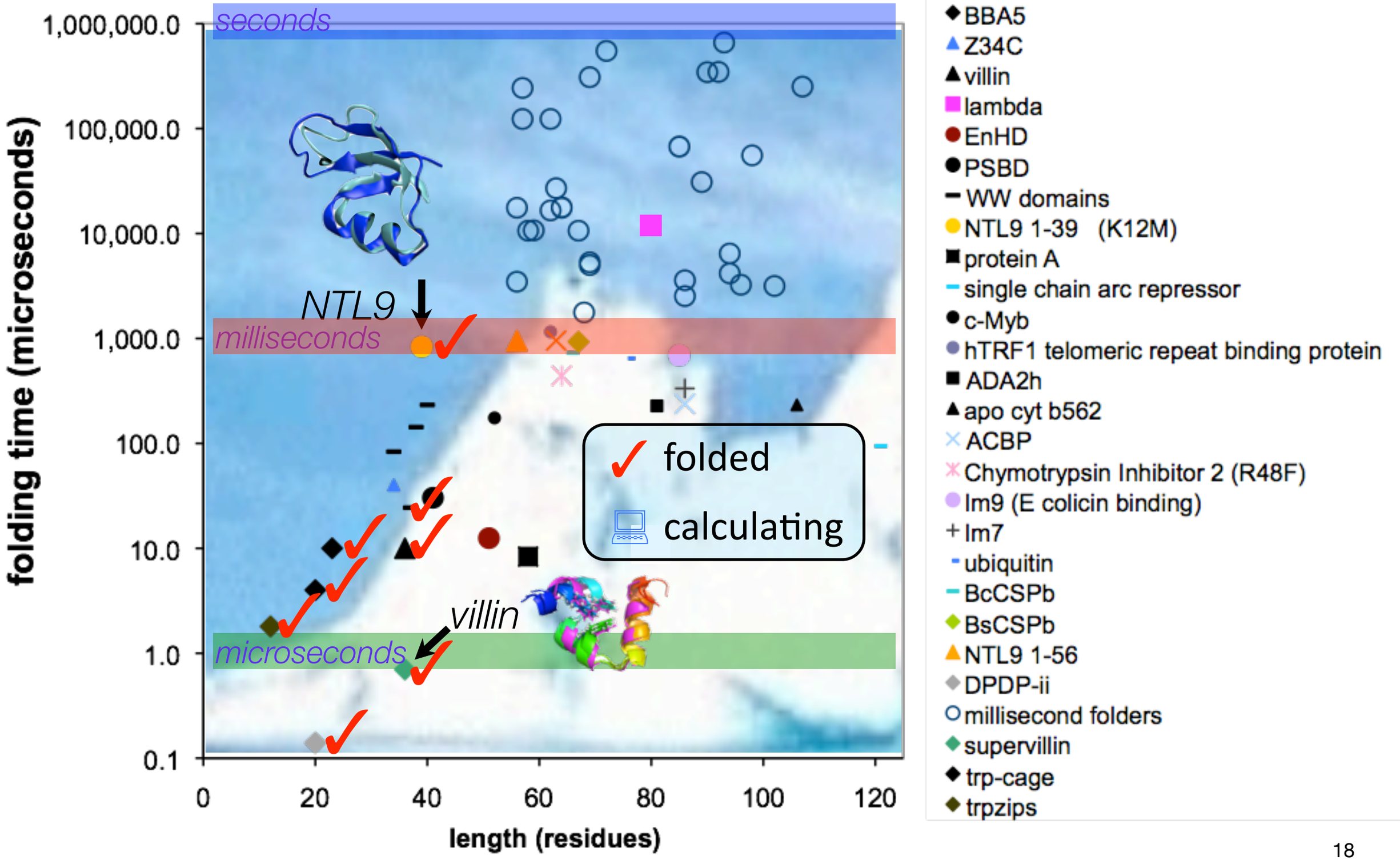
TPT: Vanden-Eijnden, *et al* (2006)

Berezhkovskii, Hummer, Szabo (2009)

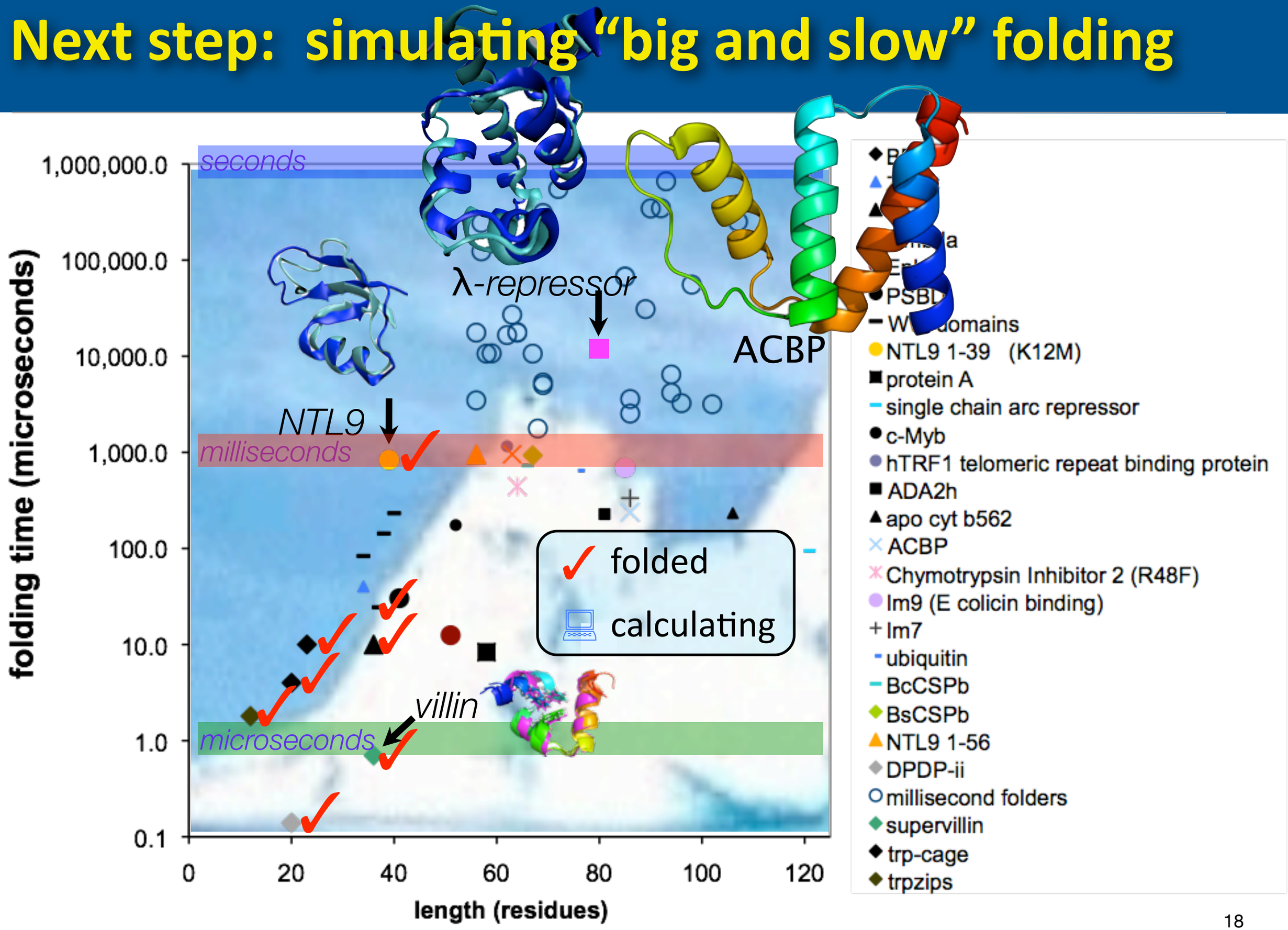
Top 10 folding pathways shows us:

- A great deal of pathway heterogeneity exists
- non-native structure plays a key role in many states
- metastability is often structurally localized (analogous to the foldon concept)

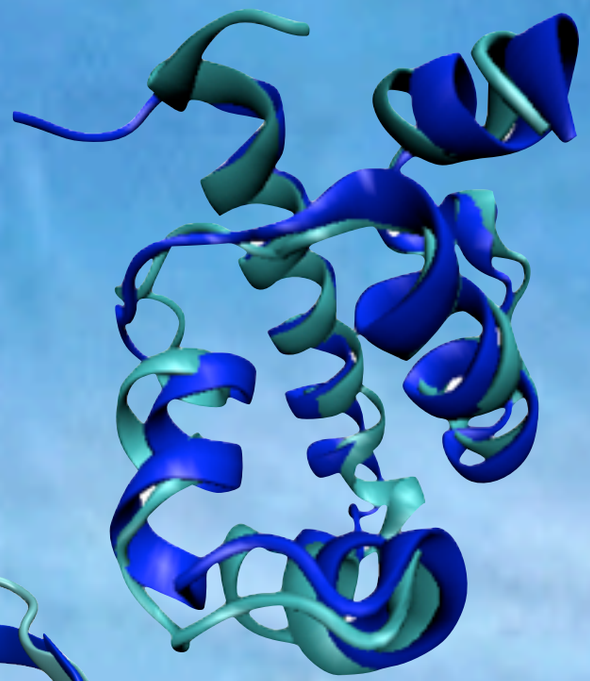
Next step: simulating "big and slow" folding



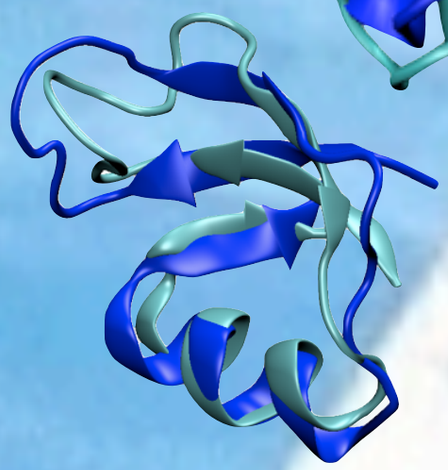
Next step: simulating "big and slow" folding



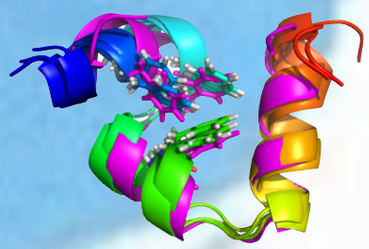
We are now getting close to the top of the mountain



Group 3/4:
Lambda repressor
(80 residues)

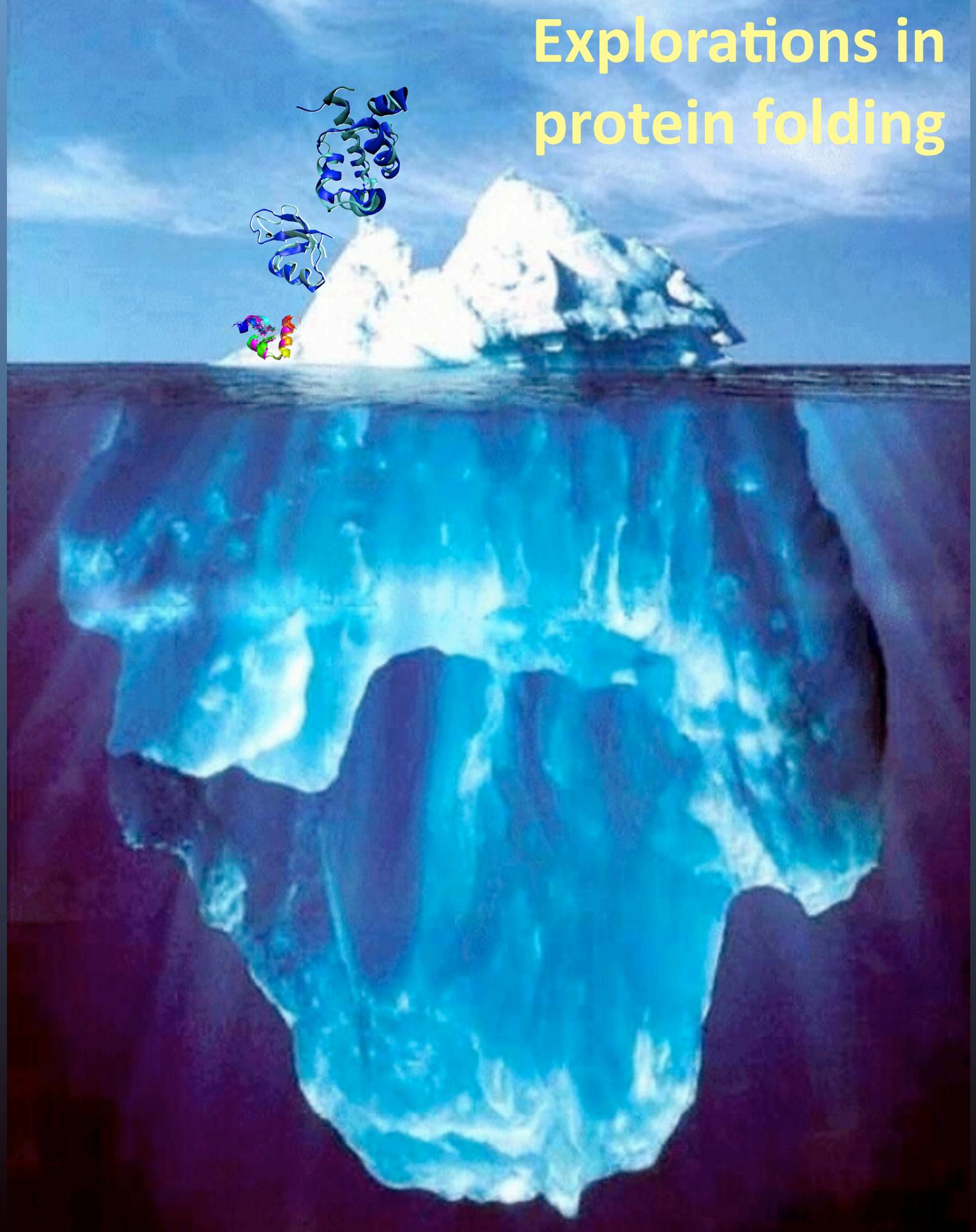


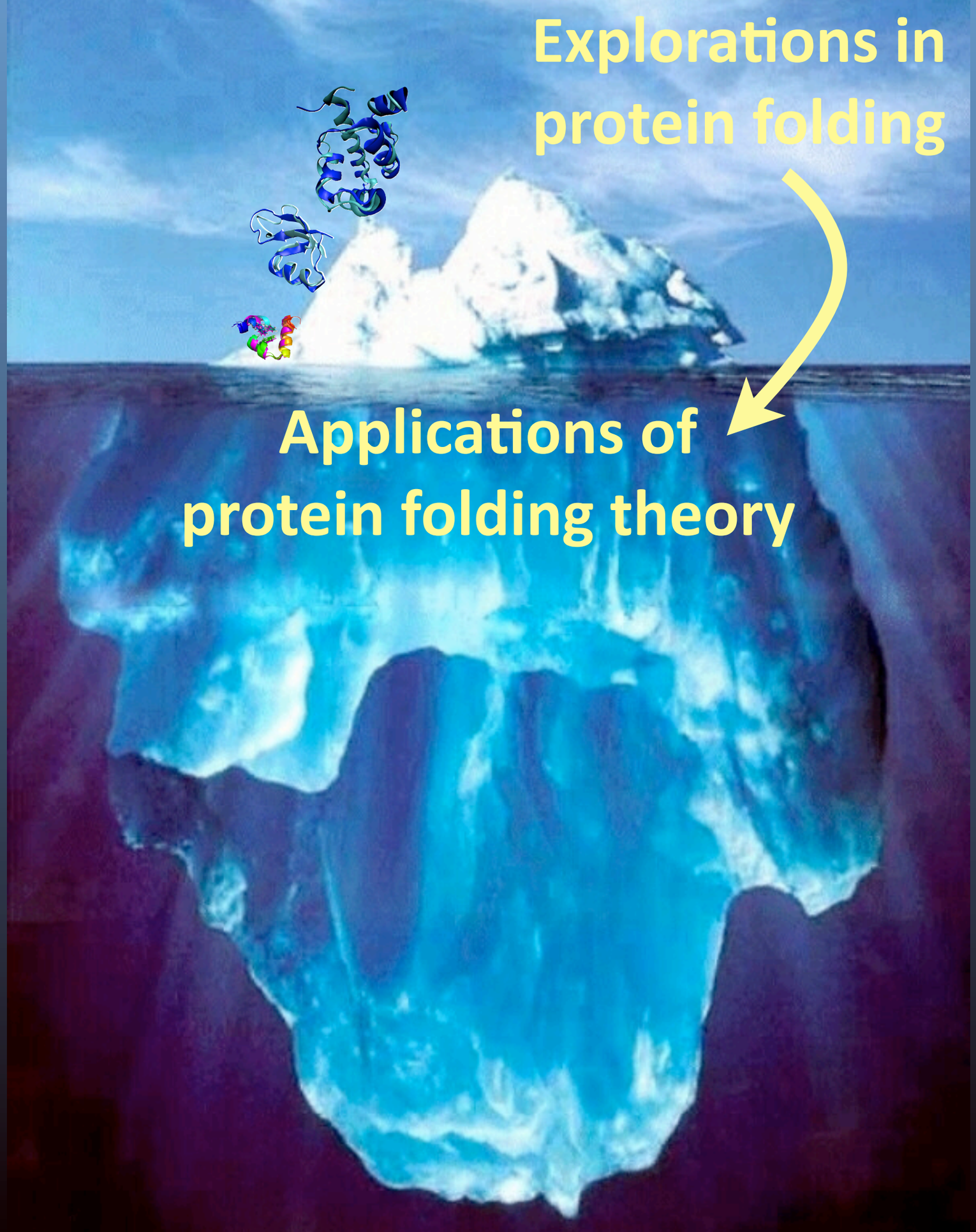
Group 2:
NTL9
(39 residues)



Group 1:
Villin headpiece
(36 residues)

Explorations in protein folding

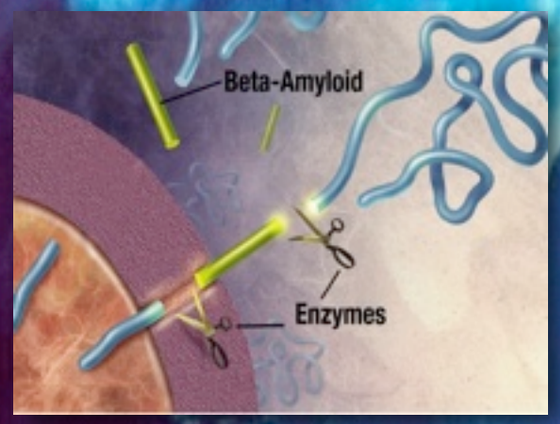



Explorations in
protein folding
Applications of
protein folding theory

Explorations in protein folding

Applications of protein folding theory

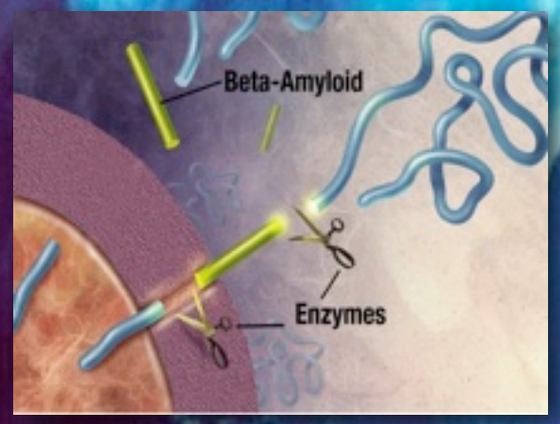
protein misfolding



Explorations in protein folding

Applications of protein folding theory

protein misfolding

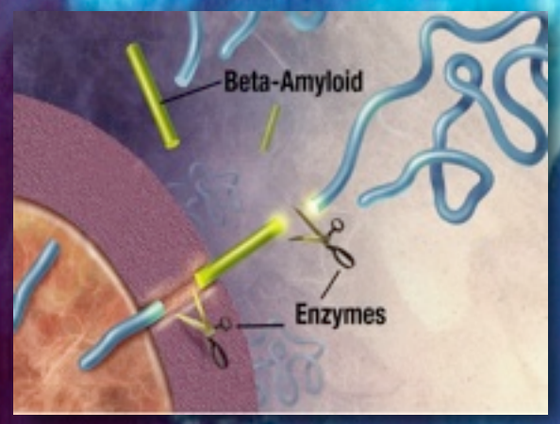


dynamics & function

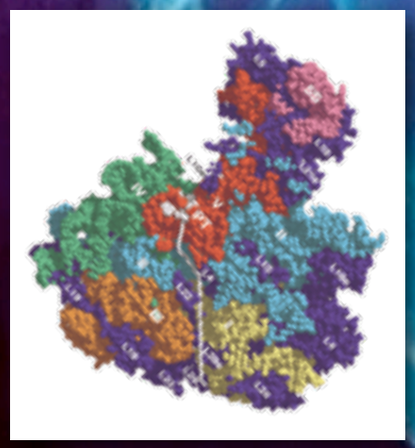
Explorations in protein folding

Applications of protein folding theory

protein misfolding

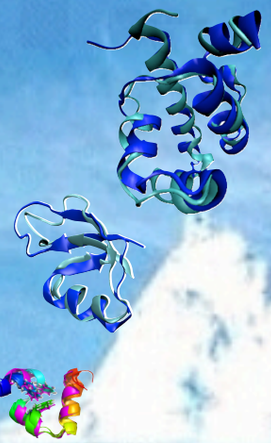


folding of nascent chains



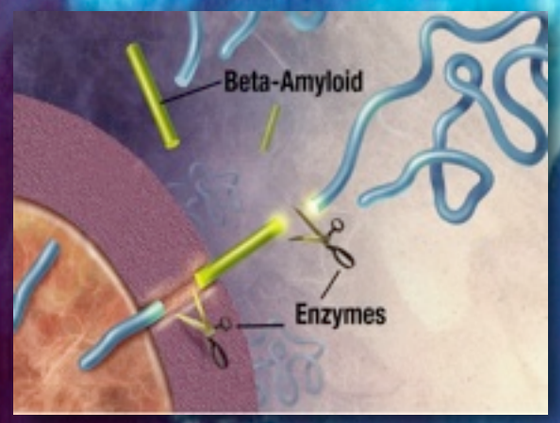
dynamics & function

Explorations in protein folding



Applications of protein folding theory

protein misfolding



dynamics & function

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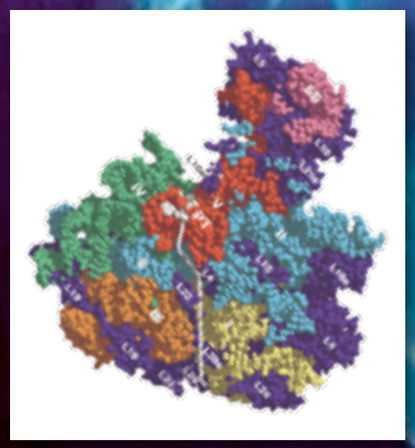
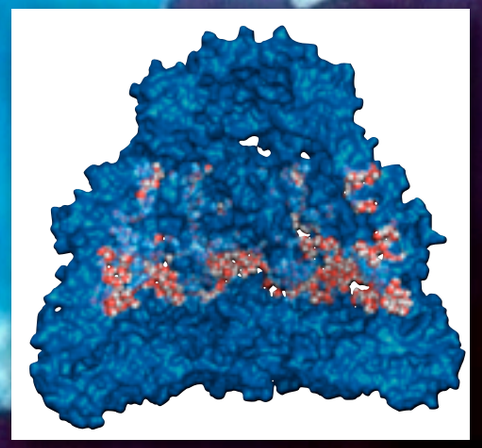
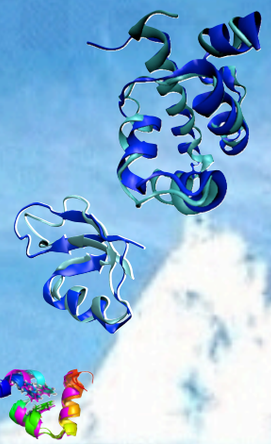




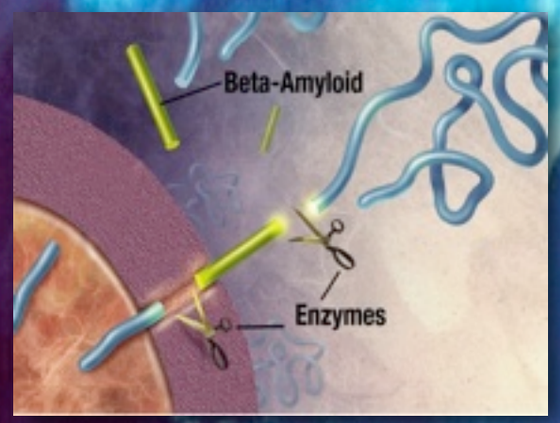
chaperonin function

Explorations in protein folding

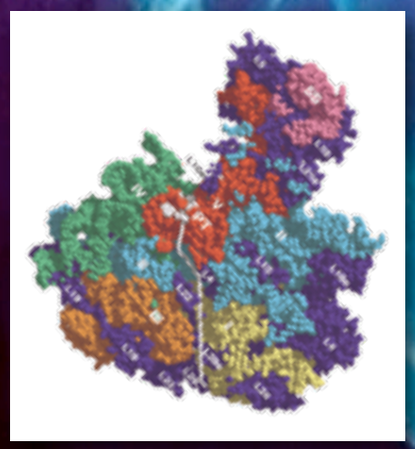


Applications of protein folding theory

protein misfolding

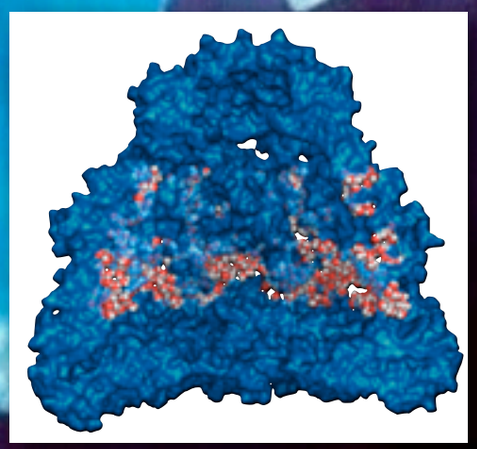


folding of nascent chains

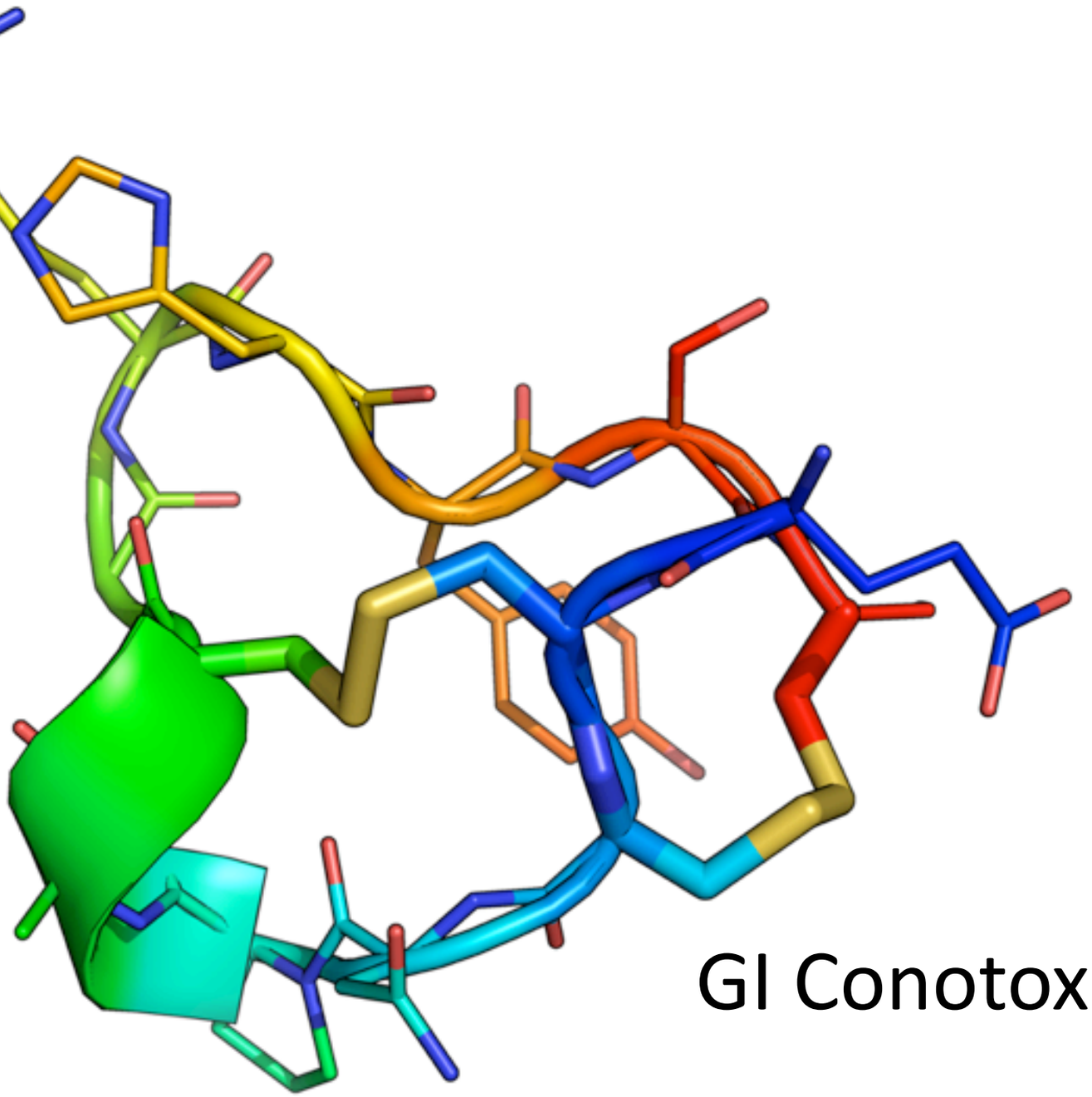


dynamics & function

chaperonin function

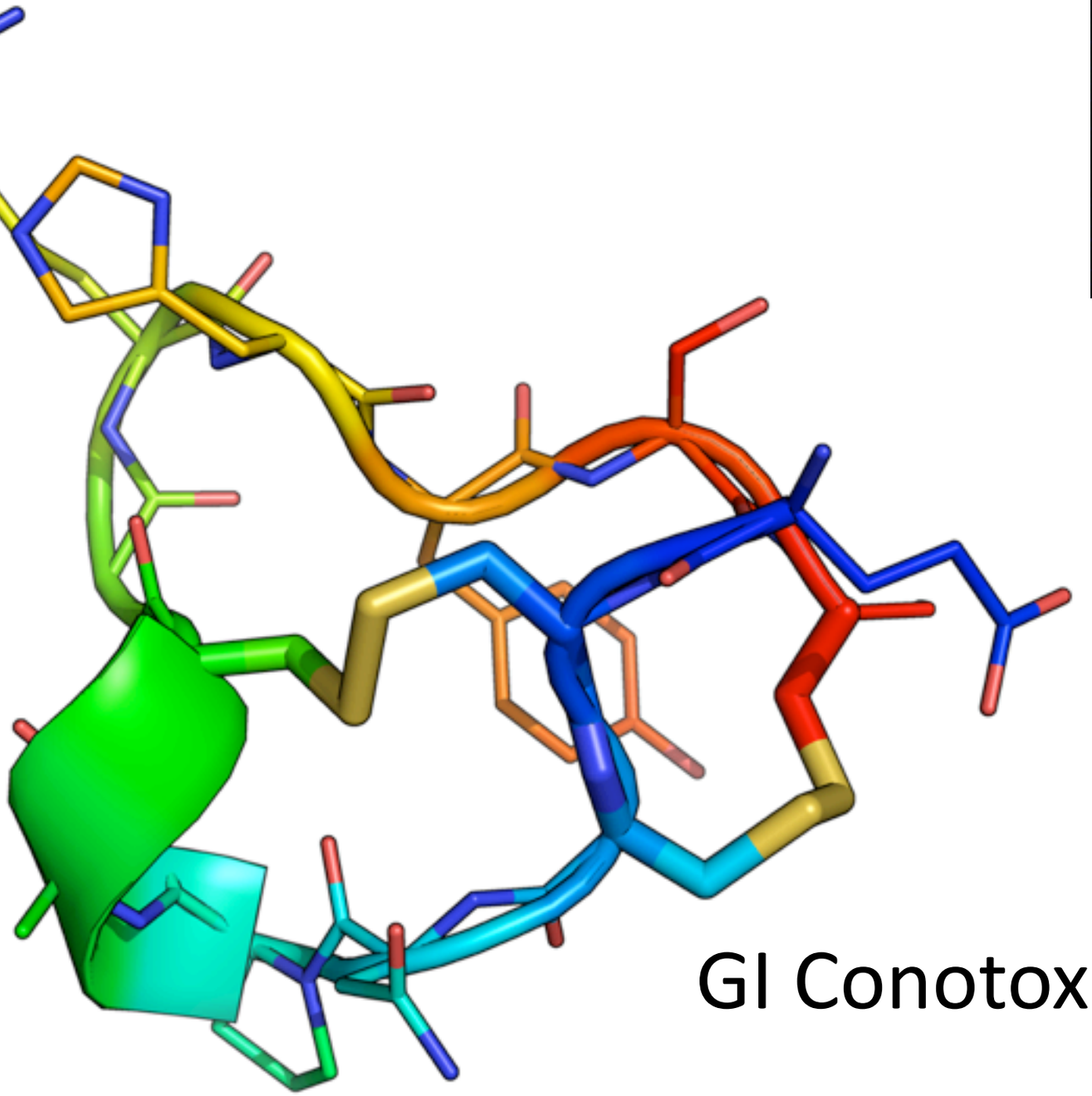


The Hope of Dynamically Derived Theraputics



GI Conotoxin

The Hope of Dynamically Derived Theraputics



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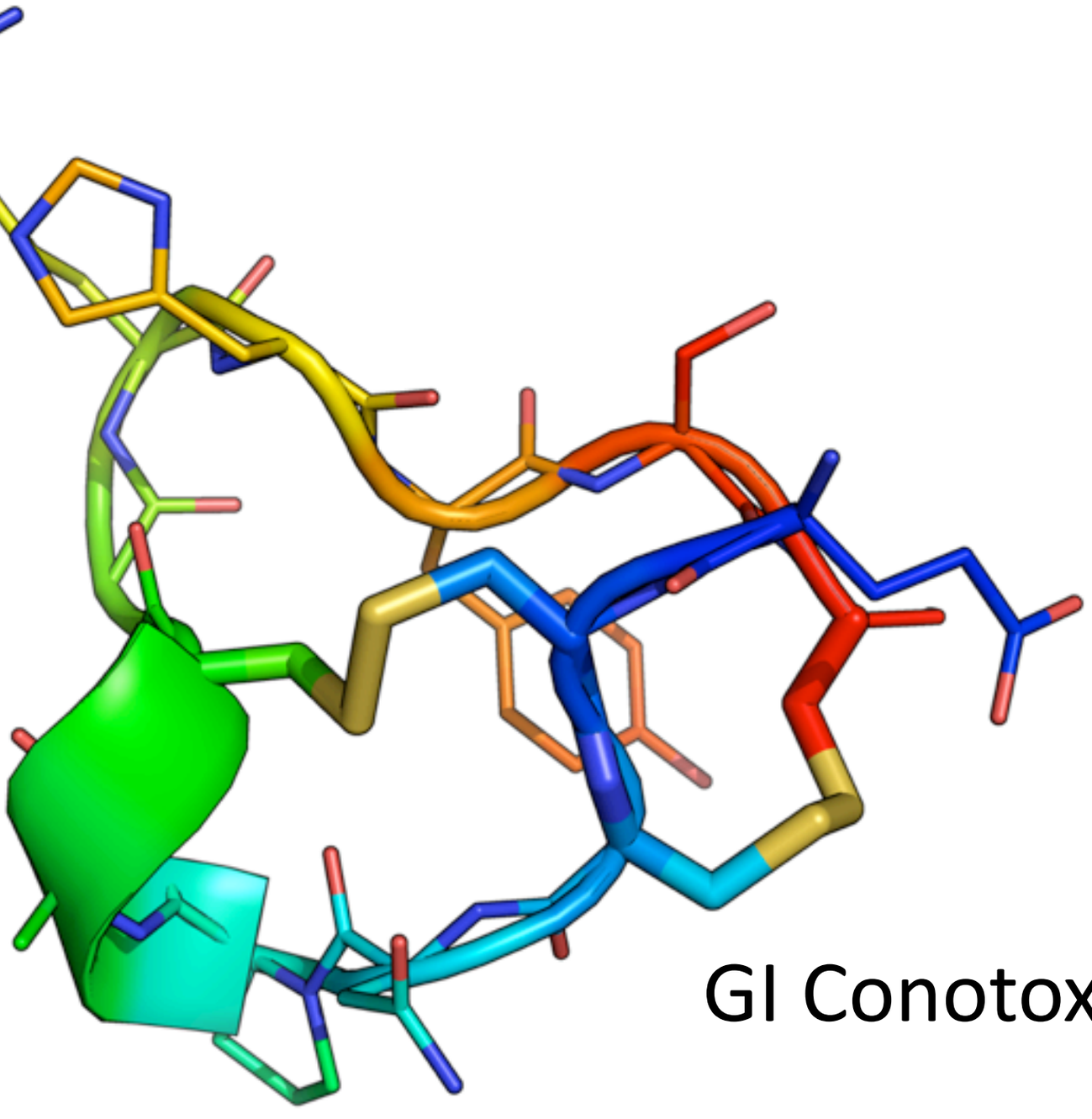
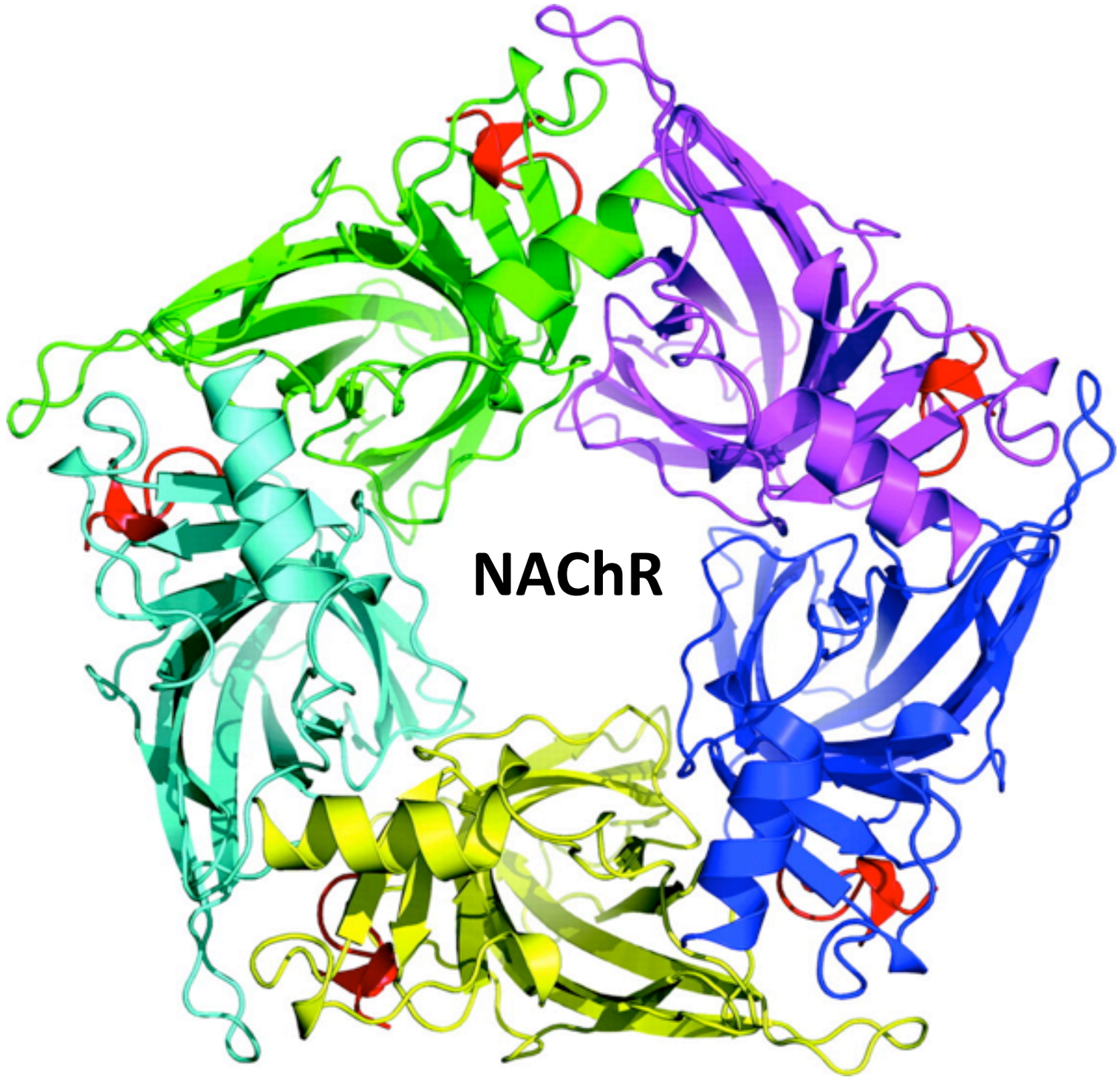


GI Conotoxin

Ziconotide (Prialt)
100-1000x as potent
as morphine

GI Offers a Number of Appealing Advantages



Ulens et. al. PNAS March 7, 2006 vol. 103 no. 10 3615-3620

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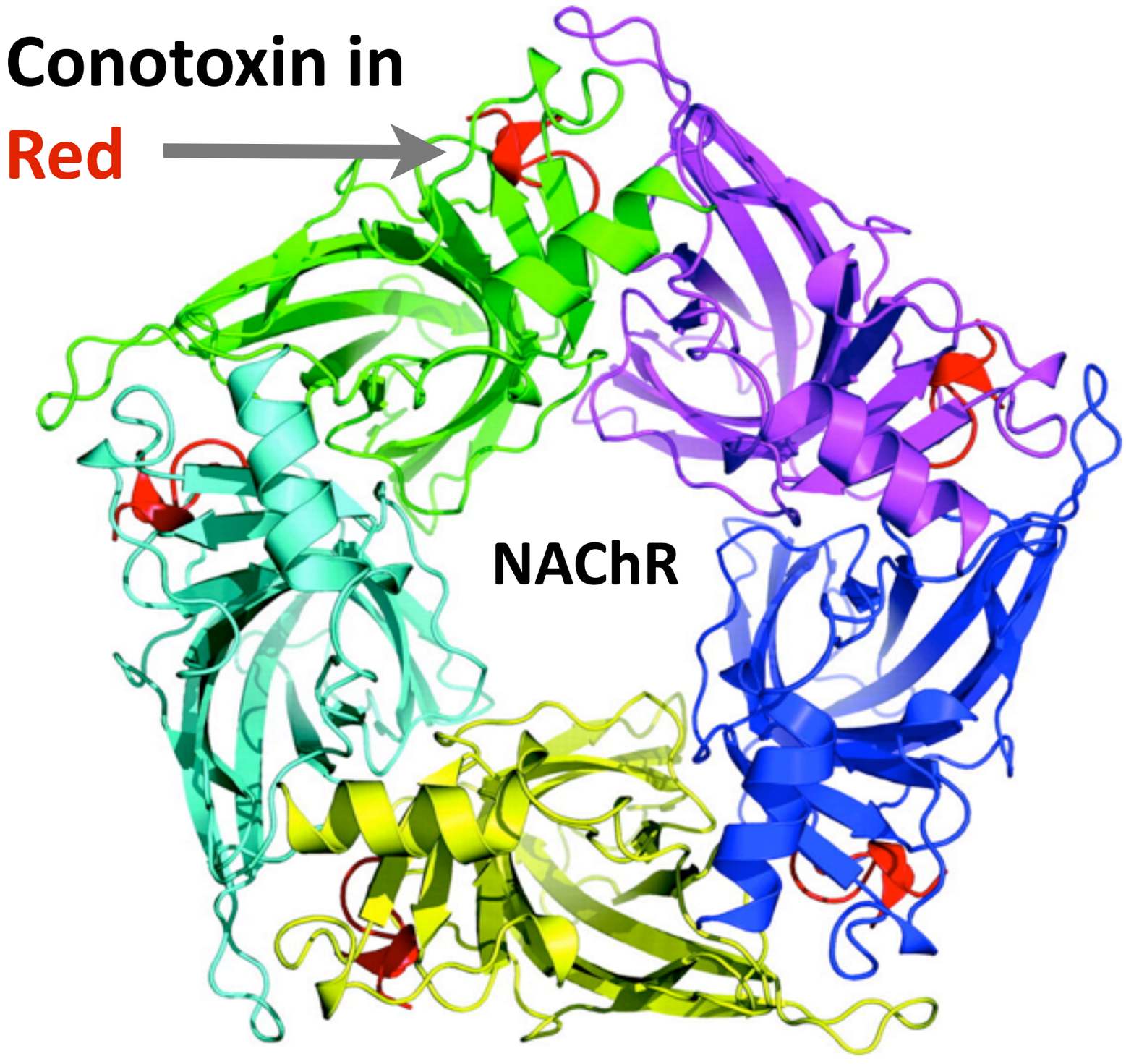

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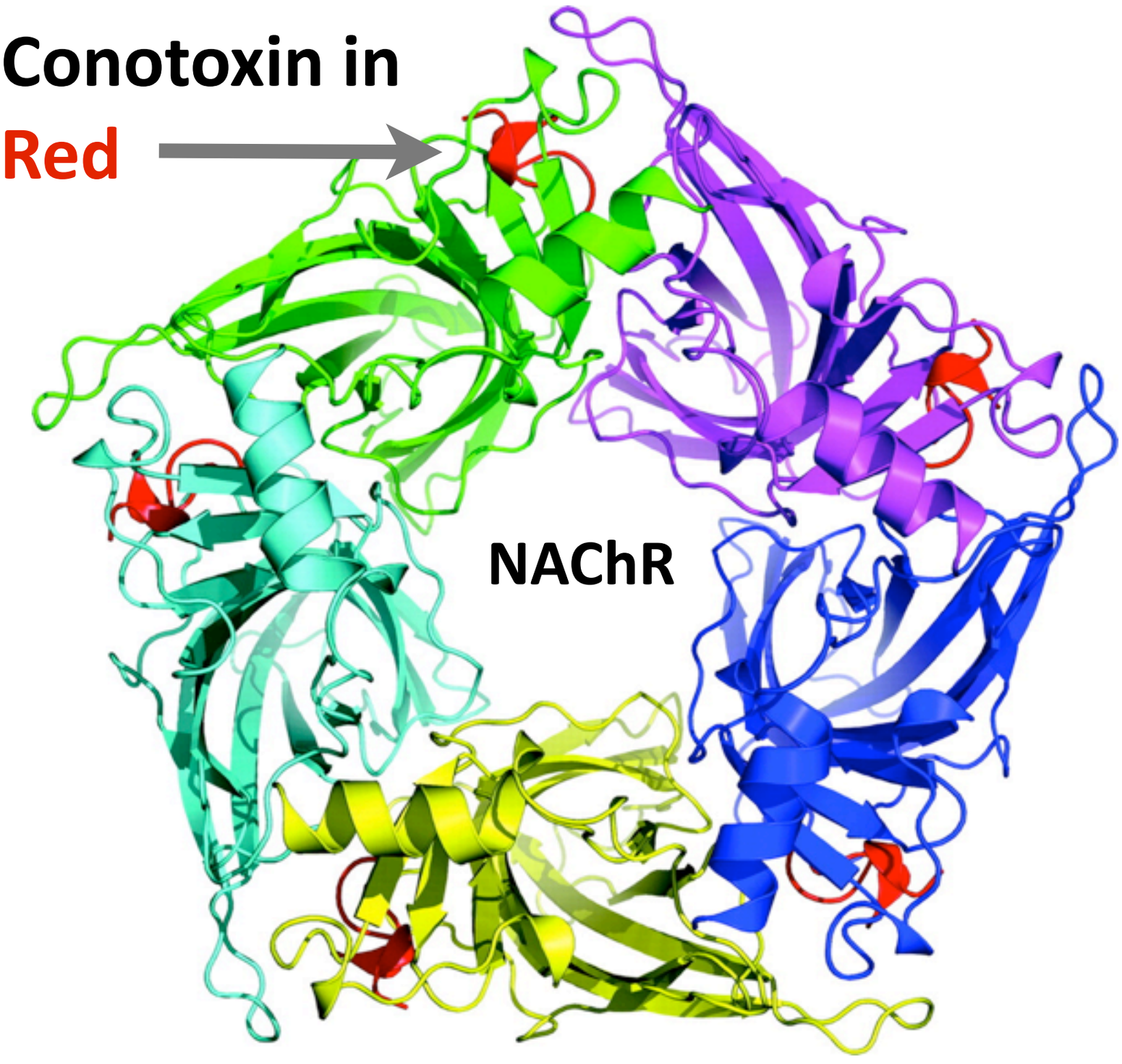
GI Offers a Number of Appealing Advantages

1. **GI is Small:** Good ADME (adsorption, distribution, metabolism, excretion)



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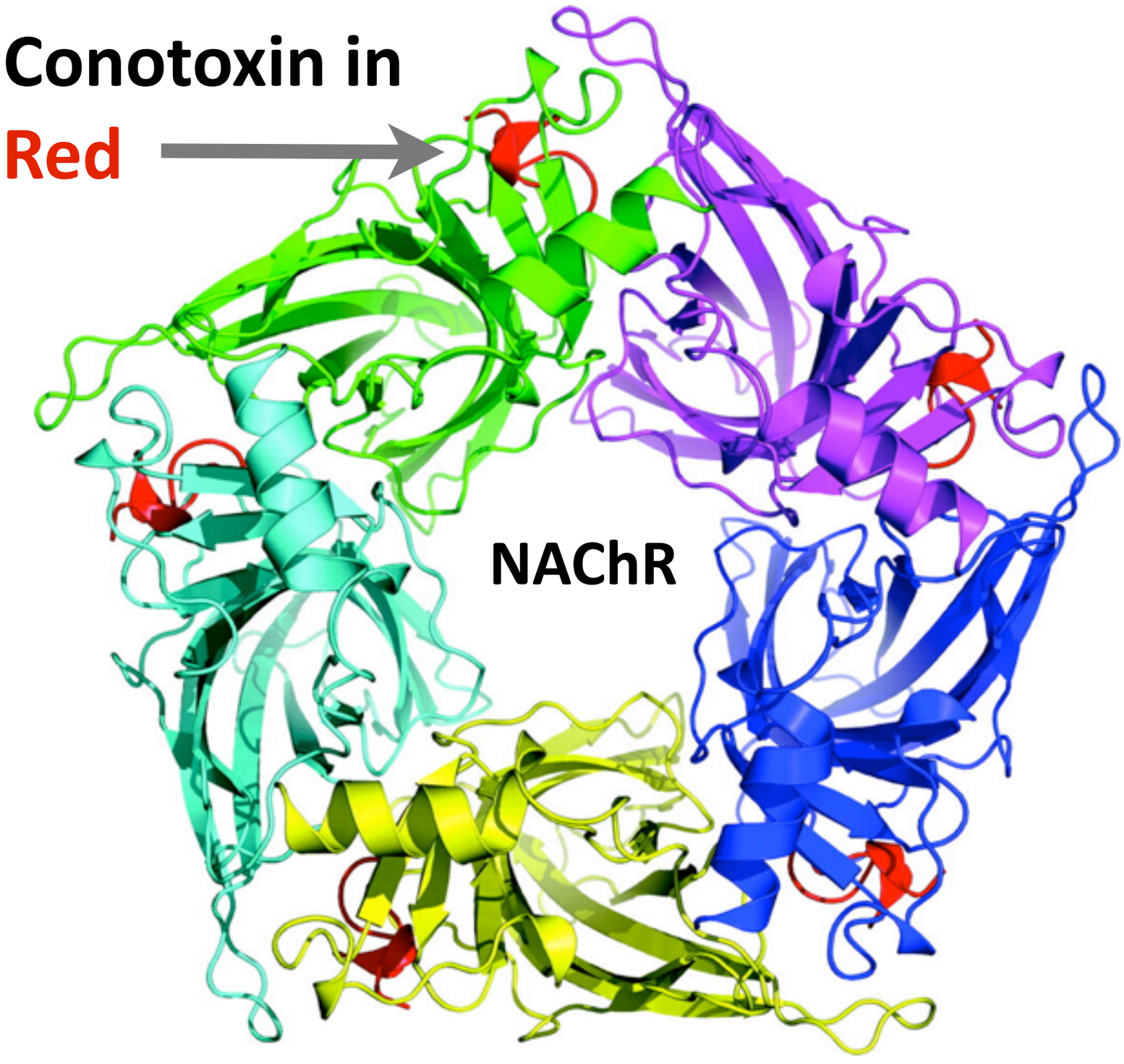

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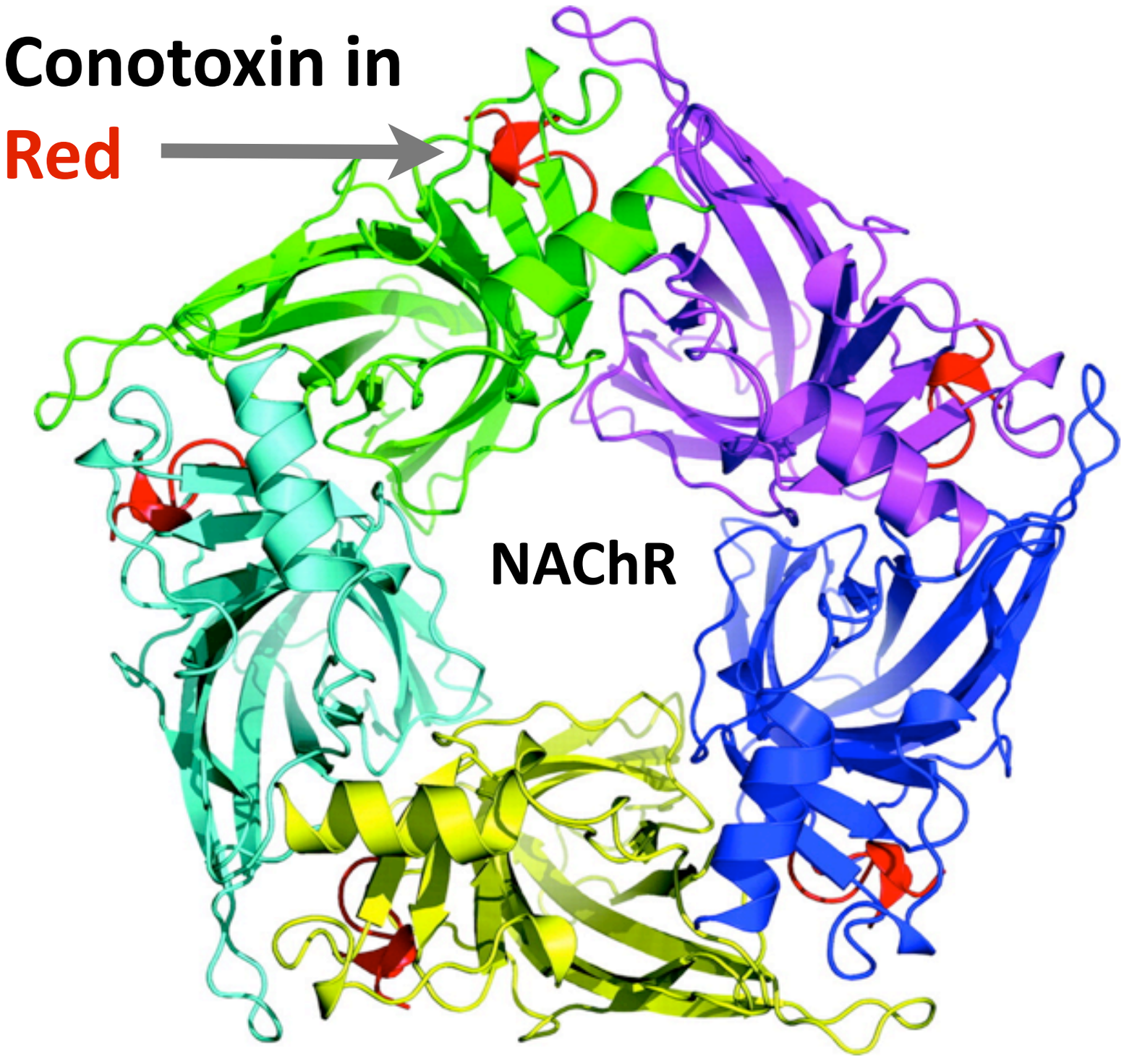

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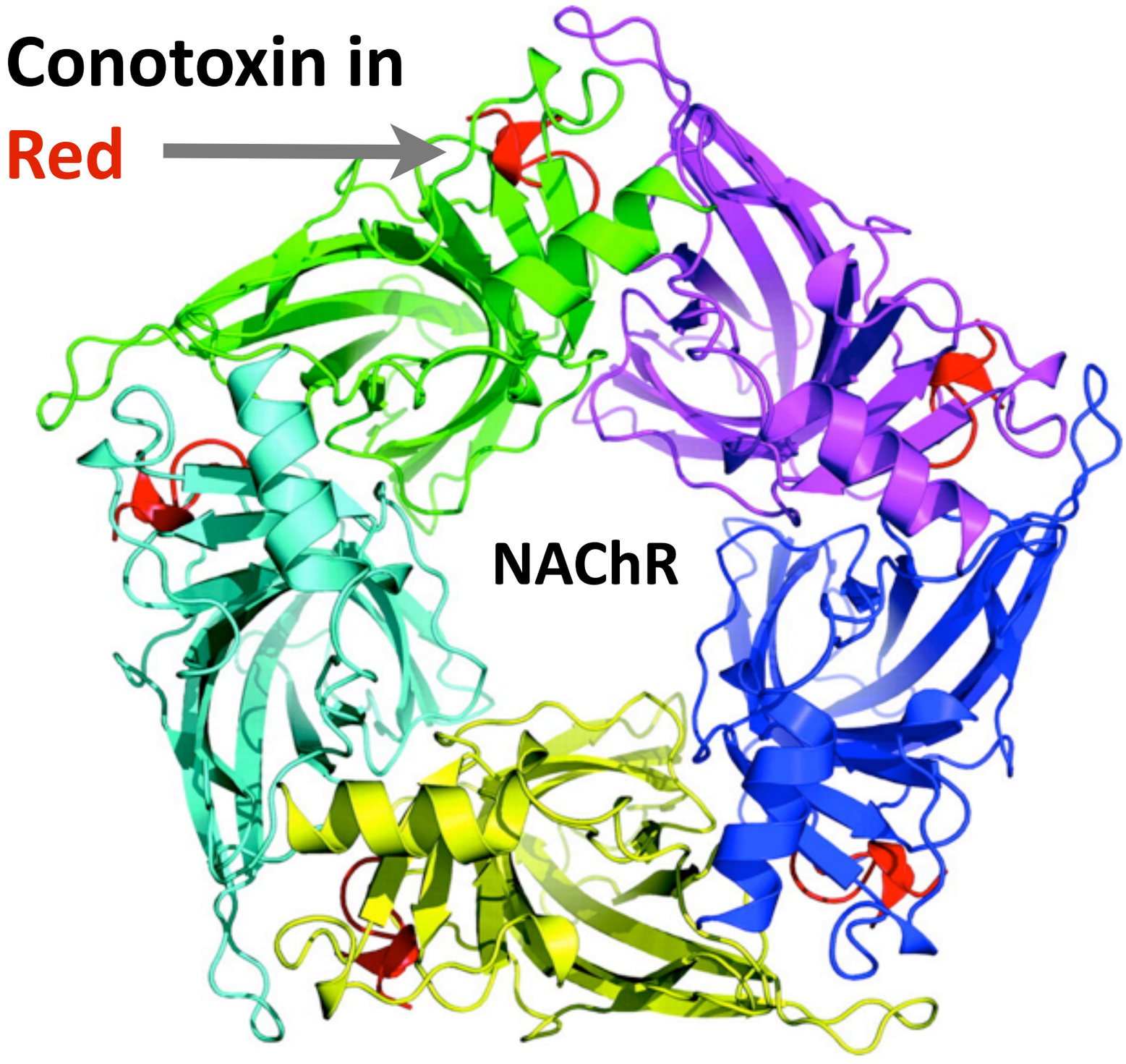
4. **There are 100s of similar "disulfide-rich" proteins**



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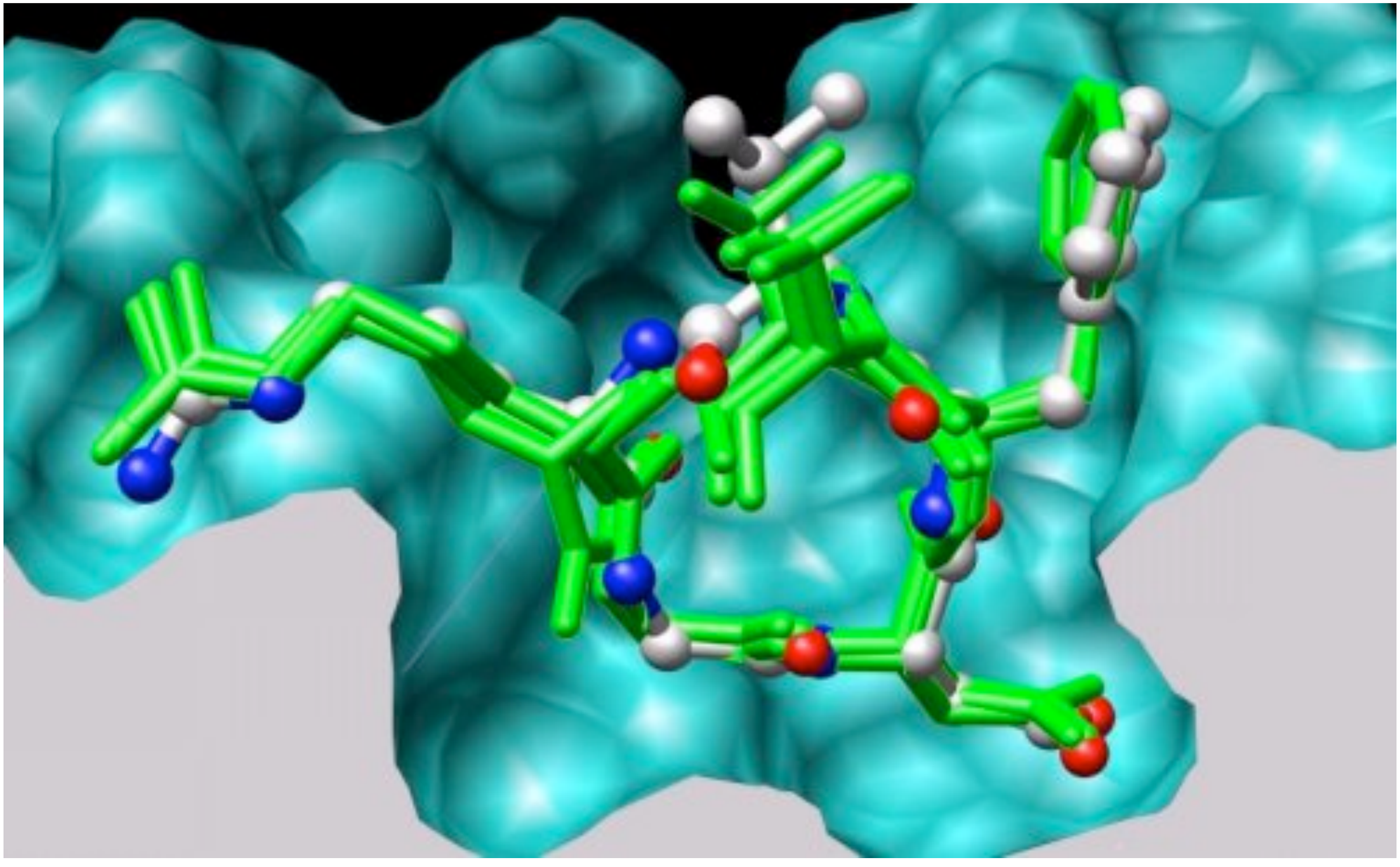
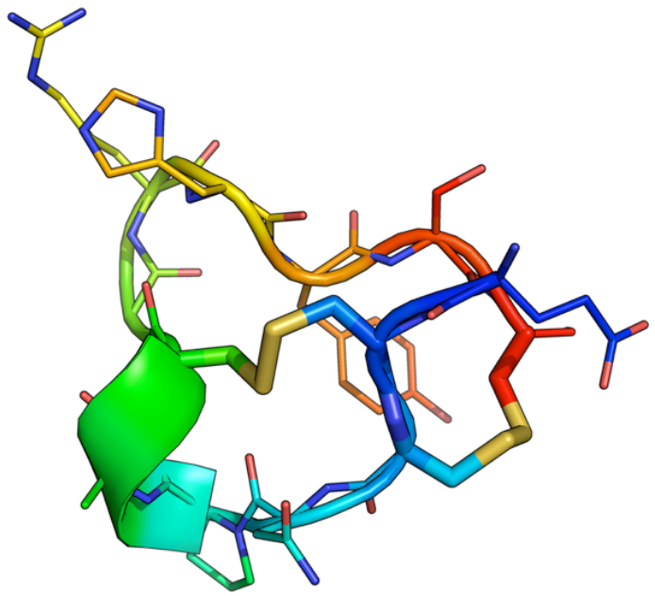
Docking



MSM Methods May Be Employed

Ligand



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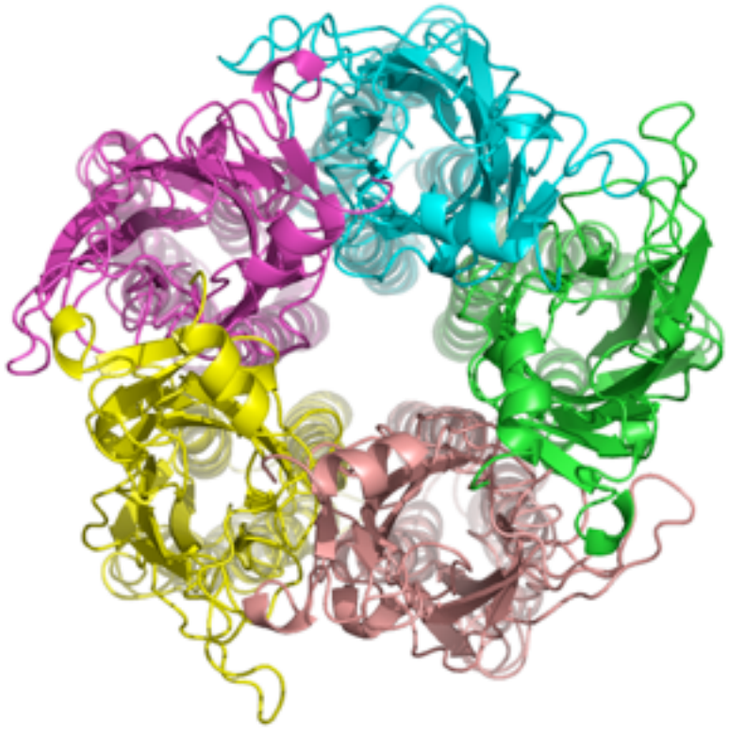

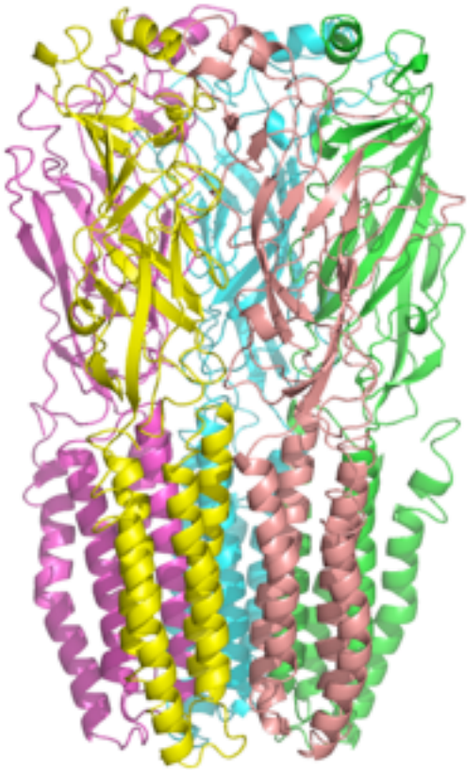

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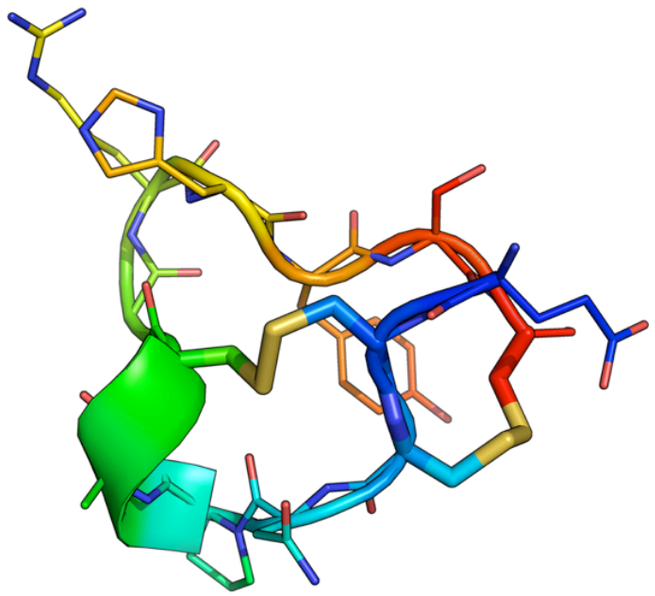

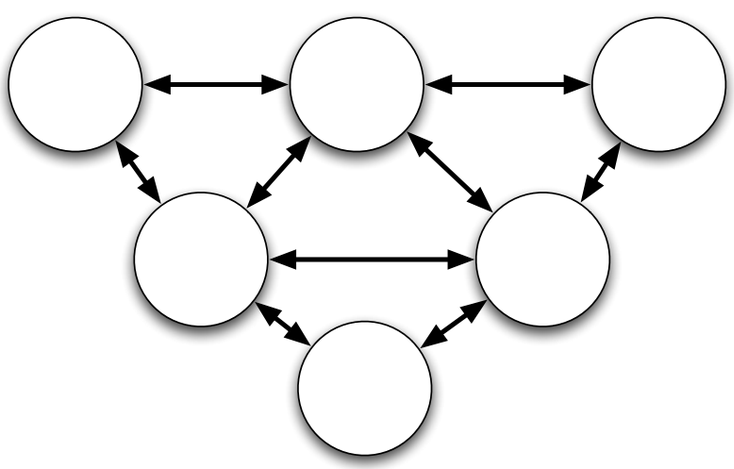

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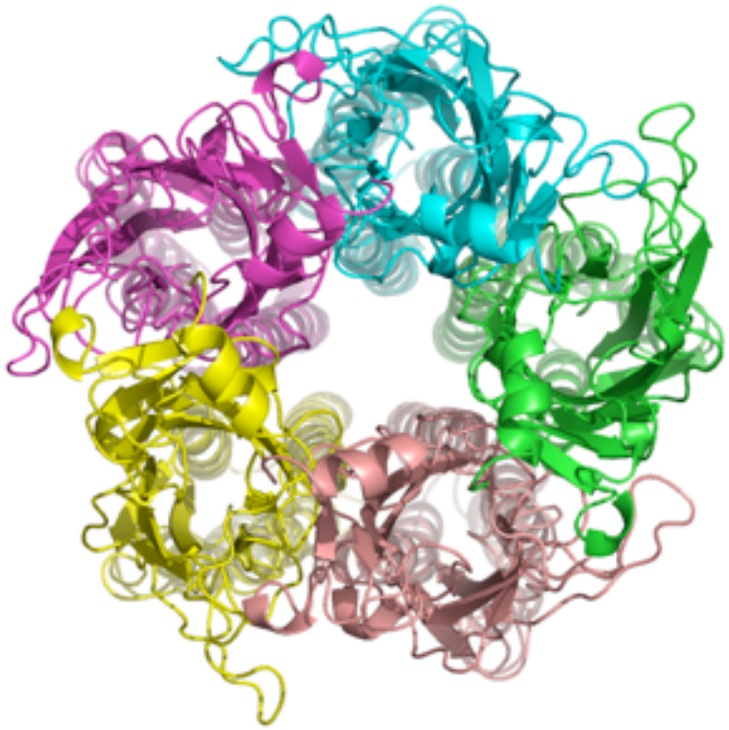

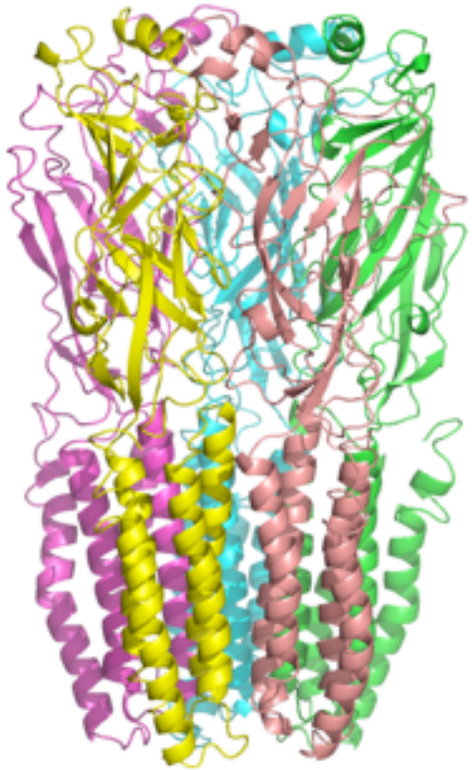

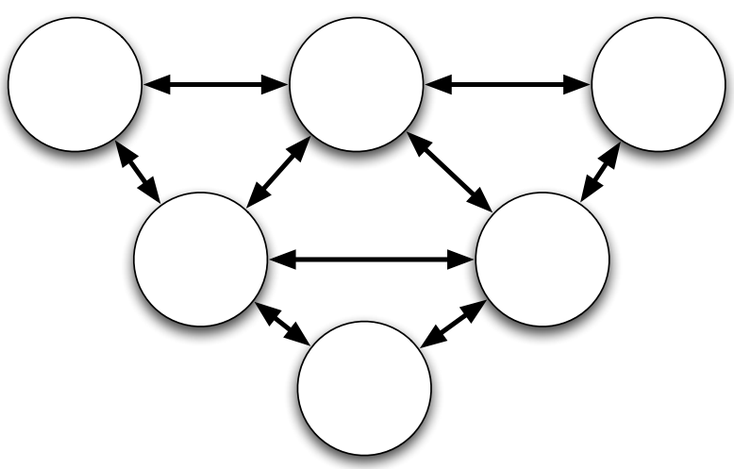

MSM Methods May Be Employed

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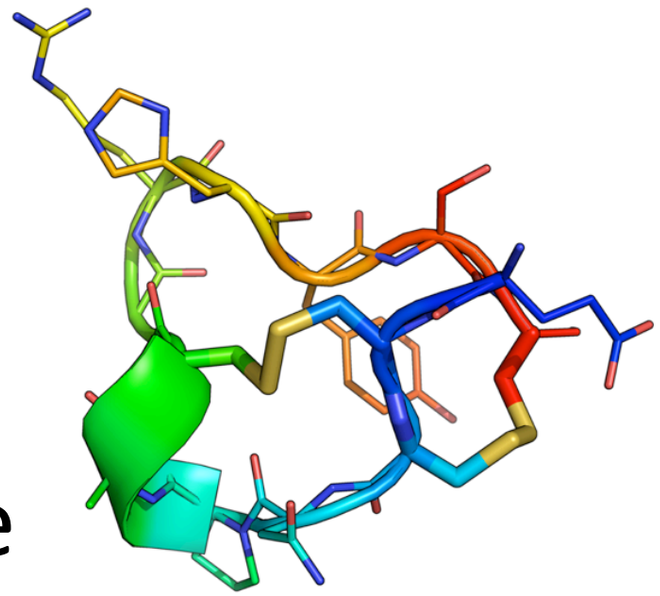

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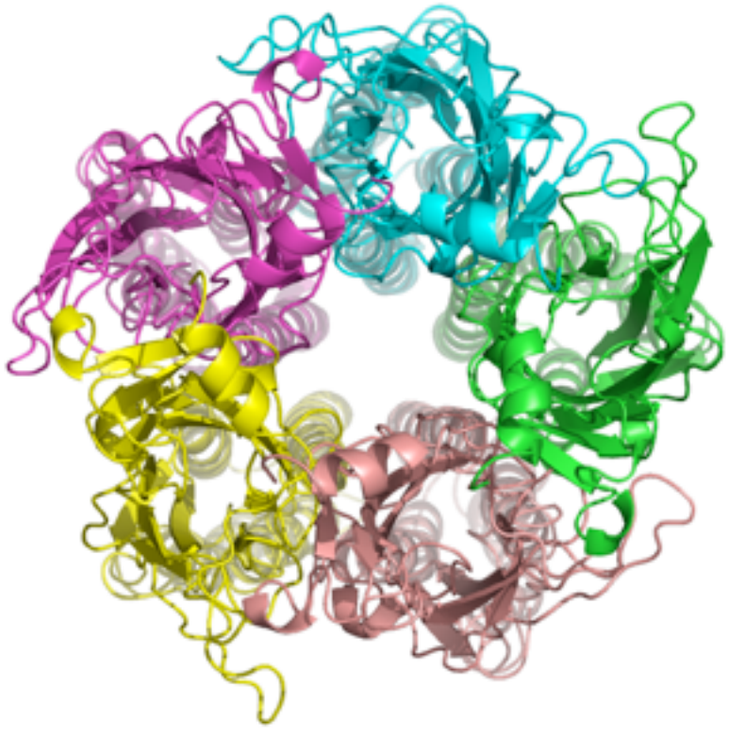
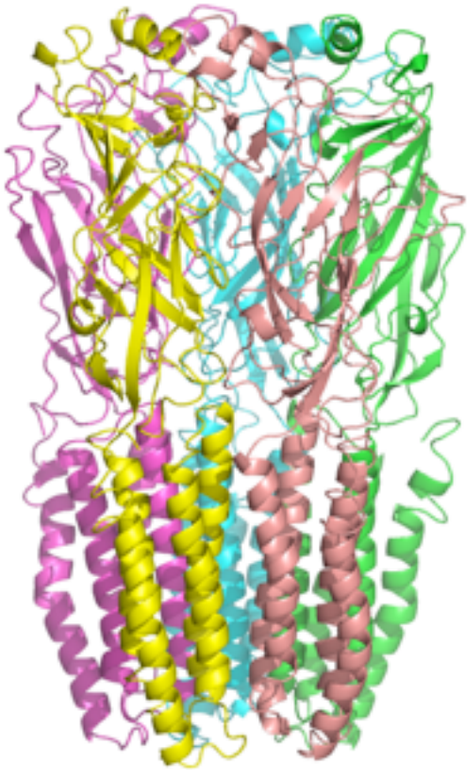
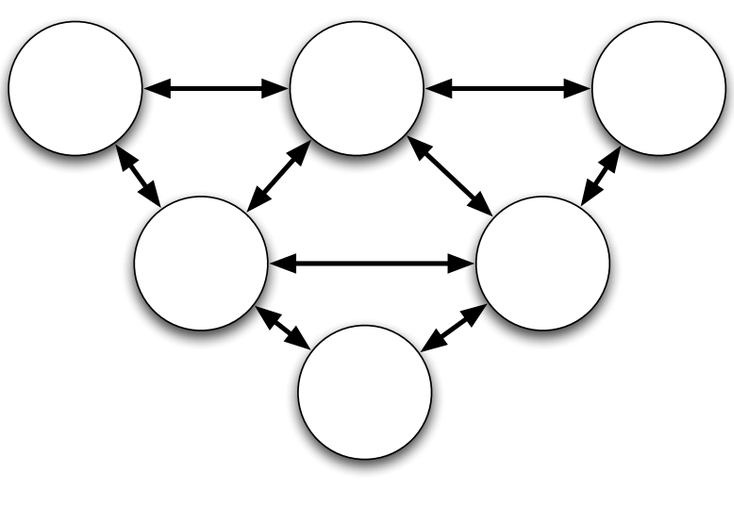
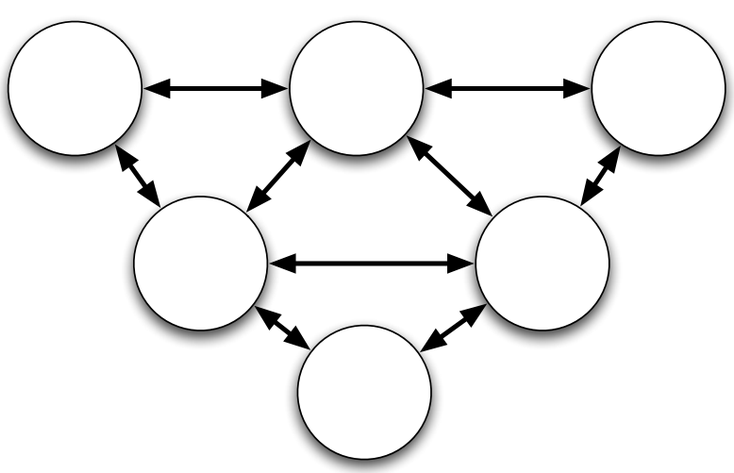




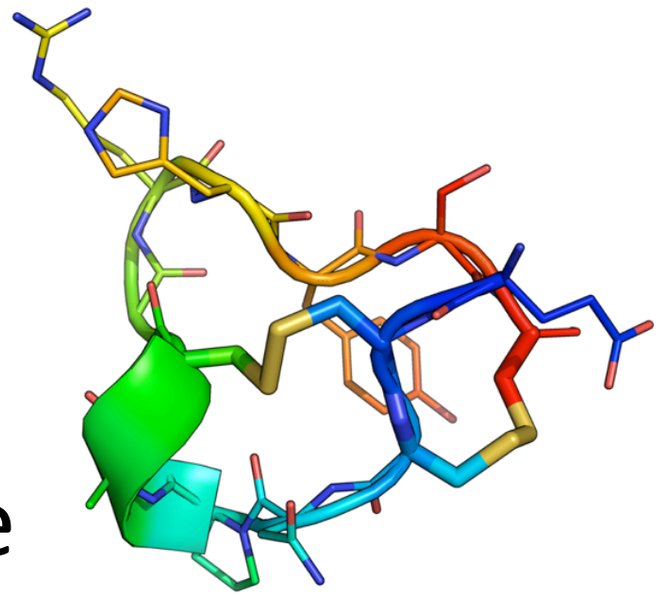
Free Energy





MSM Methods May Be Employed

Ligand



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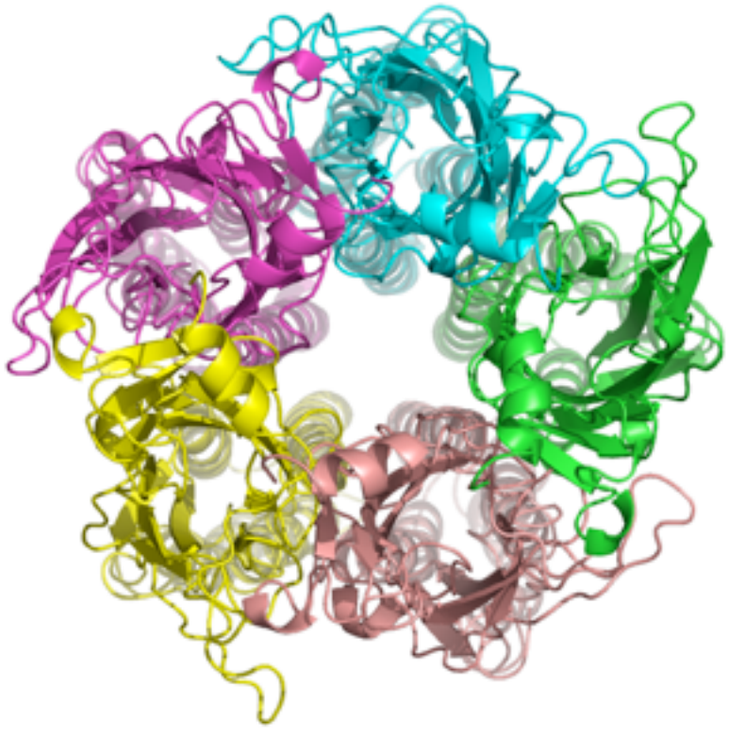
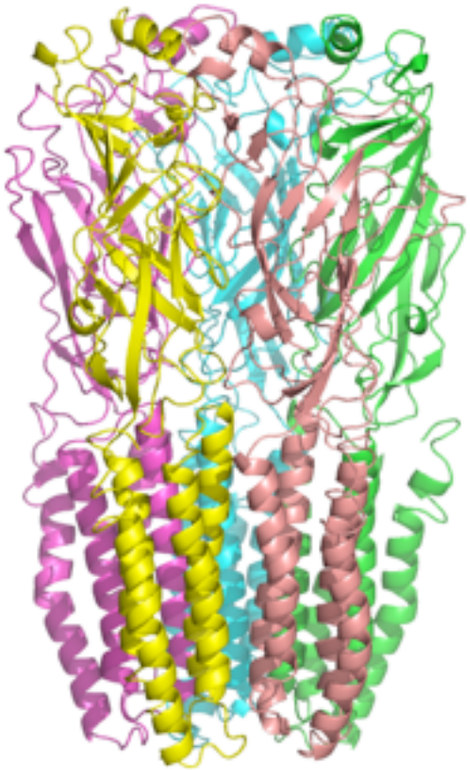


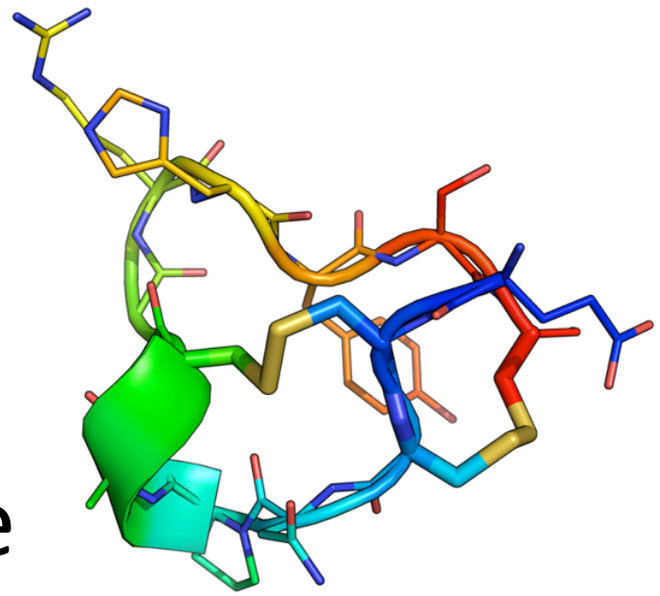


Free Energy

traditional

MSM Methods May Be Employed

Ligand



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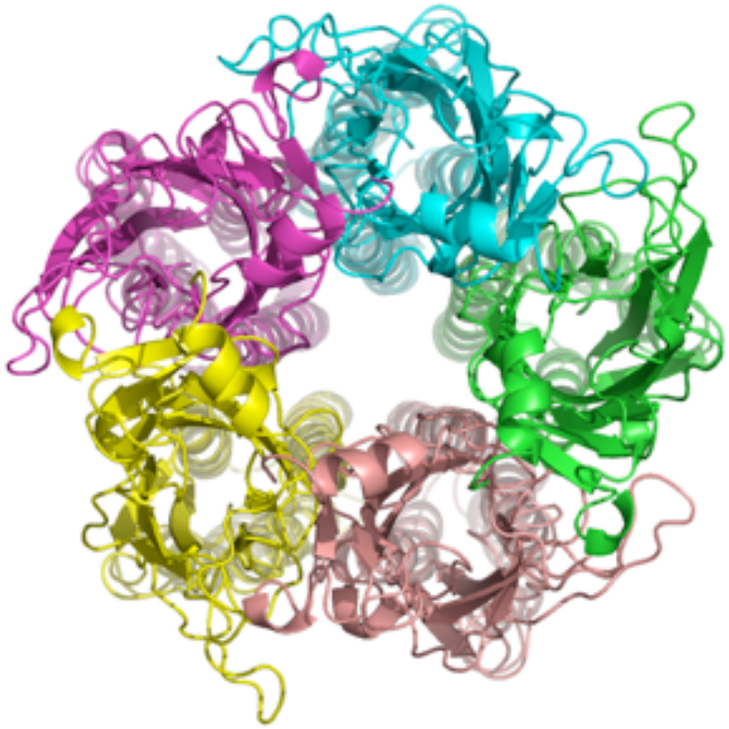
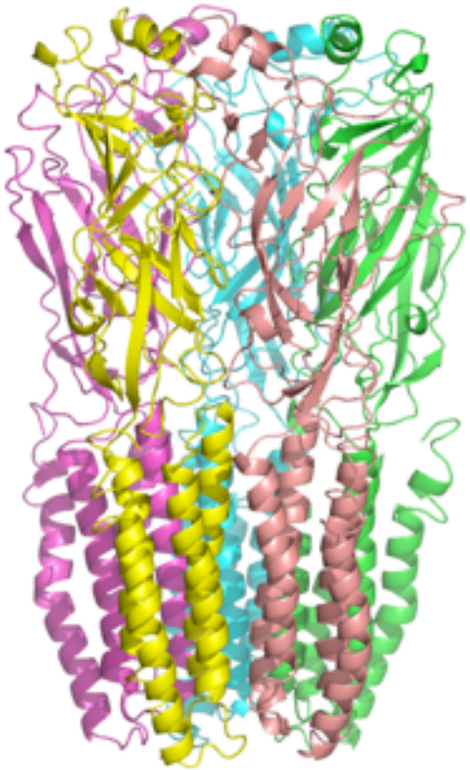
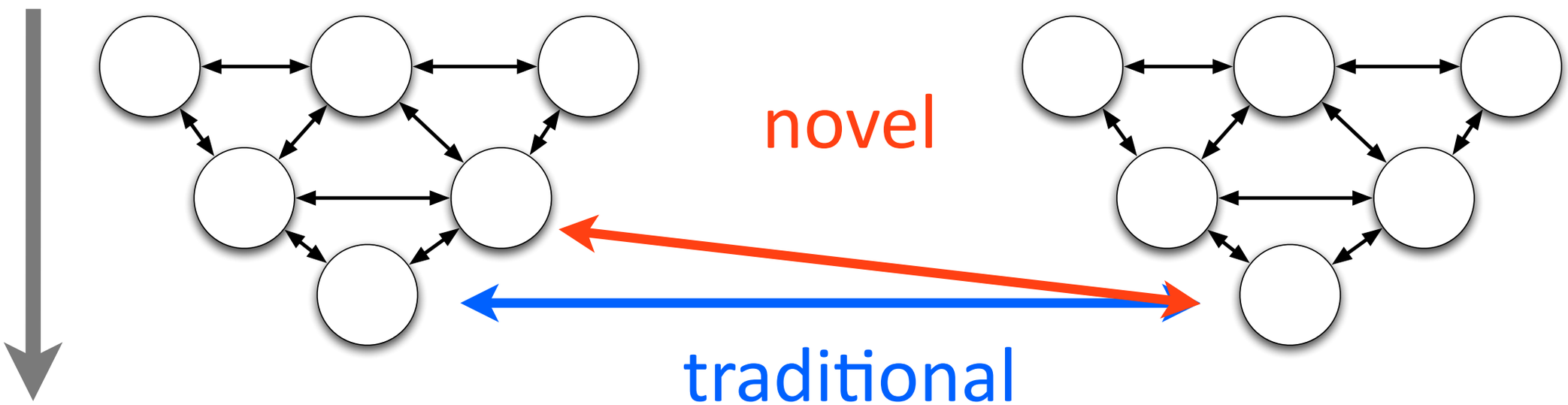


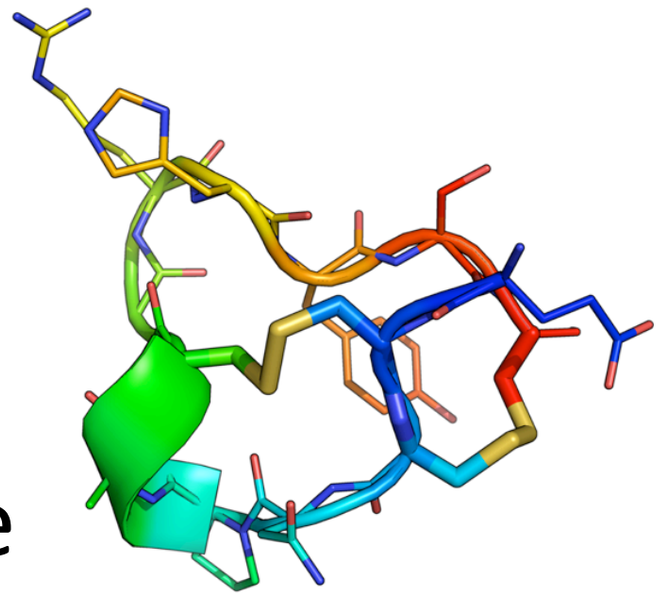


Free Energy



MSM Methods May Be Employed

Ligand



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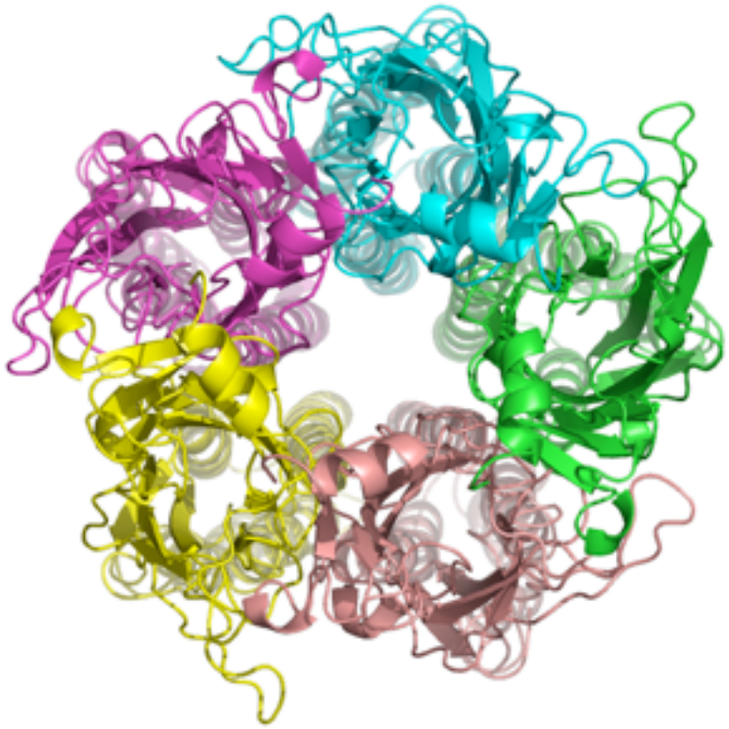
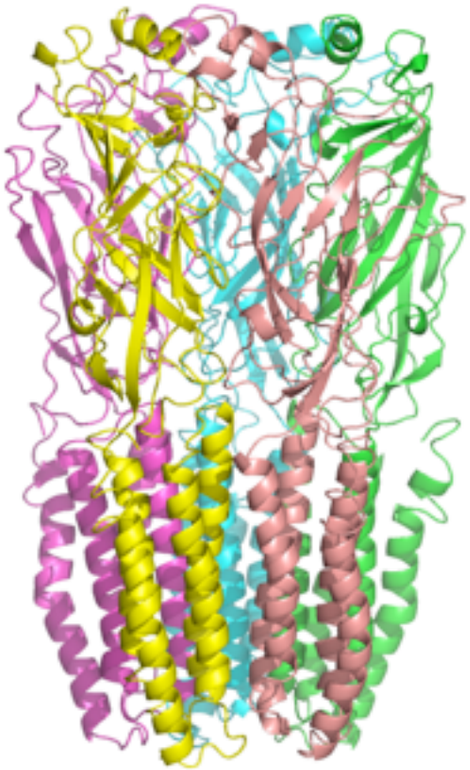
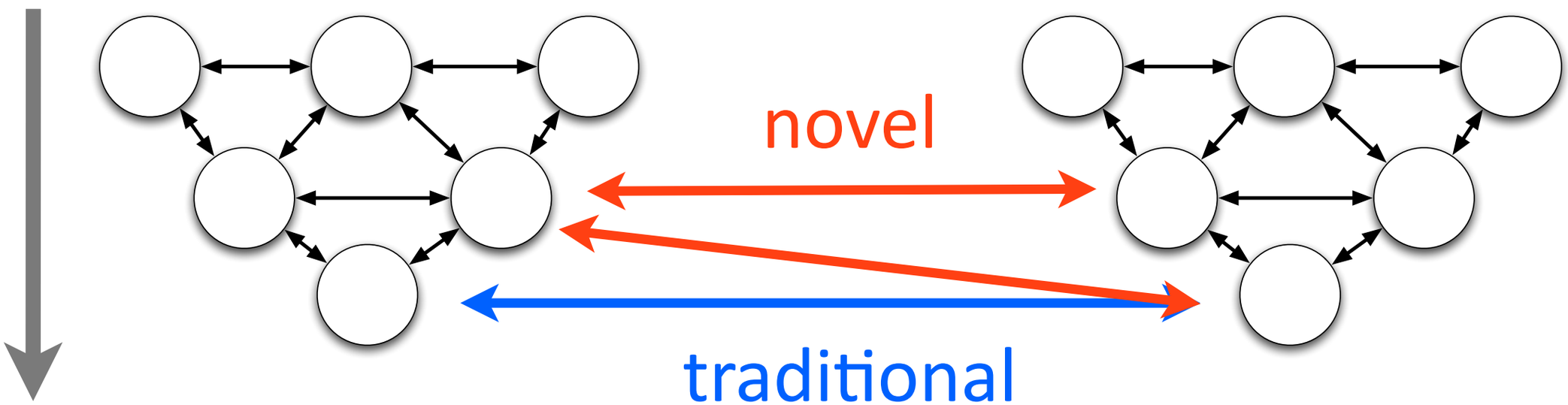
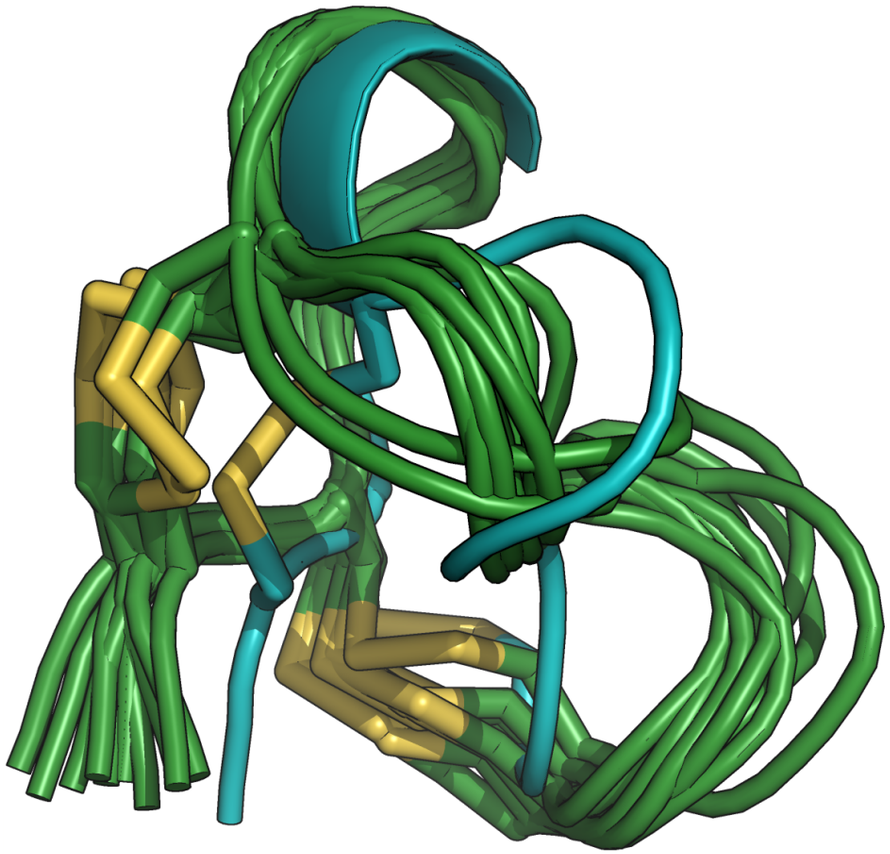


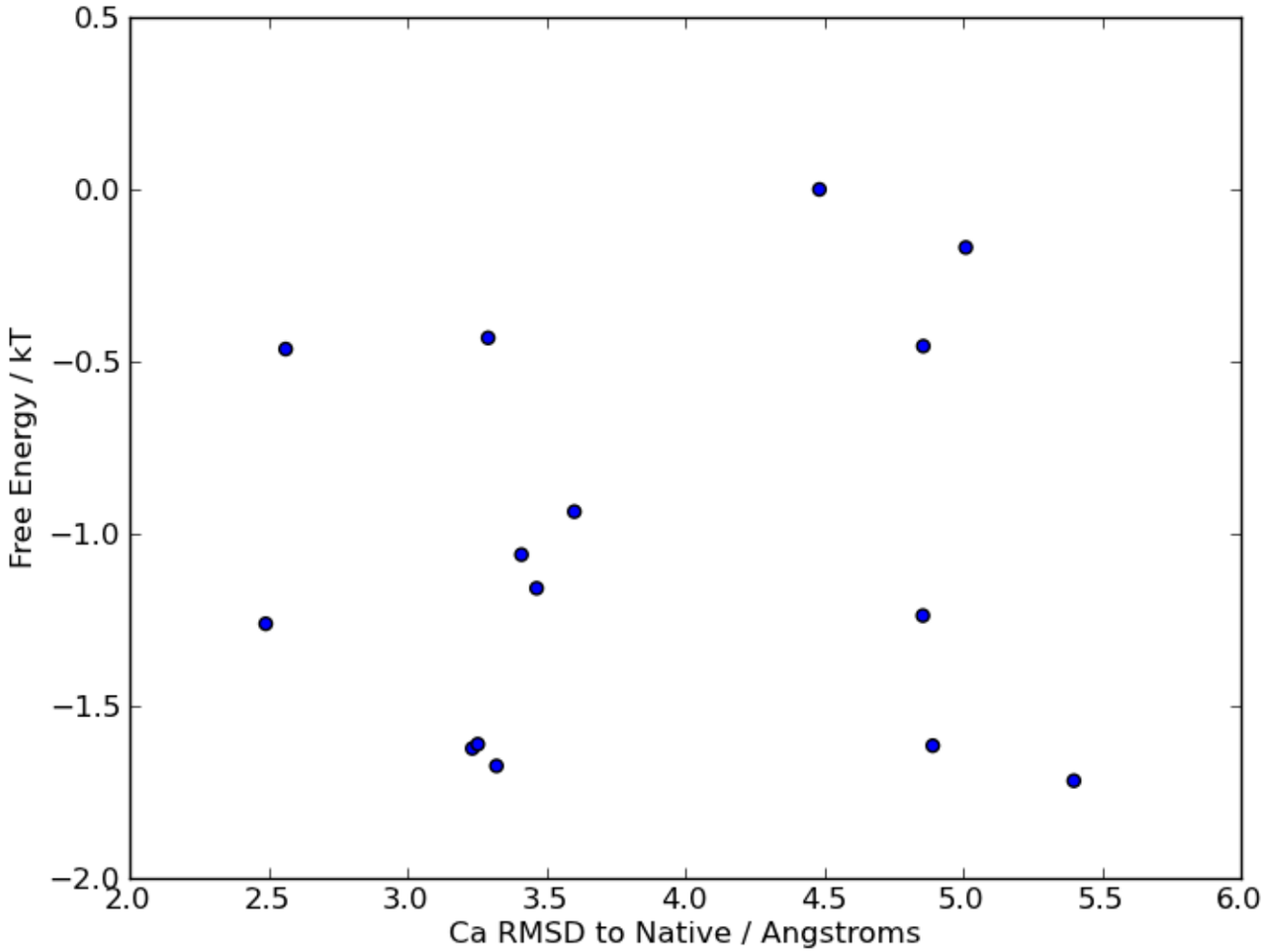


Free Energy



Some preliminary results...



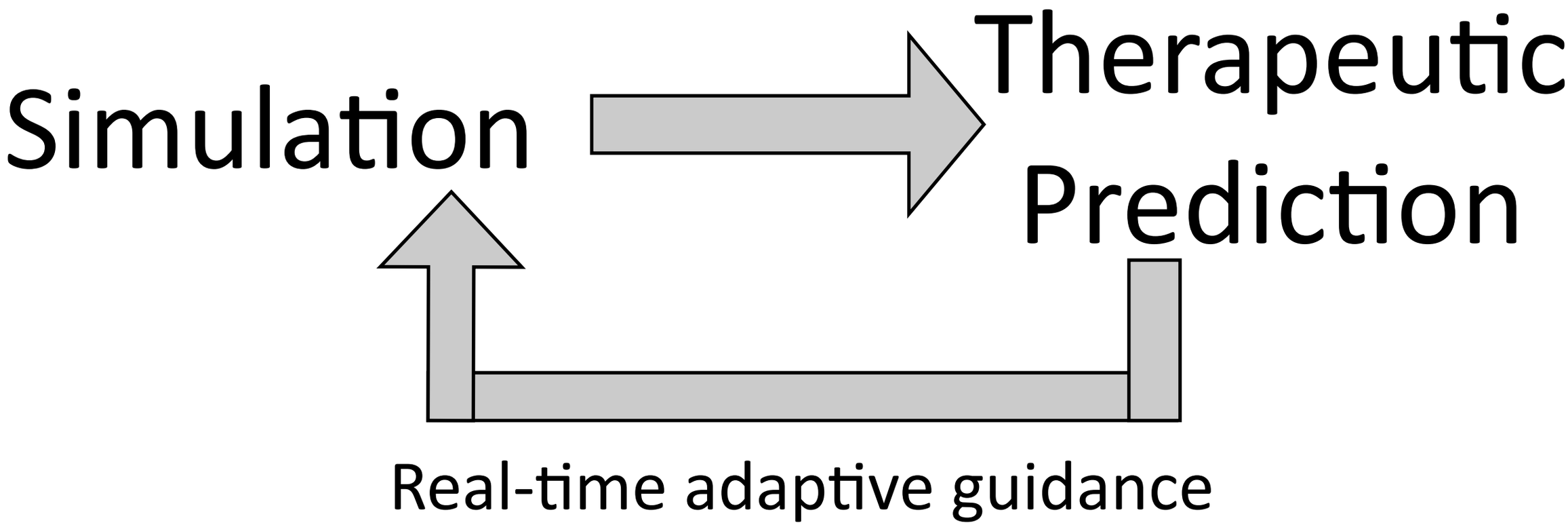


We still have some work to do for general prediction...

Why, then, a supercomputer?

Simulation → Therapeutic Prediction

Why, then, a supercomputer?



protein folding

simulations: K. Beauchamp, G. Bowman, D. Ensign, P. Kasson, V. Volez (Pande Lab, Stanford)

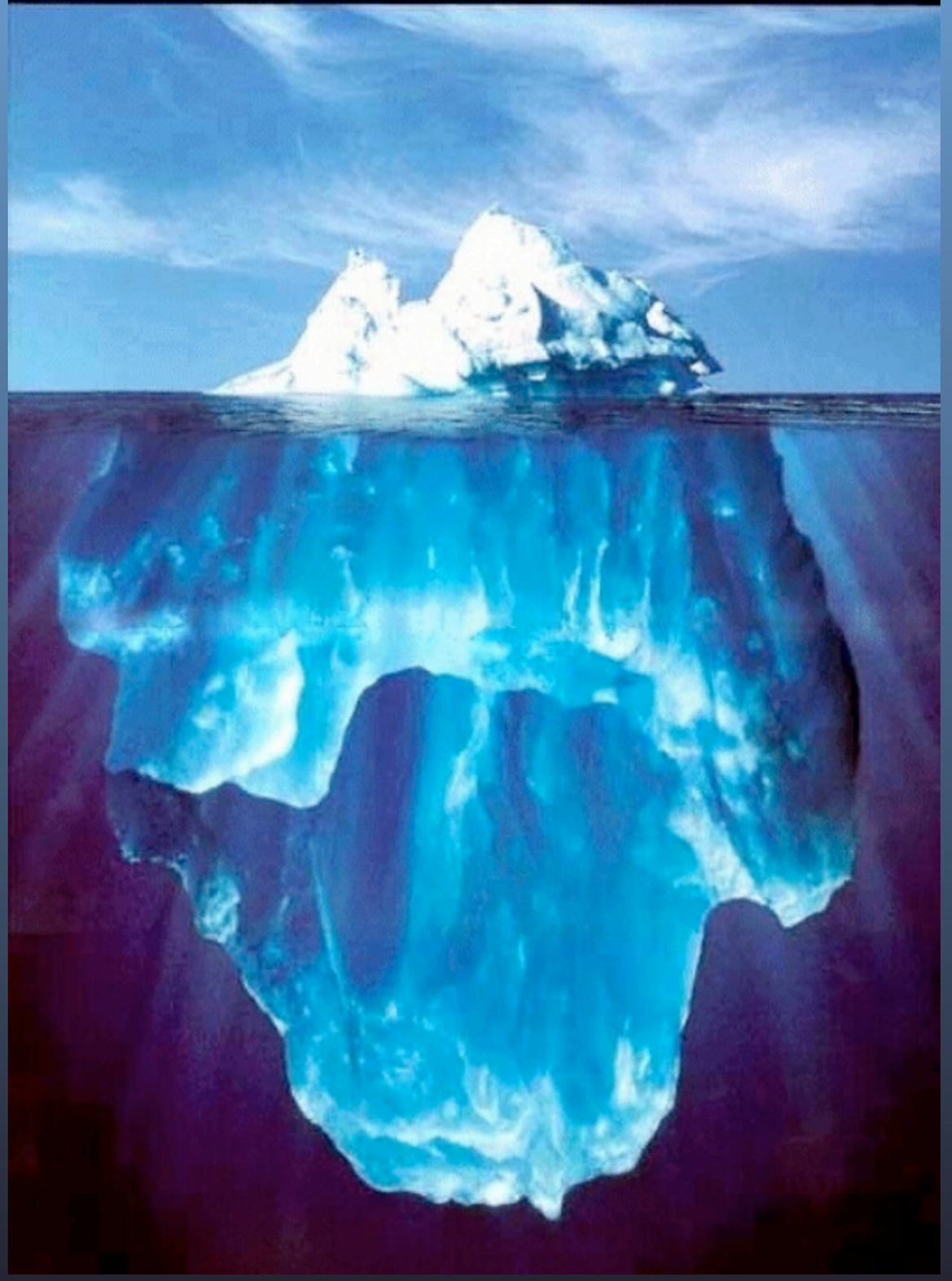
experiments: V. Singh, L. Lapidus (Lapidus Lab, Michigan State); S. Weis (UCLA)

MSM theory

S. Baccalado, K. Beauchamp, G. Bowman, J. Chodera [now @UCB], X. Huang [now @HK], S. Park [now @ANL], N. Singhal [now @Chicago] (Pande Lab, Stanford); Bill Swope & Jed Pitera (IBM); Ken Dill (UCSF)

funding

NIH Nanomedicine Protein Folding Center, NIH Roadmap Center Simbios, NIH NIGMS, NSF Chemistry, NSF Molecular Biophysics



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