Protein folding, aggregation & hydrophobicity with simple physical models

Where physics and biology meet

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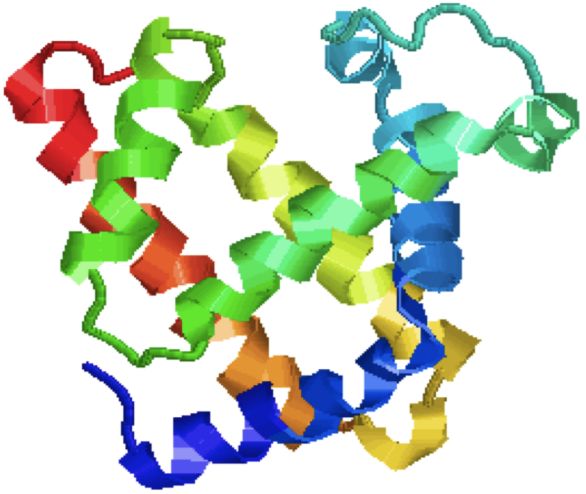
My Background

- First Degree: Computer Science / Mathematics (University of Manchester)
- PhD: Structural Bioinformatics / Biochemistry (University of Oxford)
- PostDoc: Computational (Bio)-Physics in the Frenkel group (Amolf, Amsterdam)
- Currently, Assistant Professor Bioinformatics (VU University), use all of the above

The biological approach or the physical approach?

?



TASK:

Given a protein sequence predict in which 3D structure the protein will fold.

Two approaches:

Biological Approach

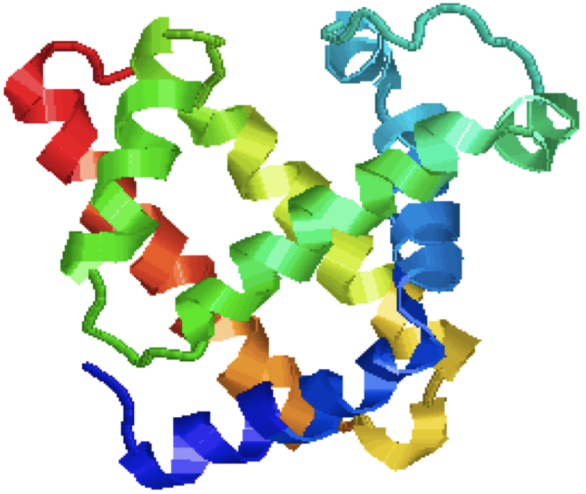
- Find a known structure with a similar sequence
- Align the sequences
- Model the unkown structure on the known structure using the alignment

Physical Approach

- Take a full atomistic force field
- Simulate as long as possible

The biological approach or the physical approach?

?



TASK:

Given a protein sequence predict in which 3D structure the protein will fold.

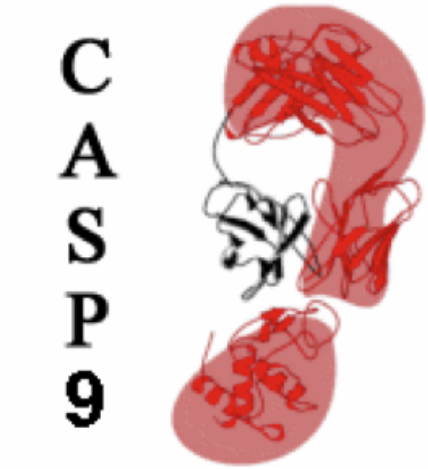
Who wins, the physical or biological approach?

CASP

Critical Assessment of protein Structure Prediction

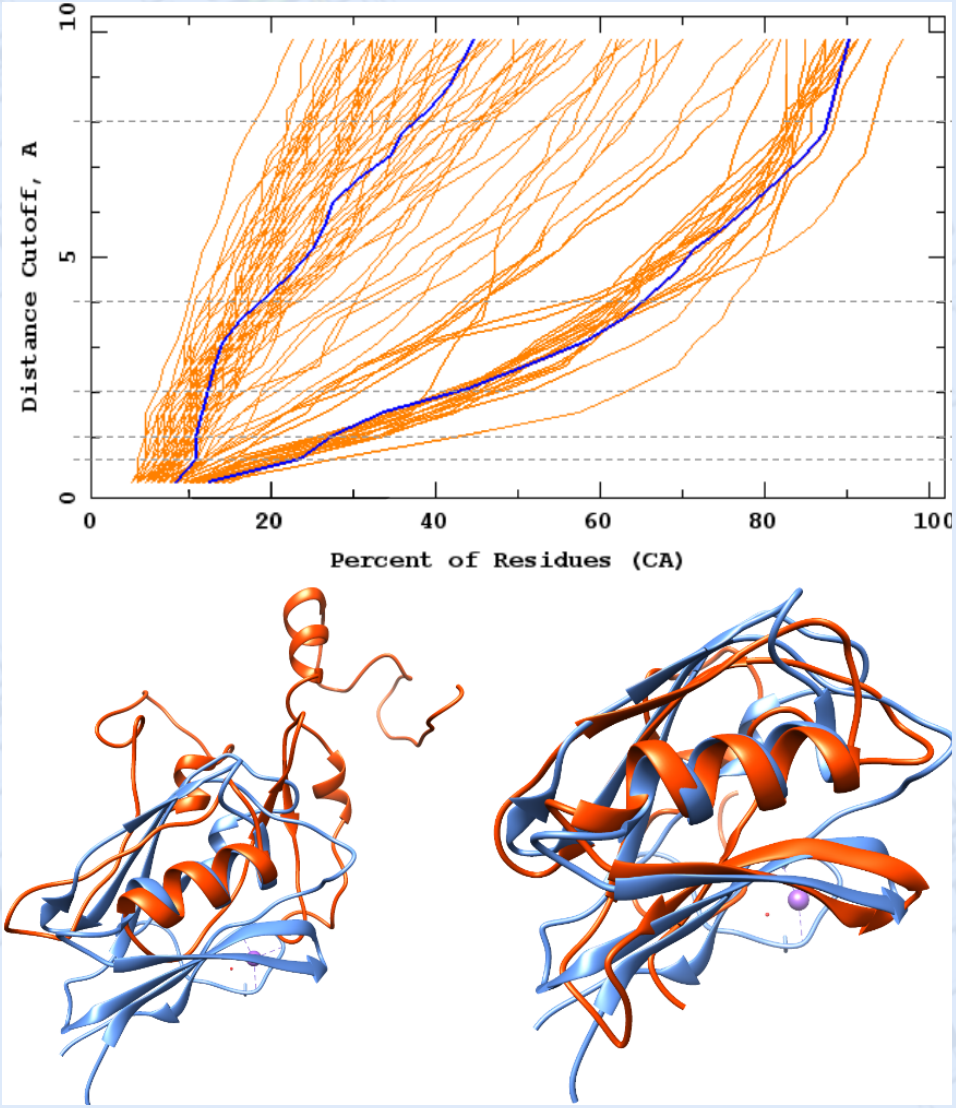
AIM: assess progress in structure prediction

- Blind test
- Ongoing for three months
- Experimentalist submit targets
- Bioinformatics groups predict structures
  - groups
  - servers

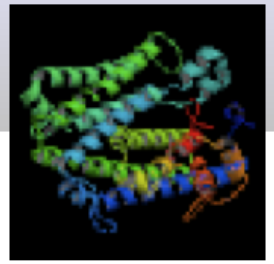


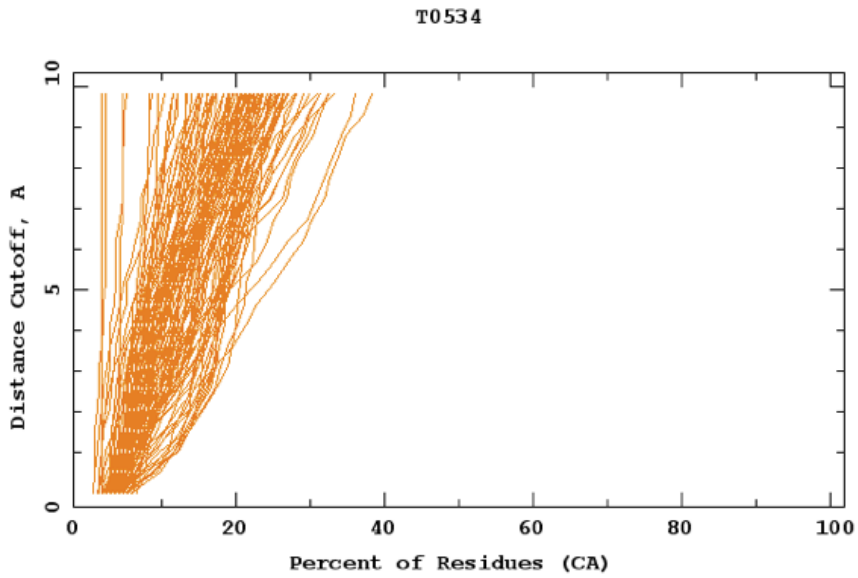
Who wins BIOLOGY or PHYSICS?

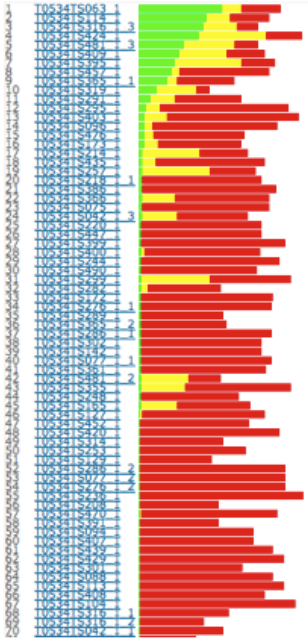
Typical CASP results



“difficult“ target







GREEN Correctly aligned residues (0 shift) according to AL0_P

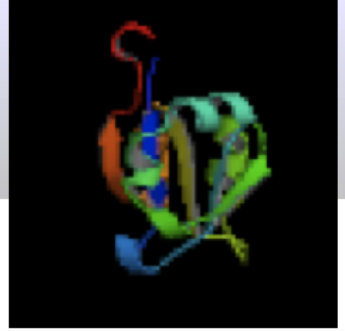
YELLOW Residues aligned within " -4 , +4 " window (4 shift) according to AL4_P

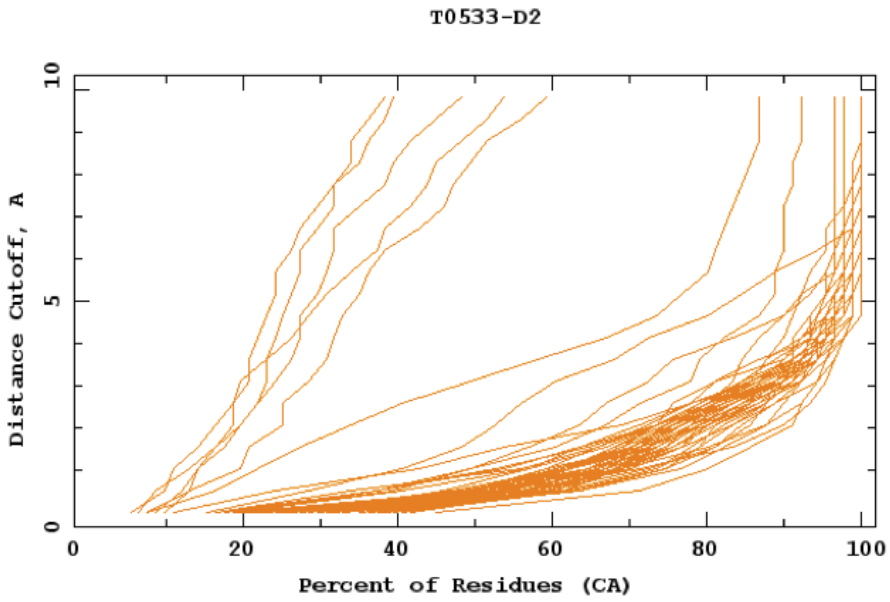
RED Residues aligned outside " -4 , +4 " window (4+ shift) according to ALI_P

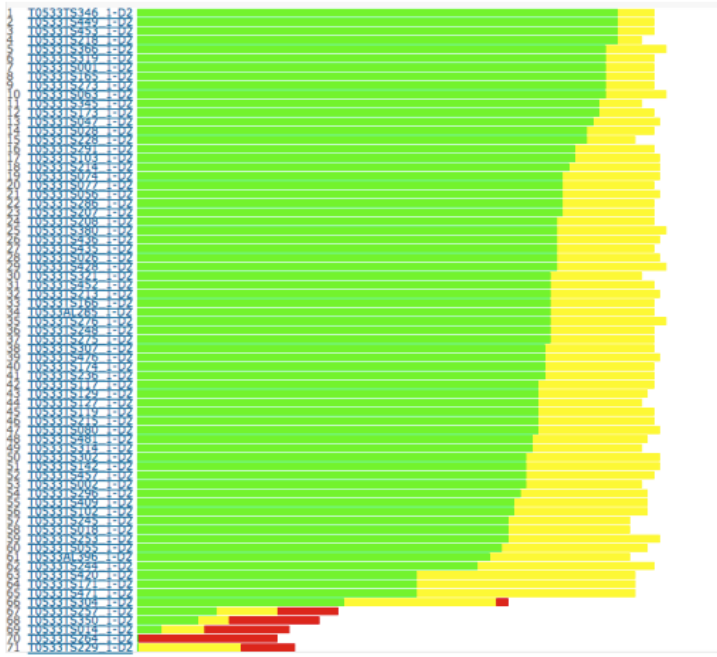
WHITE Residues not aligned or not predicted

RMSD calculated on all N residues superimposed under 5.0 Angstrom distance cutoff

“easy” target







GREEN	Correctly aligned residues (0 shift) according to AL0_P
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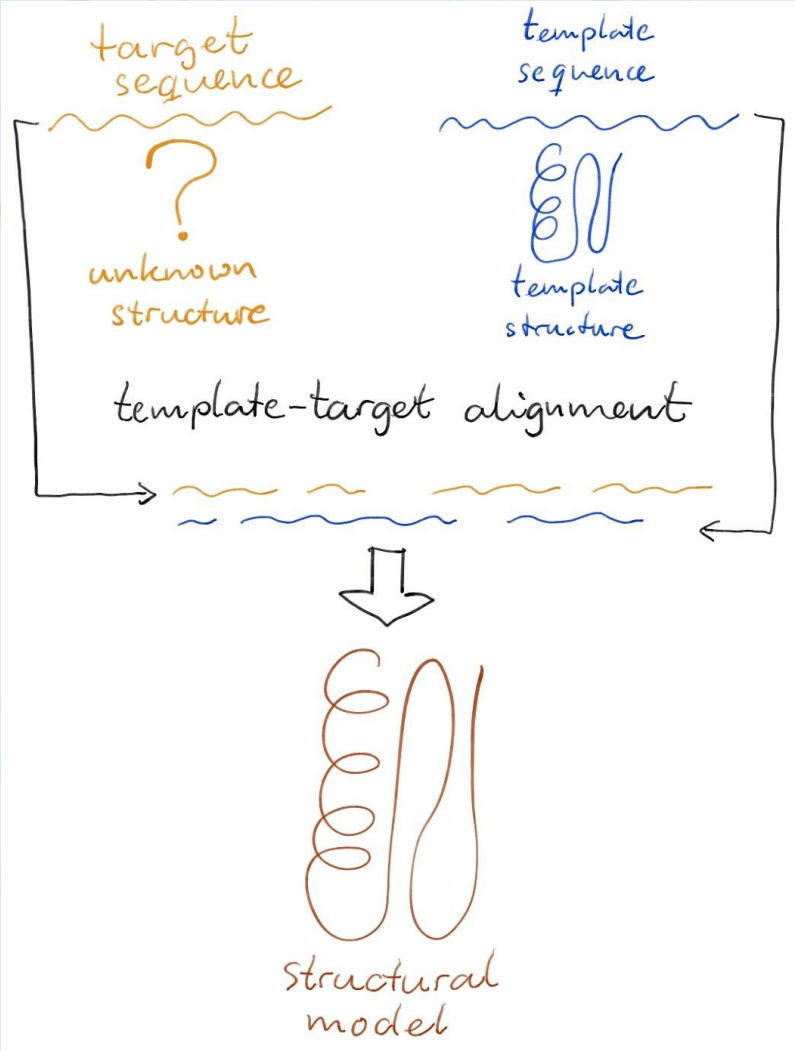
WHITE	Residues not aligned or not predicted

RMSD calculated on all N residues superimposed under 5.0 Angstrom distance cutoff

for ‘easy’ targets structures with similar sequences are available

Biology versus physical

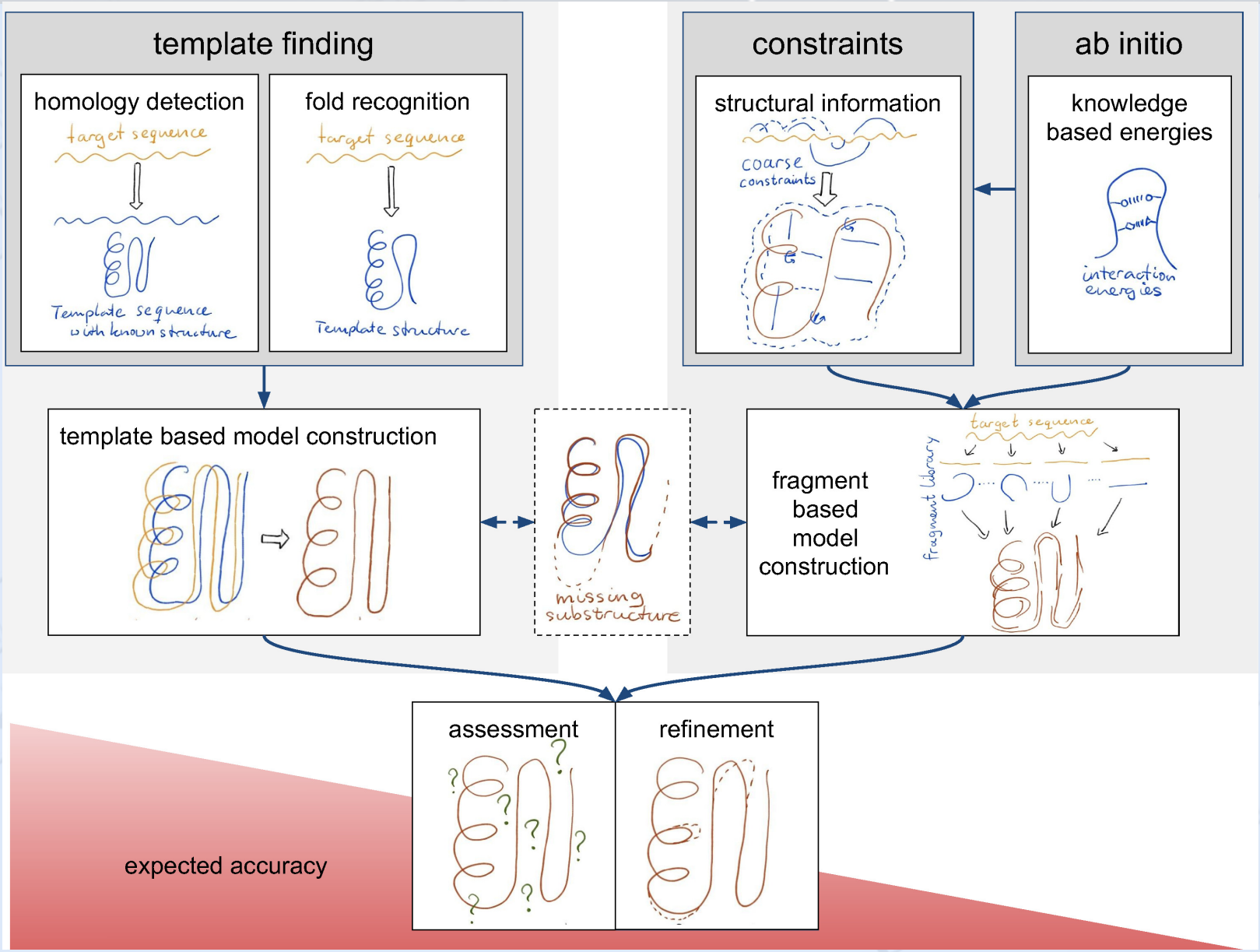


Only when a structural **template** is available, recognised by **evolutionary** sequence conservation can we model the structure correctly.

Biology wins…

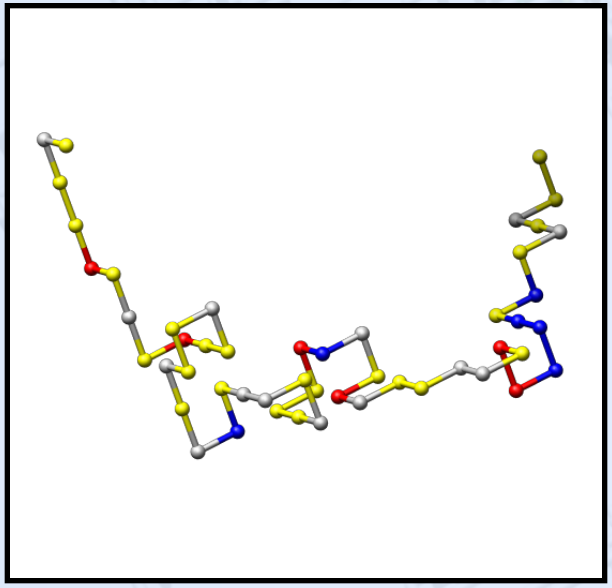
Review available https://arxiv.org/abs/1712.00407

The most successful approaches do not adhere to statistical mechanics principles

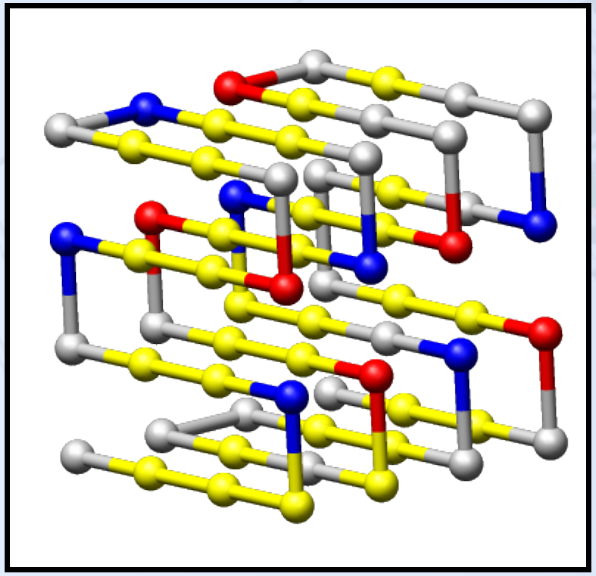


Biomolecular simulation (this afternoon)

Sequence



Structure



hydrophobic

polar (hydrophilic)

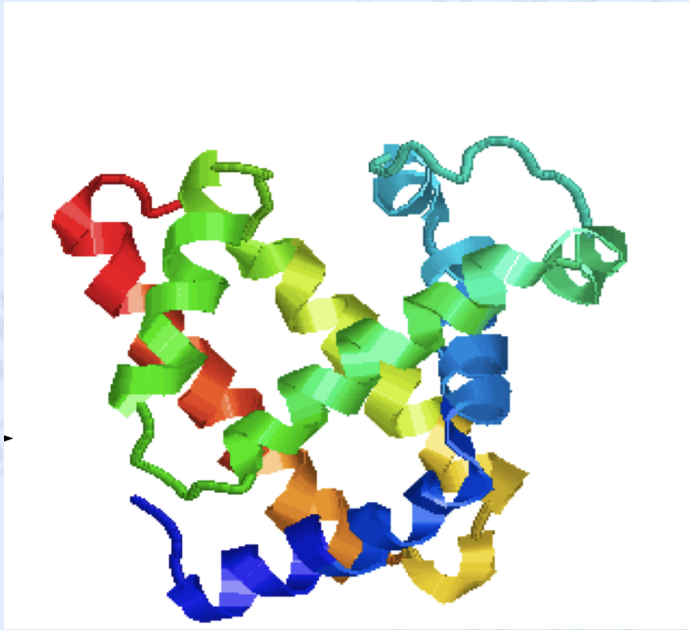
negative charge

positive charge

--	+	+	+
+			
+		+	-
+		-	+

Let’s have a look at the physical forces first

- What are the most important forces that act on a protein?
- We stay away from quantum mechanics for now.



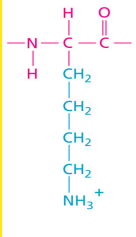
What type of forces and effects would be relevant?

- Van der Waals
- Electrostatics
- Hydrogen bonding
- Entropic effects
- **Hydrophobic effect**

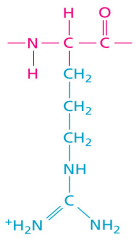
Primary Protein Structure

+ve charge

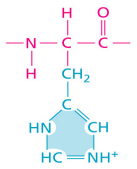
lysine (Lys, or K)



arginine (Arg, or R)

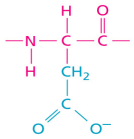


histidine (His, or H)

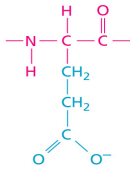


-ve charge

aspartic acid (Asp, or D)

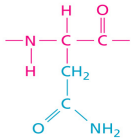


glutamic acid (Glu, or E)

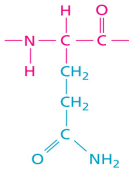


other polar

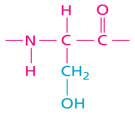
asparagine (Asn, or N)



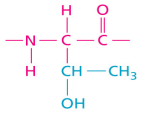
glutamine (Gln, or Q)



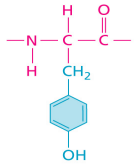
serine (Ser, or S)



threonine (Thr, or T)

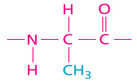


tyrosine (Tyr, or Y)

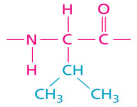


hydrophobic

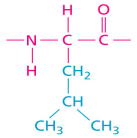
alanine (Ala, or A)



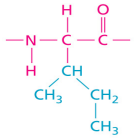
valine (Val, or V)



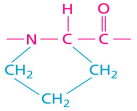
leucine (Leu, or L)



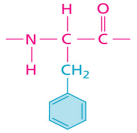
isoleucine (Ile, or I)



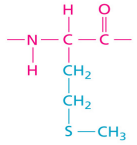
proline (Pro, or P)



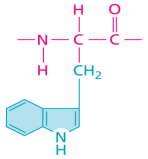
phenylalanine (Phe, or F)



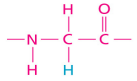
methionine (Met, or M)



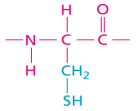
tryptophan (Trp, or W)



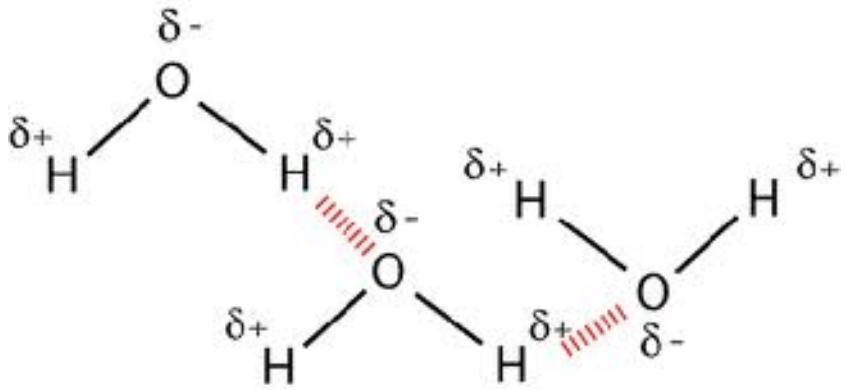
glycine (Gly, or G)



cysteine (Cys, or C)



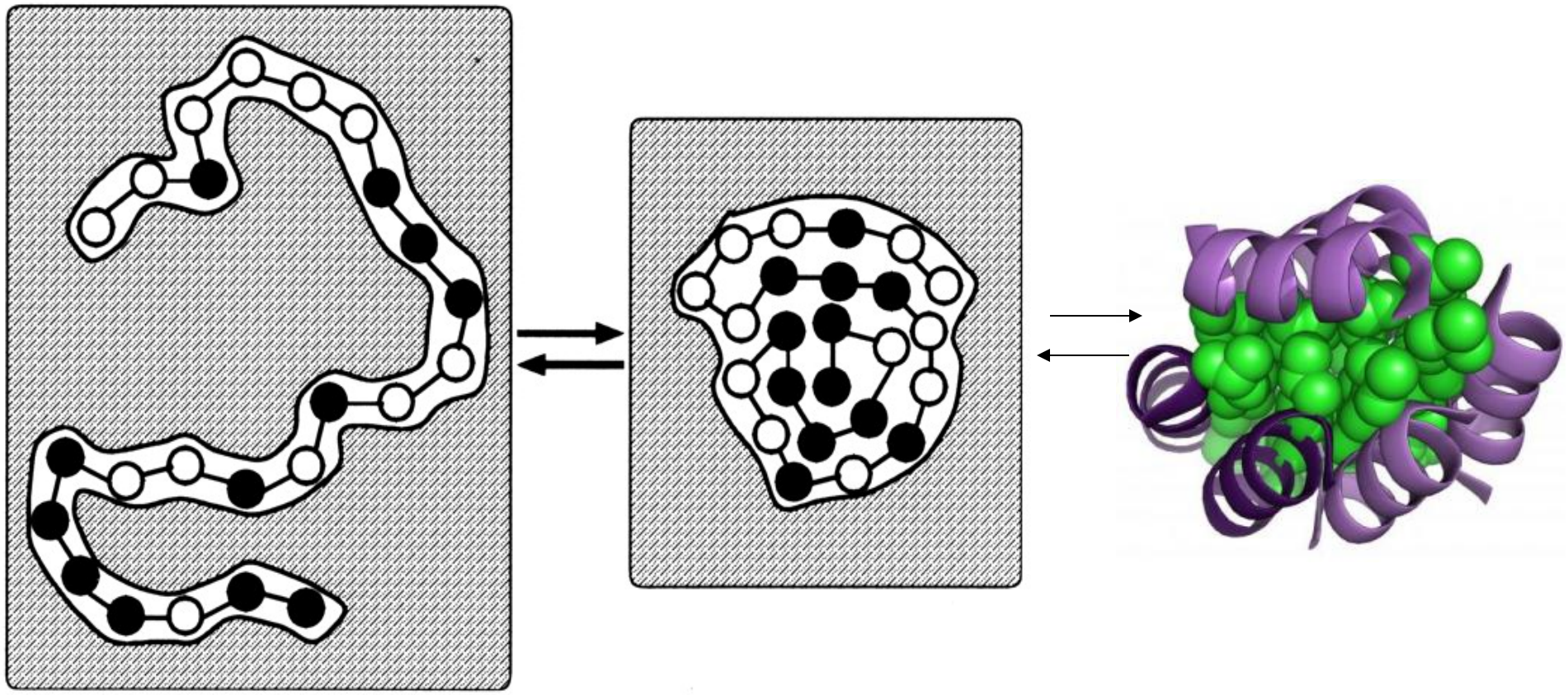
Proteins live in water



Hydrophobic effect

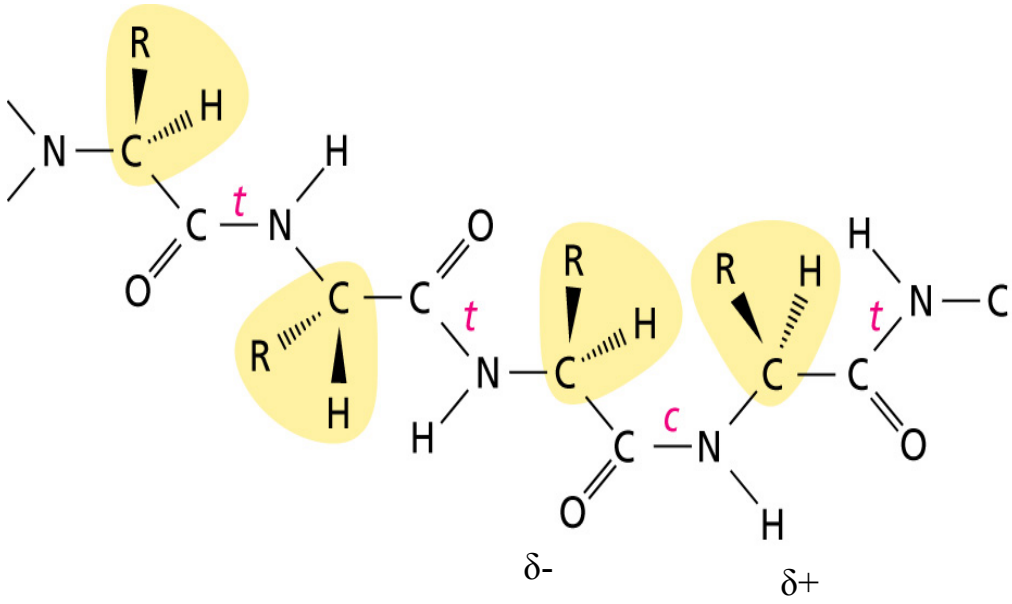
Oil and water do not mix well

Hydrophobic Collapse



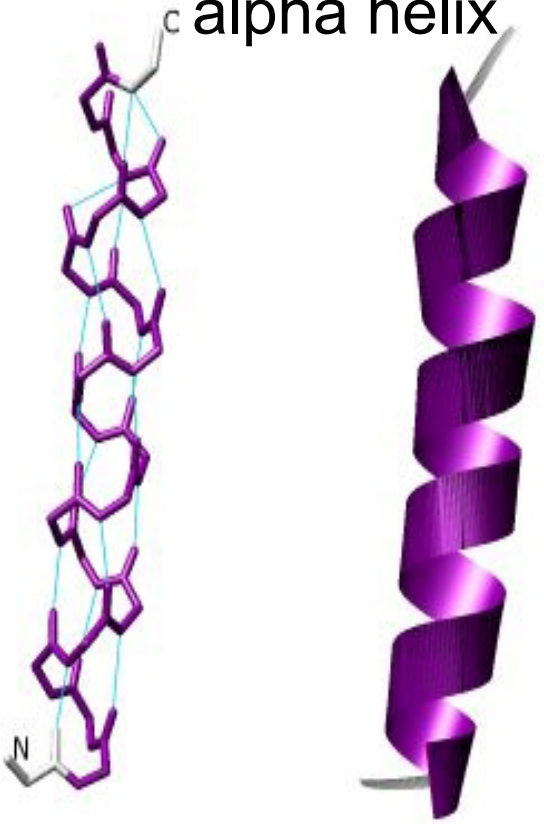
Backbone

Backbone has a hydrogen bond donor and acceptor per residue

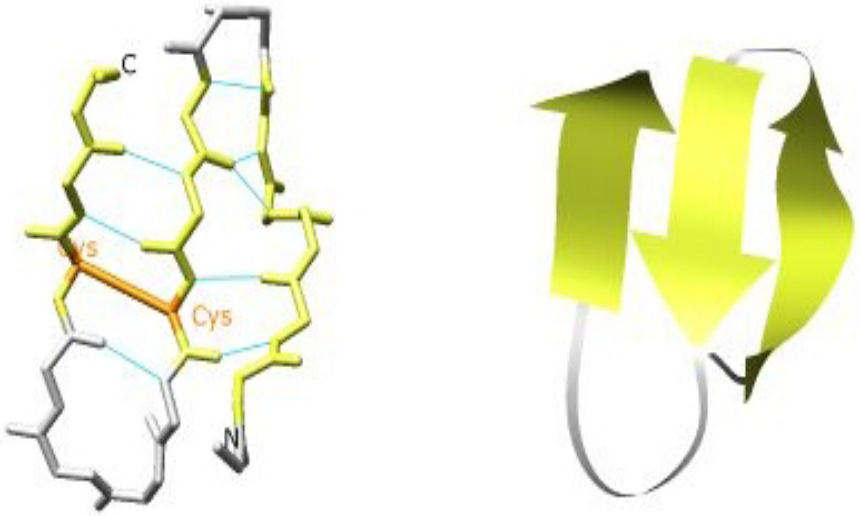


Hydrogen bonds & secondary structure of backbone

alpha helix

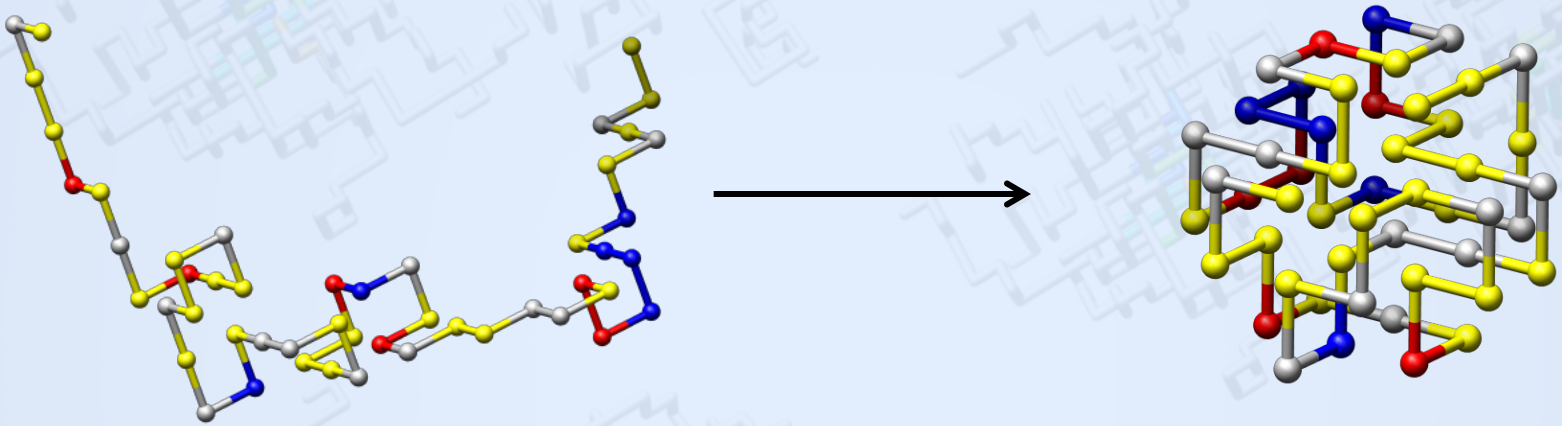


beta sheet



We will ignore this in the practical exercises!

What are the effects that contribute to a stably folded protein?

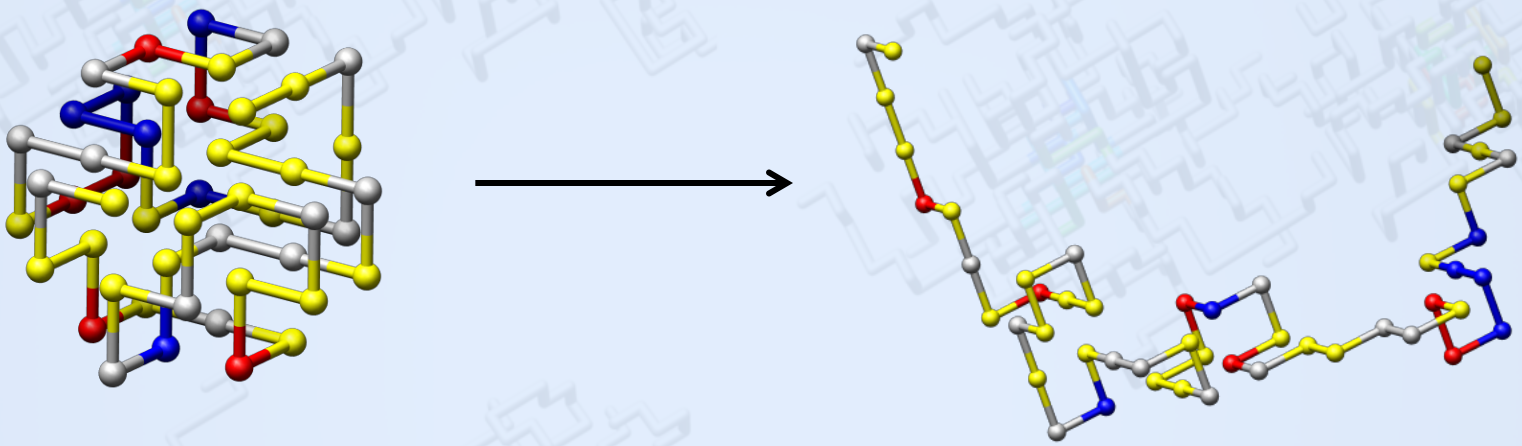


1) Hydrophobicity (oil in water)

   - note this is an effective force that contains enthalpic and entropic components

2) Hydrogen bonds form secondary structure

What forces / effects destabilize a folded protein?



1) Chain entropy!

Questions for you:

Would secondary structures form / be stable in vacuum?

What is the influence of water molecules on secondary structure formation (does it help, does it hinder formation)?

How can you explain secondary structure formation in an aqueous environment?

The biological approach or the physical approach?

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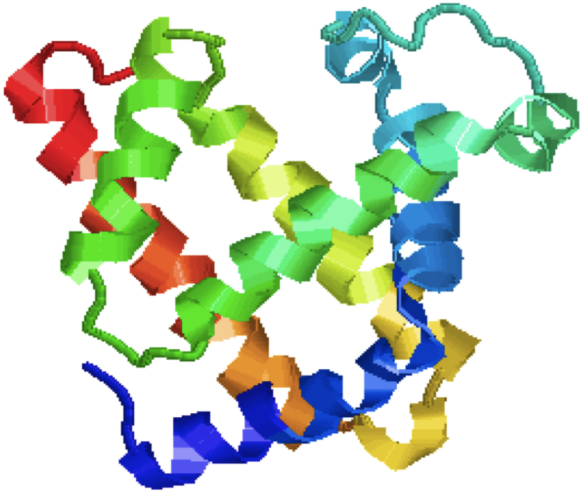
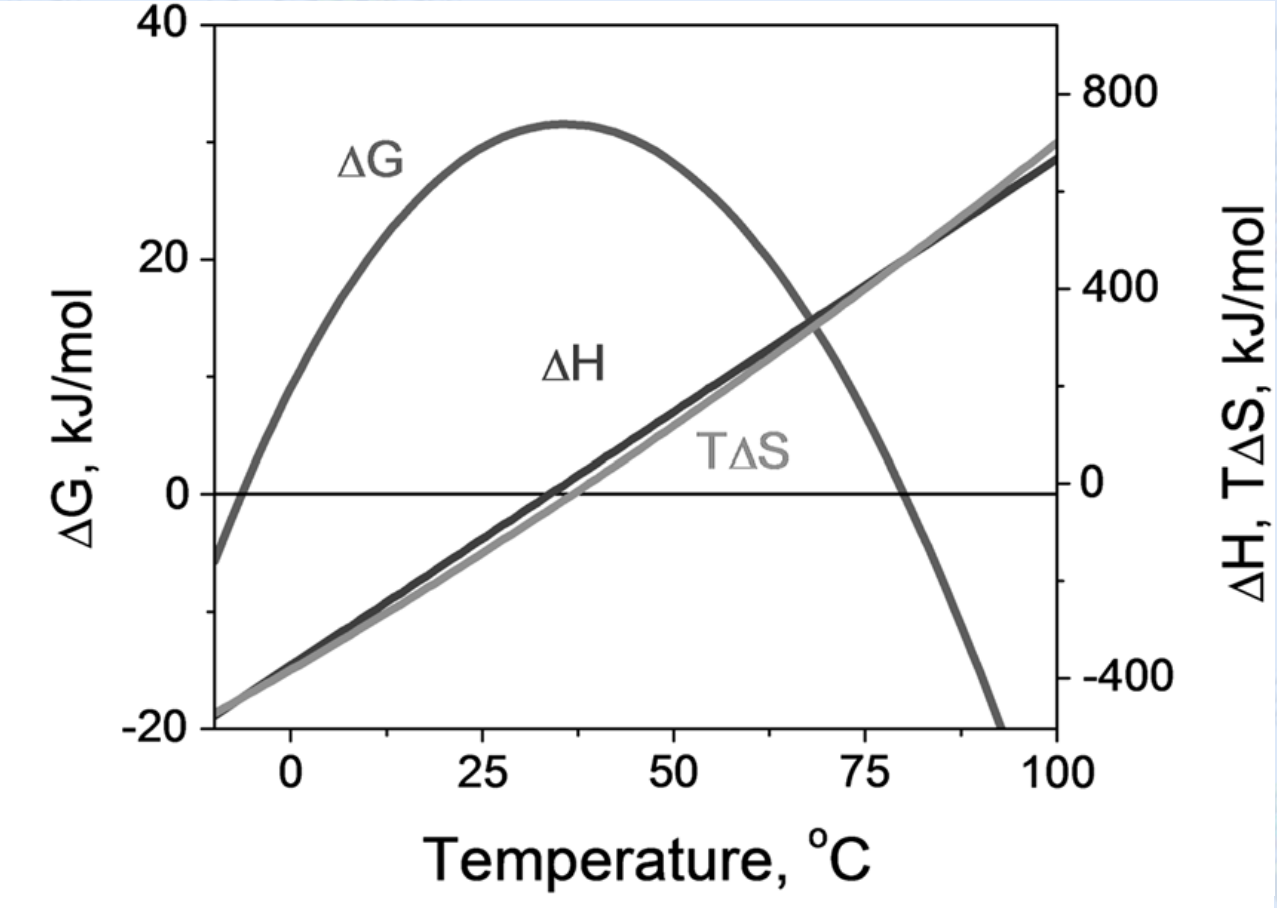


TASK:

Given a protein sequence predict in which 3D structure the protein will fold.

So **WHY** does biology win?

Entropic and enthalpic contributions compensate (experimental)

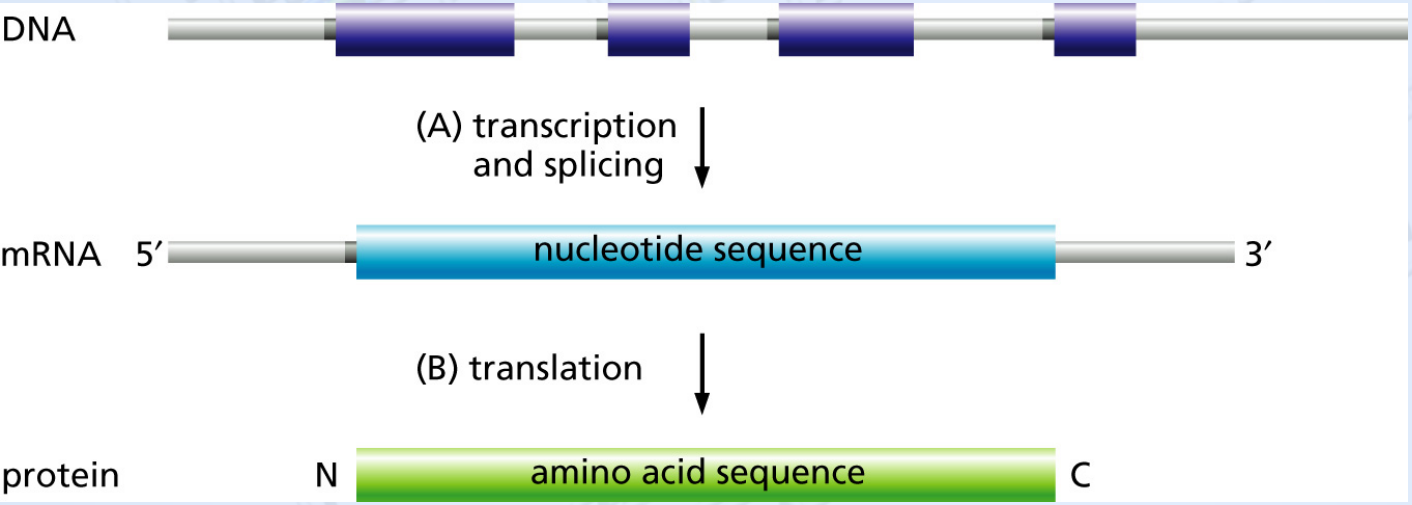


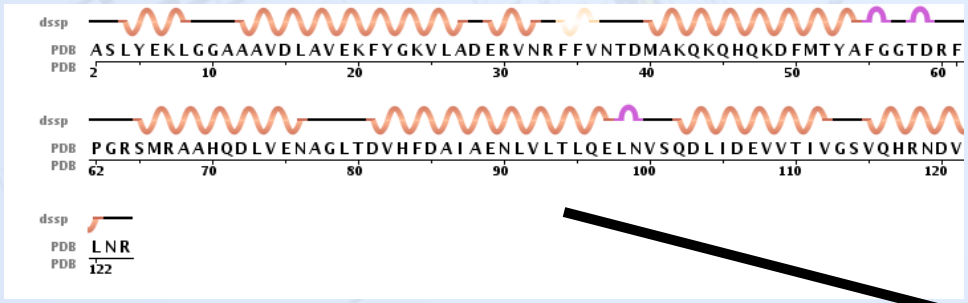
Look at the scale of the axes!

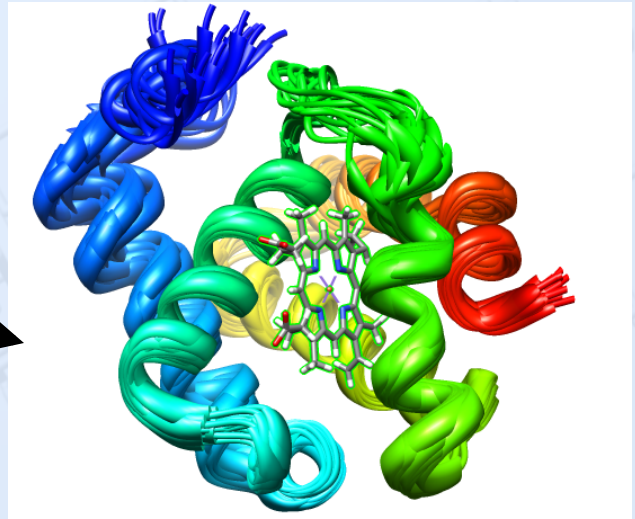
Physics & Biology: folding specificity

Unique characteristic:

The sequence of a protein determines and specifies its structure

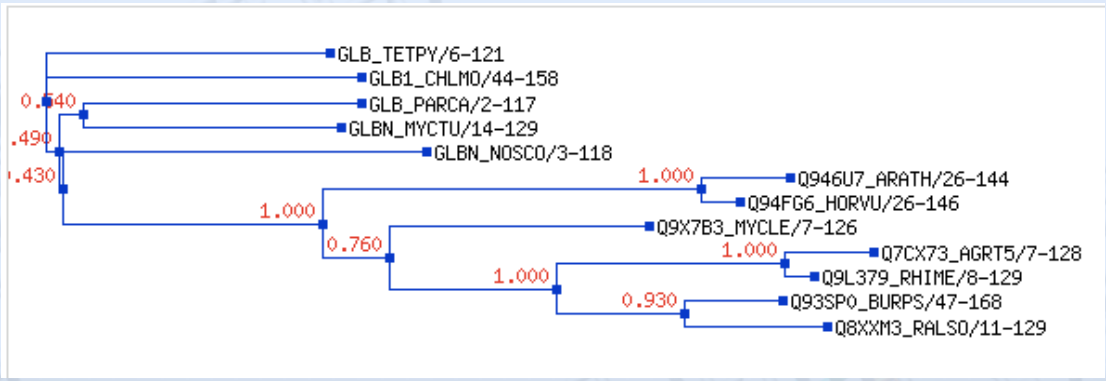


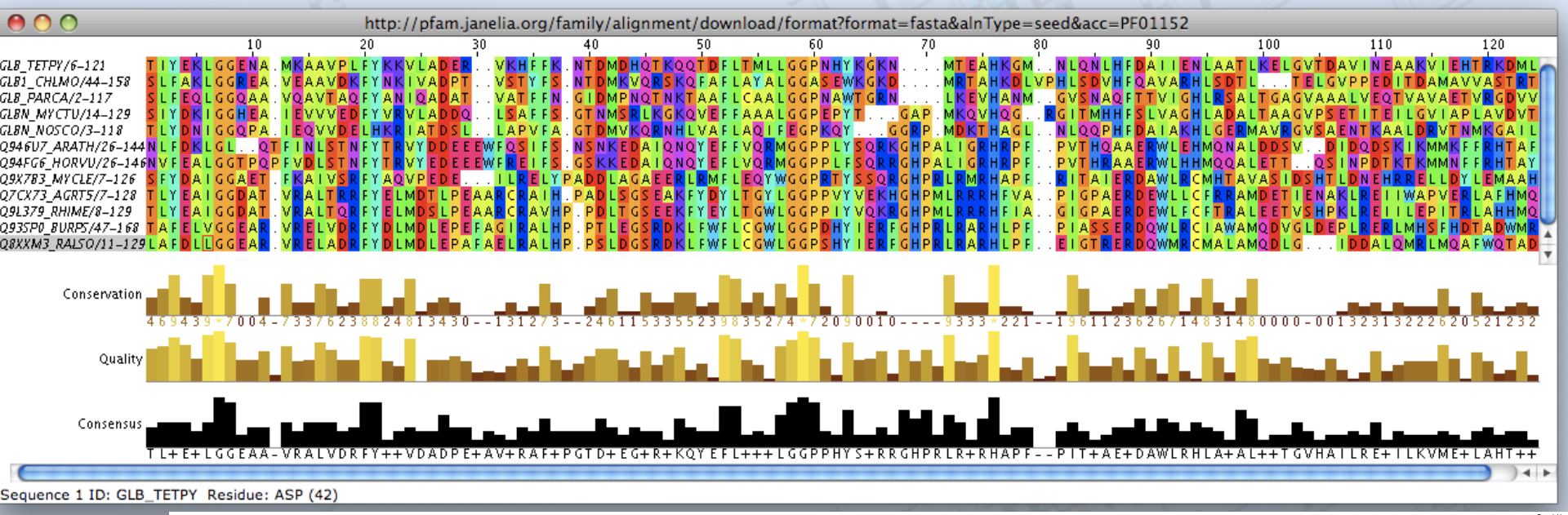


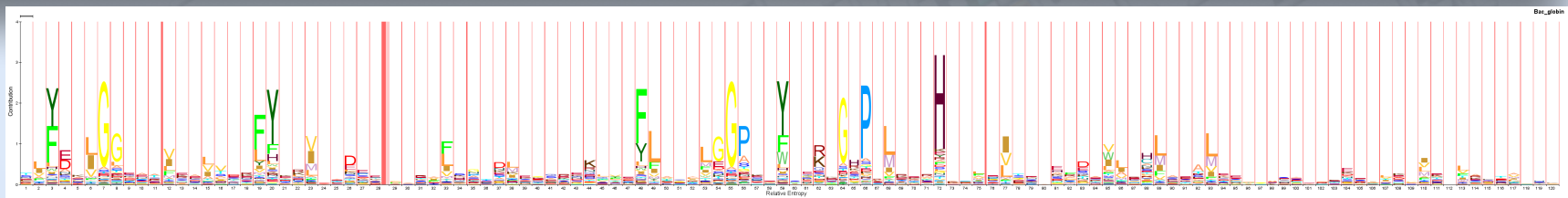


Sequences evolve!

What can evolutionary history tell us?







Biology: structure is more conserved than sequence

1L9H:A(size=349) vs 1GUE:A(size=239)
Structure Alignment

Rmsd = 4.0Å Z-Score = 5.5
Sequence identity = 7.4%
Aligned/gap positions = 202/92

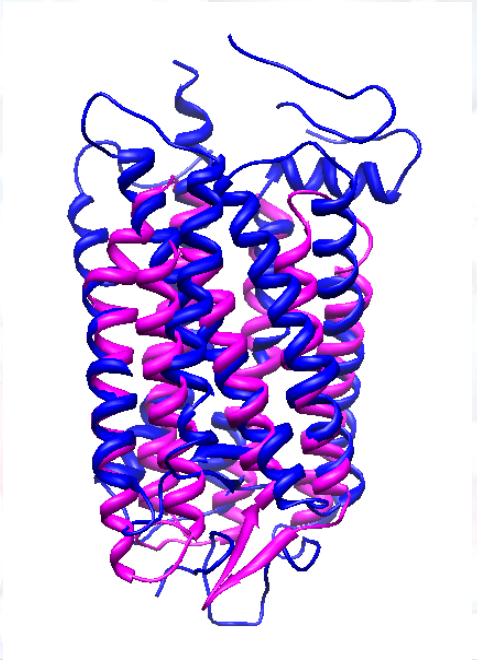
Sequence alignment based on structure alignment.

Sequence alignment based on structure alignment. Position numbers according to sequence (starting from 1) and according to PDB are given as SSSS/PPPP, SSSS - sequence, PPPP - PDB.

1L9H:A - MOL_ID: 1; MOLECULE: RHODOPSIN; CHAIN: A, B

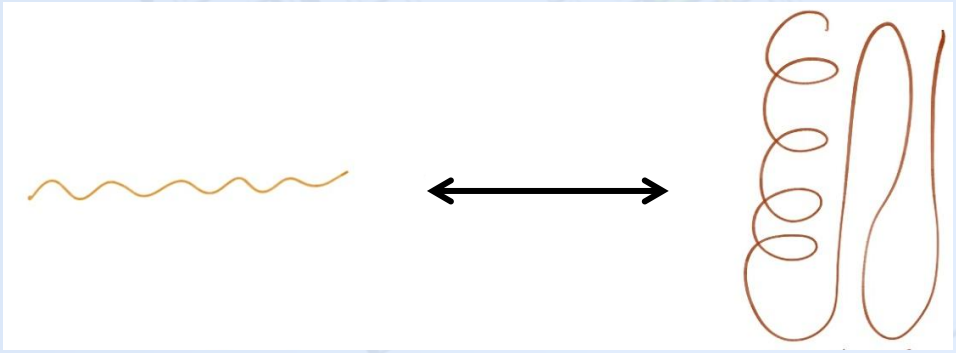
1GUE:A - MOL_ID: 1; MOLECULE: SENSORY RHODOPSIN II; SYNONYM: SR-II; CHAIN: A; ENGINEERED: YES; OTHER_DETAILS: K-STATE, REFINED WITH EXTRAPOLATED DATA

```
1L9H:A    33/33    AEPWQFSMLAAYMFLLIMLGFPINFLTLYVTVQHKKLRTPLNYILLNLAVADLFMVFGGF
1GUE:A     3/4     GLTTLFWLGAIGMLVGTLAFAWAGRDA--GSG-----------ERRYYVTLVGISGIAA

1L9H:A    93/93    TTTLYTSLHGYFVFG--------PTGCNLEGFFATLGGEIALWSLVVLAIERYVVVCKPM
1GUE:A    49/50    VAYVVMALG---VGWVPVAERTVFAPRYIDWILTTPLIVYFLGLLAG------------

1L9H:A   145/145   SNFRFGENHAIMGVAFTWVMALACAAPPLVGWSRYIPEGMQCSCGIDYYTPHEETNNESF
1GUE:A    93/94    ------------LDSREFGIVITLNTVVM--LAGFA---------GAMVPGIERYALFGM

1L9H:A   205/205   VIYMFVVHFIIPLIVIFFCYGQLVFTVKEAAAQQQESATTQKAEKEVTRMVIIMVIAFLI
1GUE:A   130/131   GAVAFLGLVYYLVGPMTESASQ----------------------RSSGIKSLYVRLRNL

1L9H:A   265/265   CWLPYAGVAFYIFTH---QGSDFG----PIFMTIPAFFAKTSAVYNPVIYIMMN
1GUE:A   167/168   TVI-LWAIYPFIWLLGPPGVALLTPTVDVALIVYLDLVTKVGFGFIALDAAATL
```



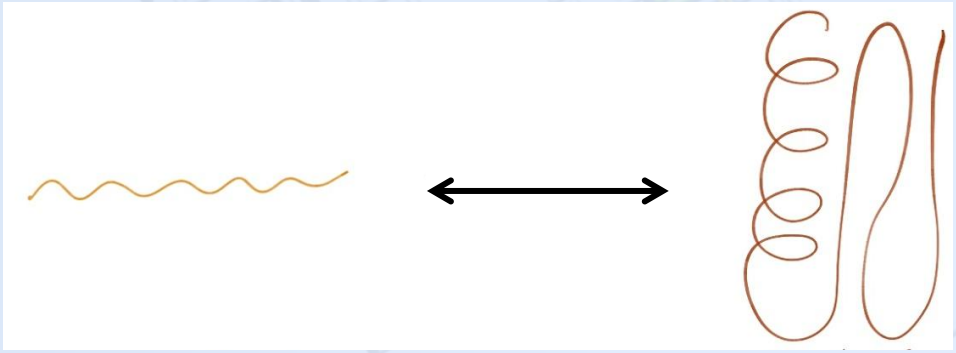
So if we have a protein with a known structure that has a similar sequence – we have solved our problem.

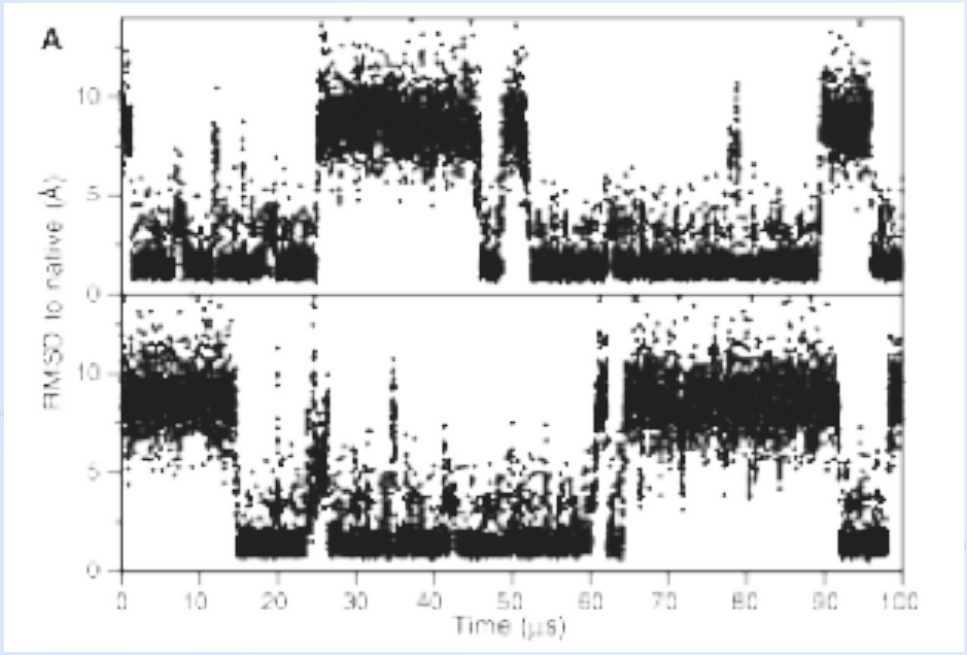
So is there any role for physics based approaches?



- Biological questions (qualitative):
  - What is the function of this protein in the cell?
  - What happens if we change the sequence of the protein?
  - Where does the substrate bind?
  - Do evolutionary related proteins bind the same substrate
- Physical questions (quantitative):
  - How stable is this protein
  - Under which conditions will this protein fold?
  - How strong is the binding to a substrate?

So is there any role for physics based approaches?

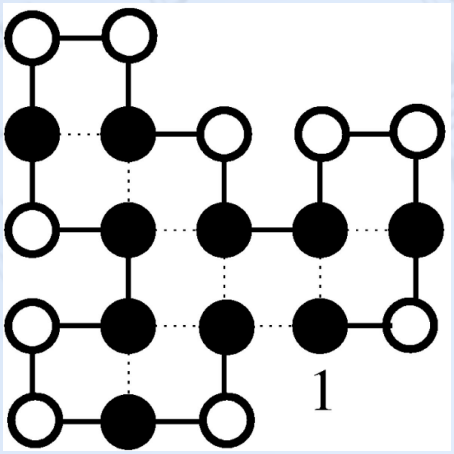




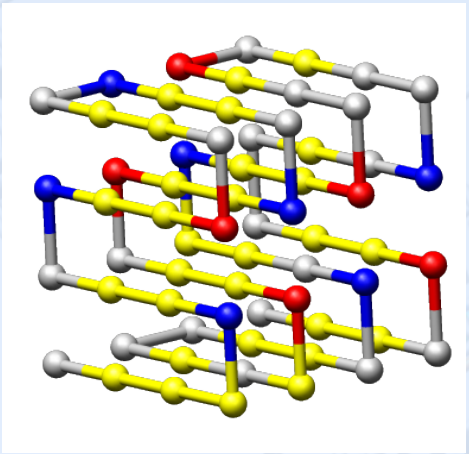
- Fundamental understanding of mechanisms and forces involved in folding
- Detailed simulation under (experimental) constraints.

Why use simple models?

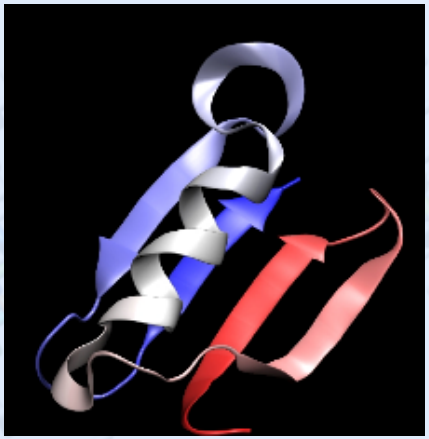
HP model - minute



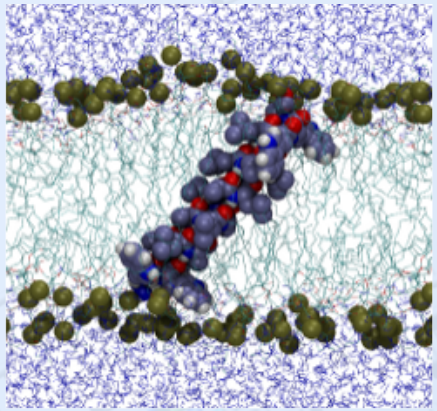
cubic lattice model - hour



backbone model - week



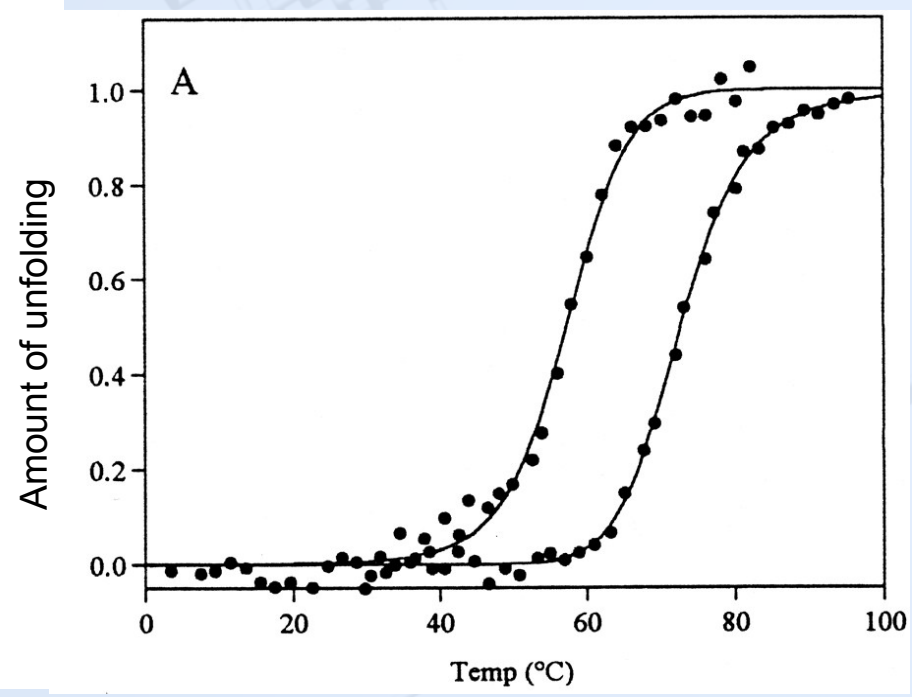
full atomistic model - year(s)

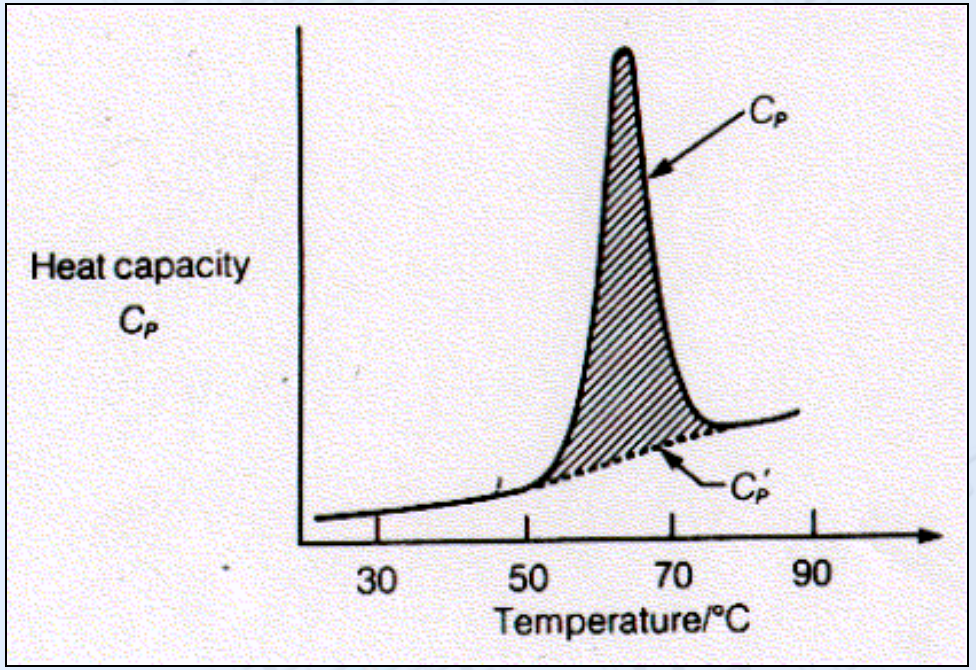


- Sampling lowest free energy state
- Different conditions
- Larger systems

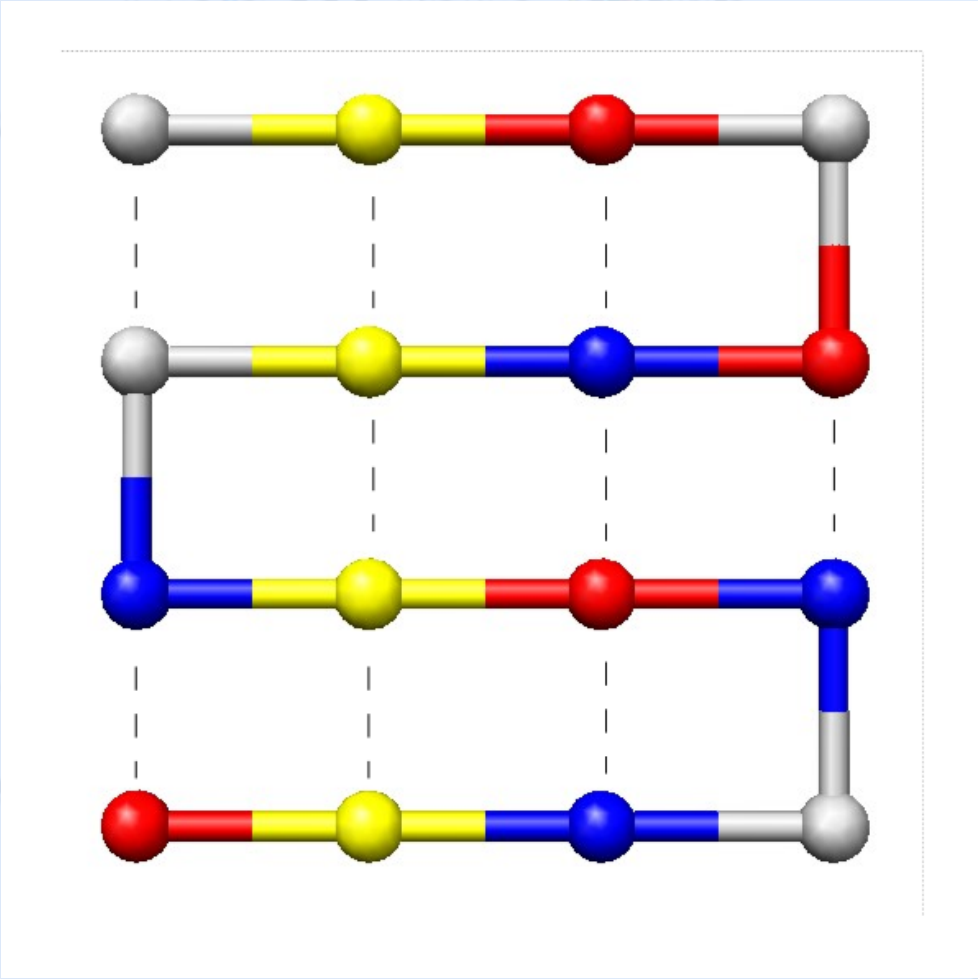
Physics: folding specificity - perfect self assembly

Experimental curves – can we understand these?





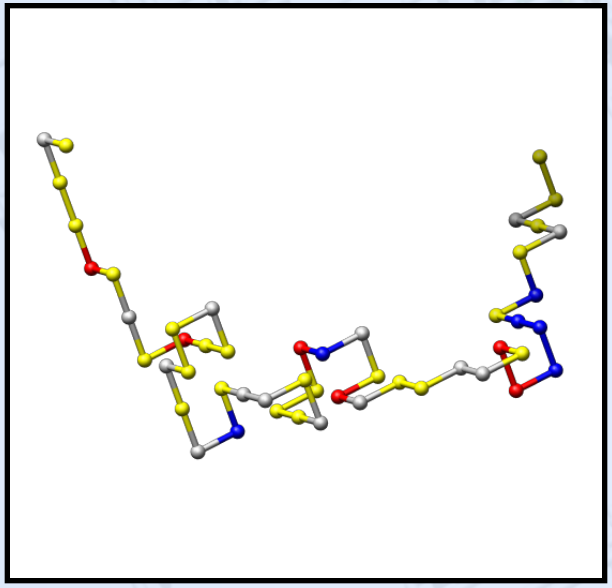
A very simple model



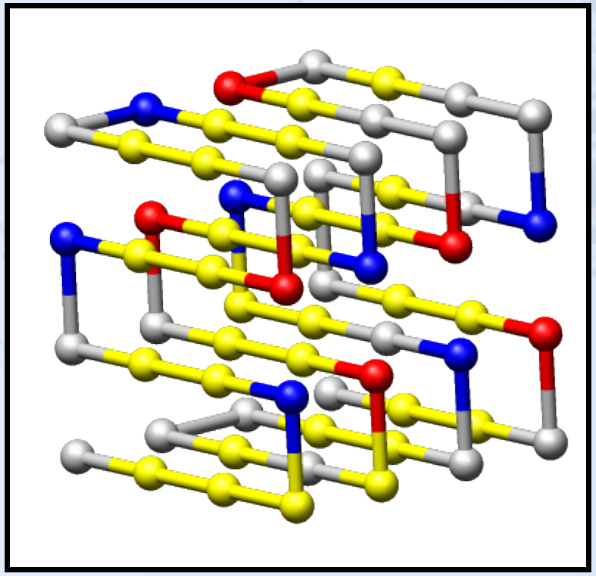
- 3D for research
- 2D in practical

Lattice Model

Sequence



Structure



hydrophobic

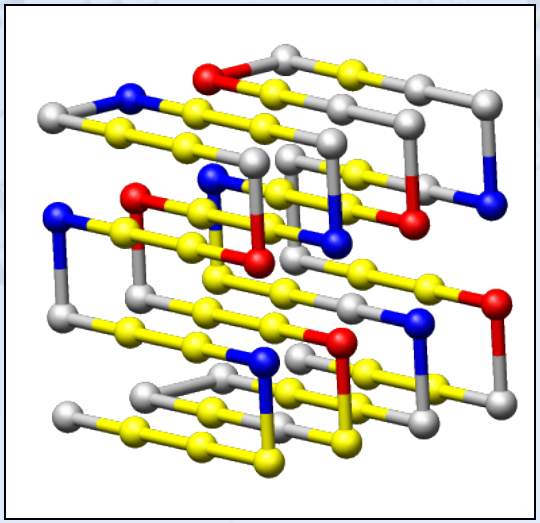
polar (hydrophilic)

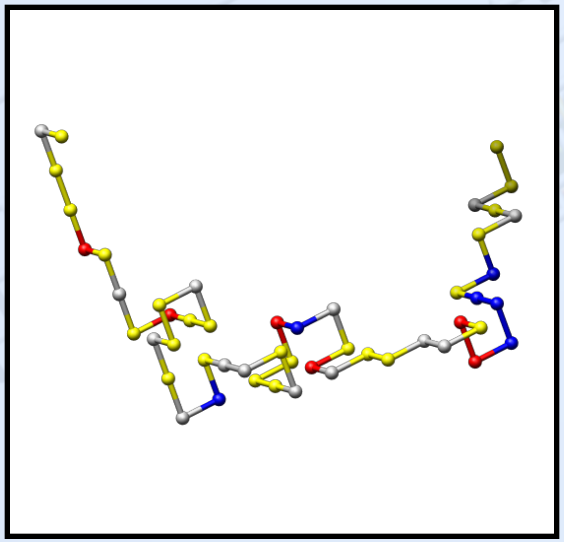
negative charge

positive charge

	--	+	+	+
	+			
	+		+	-
	+		-	+

Cubic Lattice Model





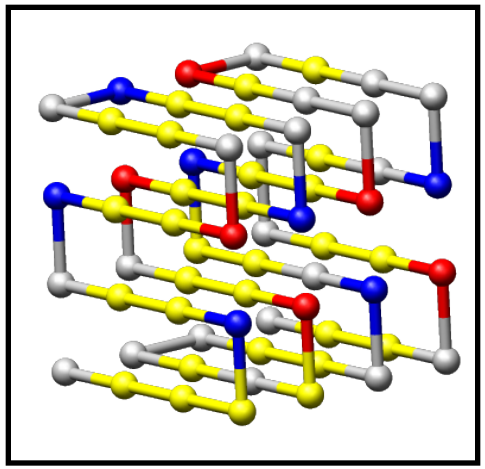
- Cheap & simple
  - Use for right purpose
- Can model:
  - General trends
  - Folding specificity
  - Heat capacity
  - Binding and unbinding
- Not captured:
  - Secondary structure
  - Hydrophobic effect (cold denaturation)
  - Structure predictions for specific proteins

Shakhnovich & Gutin 1993 PNAS 90

Coluzza et al 2003 Phys Rev E 68

Lattice Model, Potential, Design & Simulation

Sequence Design



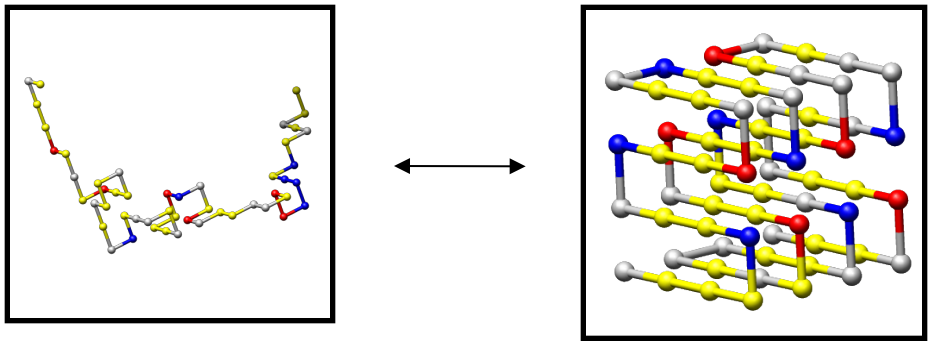
hydrophobic

polar (hydrophilic)

negative charge

positive charge

Folding Simulation



Interaction Potential

	--	+	+	+
	+			
	+		+	-
	+		-	+

hydrophobic

polar (hydrophilic)

negative charge

positive charge

Simulation: interaction potential

$$E = \frac{1}{2}\sum_{i}^{N}\sum_{j}^{N}\epsilon_{a(i),a(j)}C_{ij}$$

energy

contact

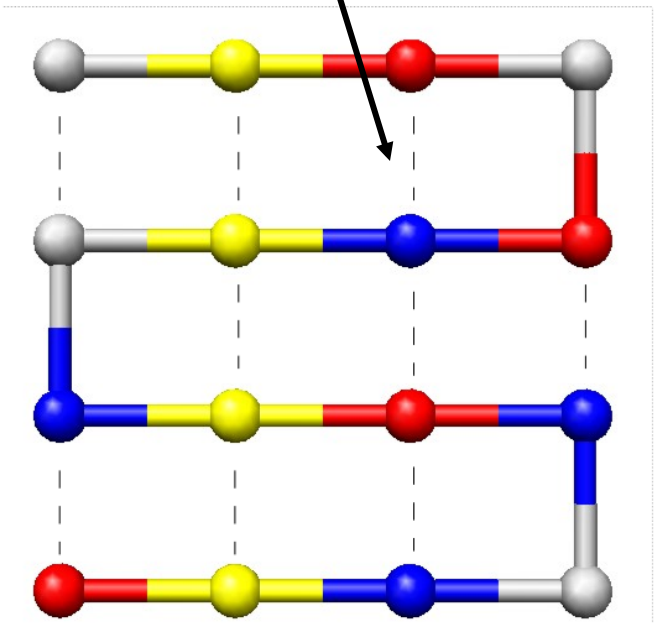
hydrophobic

polar (hydrophilic)

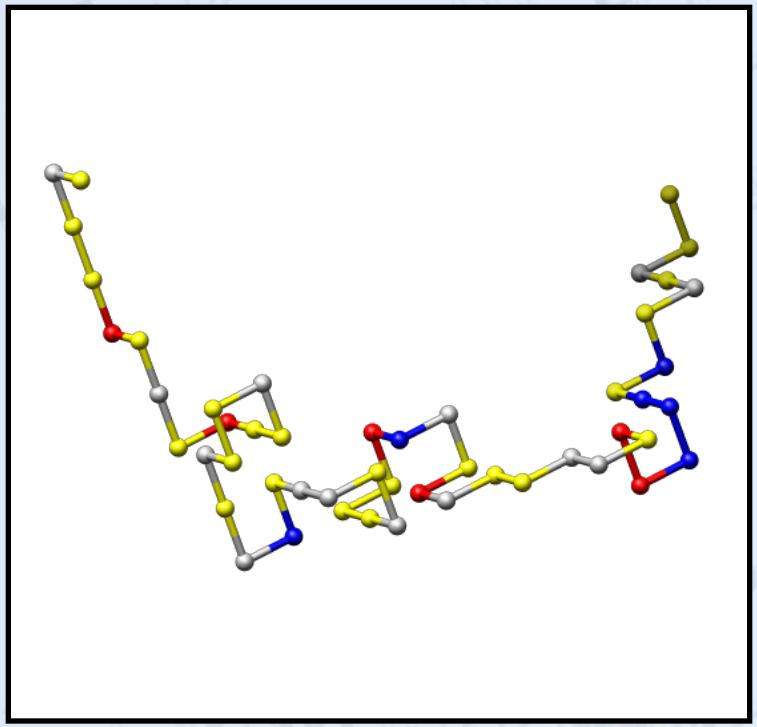
negative charge

positive charge

	--	+	+	+
	+			
	+		+	-
	+		-	+



Simulation: Monte Carlo



Monte Carlo:

- Choose a residue (or region)
- Change its position
- Calculate new interaction energy
- Accept with Monte Carlo criterion

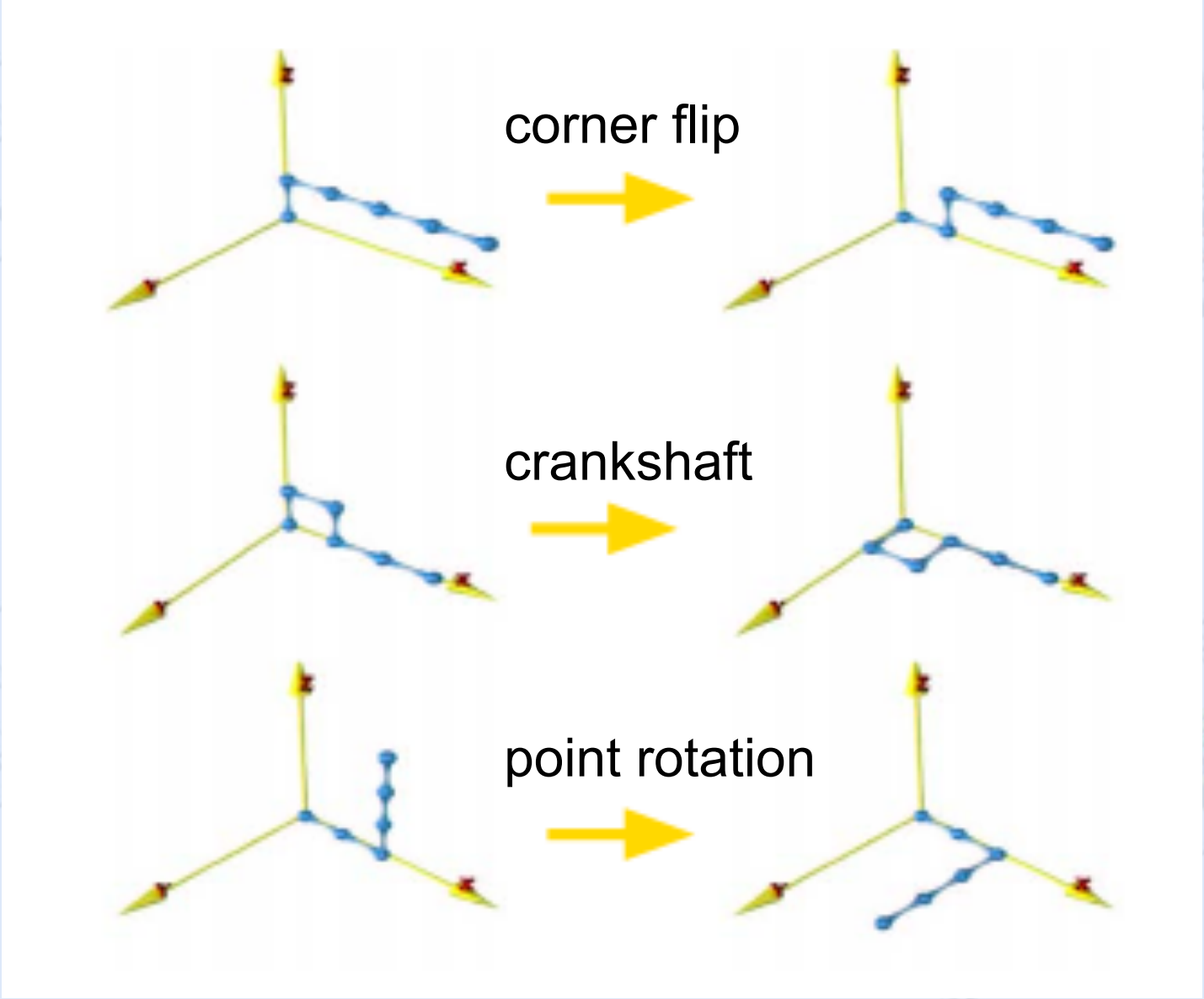
$$P_{\mathrm{acc}} = \min\left\{1, \exp\left(\frac{E_{\mathrm{old}} - E_{\mathrm{new}}}{kT}\right)\right\}$$

Shakhnovich & Gutin 1993 PNAS 90

Coluzza et al 2003 Phys Rev E 68

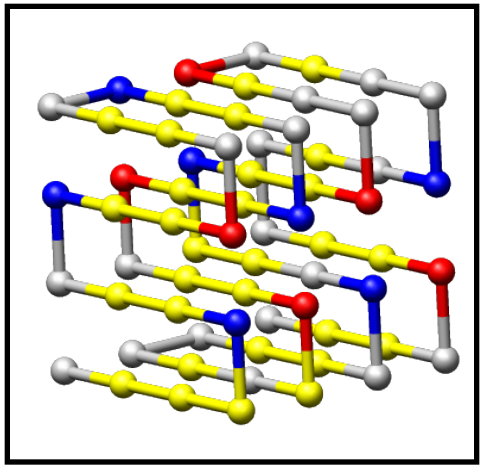
Betancourt & Thirumalai 1999 Protein Sci 8

Simulation: Lattice Moves



Sequence Design

Design



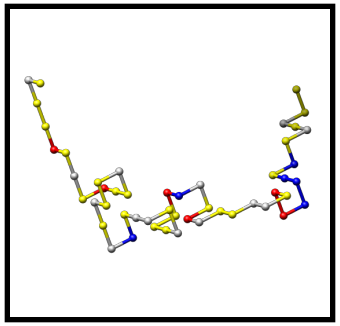
hydrophobic

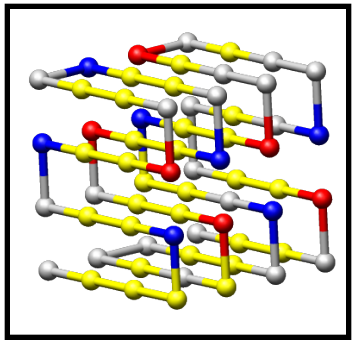
polar (hydrophilic)

negative charge

positive charge

Simulation





Potential

	hydrophobic	polar	negative	positive
hydrophobic	--	+	+	+
polar	+			
negative	+		+	-
positive	+		-	+

hydrophobic

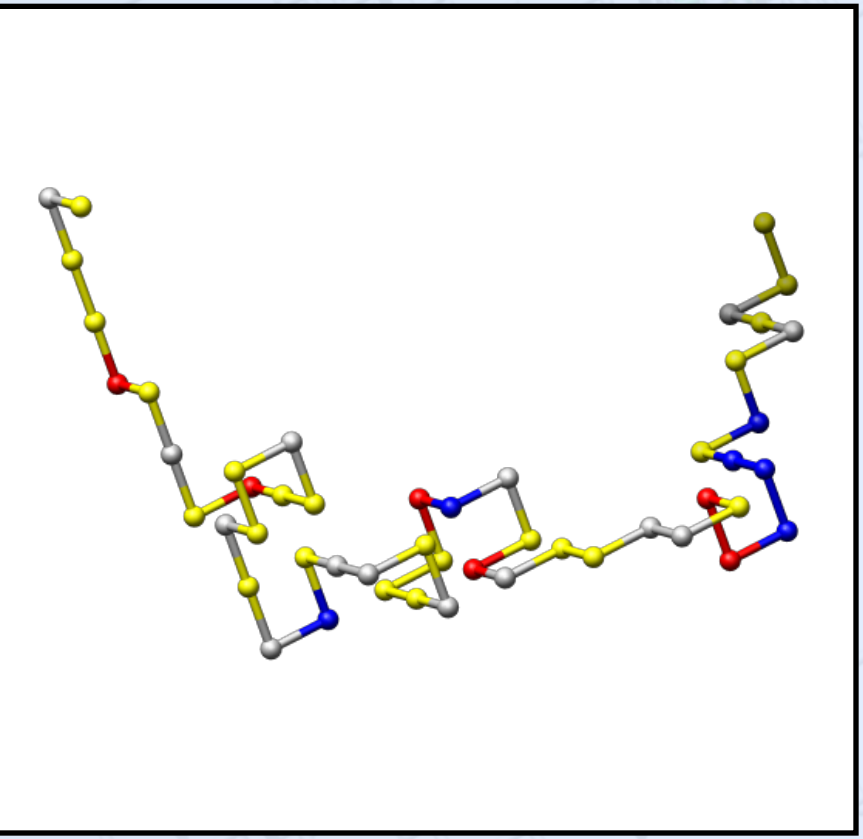
polar (hydrophilic)

negative charge

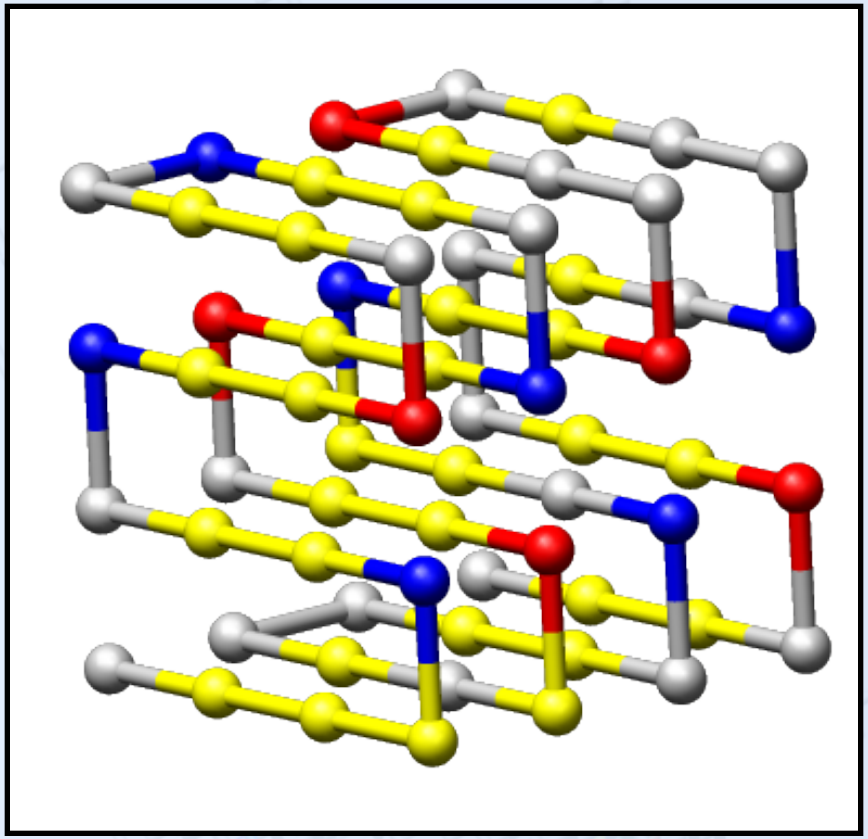
positive charge

Problem: how to create a folding sequence?

We cannot take real protein sequences (why not?)



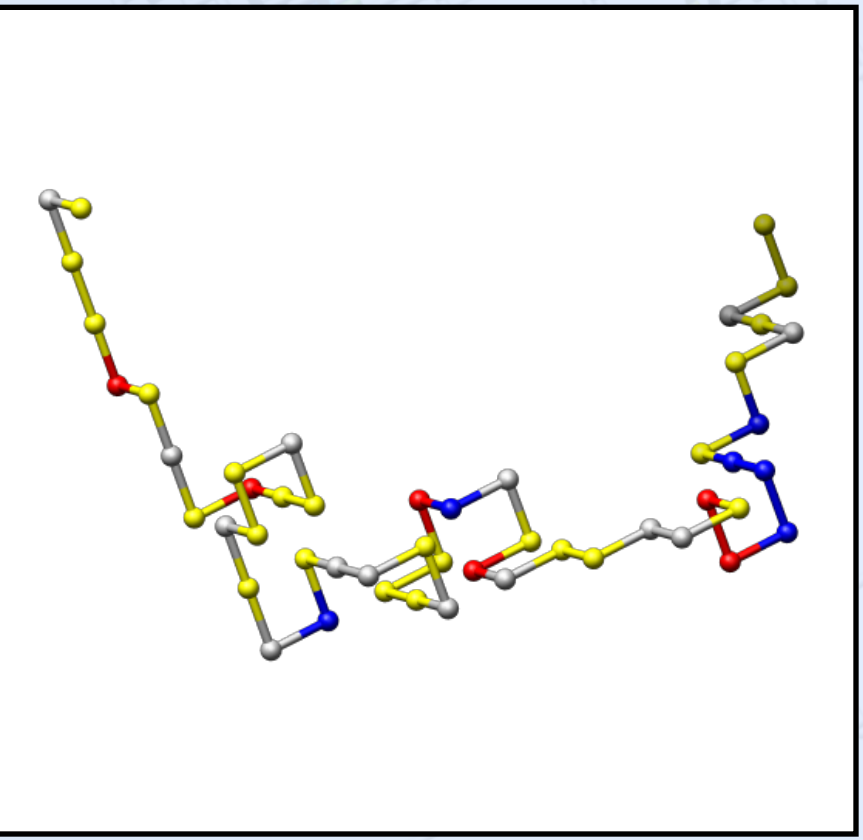
?



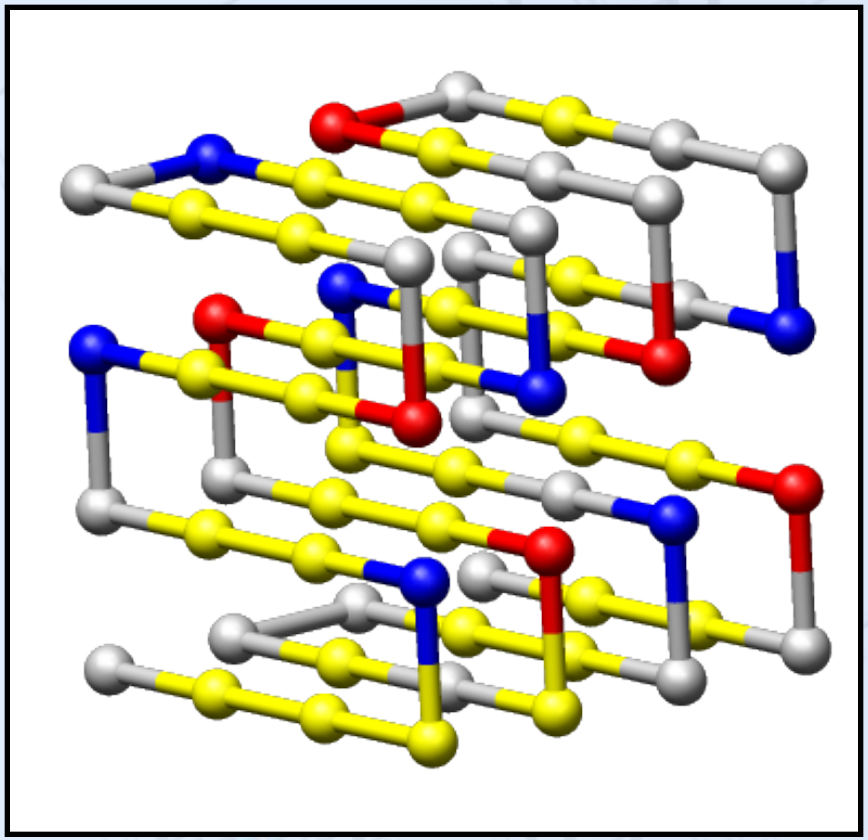
In nature evolution ensures folding...

Solution: energy minimization

Given a structure, what are sequences with a low (potential) energy?

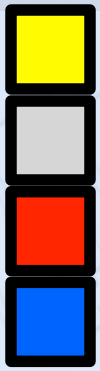


?



we can simulate evolution by changing the sequence with random substitutions

Lattice Model: design



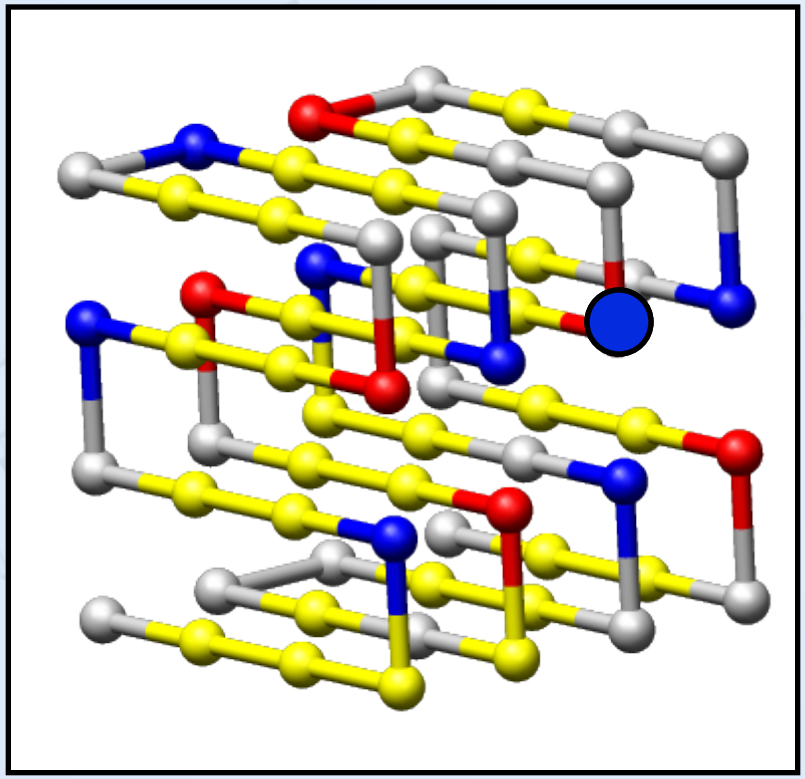
hydrophobic

polar (hydrophilic)

negative charge

positive charge

	--	+	+	+
	+			
	+		+	-
	+		-	+

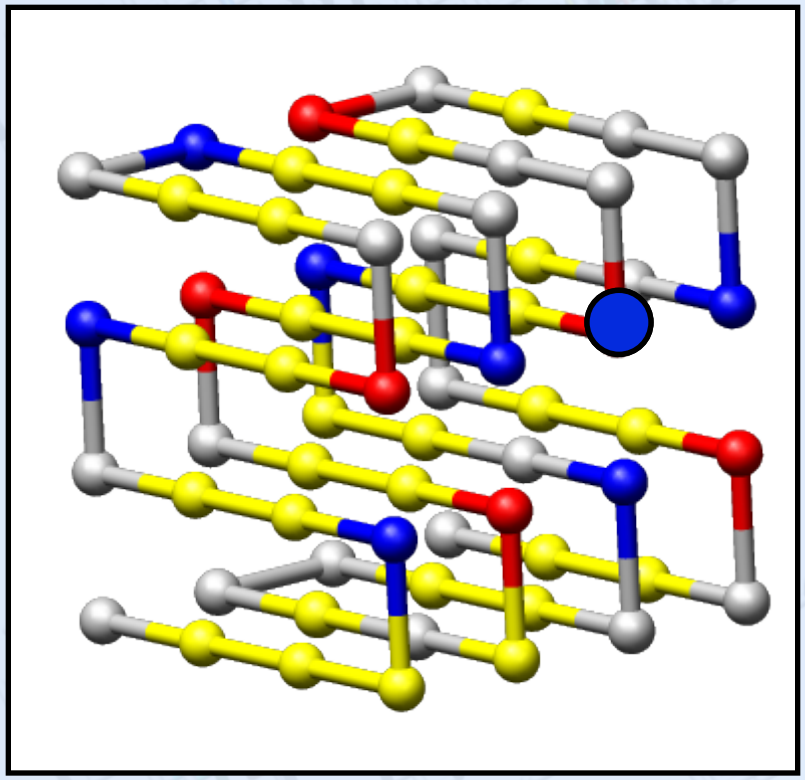


Design loop:

-Initiation: choose a structure, keep it frozen

- Design loop:
  - Choose a residue
  - Change the amino acid
  - Calculate new interaction energy
  - Accept with Monte Carlo criterion based on energy and variance

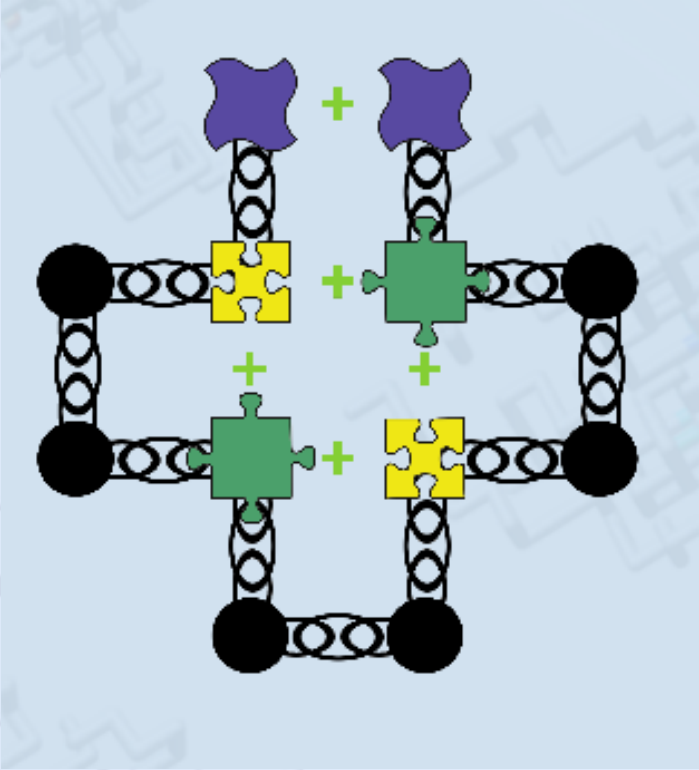
Sequence design: energy **minimization**



$$P_{\text{acc}} = \min\left\{1, \exp\left(\frac{E_{\text{old}} - E_{\text{new}}}{kT}\right)\right\}$$

Note that this is an “ad hoc” algorithm – no statistical mechanics, pure energy minimisation

Interactions: toy example 2D

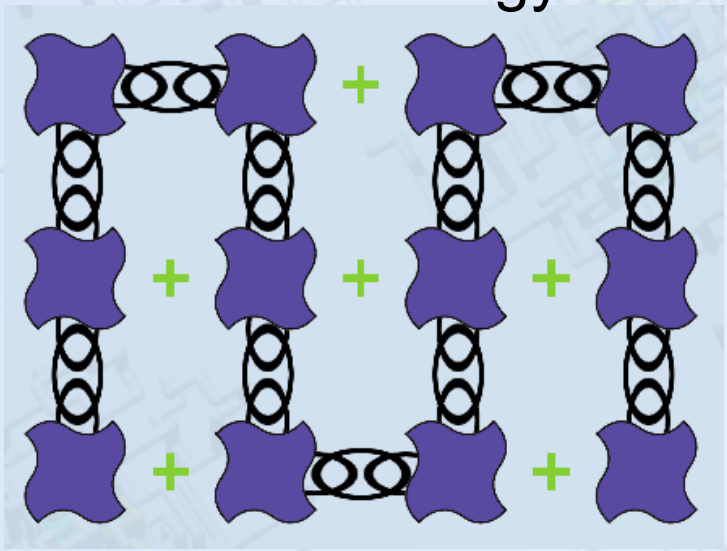


matching puzzle pieces indicate favourable interaction energies

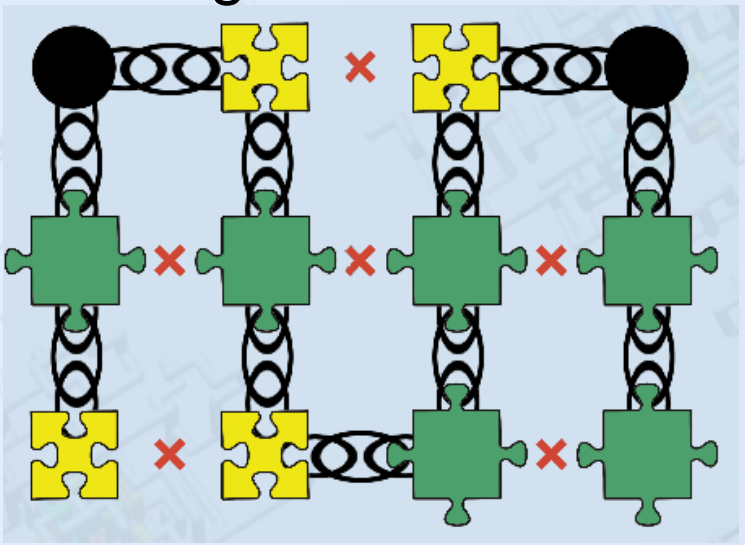
Tutorial code is based on this toy example

Sequence Design: what would be a good (specific) folder

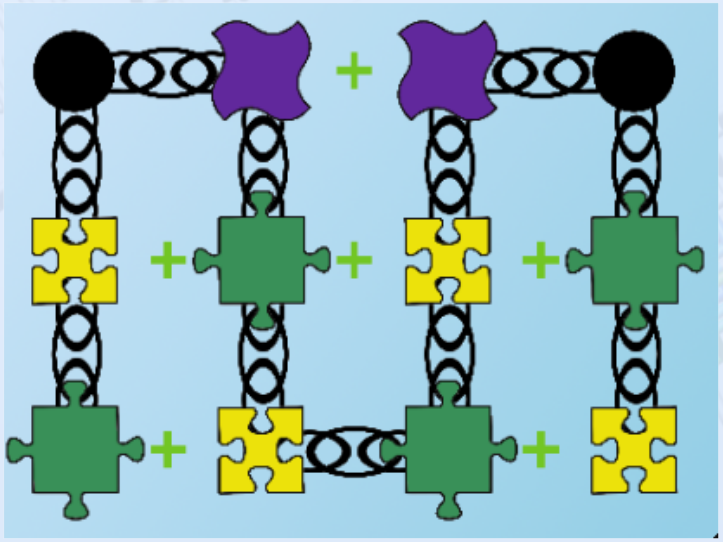
Low energy



High variance



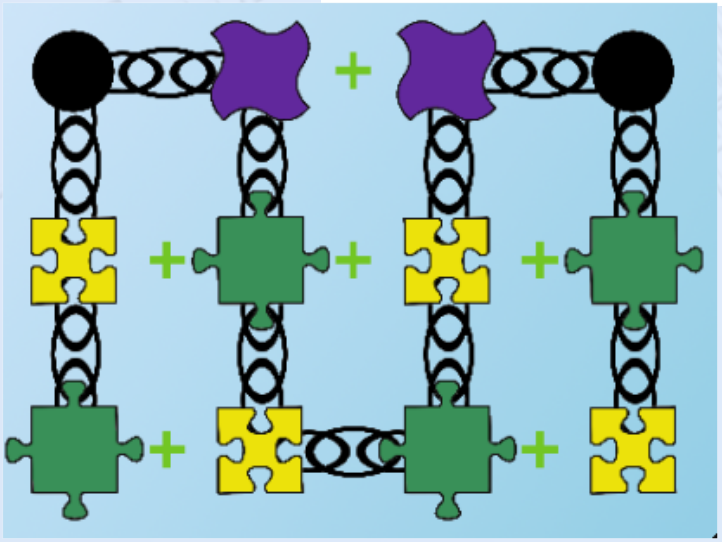
Good folder

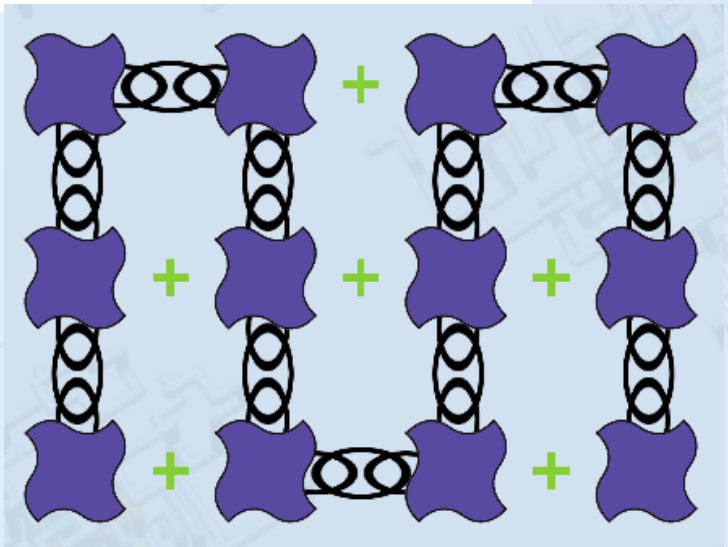


Sequence Variance

$$N_p = \frac{N!}{n_1!n_2!...n_{N_A}!}$$

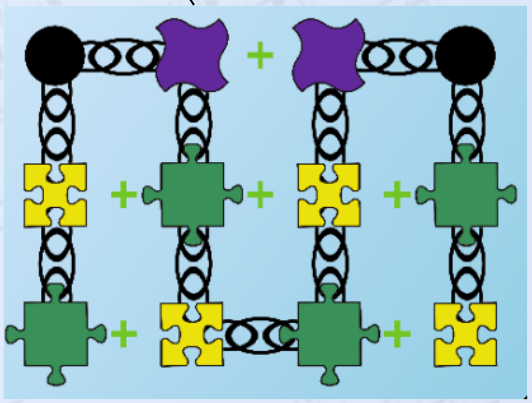
$$P_{\text{acc}} = \min\left\{1, \left(\frac{N_p^{\text{new}}}{N_p^{\text{old}}}\right)^{1/q}\right\}$$

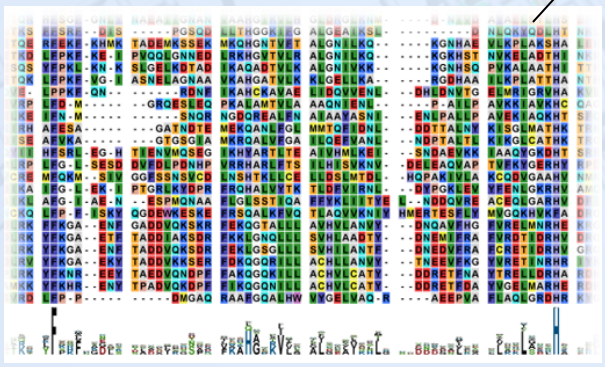




Sequence Variance & Biology

$$d = \sum_{a=0}^{a=20} (p_a - s_a)^2$$

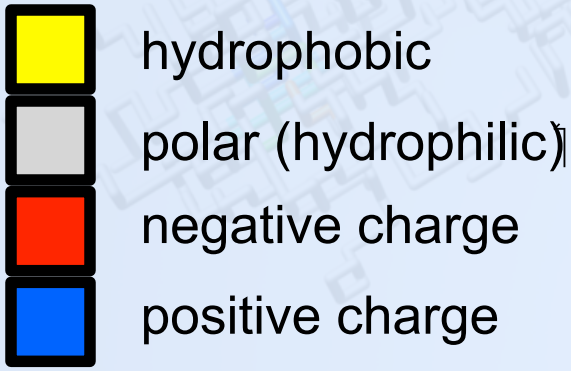


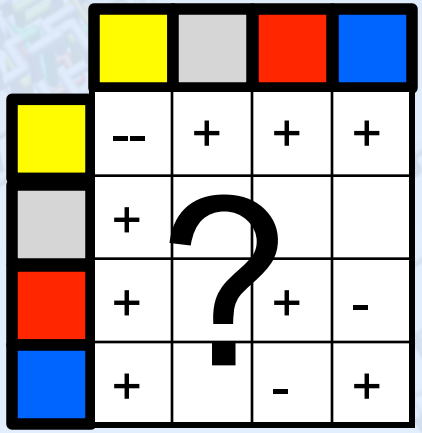


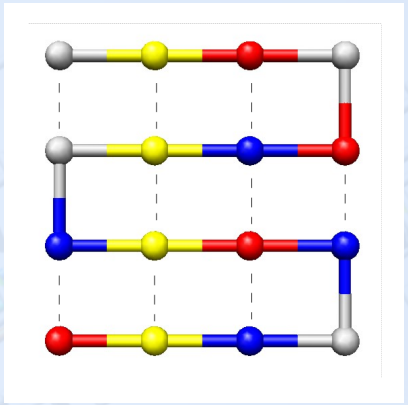
$$P_{\text{acc}} = \min\left\{1, e^{-1/q(d_{\text{new}} - d_{\text{old}})}\right\}$$

Take variance estimates from amino acid type occurrence

How to derive a potential?







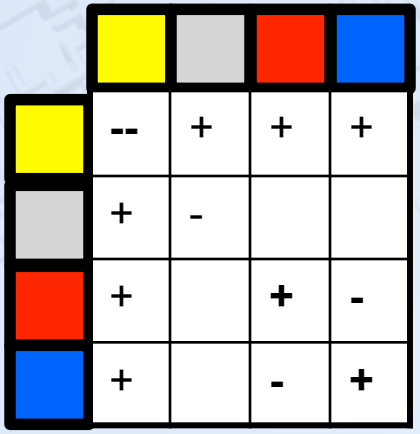
$$E = \frac{1}{2}\sum_{i}^{N}\sum_{j}^{N}\epsilon_{a(i),a(j)}C_{ij}$$

Can we use experimental biological data?

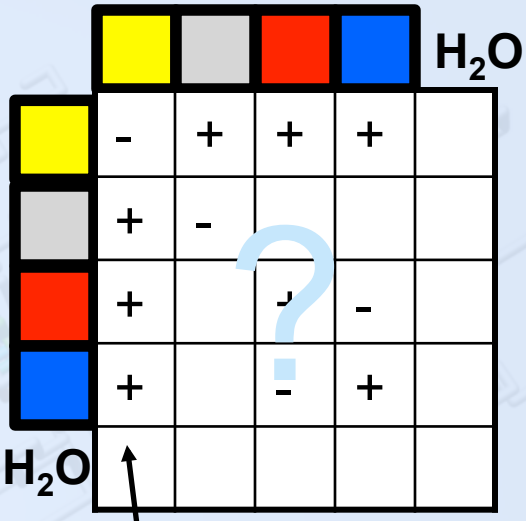
“Knowledge Based” Amino Acid Pair Potentials

- Sample the PDB
- Nearly 100.000 protein structures (X-ray, NMR, Cryo)
- Assumption:
  PDB is a representative ensemble of well mixed amino acids

“Knowledge Based” Amino Acid Pair Potentials



hydrophobic
polar (hydrophilic)
negative charge
positive charge

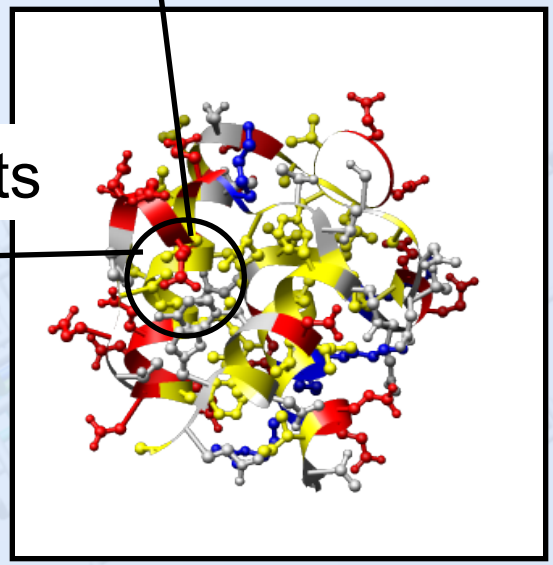


Miyazawa & Jernigan 1993 Protein Eng 6
Betancourt & Thirumalai 1999 Protein Sci 8

observed contacts

$$\epsilon_{i,j} = -kT \ln \left(\frac{c_{i,j}}{\omega_{i,j}} \right)$$

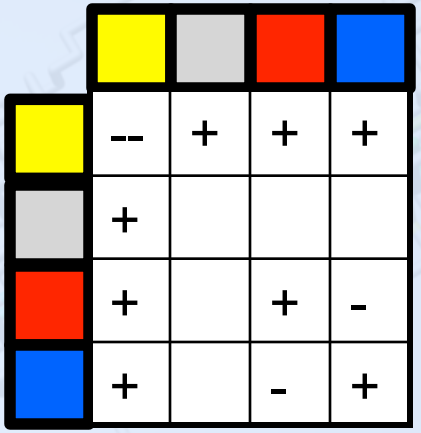
expected contacts

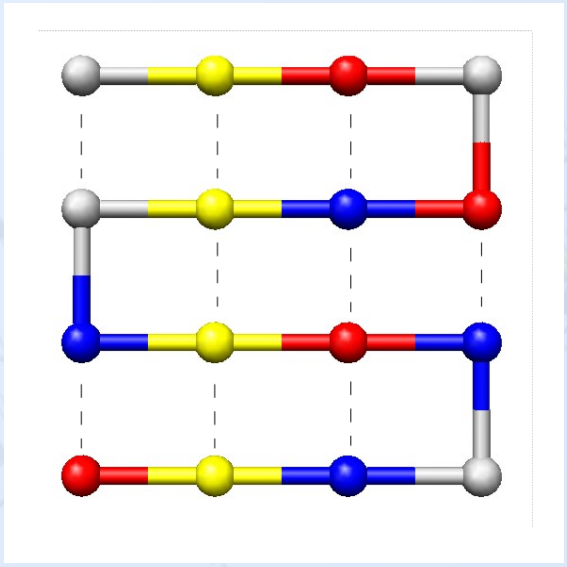


“Knowledge Based” Amino Acid Pair Potentials

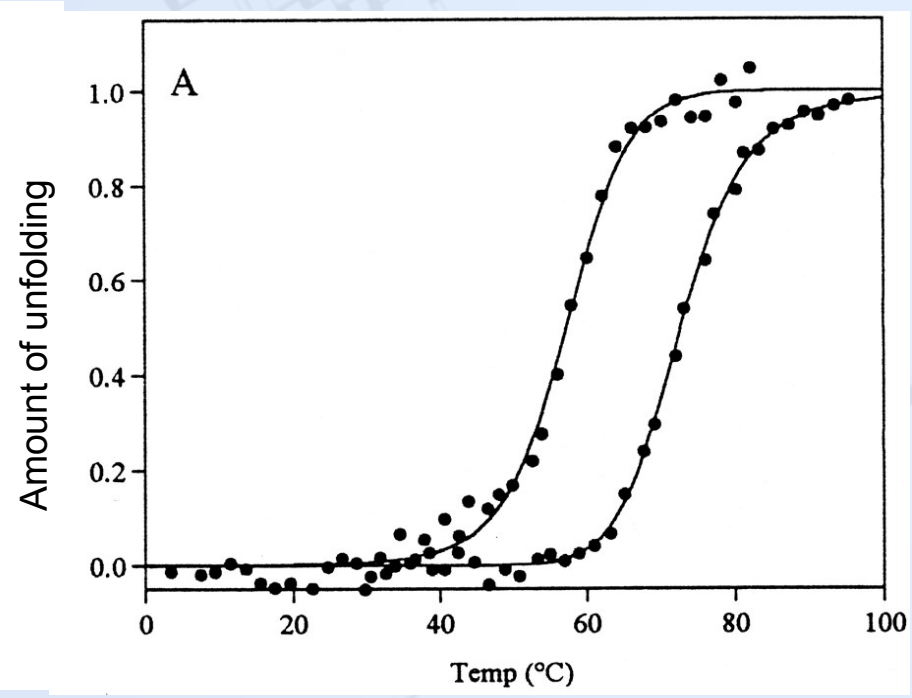
$$\epsilon_{i,j} = kT \ln \left(\frac{c_{i,j}}{\omega_{i,j}} \right)$$

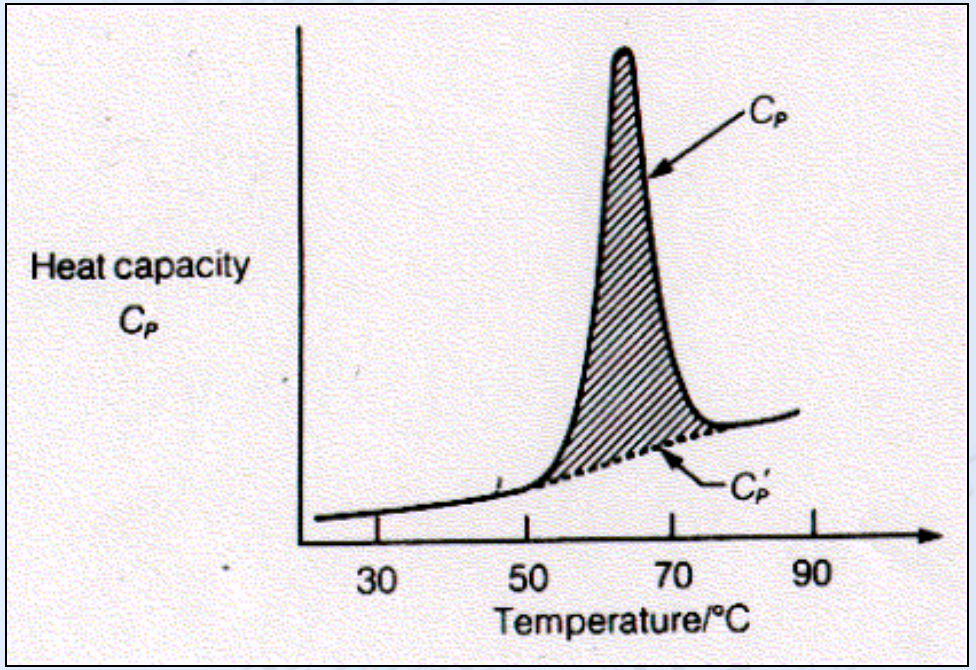
$$\omega_{i,j} = \frac{n_i q_i n_j q_j}{\sum_k q_k n_k}$$



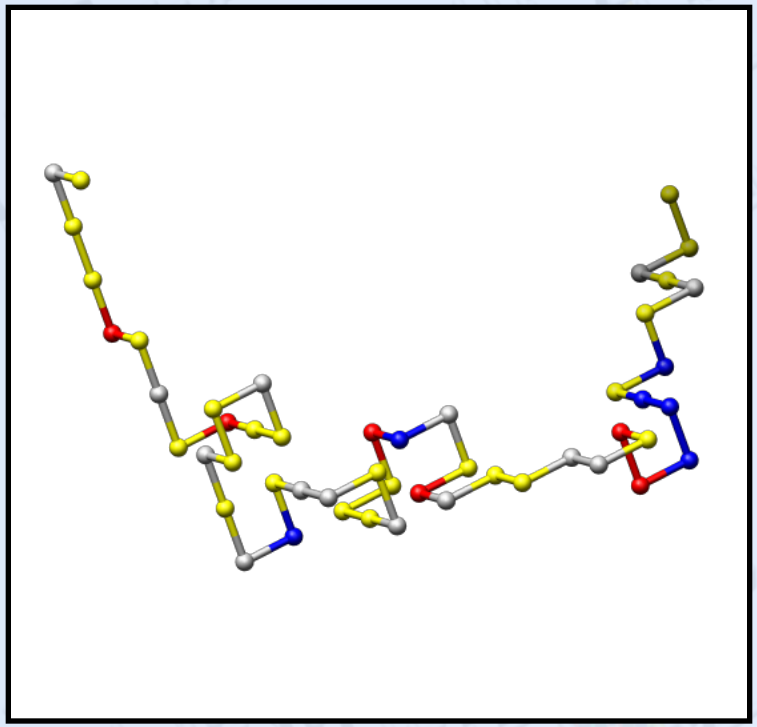


Are experimental results captured by the model?





Let's start the Monte Carlo Simulation



Monte Carlo:

- Choose a residue (or region)
- Change its position
- Calculate new interaction energy
- Accept with Monte Carlo criterion

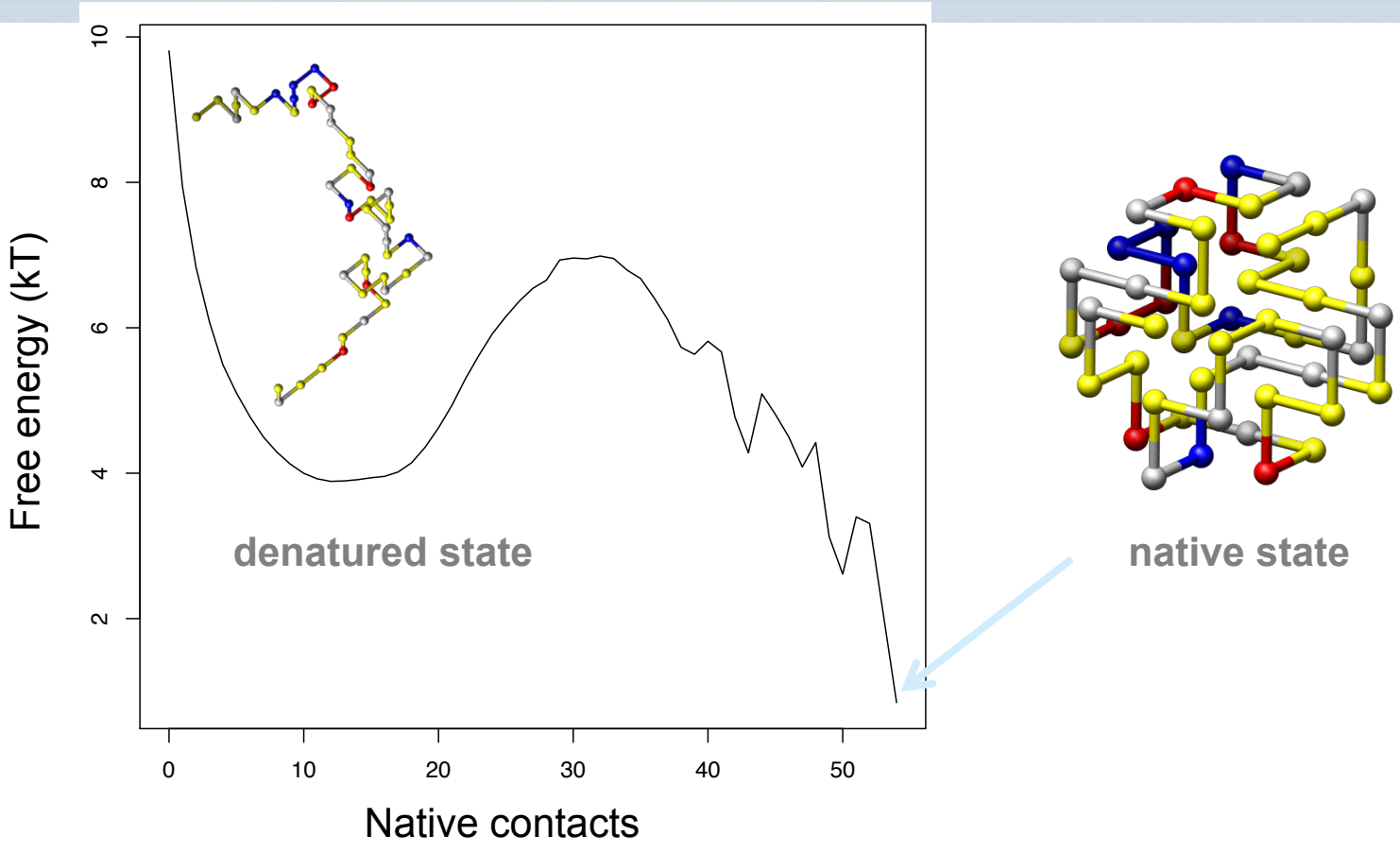
$$P_{\text{acc}} = \min\left\{1, \exp\left(\frac{E_{\text{old}} - E_{\text{new}}}{kT}\right)\right\}$$

Shakhnovich & Gutin 1993 PNAS 90

Coluzza et al 2003 Phys Rev E 68

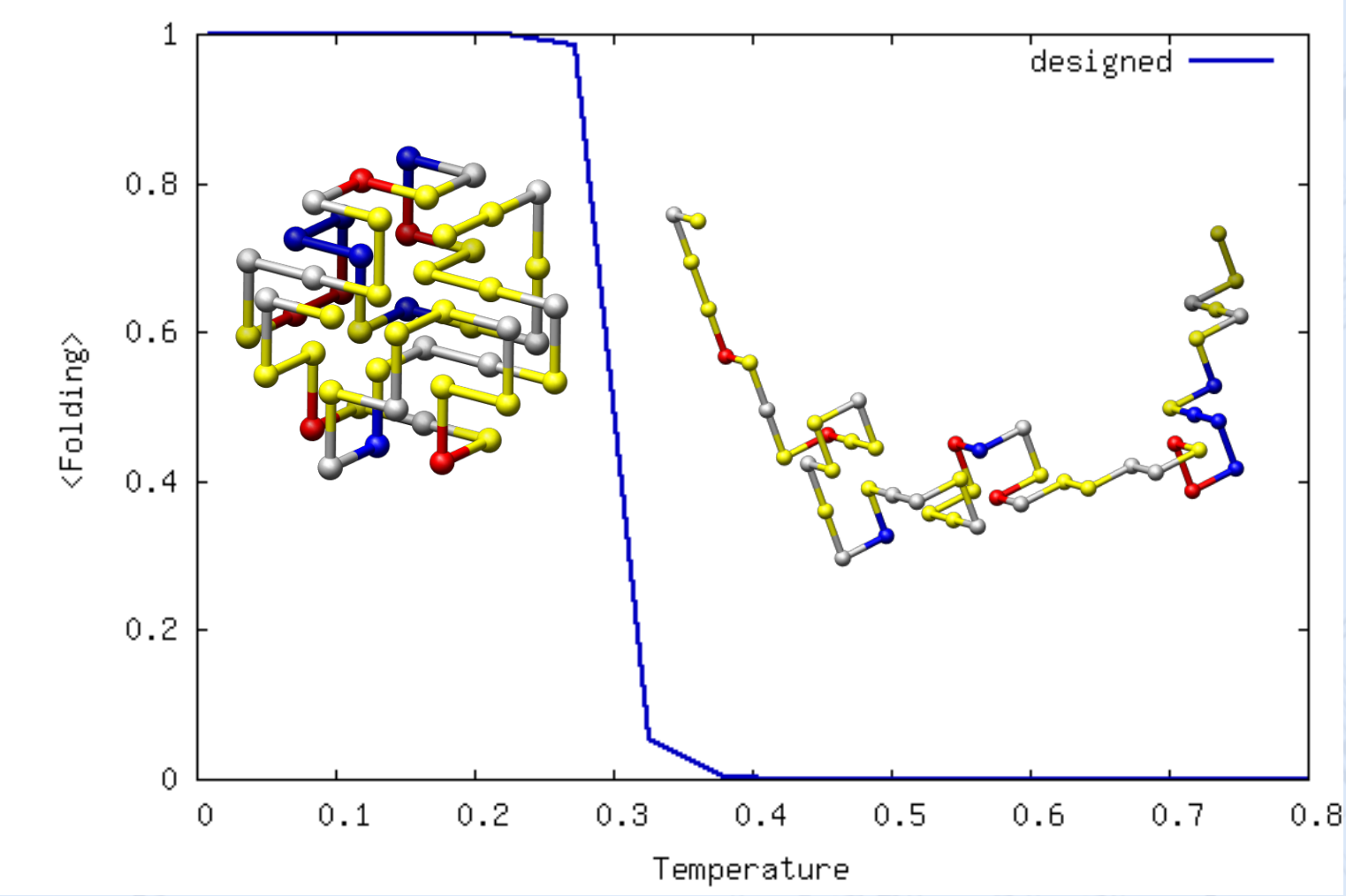
Betancourt & Thirumalai 1999 Protein Sci 8

Free energy curve of folding

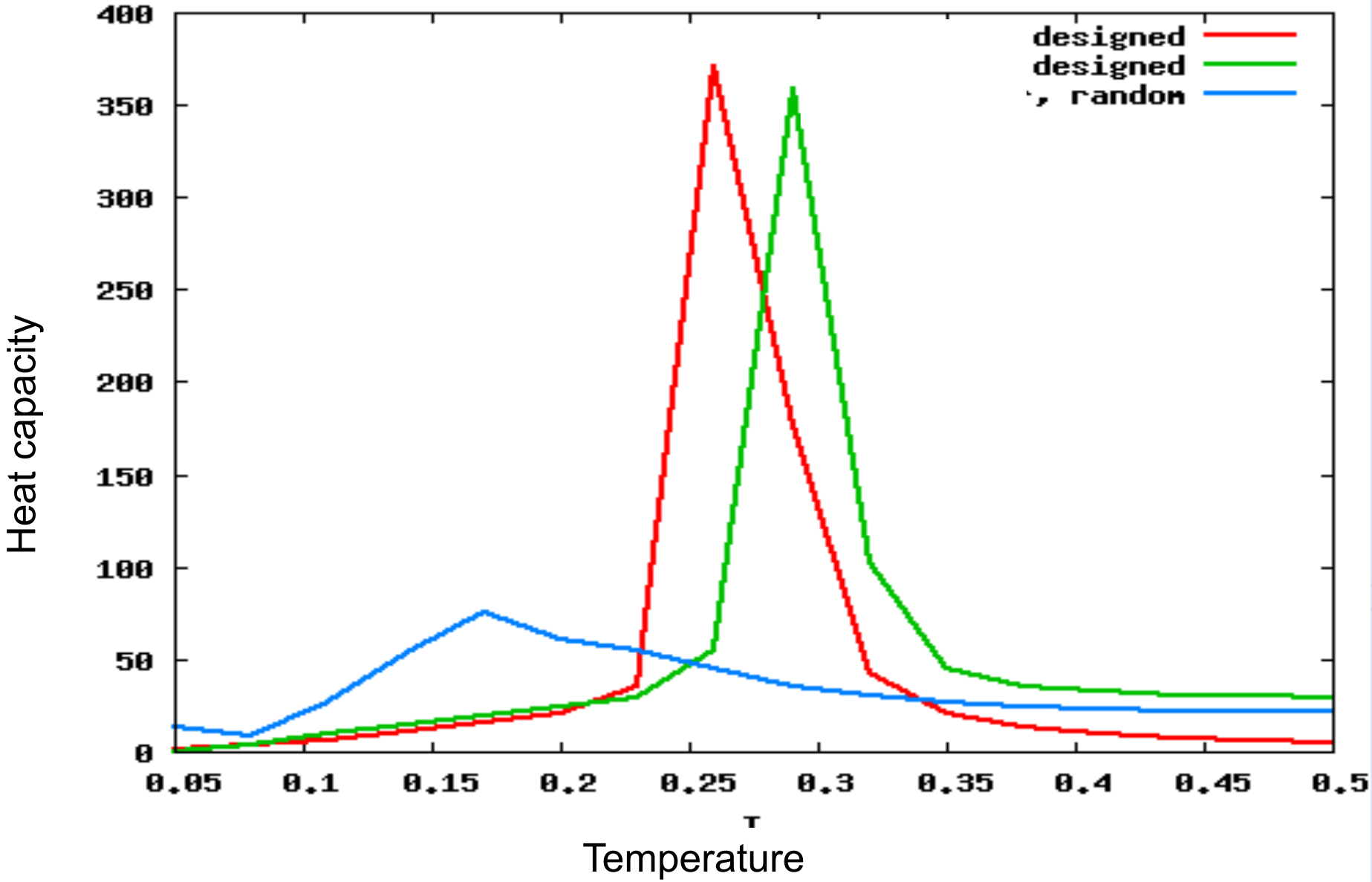


- Proteins fold into a specific native structure, given their sequence
- What would happen if we raise the temperature?

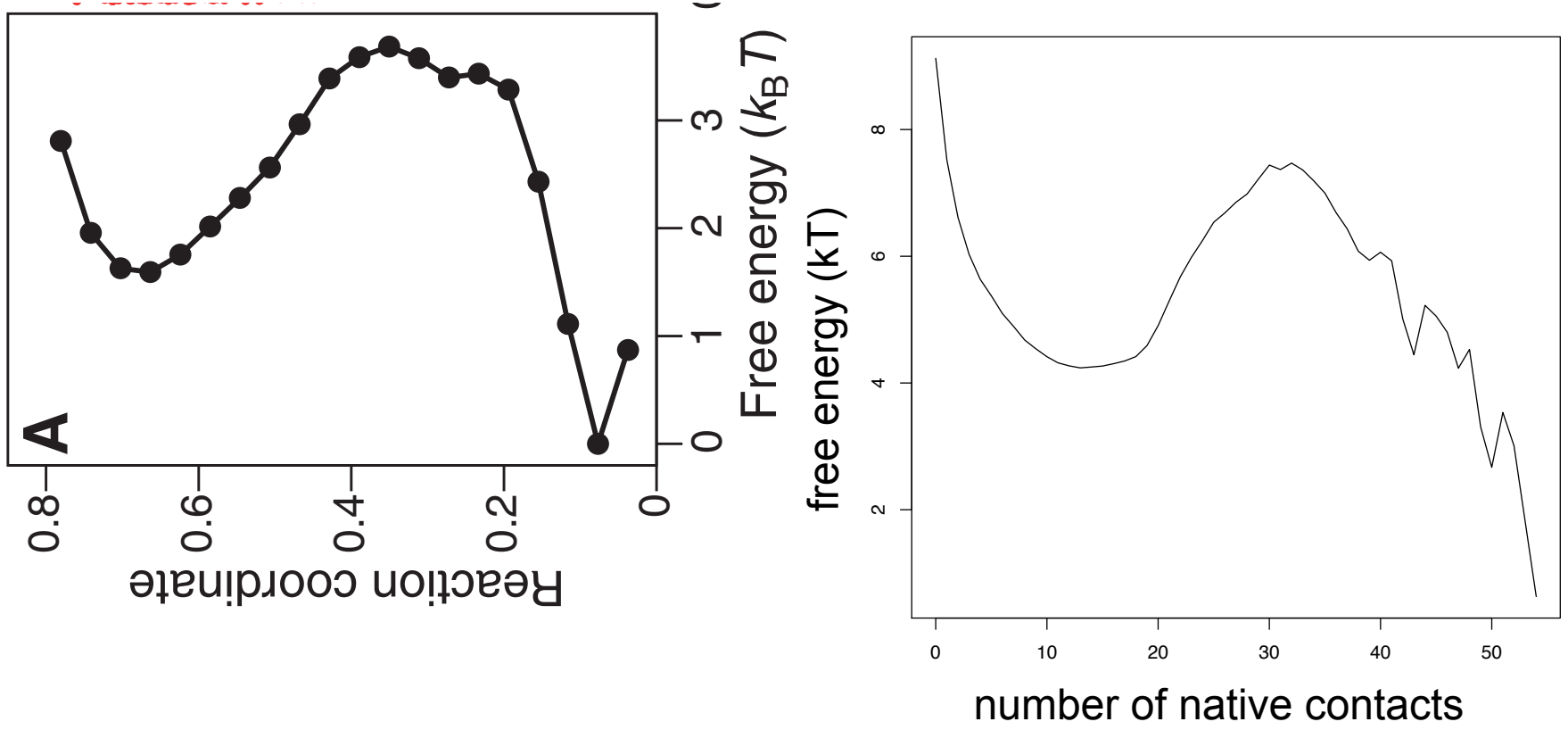
Folding Specificity on the Lattice



Foldable, with high specificity

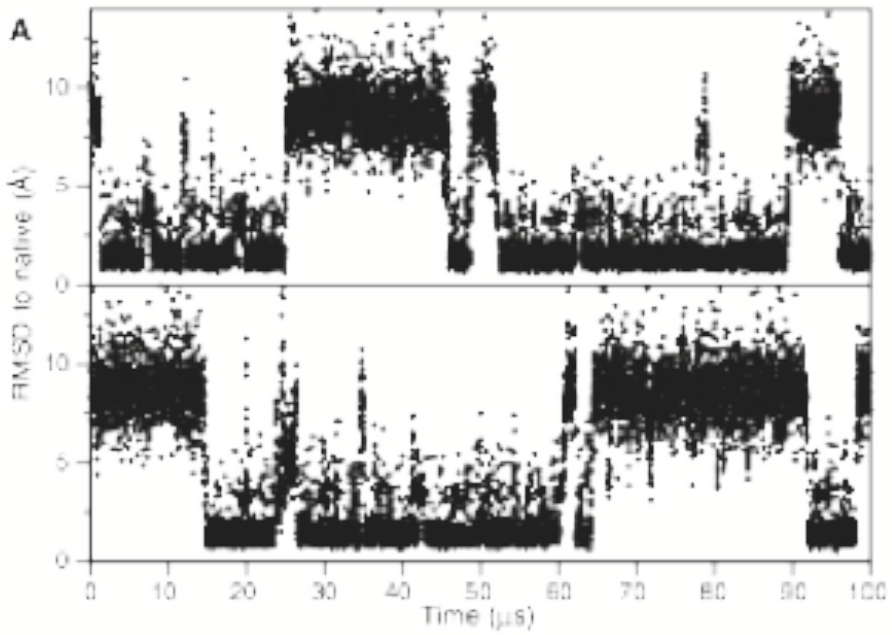


Full atom vs coarse grained folding

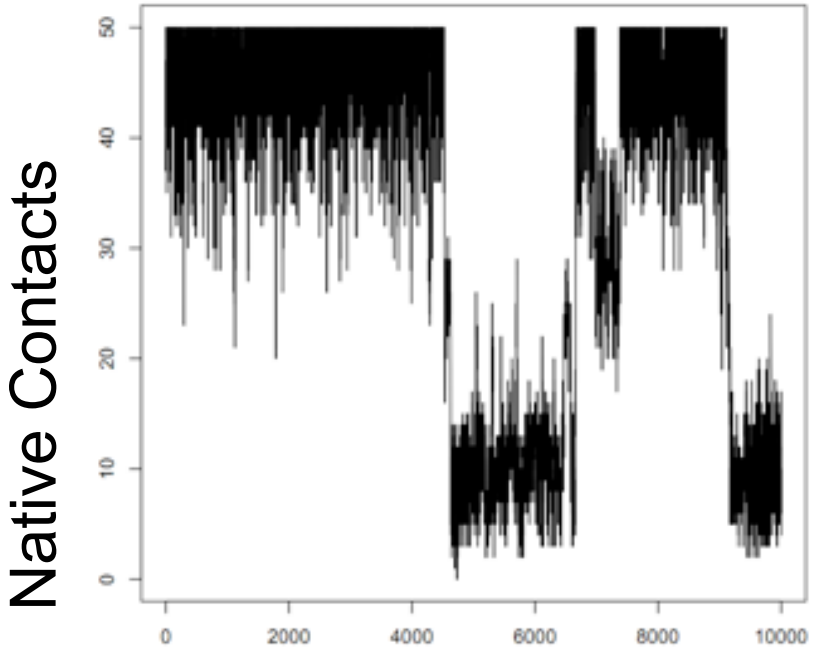


Shaw, D. E., et al. (2010) Science, 330

Full atom vs coarse grained folding



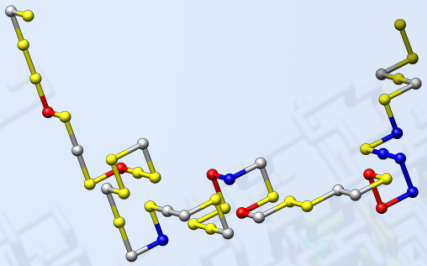
Shaw, D. E., et al. (2010) Science, 330



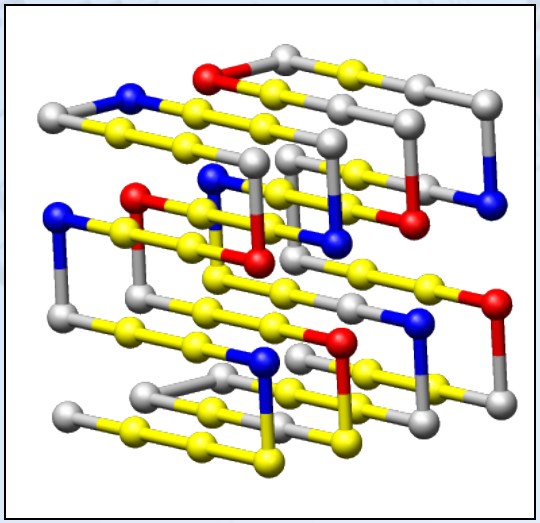
(thanks to Erik van Dijk)

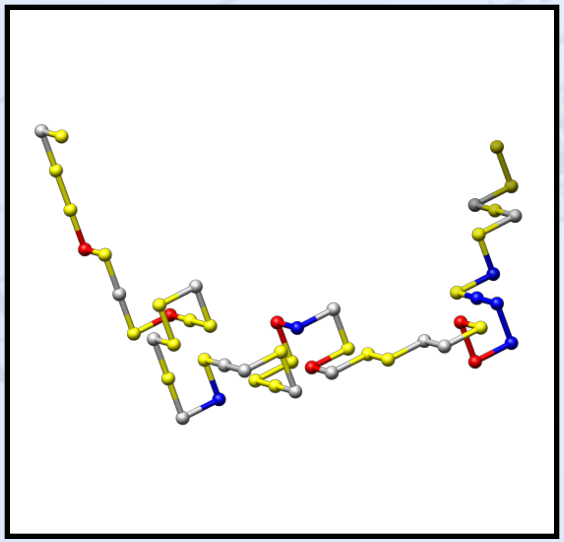
Protein folding Specificity

- Proteins fold into a specific native structure
- Folded structure => energetically favorable
- Unfolded structure => entropically favorable
- At higher temperatures, proteins become unstructured



Cubic Lattice Model





- Cheap & simple
  - Use for right purpose
- Can model:
  - General trends
  - Folding specificity
  - Heat capacity
  - Binding and unbinding

- **Not captured:**
  - **Secondary structure**
  - **Hydrophobic effect (cold denaturation)**
  - Specific proteins

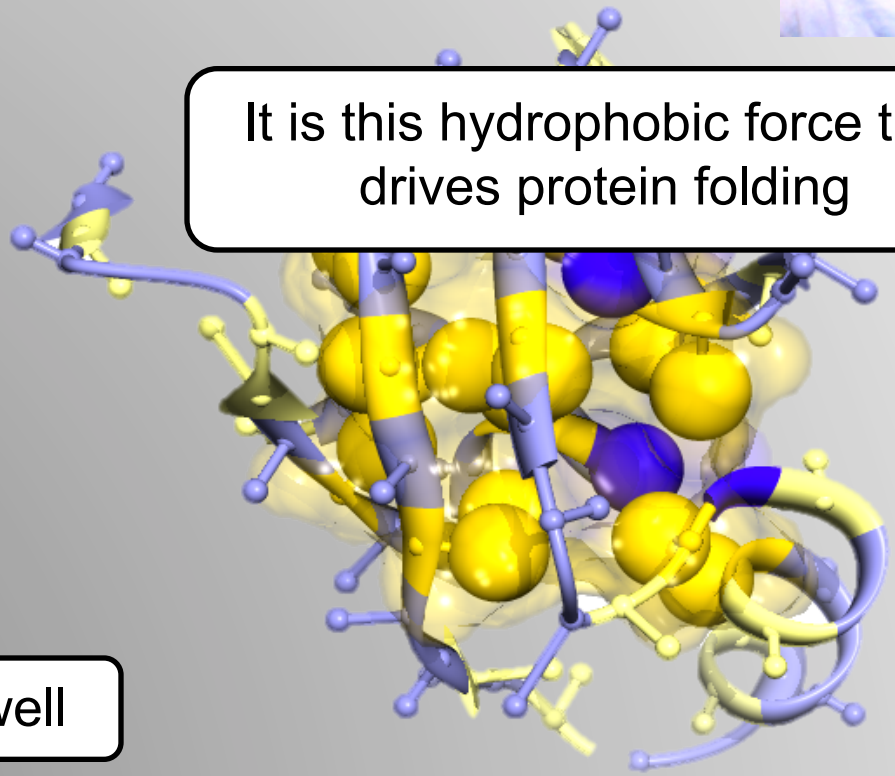
Shakhnovich & Gutin 1993 PNAS 90

Coluzza et al 2003 Phys Rev E 68

Consistent treatment of hydrophobicity in protein lattice models accounts for cold denaturation

Erik van Dijk & Sanne Abeln

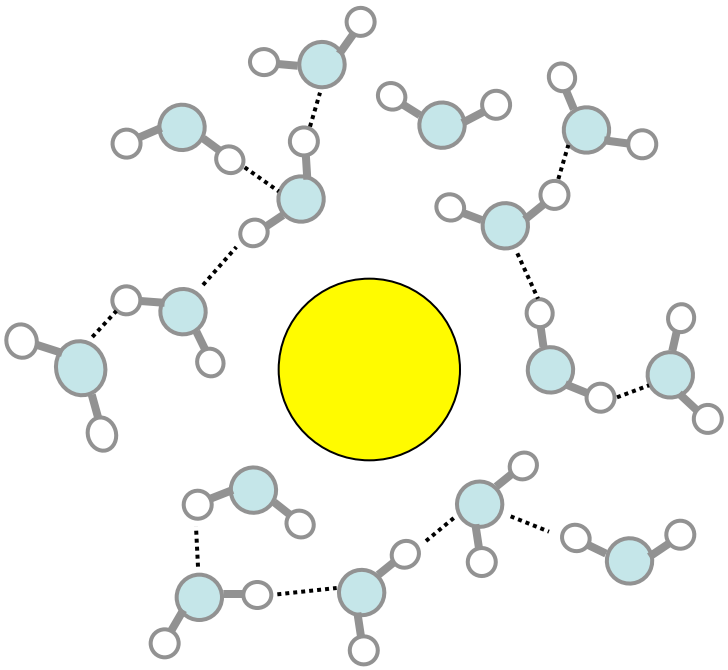
Oil and water do not mix well



It is this hydrophobic force that drives protein folding

PRL 116(7) 2016 & PLOS CB 11(5) 2015

Molecular picture of hydrophobicity?



Hydrophobicity is a an emergent force from collective interactions between water and oily-groups

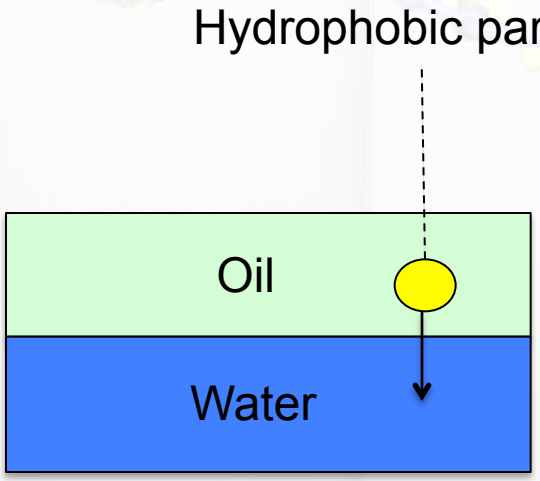
Water likes itself ‘better’

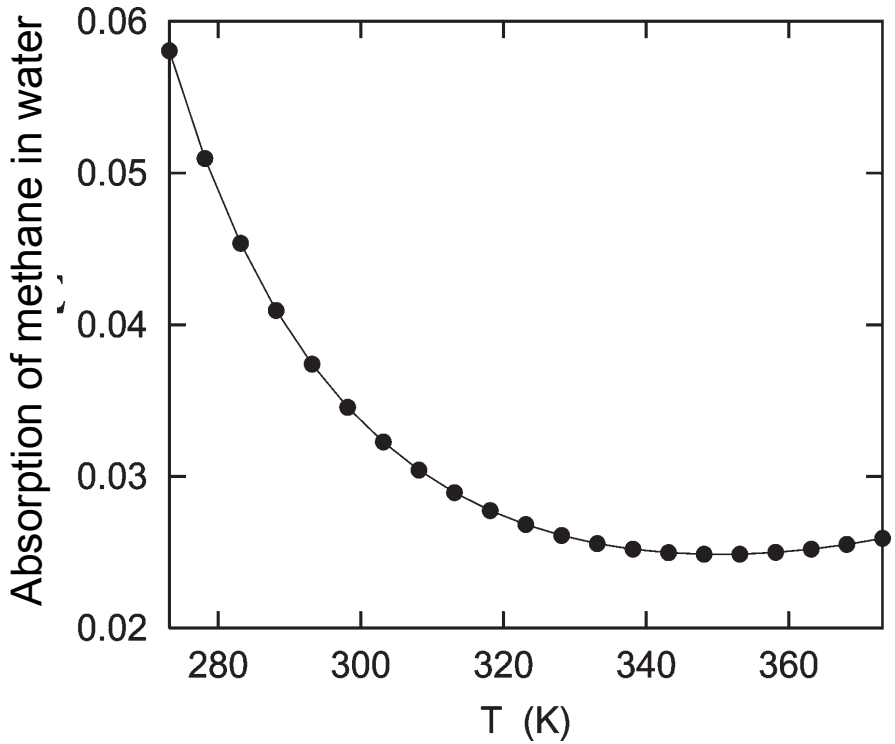
Exact molecular picture still unclear

- Entropic component
- Enthalpic component

Emergent behaviour (entropy & enthalpy)

Hydrophobic force has a maximum around 70 - 80 °C



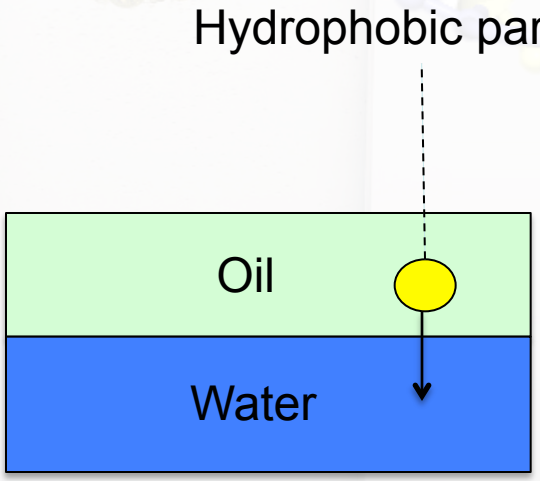


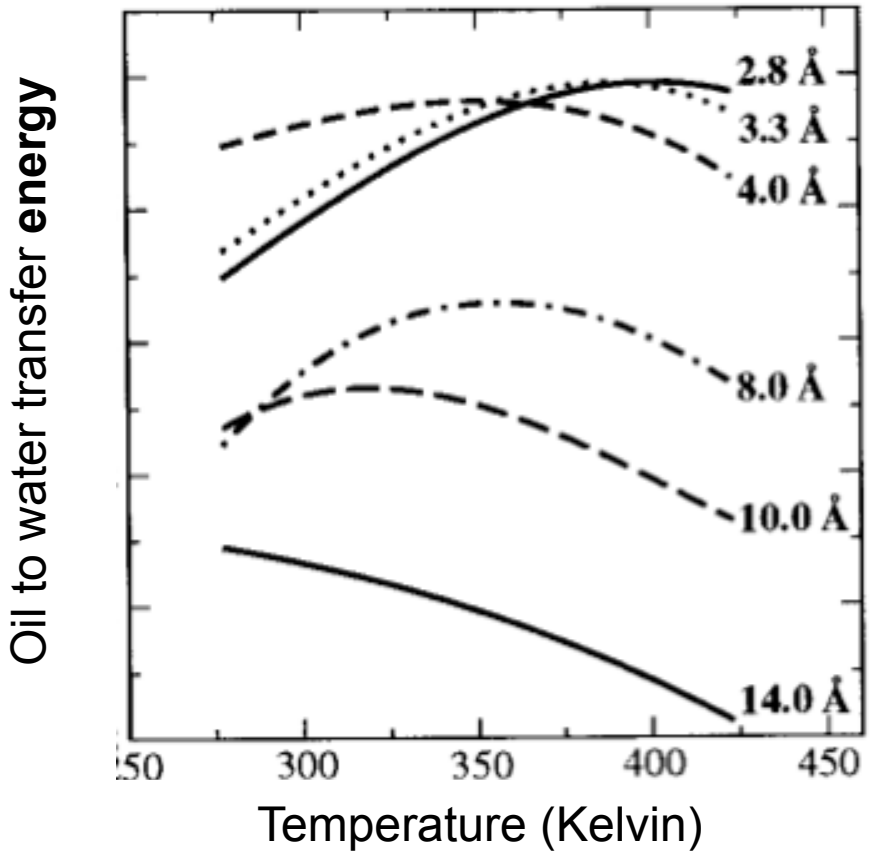
Widom Phys. Chem. Chem. Phys., 2003; Gallagher 2003, JACS; Huang and Chandler PNAS 2000

Emergent behaviour (entropy & enthalpy)

Hydrophobic force has a maximum around 70 - 80 °C

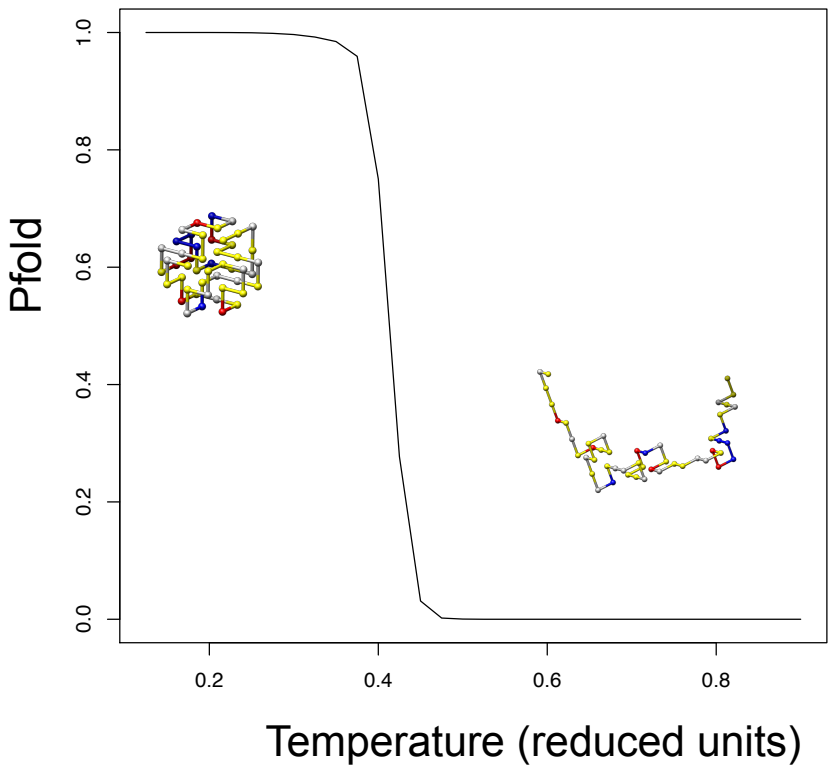
Can this emergent behaviour influence protein folding?

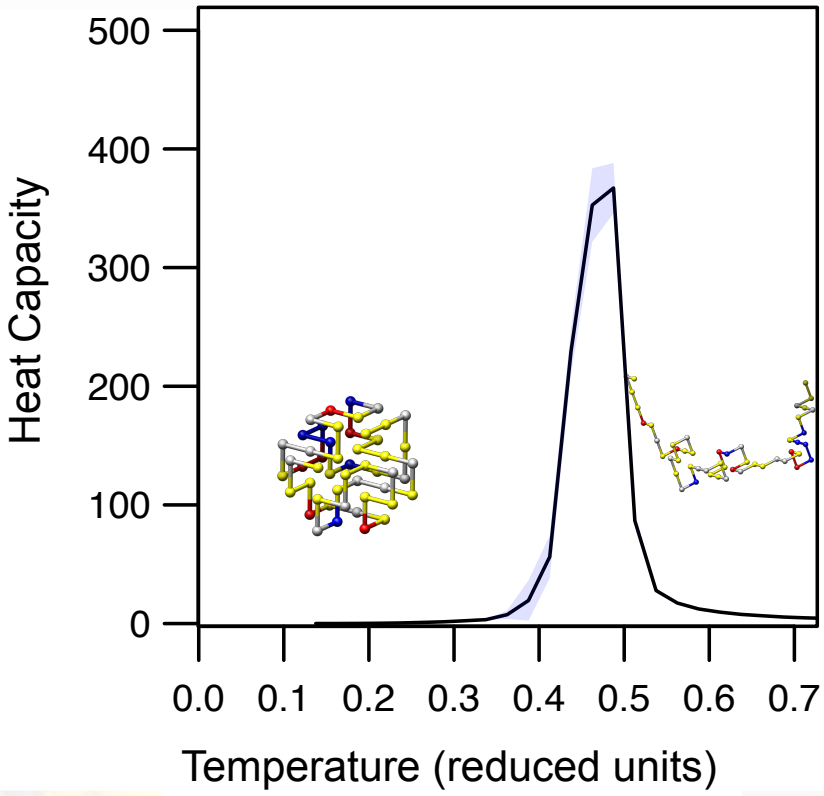




Widom Phys. Chem. Chem. Phys., 2003; Gallagher 2003, JACS; Huang and Chandler PNAS 2000

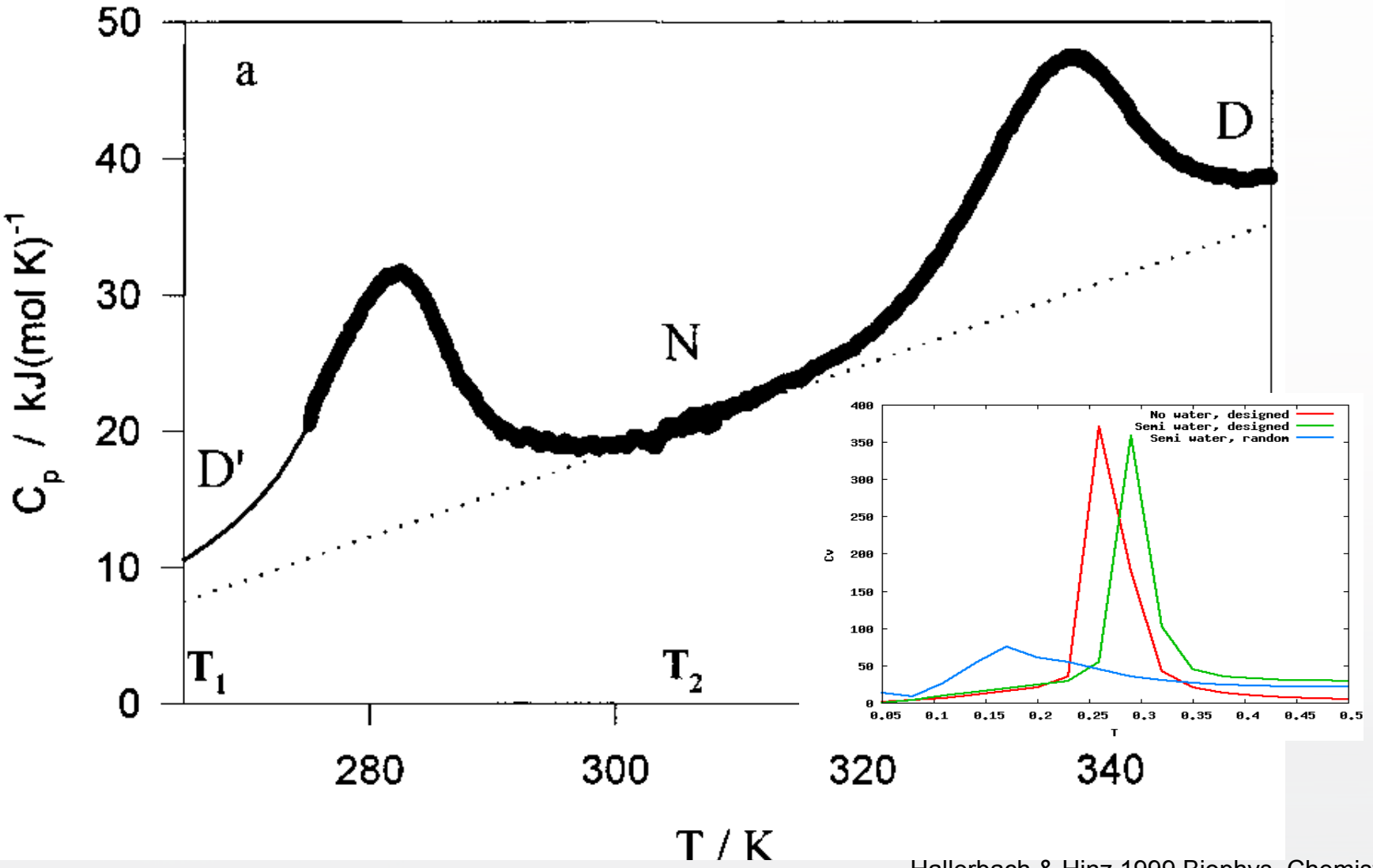
Lattice model for protein folding





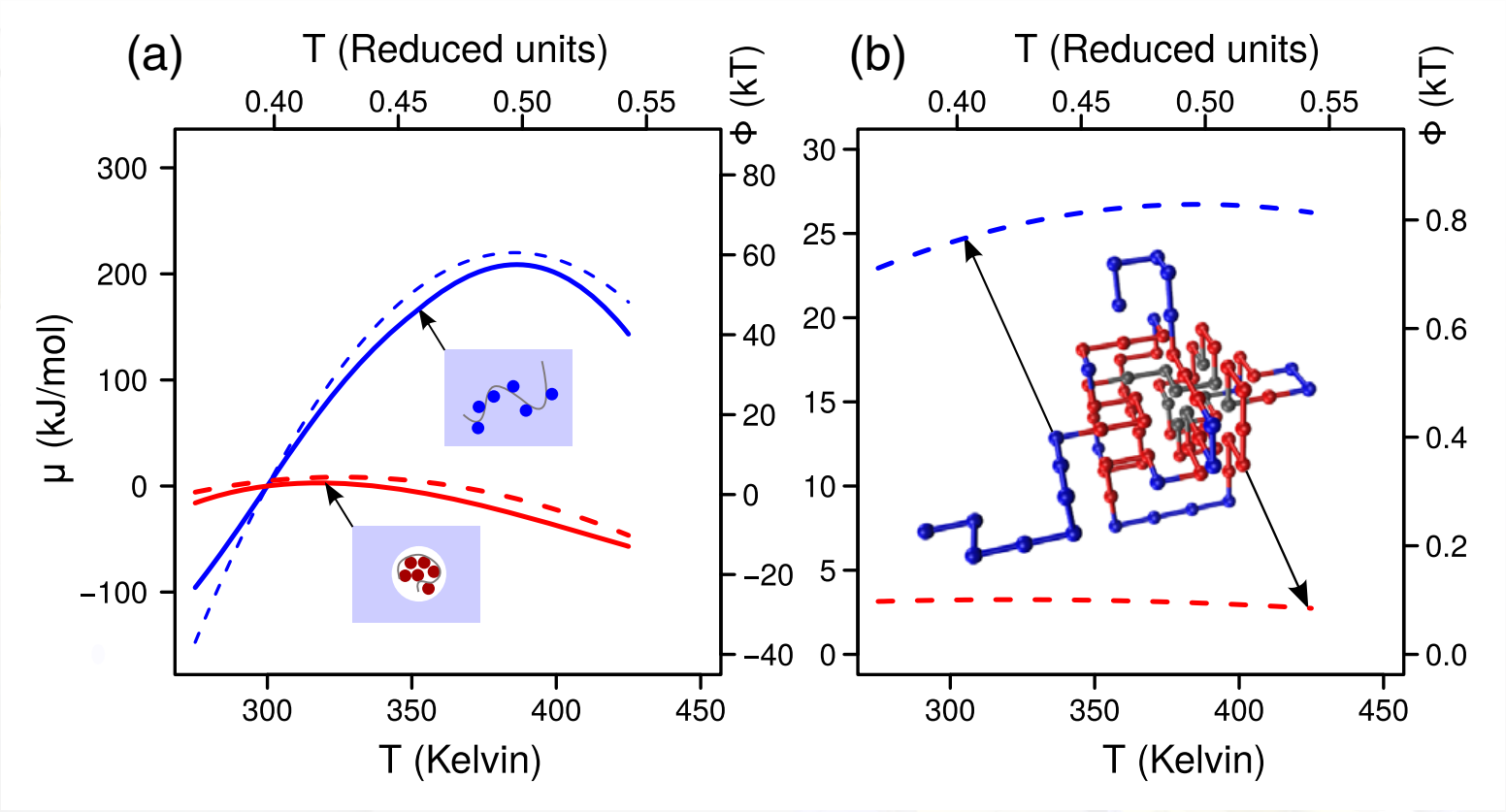
- At higher temperatures, proteins become unstructured
  - (chain) entropy becomes dominant in partition function

Heat capacity of myoglobin



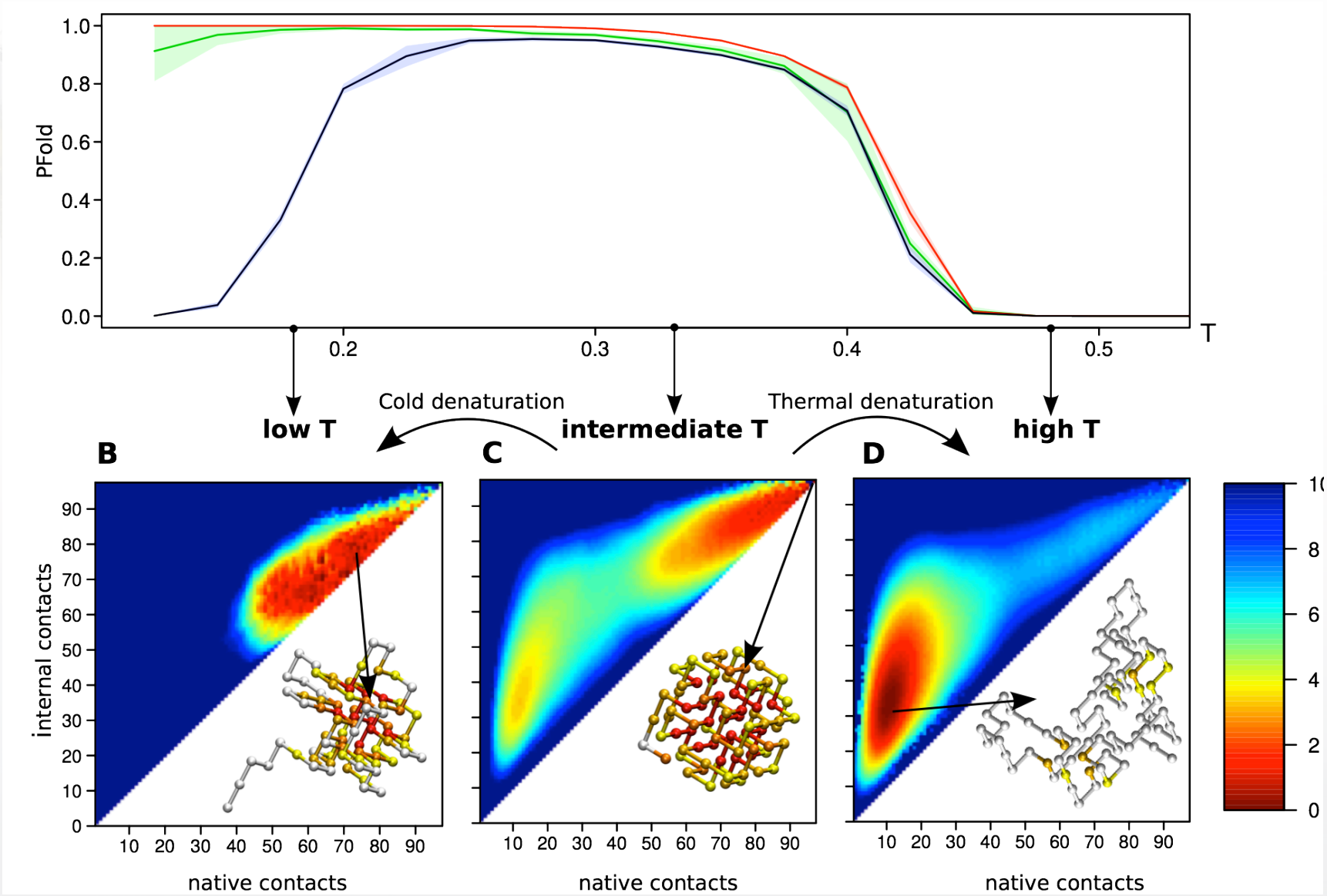
Hallerbach & Hinz 1999 Biophys. Chemistry

Adding the temperature dependence to the model



$$F_{\mathrm{hydr}} = -\alpha N_{\mathrm{h}}(T - T_0)^2$$

Cold denaturation & compact state



Model predicts linearity of heat capacity baseline

In our model, we model the free energy of a water - hydrophobic contact as:

$$F_{\text{hydr}} = -\alpha N_{\text{h}}(T - T_0)^2 \tag{1}$$

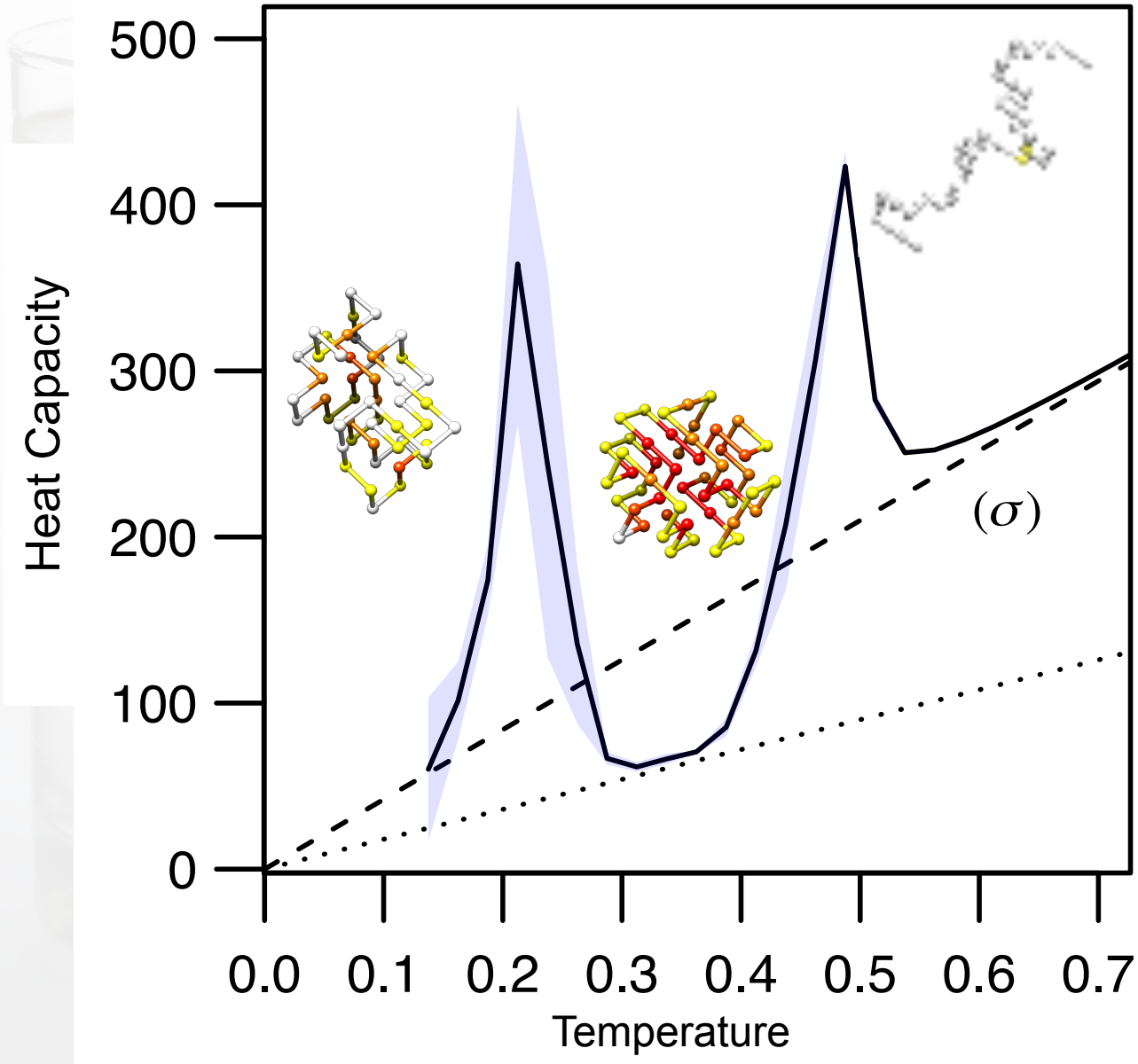
Multiplying both sides by β, taking derivative with respect to β and using that $\frac{d\beta F}{d\beta} = \langle E \rangle$ we get:

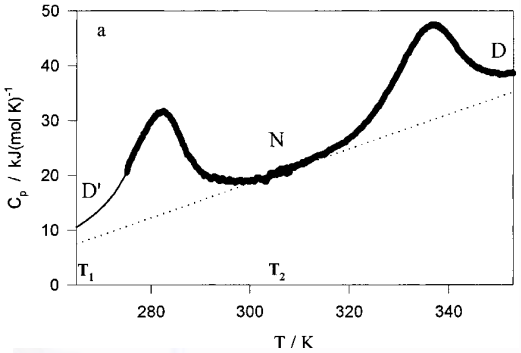
$$\langle E_{\text{hydr}} \rangle = -\alpha N_h(T_0^2 - T^2) \tag{2}$$

This yields a simple rule for theslope of heat capacity, under the assumption no phase transition, such as folding, take place.

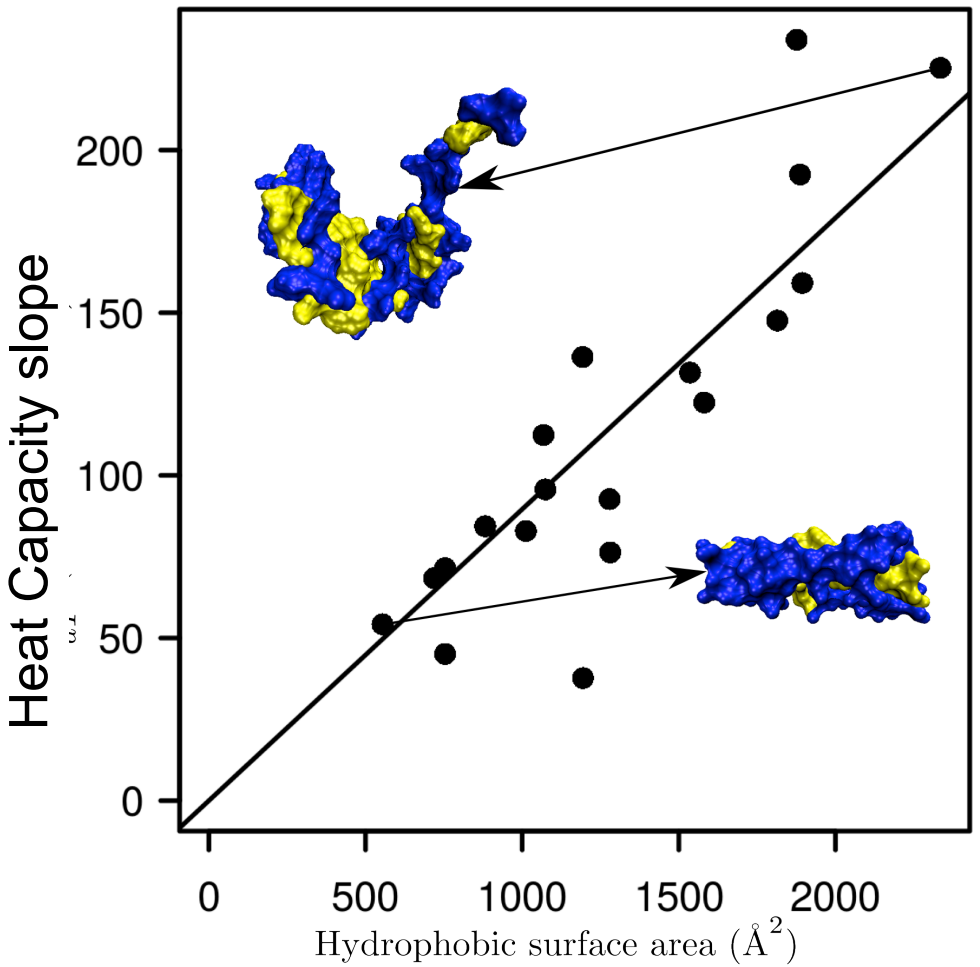
$$C_V(T) = \frac{d\langle E \rangle}{dT} = 2\alpha N_h T \tag{3}$$

Heat capacity native-denatured





Cv slope for real proteins

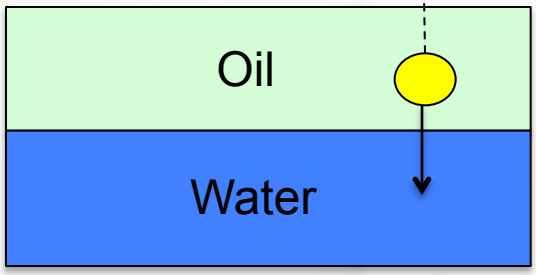


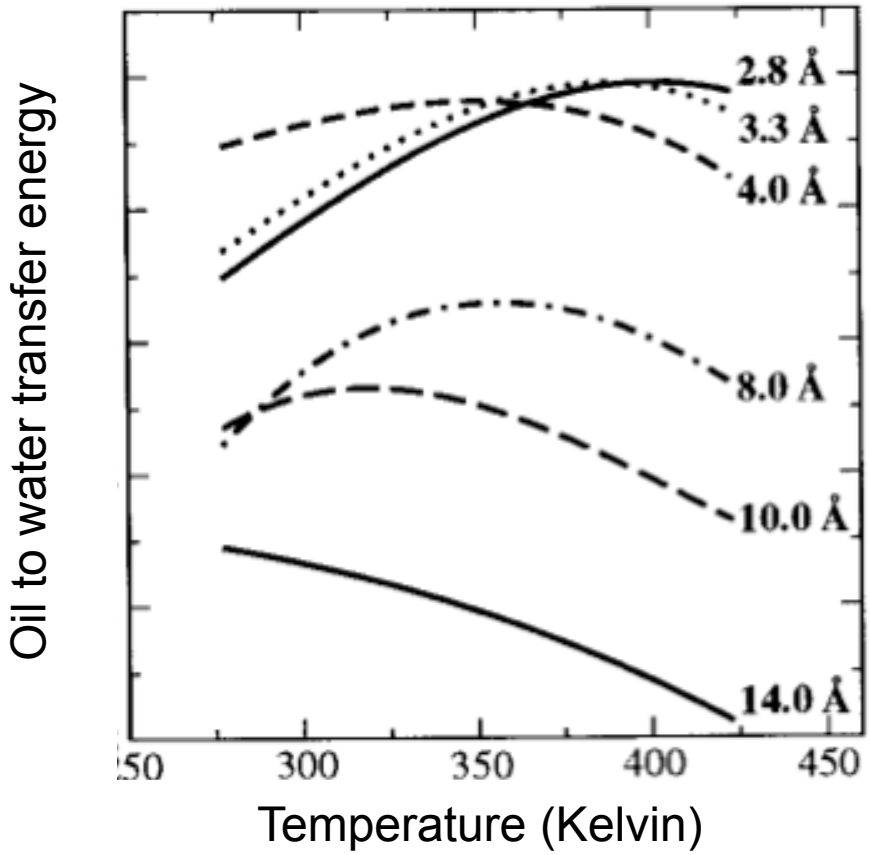
$$C_V(T) = \frac{d\langle E \rangle}{dT} = 2\alpha N_h T$$

Emergent behaviour (entropy & enthalpy)

Hydrophobic force has a maximum around 70 - 80 °C

Can we measure this emergent behaviour for amino acids in protein structures?



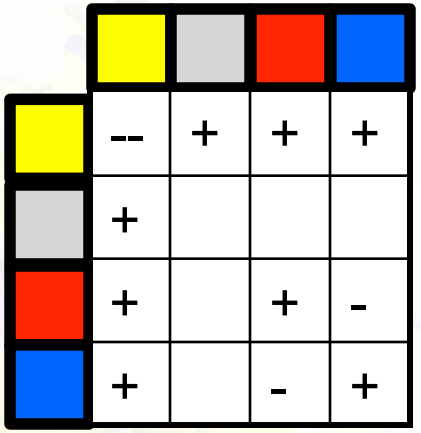


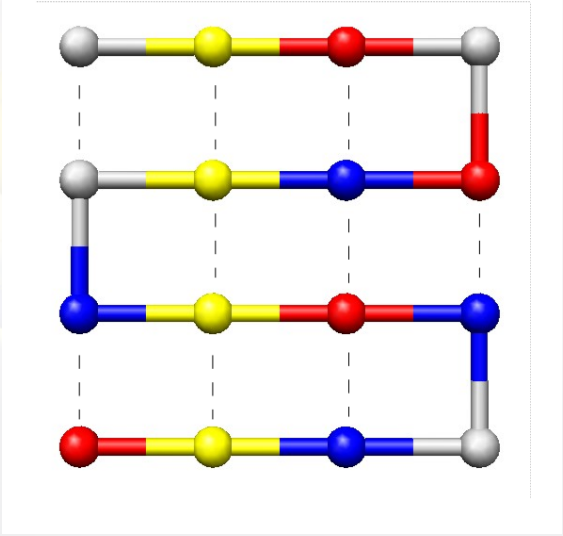
Widom Phys. Chem. Chem. Phys., 2003; Gallagher 2003, JACS; Huang and Chandler PNAS 2000

“Knowledge Based” Amino Acid Pair Potentials

$$\epsilon_{i,j} = kT \ln \left(\frac{c_{i,j}}{\omega_{i,j}} \right)$$

$$\omega_{i,j} = \frac{n_i q_i n_j q_j}{\sum_k q_k n_k}$$



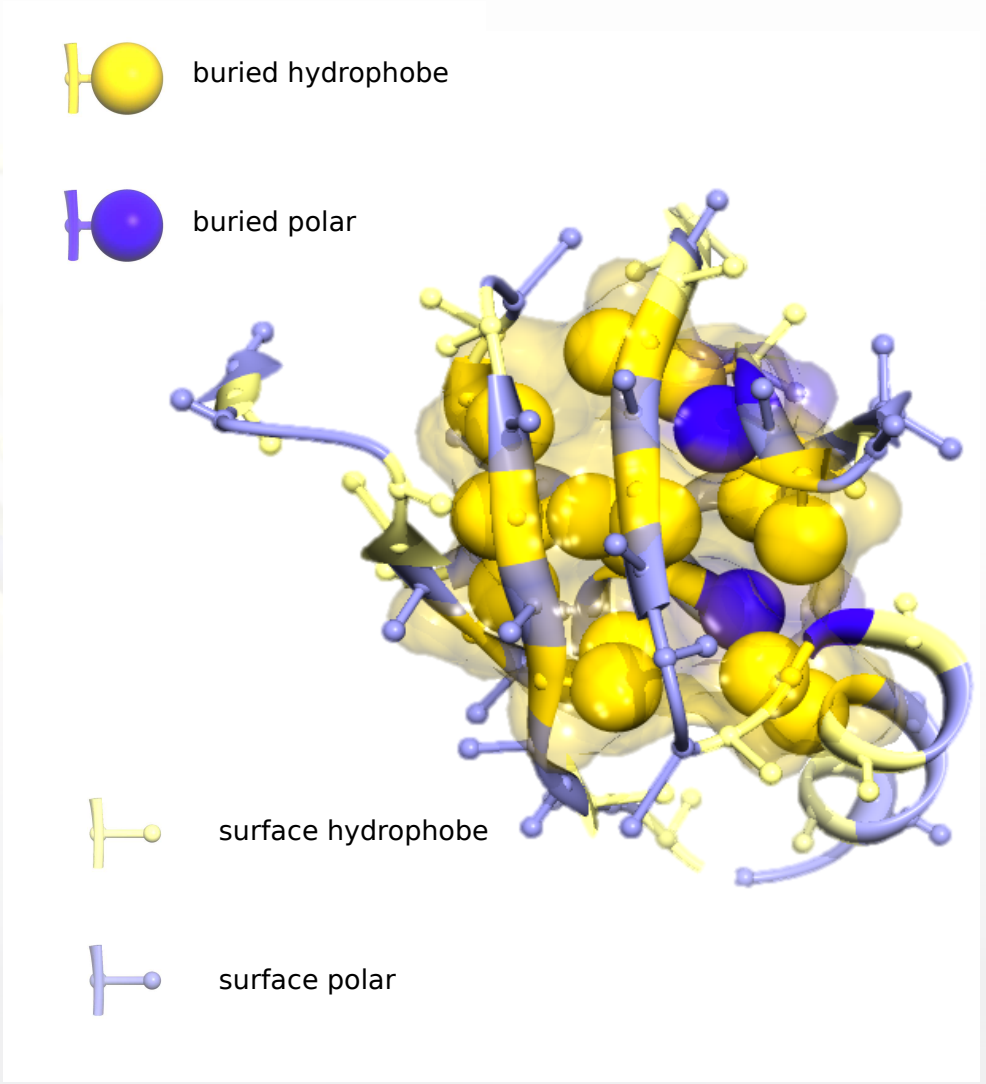


Calculating hydrophobicities for amino acids

- Mine set of protein structures resolved with NMR at different temperatures
- Consider buried versus surface residues
  - Simplest approach: propensity for being buried

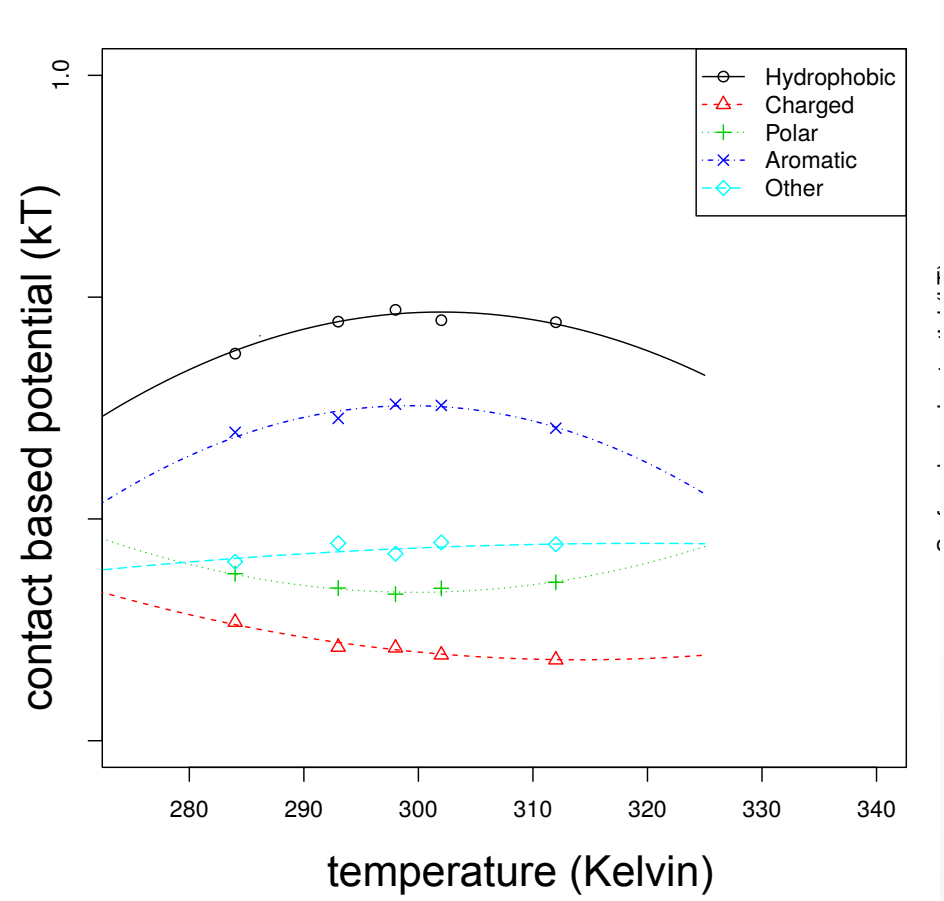
$$P^*_{a,b} = \frac{p^*_{a,b}}{p^*_{a,nb}} = \frac{N_{a,b}/N_{a,nb}}{N_b/N_{nb}}$$

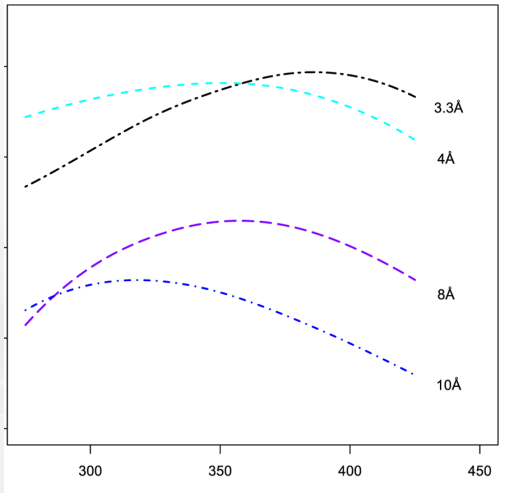
  - We use three different approaches to calculate approximate free energy terms



Temperature dependence of amino acids

- We calculate the propensities for each type of amino acid at different temperatures
- We see a clear temperature dependence for the hydrophobic amino acids
- This nicely matches theoretical predictions





van Dijk et al. PLOS Compl Biol, 11(5) 2015

Is this temperature dependence significant?

- To test statistical significance we use a resampling procedure (shuffling temperatures)

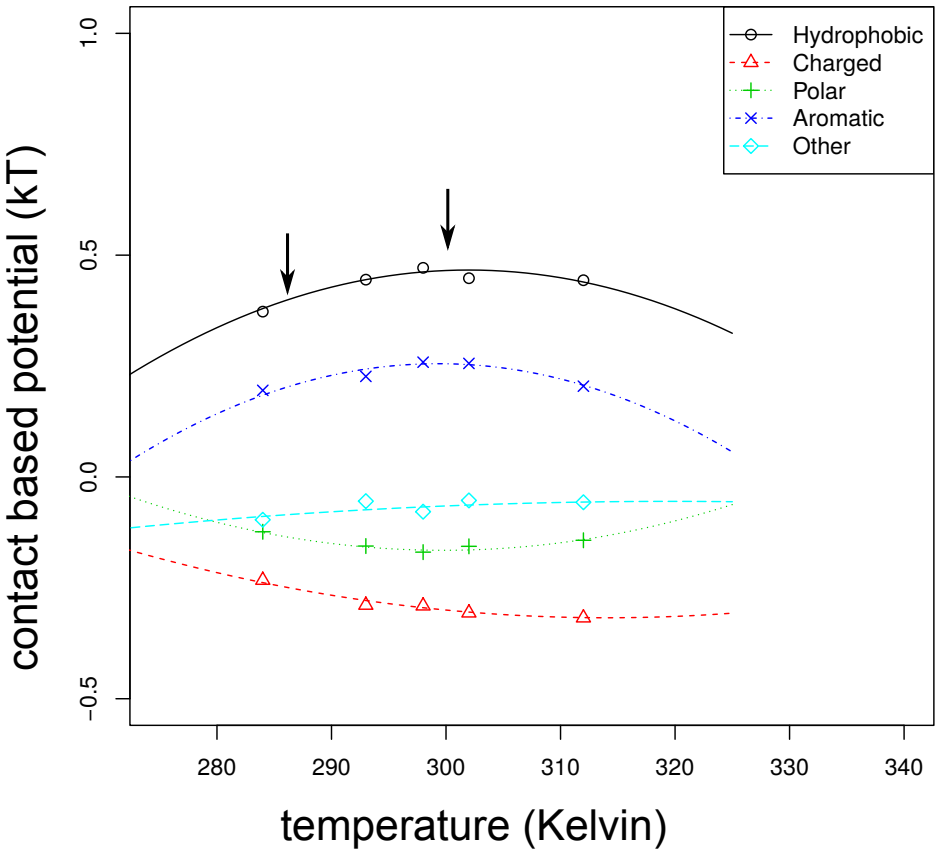
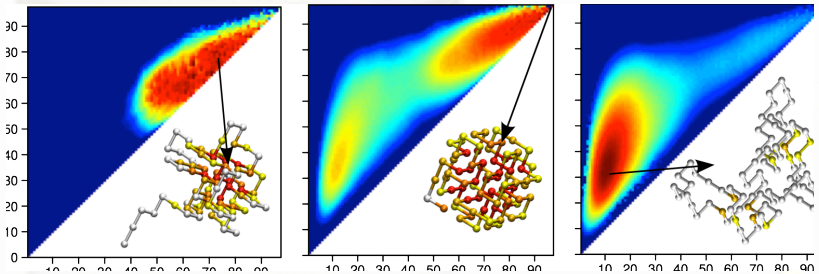


Table 3. Significance of hydrophobic temperature dependence pooled.

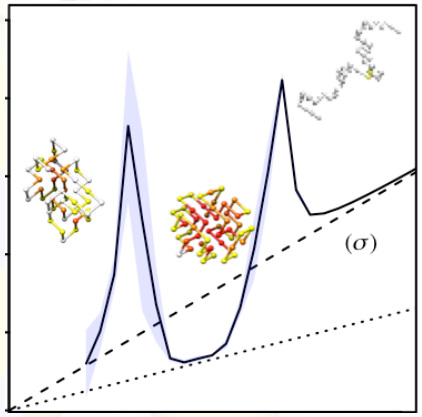
amino acid class	p-value contacts	p-value surface	ΔΔ*G* contacts	ΔΔ*G* surface
hydrophobic	< 0.01	< 0.01	0.10	0.32
polar	< 0.01	0.23	-0.05	0.13
charged	< 0.01	0.80	-0.06	-0.04
aromatic	0.04	< 0.01	0.06	0.32
other	0.32	< 0.01	0.02	0.41

Impact of understanding hydrophobicity

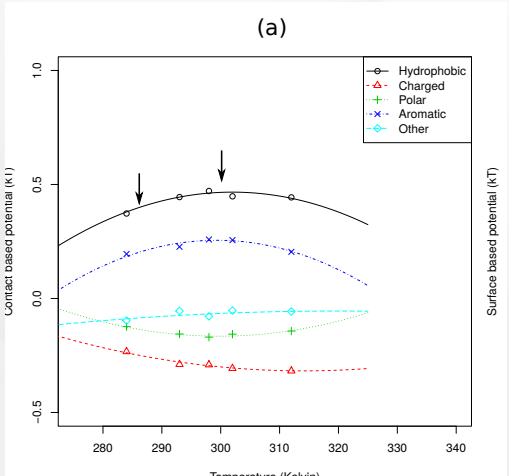
We can explain cold denaturation



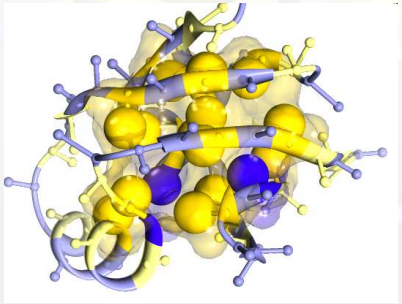
We can understand heat capacity curves

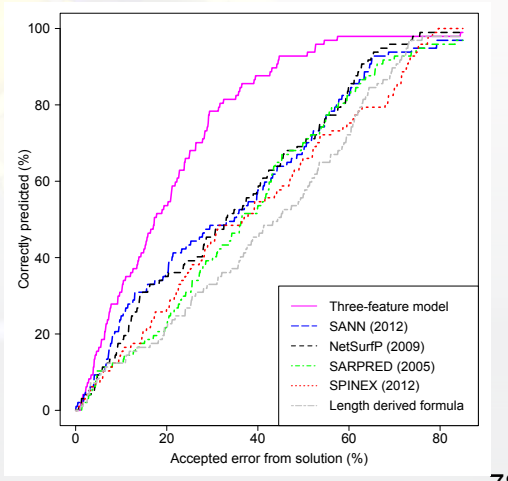


Extract hydrophobic temperature dependence form structures



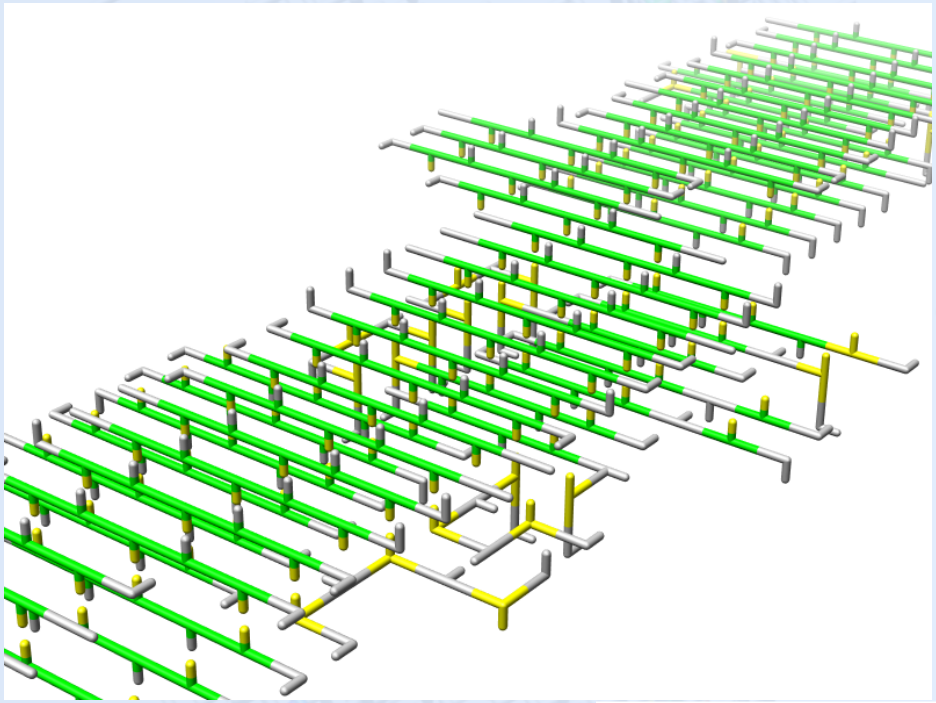
Predict total hydrophobic surface area





Model can reproduce formation of fibres

Abeln, S., Vendruscolo, M., Dobson, C. M., & Frenkel, D. (2014). A Simple Lattice Model That Captures Protein Folding, Aggregation and Amyloid Formation. PLoS ONE, 9(1), e85185

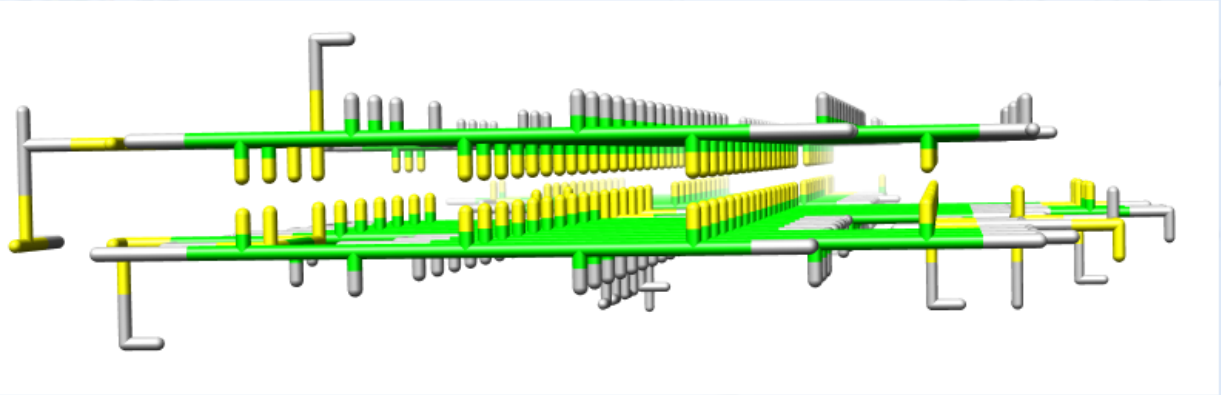


- Fibres
  - Formation depends on sequence properties
  - Hydrophobic inner layers
  - Fast simulation

hydrophobic

polar (hydrophilic)

beta-strand



Vacancy for PhD student

- 4 years
- Protein folding & amyloid formation – coarse-grained protein models
- Close connection to experimental work on force unfolding and amyloid formation in collaboration with Gijs Wuite en Alexander Buell
- Contact: s.abeln@vu.nl

References

Abeln, S., & Frenkel, D. (2008). Disordered flanks prevent peptide aggregation. *PLoS Comput. Biol.*, *4*(12), e1000241. doi:10.1371/journal.pcbi.1000241

Abeln, S., & Frenkel, D. (2011). Accounting for protein-solvent contacts facilitates design of nonaggregating lattice proteins. *Biophys. J.*, *100*(3), 693–700. doi:10.1016/j.bpj.2010.11.088

Abeln, S., Vendruscolo, M., Dobson, C. M., & Frenkel, D. (2014). A Simple Lattice Model That Captures Protein Folding, Aggregation and Amyloid Formation. *PLoS ONE*, *9*(1), e85185. doi: 10.1371/journal.pone.0085185

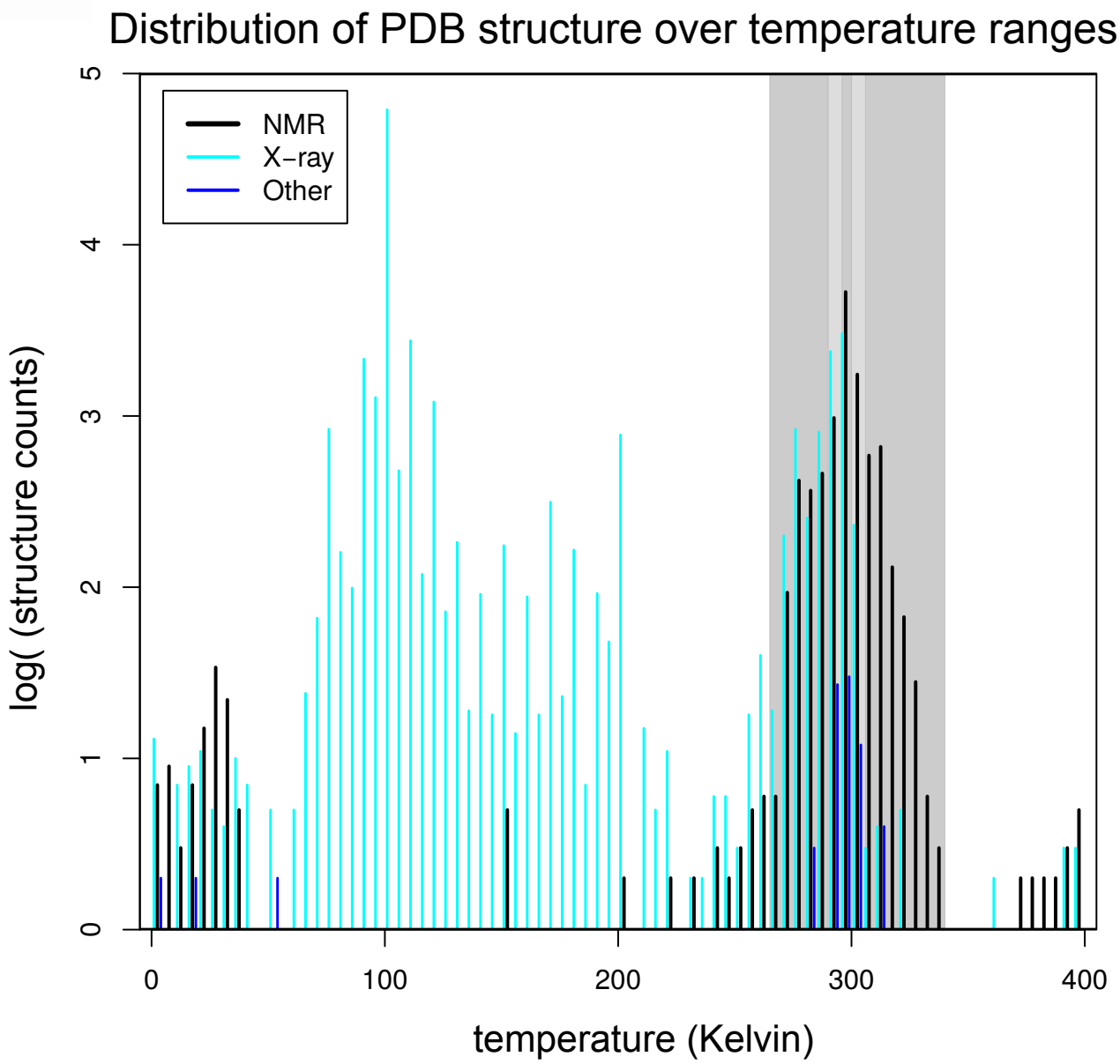
Ni, R., Abeln, S., Schor, M., Cohen Stuart, M. A., & Bolhuis, P. G. (2013). Interplay between Folding and Assembly of Fibril-Forming Polypeptides. *Physical Review Letters*, *111*(5), 058101. doi: 10.1103/PhysRevLett.111.058101

Ni, R., Kleijn, J. M., Abeln, S., Cohen Stuart, M. a., & Bolhuis, P. G. (2015). Competition between surface adsorption and folding of fibril-forming polypeptides. *Physical Review E*, *91*, 1–5. doi: 10.1103/PhysRevE.91.022711

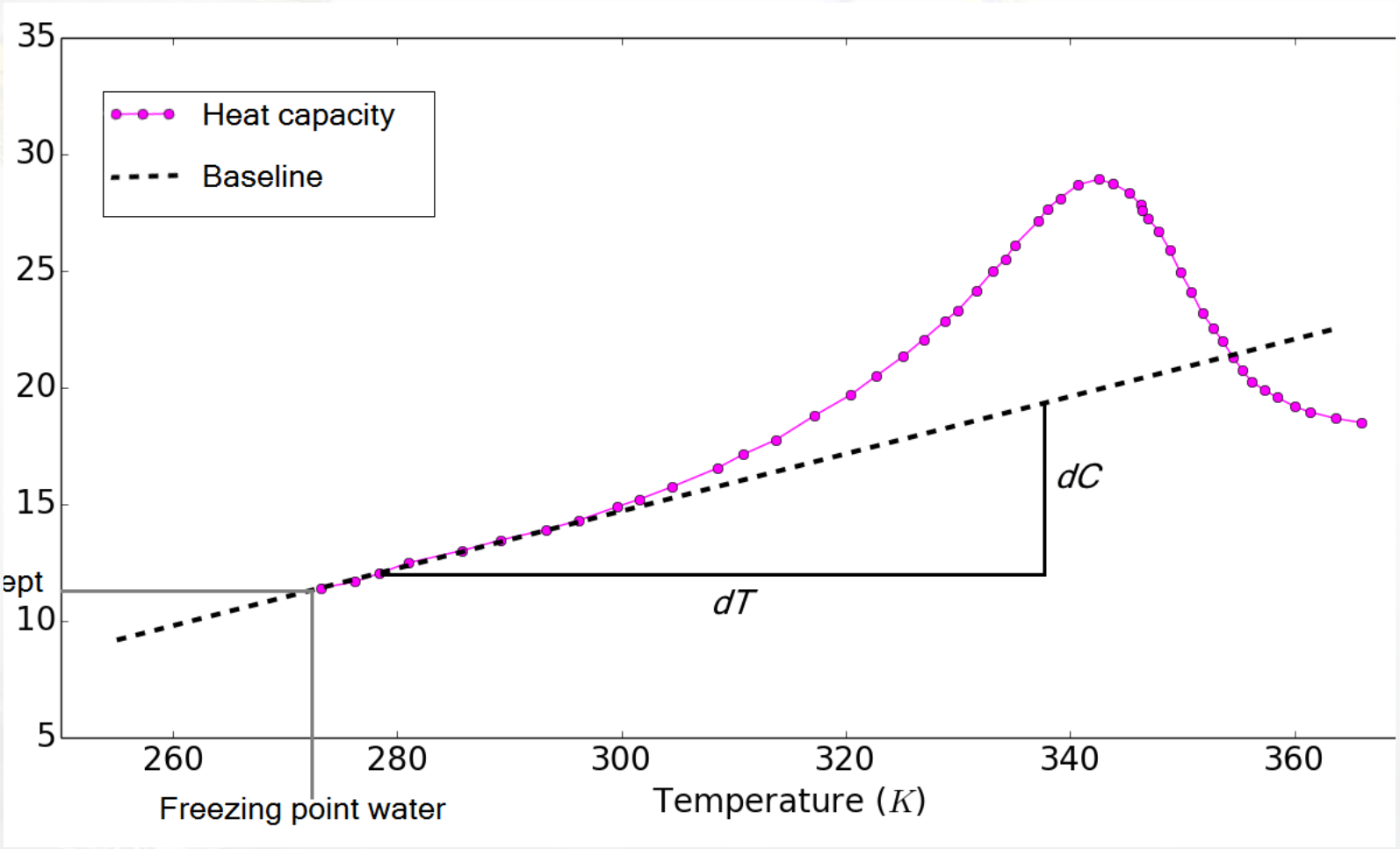
van Dijk, E., Hoogeveen, A., & Abeln, S. (2015). The Hydrophobic Temperature Dependence of Amino Acids Directly Calculated from Protein Structures. *PLOS Computational Biology*, *11*(5), e1004277. doi:10.1371/journal.pcbi.1004277

van Dijk, E.; Varilly, P.; Knowles, T.; Frenkel, D.; Abeln, S. Consistent treatment of hydrophobicity in protein lattice models accounts for cold denaturation. ArXiv e-prints 2015, [arXiv:cond-mat.soft/ 1511.06590] – accepted PRL

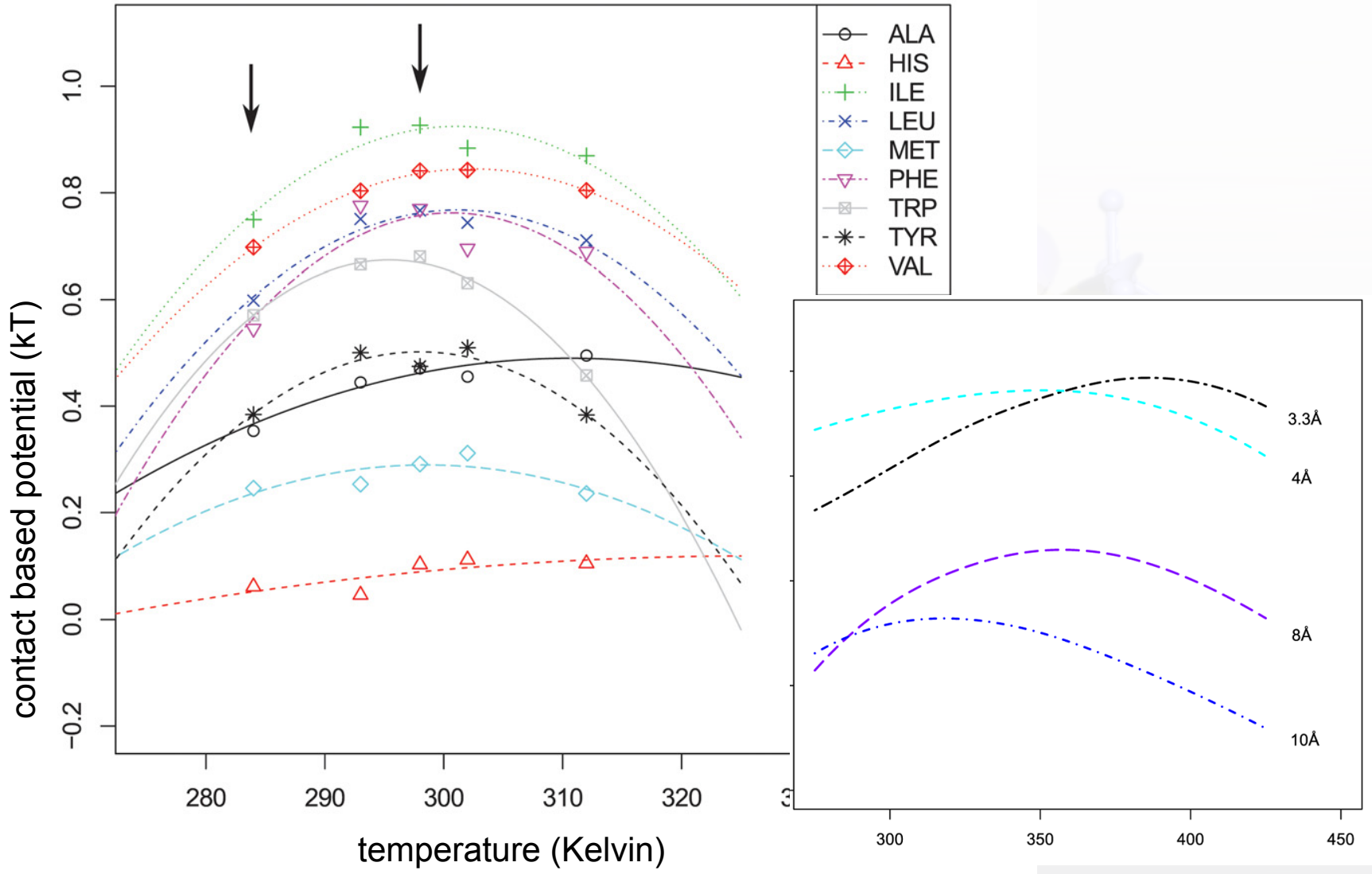
Consider NMR structures at different temperatures



Heat capacity: linear slope



Hydrophobicity of amino acids



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