Design and Stability of Proteins and Biopolymers in explicit water: A Coarse-Grain Approach

Valentino Bianco, Ivan Coluzza

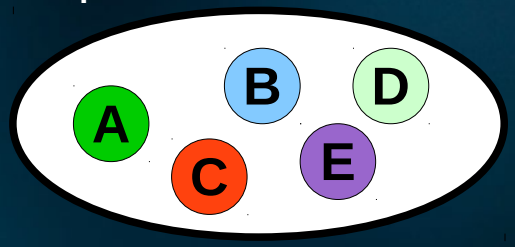
universität wien

Relevance of Water in Design and Folding of bio-polymers

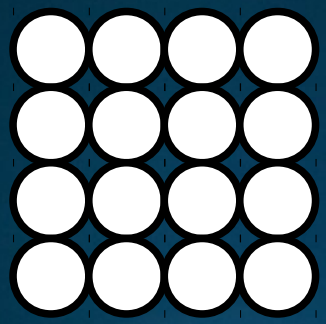
Design

Designing of a protein consists in sampling all the possible sequences,
on top of a target structure and according to a given alphabet of “letters” (amino-acids),
such that we maximize the probability to fold into the target structure

Alphabet of residues



Target structure



Designed sequences

Folding

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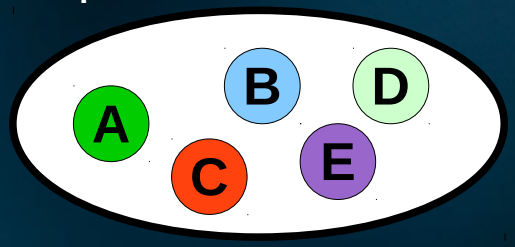
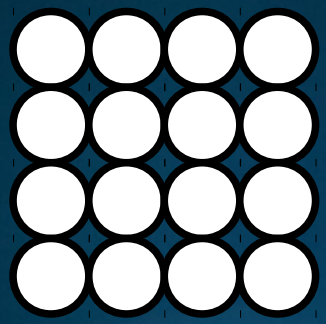


Target structure



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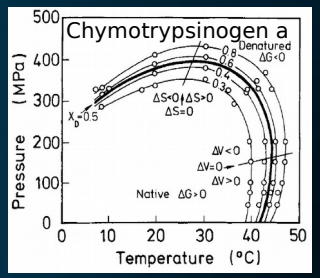
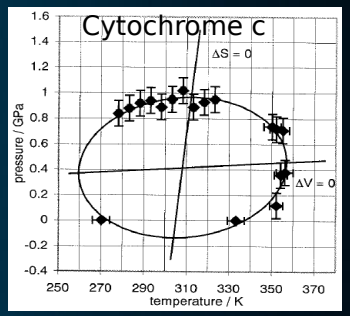
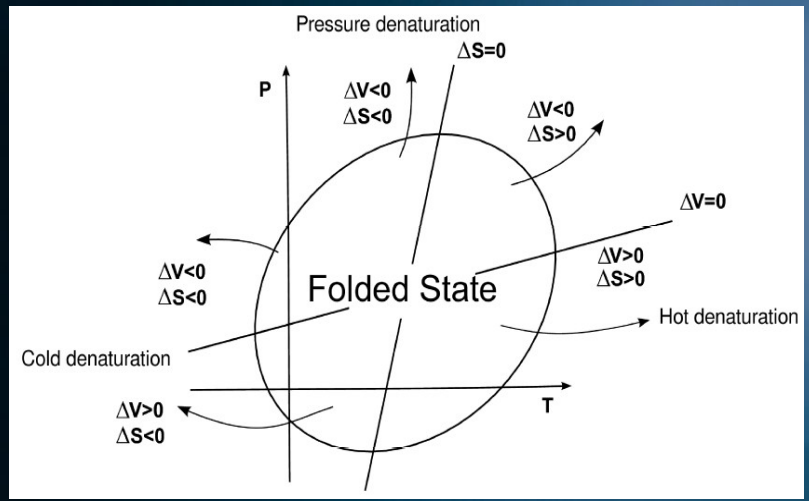




Stability region of the designed proteins



Folding

Hawley, Biochem (1975) ... Gross et al, Eur J Biochem (1994) ... Lesch et al, Biophys J (2002) ...

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Design

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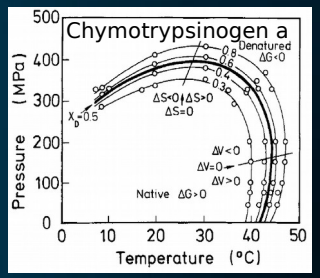
Alphab

A

Can we account for the hydration water properties?
How water influence the stability of the designed sequences?



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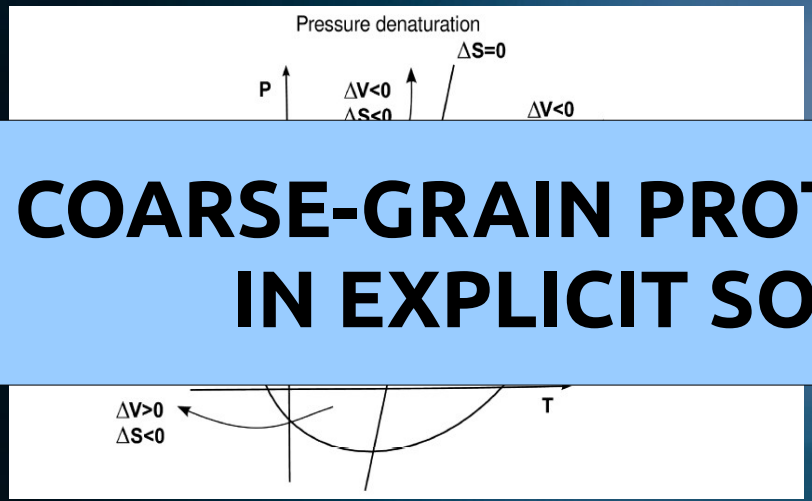
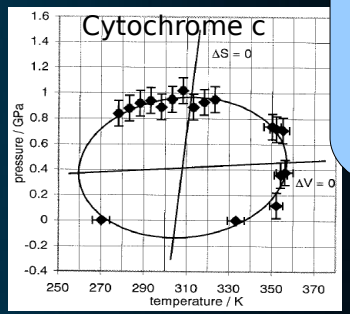
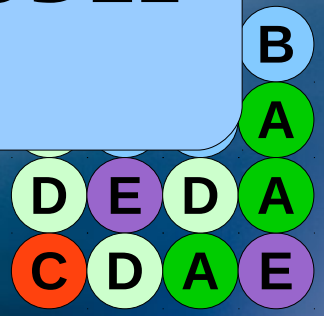




COARSE-GRAIN PROTEIN MODEL IN EXPLICIT SOLVENT

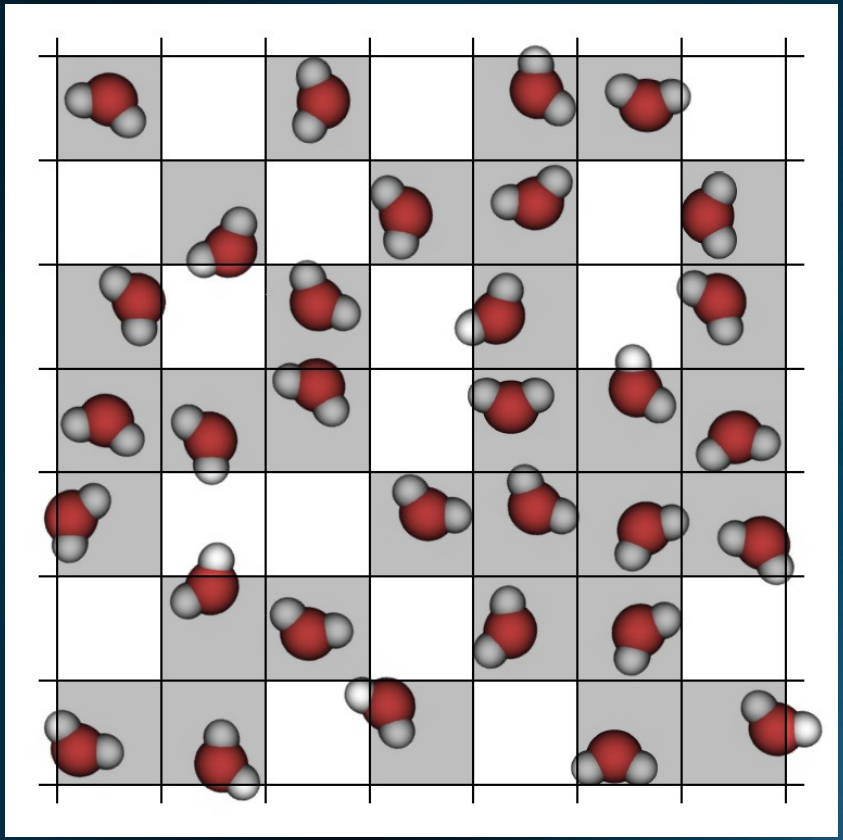
Folding



Hawley, Biochem (1975) ... Gross et al, Eur J Biochem (1994) ... Lesch et al, Biophys J (2002) ...

MANY-BODY MODEL FOR WATER

We coarse grain the spatial structure dividing the available volume in cells of the molecular size



Stokely et al, PNAS, 2010
Strekalova et al, PRL, 2011
Mazza et al, PNAS, 2011
Bianco et al, J Biol Phys, 2012
Bianco et al, Sci Rep, 2014
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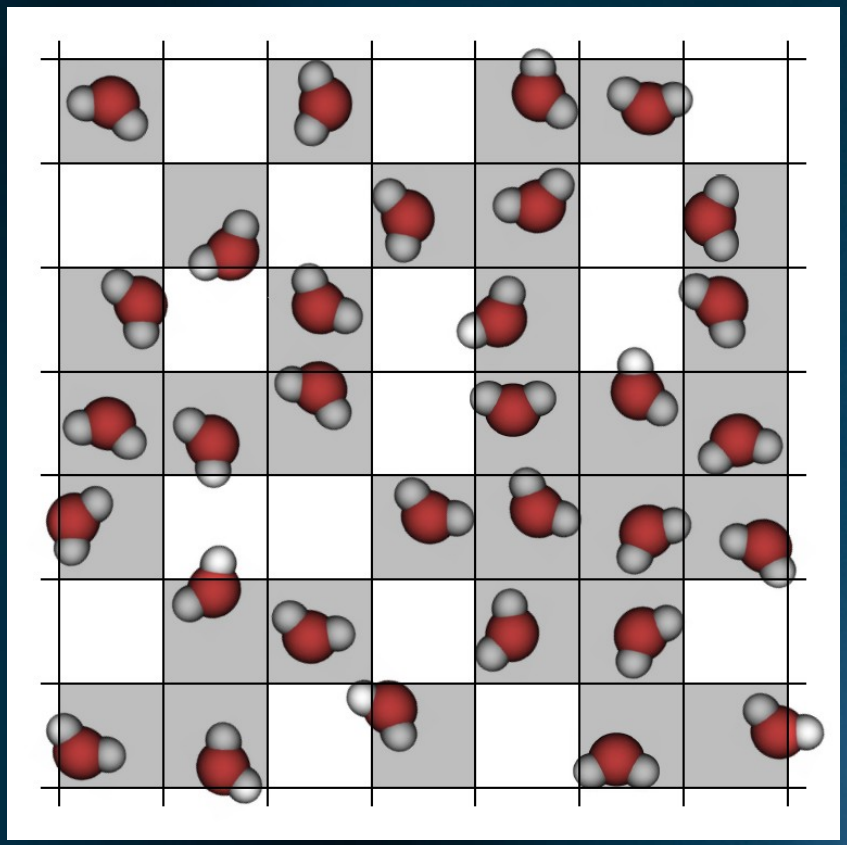
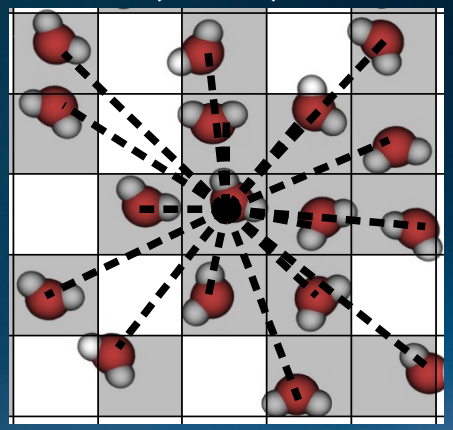


Isotropic Interaction (vdW)



$$E=U(r)$$

Stokely et al, PNAS, 2010
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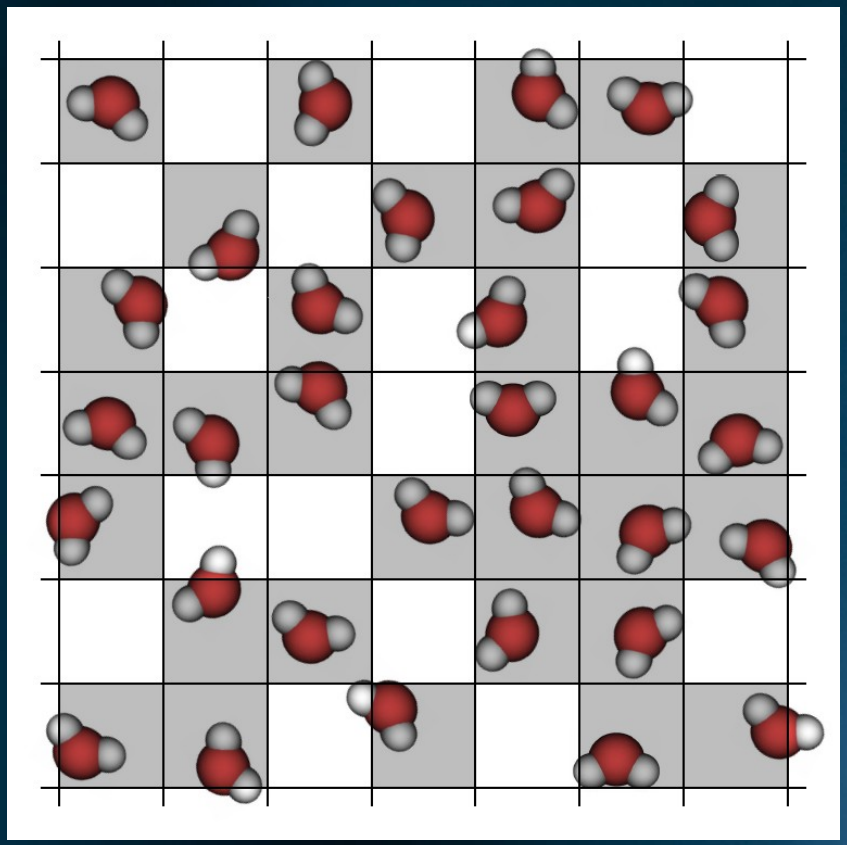

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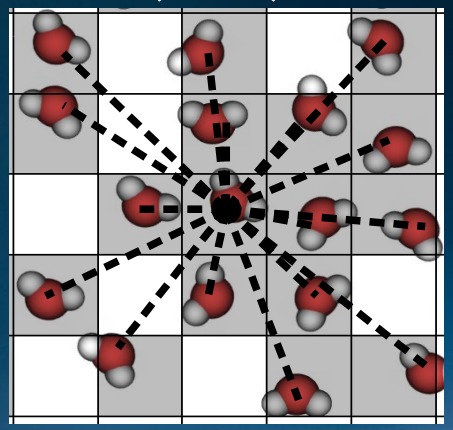
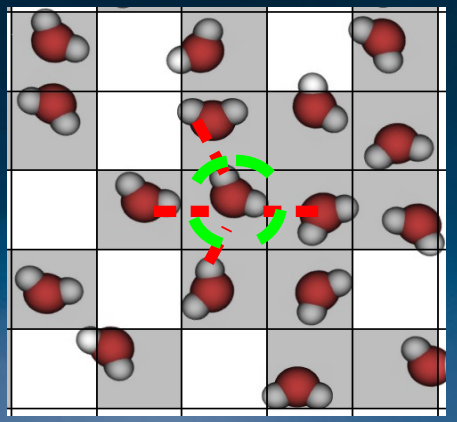


Hydrogen Bond as directional + cooperative interaction



$$E = U(r) - JN_{HB} - J\sigma N_{coop}$$

The volume depends on the number of HBs

$$V = Nv_0 + N_{HB}v_{HB}$$

Stokely et al, PNAS, 2010
Strekalova et al, PRL, 2011
Mazza et al, PNAS, 2011
Bianco et al, J Biol Phys, 2012
Bianco et al, Sci Rep, 2014
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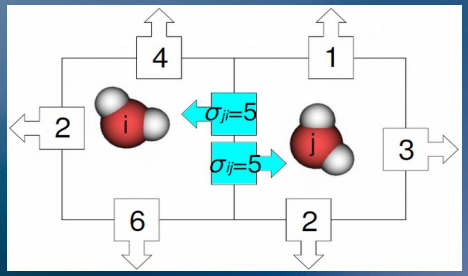
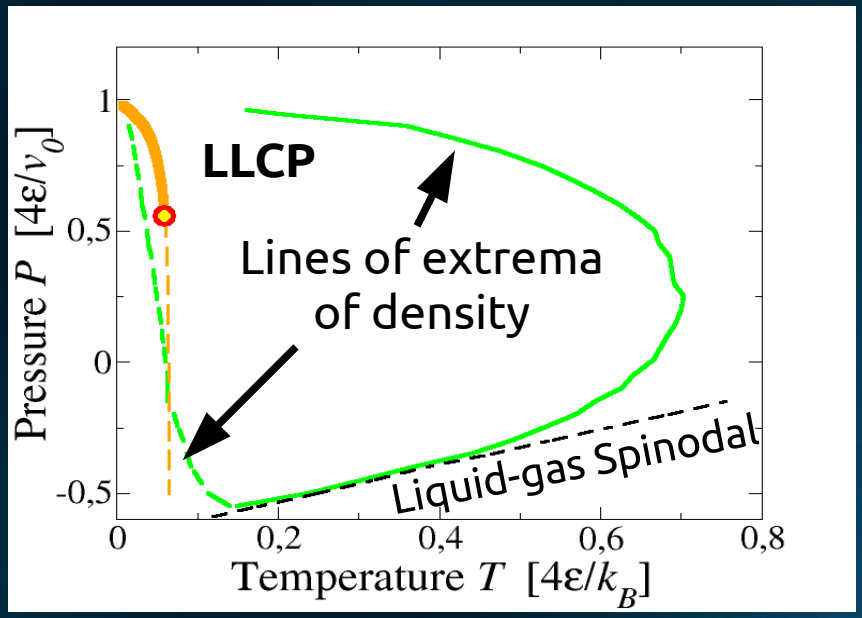
The state of a water molecule is described introducing 4 bonding variables

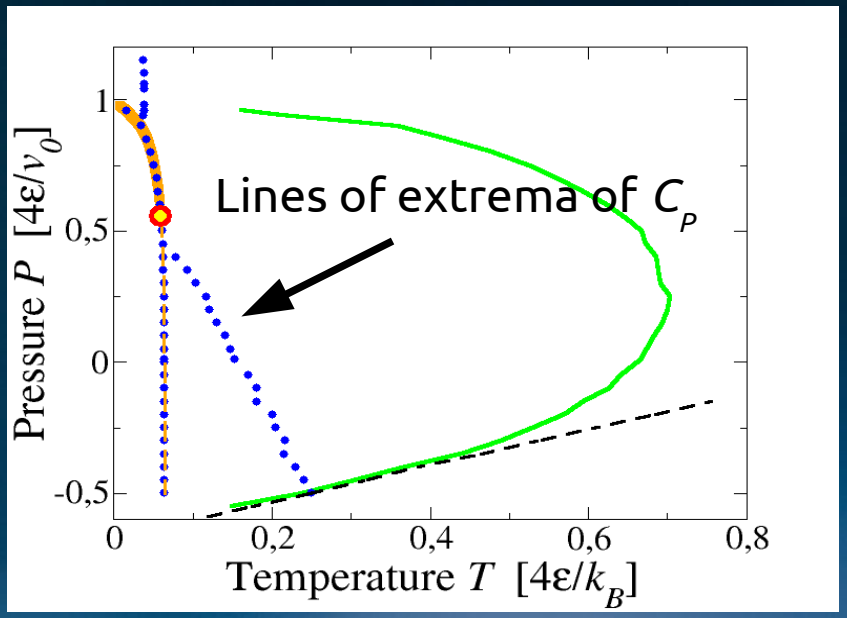


THERMODYNAMICS OF MANY-BODY WATER

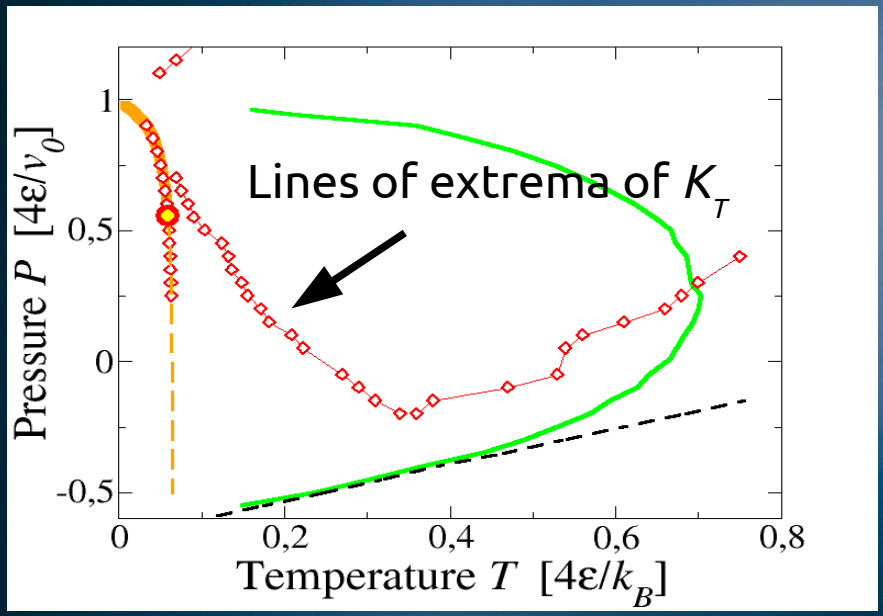
Anomalous behavior of Density



Anomalous behavior of Specific Heat C_P



Anomalous behavior of Isothermal Compressibility K_T

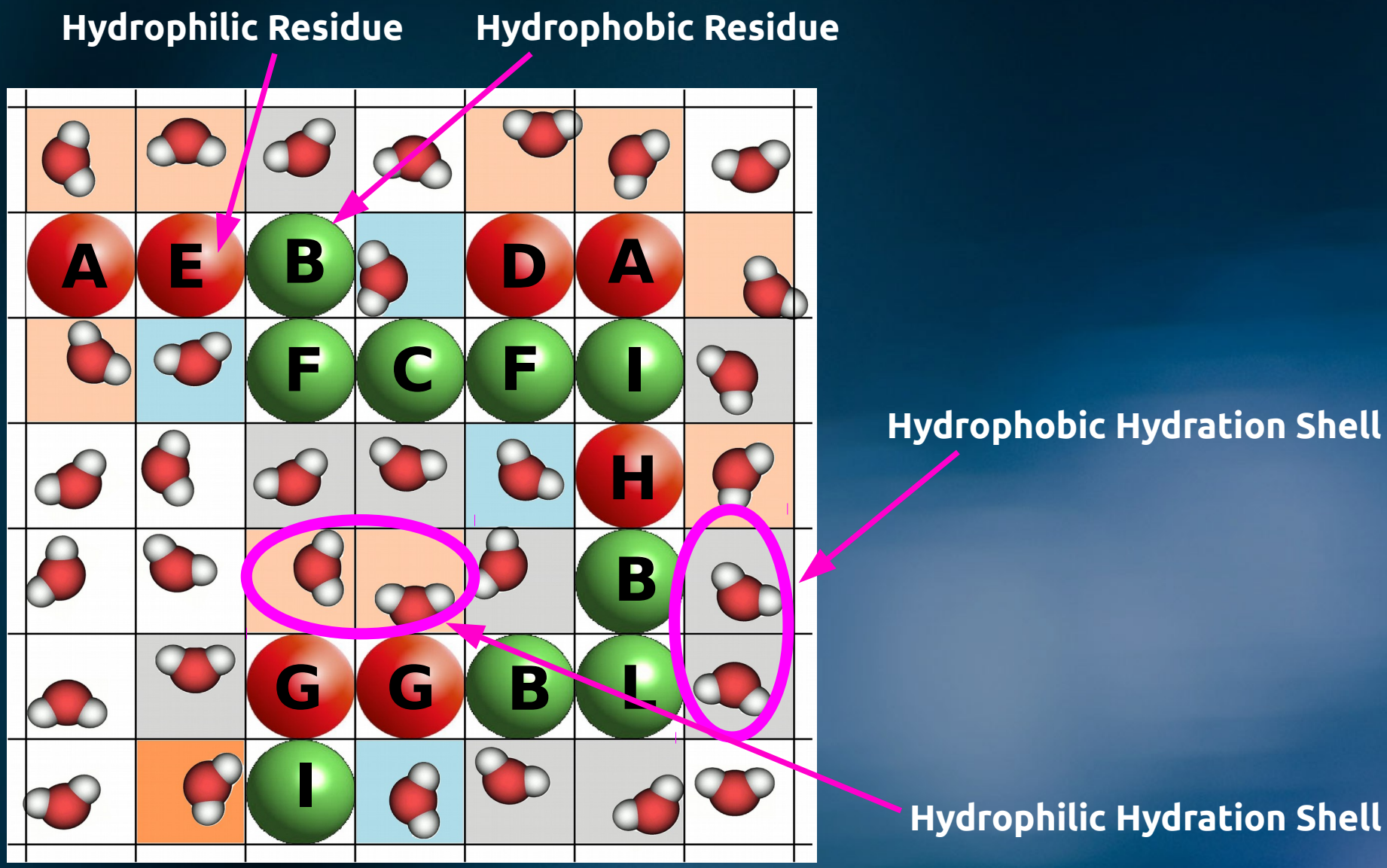


… consistent with Mazza et al, PNAS 2011

… reported by Sastry et al, PRE 1996

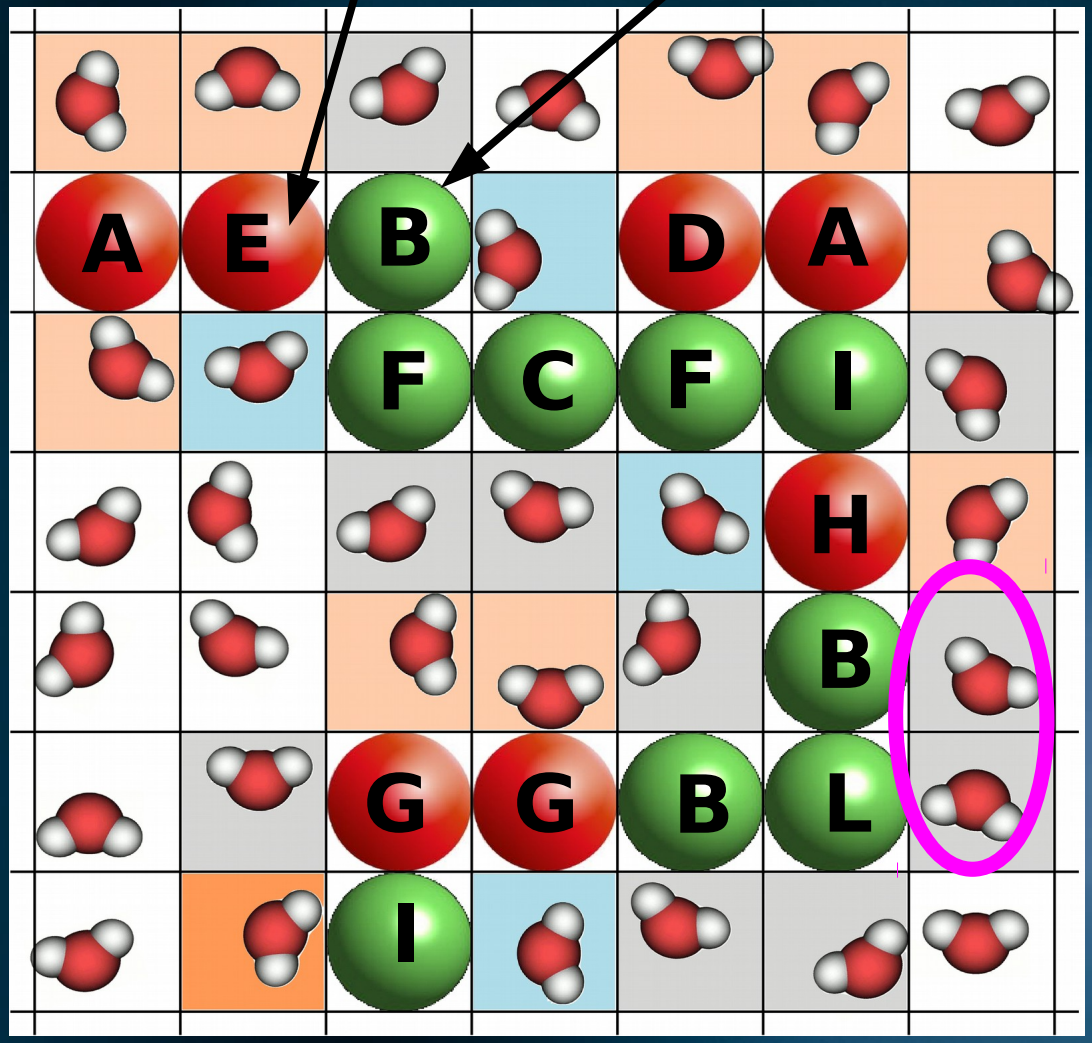
Bianco & Franzese, Sci Rep, 2014

Water-Protein Coarse Grain Model



We introduce a residue-residue interaction matrix; residue-water interaction energy

Water-Protein Coarse Grain Model



The protein affects the water-water interaction in the hydration shell

More persistent hydrogen bonds at the hydrophobic interface

Consistent with:
Dias et al, PRL 2008
Peterson et al, JCP 2009
Sarupria et al, PRL 2009
Davis et al, Nature 2012
...

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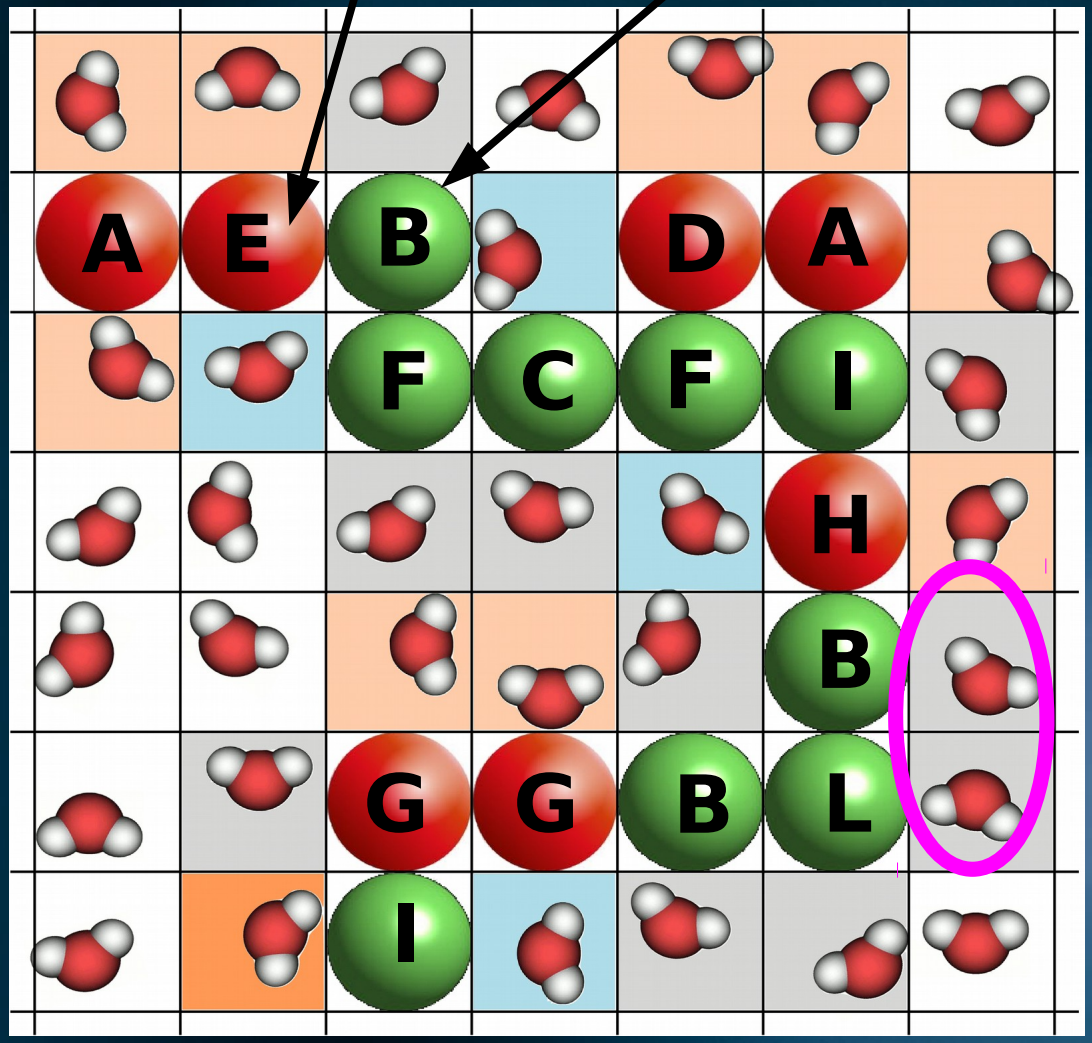

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Sarupria et al, PRL 2009
Davis et al, Nature 2012
...

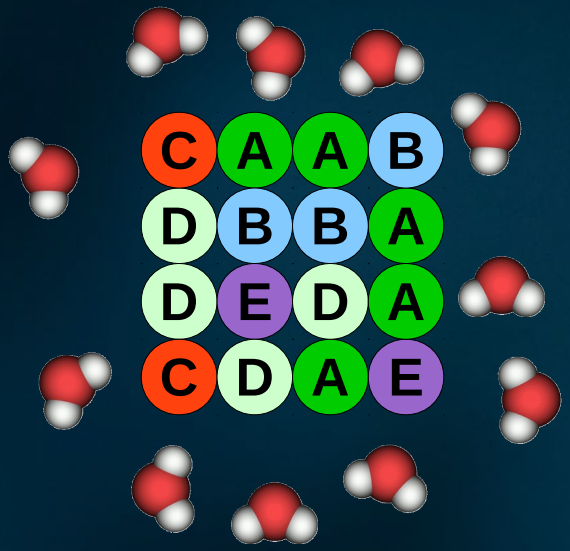
Increase of density of hydration water upon pressurization at the hydrophobic interface

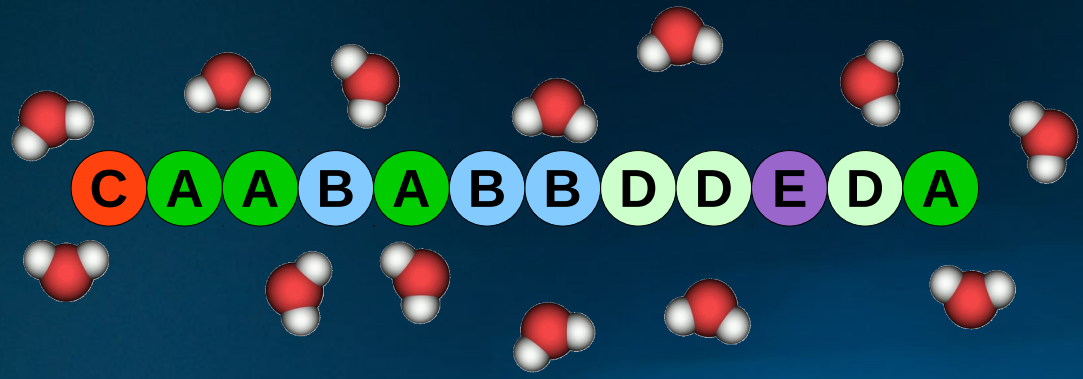
Consistent with:
Lum et al, JCPB 1999
Sarupria et al, PRL 2009
Das et al, JCPB 2012
...

We introduce a residue-residue interaction matrix; residue-water interaction energy

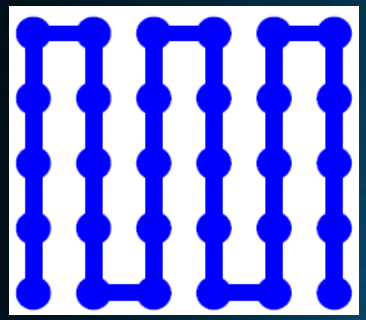
Design in explicit water

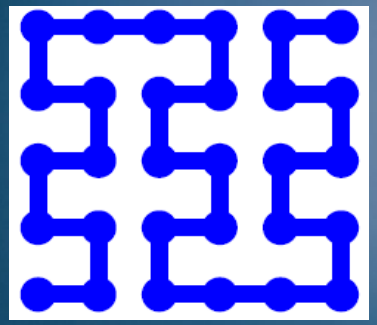
We maximize the enthalpy gap between the folded and stretched proteins, including also the average contribution coming form the hydration water.

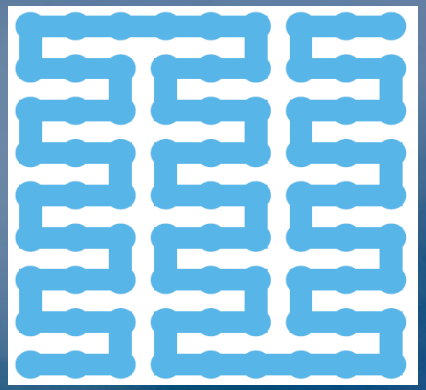




Target structures

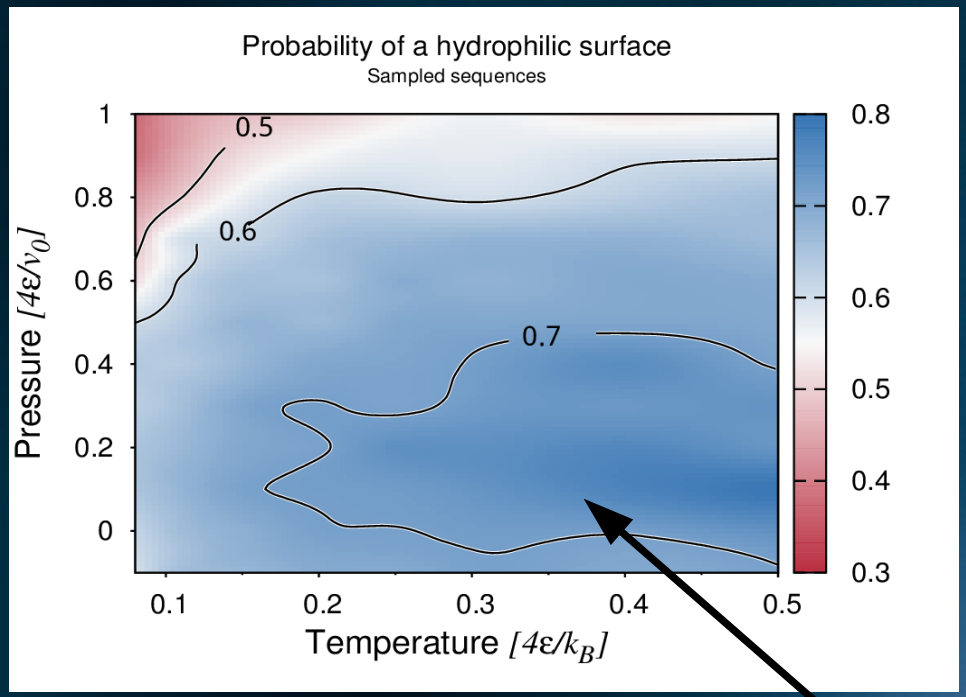


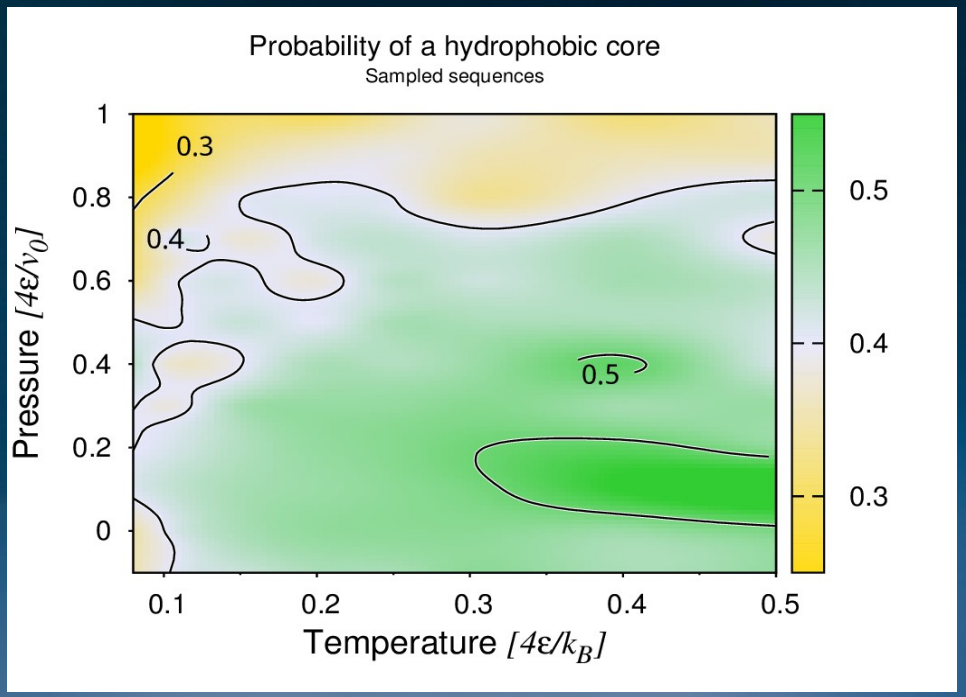




Hydrophilic/Hydrophobic profile of the designed sequences

We calculate the probability that the designed sequences have a hydrophilic surface and a hydrophobic core, in abroad range of temperatures and pressures.





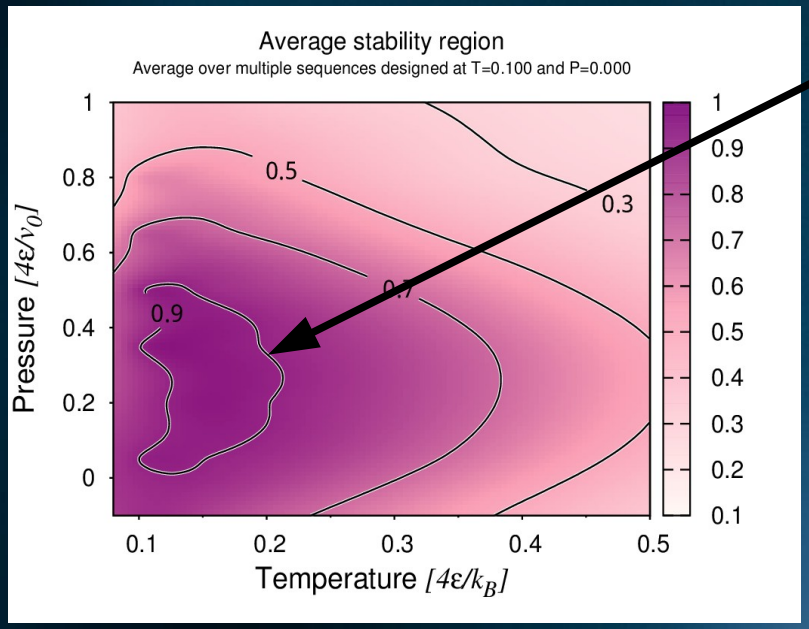
Ambient conditions

The water is a good solvent at low T and high P, leading to an increase of the probability to have hydrophobic residues on the surface

Average Stability Regions of Designed Sequences

We calculate, via Monte Carlo simulations, the probability that the designed proteins fold into the native structure.

Designed at **low-T and low-P**



Close stability region

Average Stability Regions of Designed Sequences

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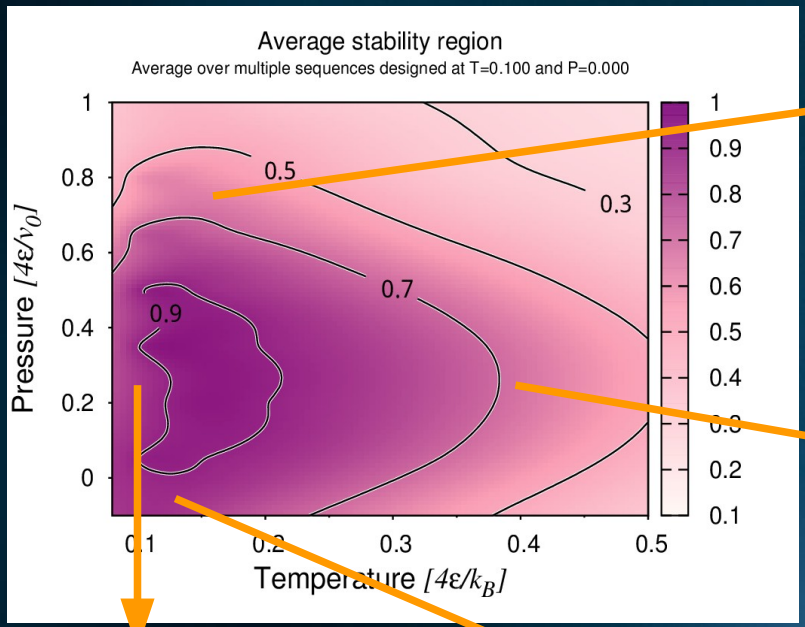
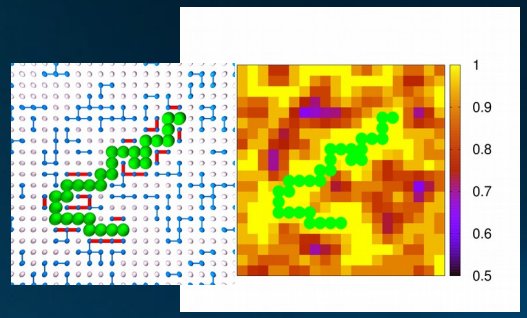
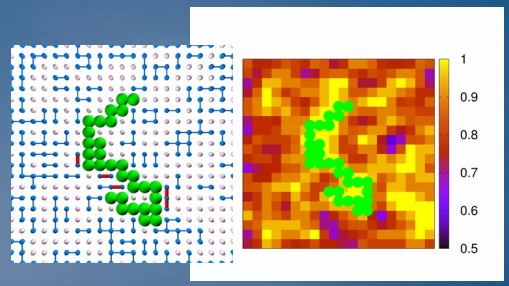


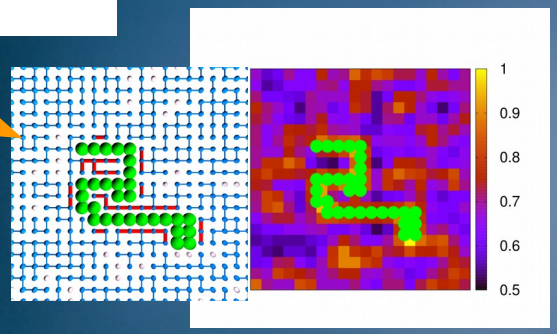
Density driven high-P denaturation



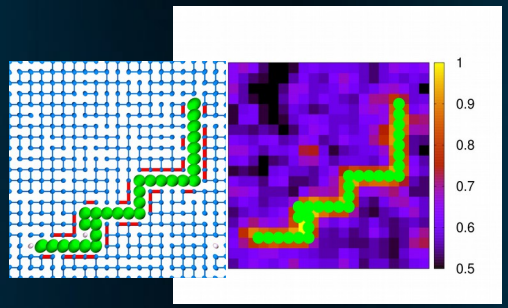
Entropy driven thermal denaturation at high T



Enthalpy driven low-P denaturation



Energy driven cold denaturation at low T



Denaturation mechanisms explained in :

PRL 115, 108101 (2015) PHYSICAL REVIEW LETTERS week ending 4 SEPTEMBER 2015

Contribution of Water to Pressure and Cold Denaturation of Proteins

Valentino Bianco and Giancarlo Franzese*

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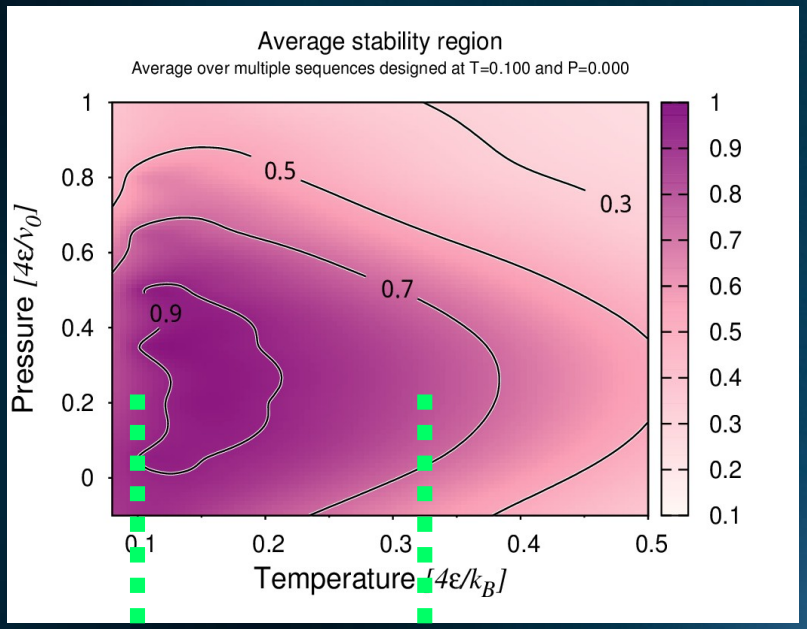

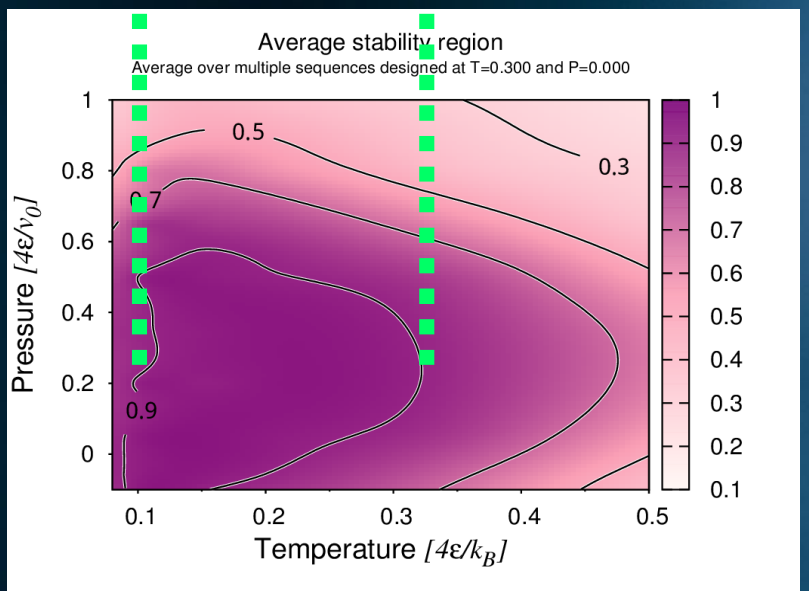

Designed at **high-T and low-P**

Average Stability Regions of Designed Sequences

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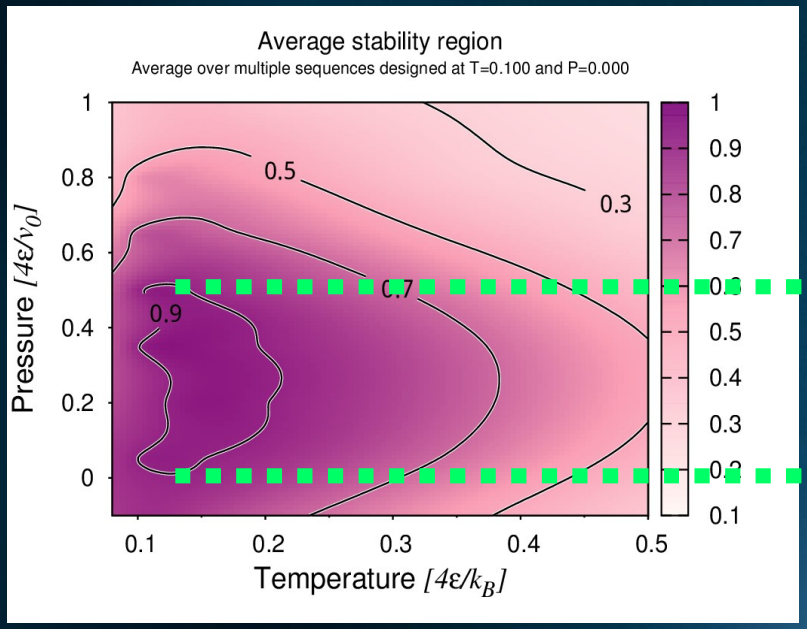
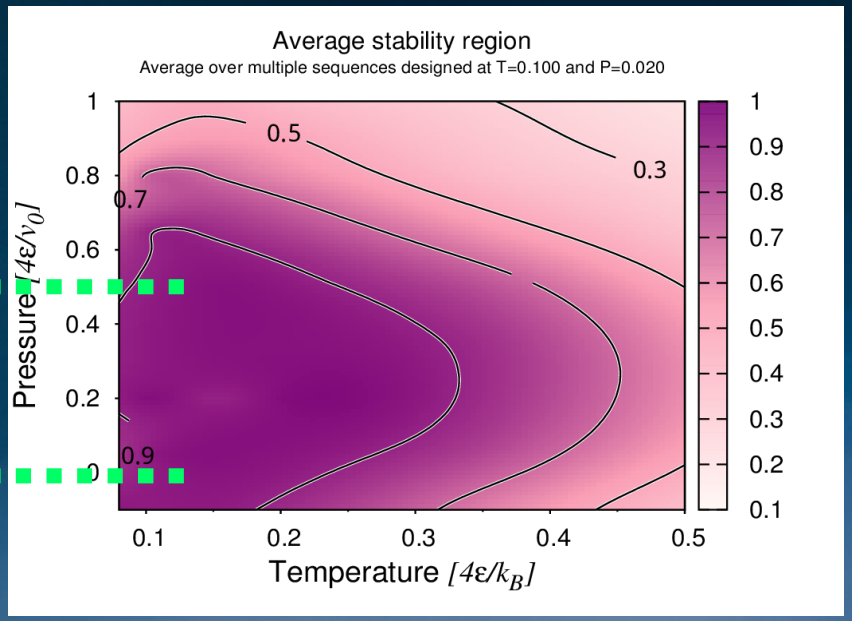
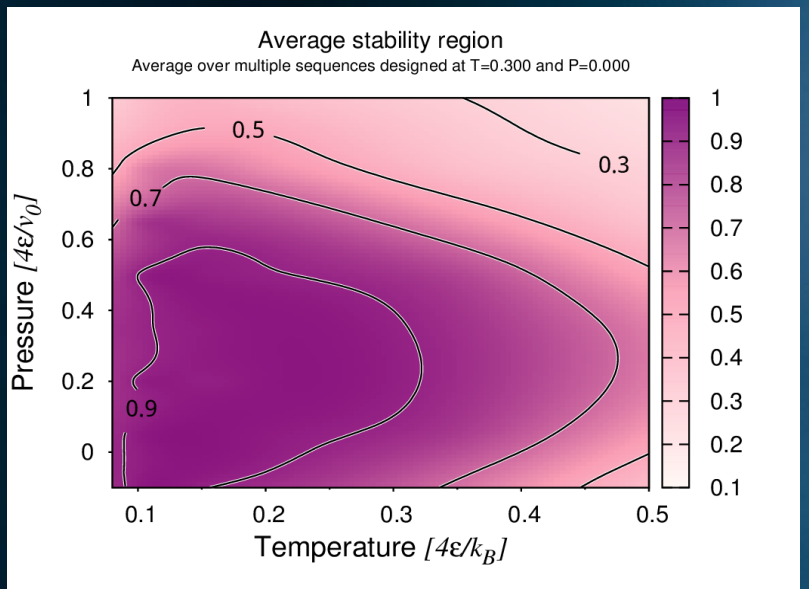
Designed at **low-T and low-P**



Designed at **low-T and high-P**





Designed at **high-T and low-P**

Take Home Message

1) We propose a coarse-grain model for water-protein to study how water influences the design and folding of proteins and, more in general, bio-polymers.
2) We show that, accounting for the properties of the protein hydration water, the designed sequences change as function of temperatures and pressure.
3) The stability region of the designed proteins is a close region in the P-T plane. The model reproduces the hight-T, low-T, low-P and high-P denaturation of proteins.
4) Designed sequences at different values of T and/or P exhibit different stability regions. Sequences designed at higher temperatures/pressures (T/P) are stable, in average, In a broader range of T/P with respect the ones designed at lower T/P.

Thanks to

Ivan Coluzza
Chiara Cardelli
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Christoph Dellago

universität wien

Lorenzo Rovigatti
Emanuele Locatelli
Barbara Capone

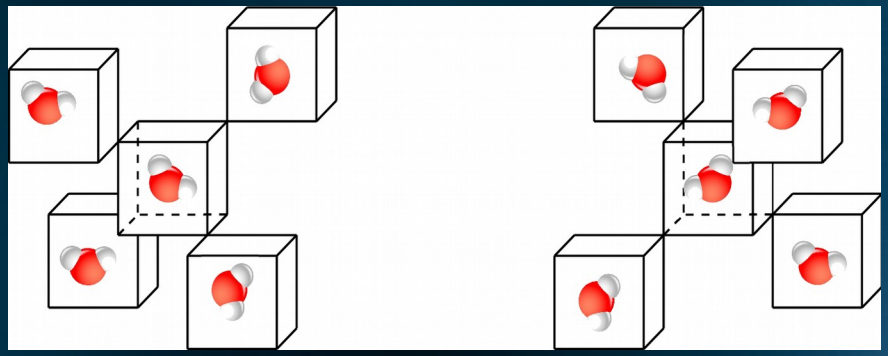
universität wien

Giancarlo Franzese
Arne Zantop

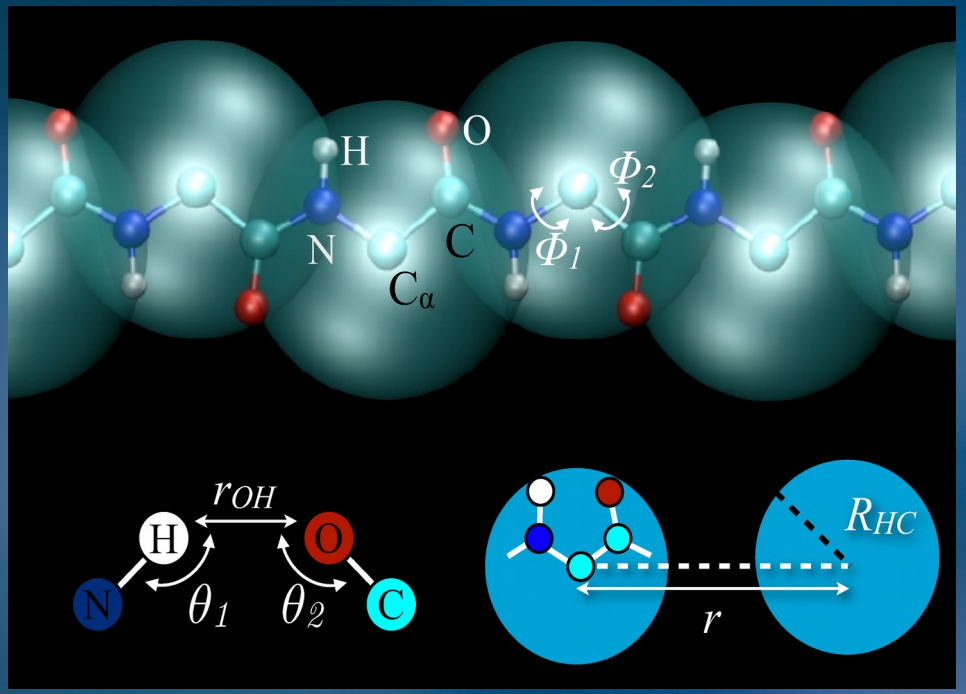
Universitat de Barcelona

PERSPECTIVES

3D Water Model



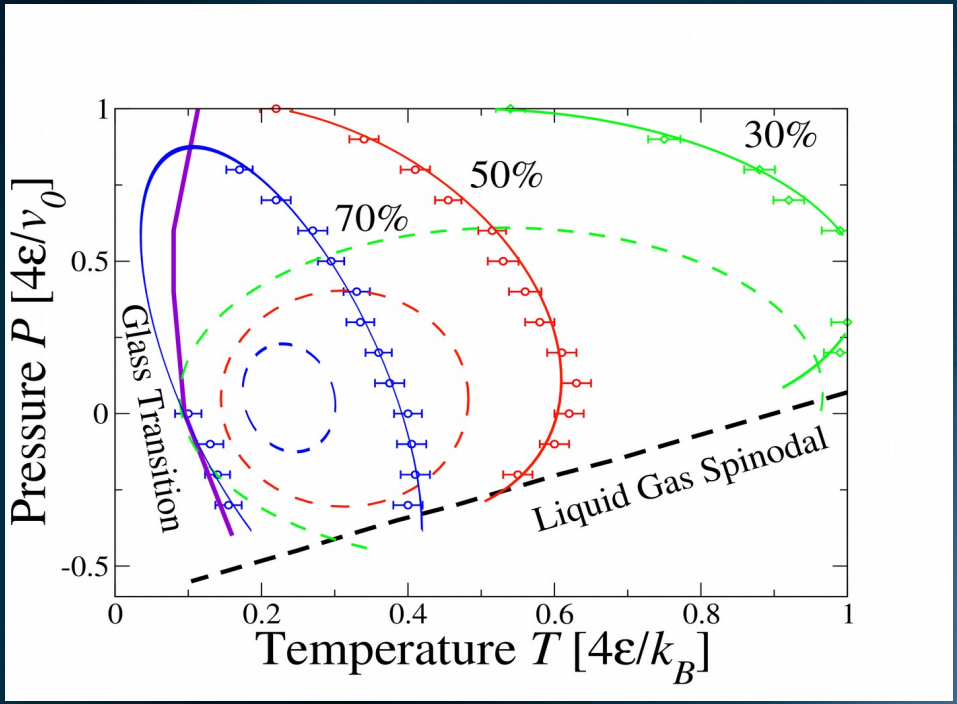
Caterpillar Model



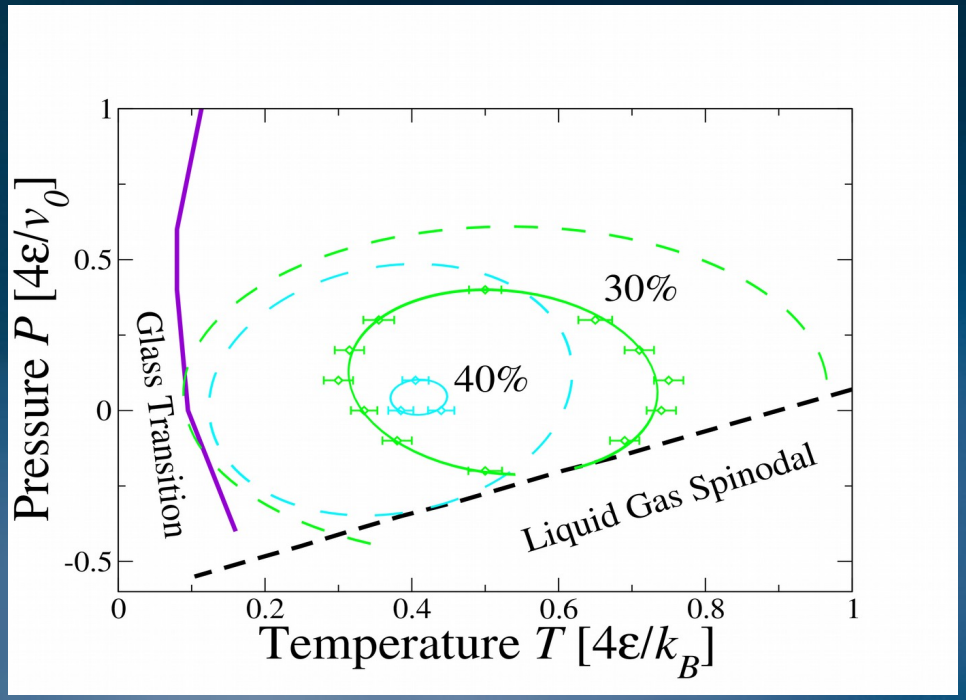
Coluzza, PLOS, 2011
Coluzza, Plos One, 2014

Tune of the Model Parameters

Decrease of the strength of HBs in the hydrophobic hydration shell

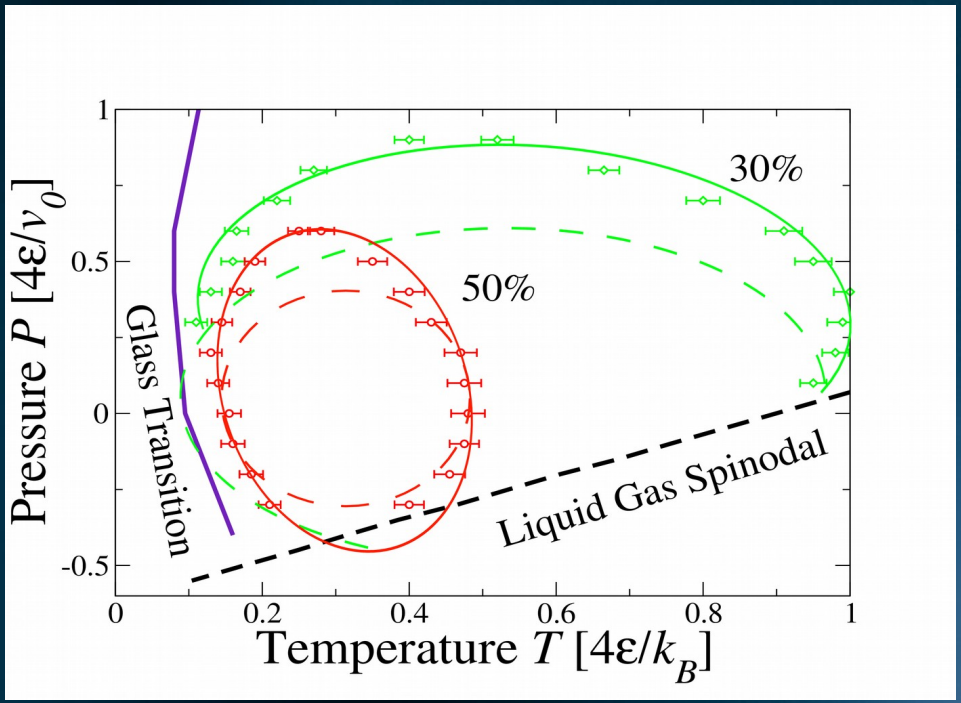


Increase of the strength of HBs in the hydrophobic hydration shell

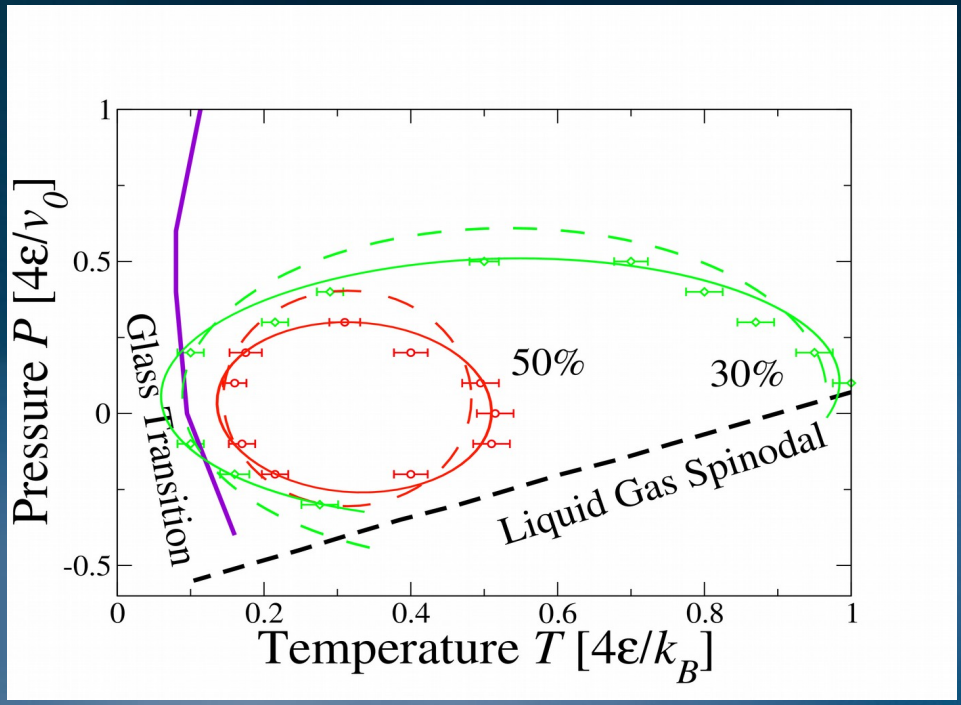


Tune of the Model Parameters

Decrease of the compressibility factor in the hydrophobic hydration shell

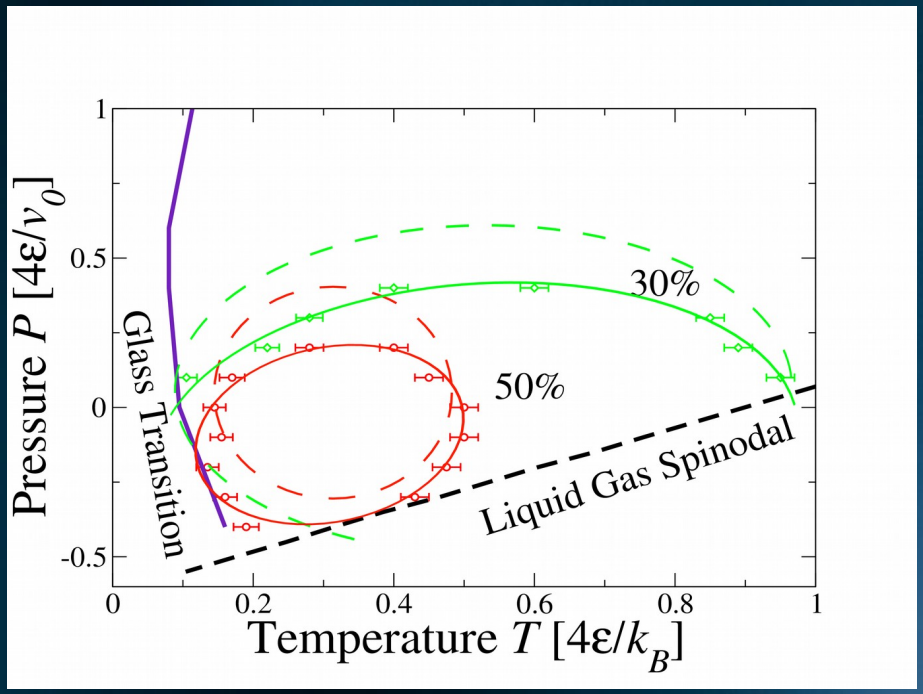


Increase of the compressibility factor in the hydrophobic hydration shell

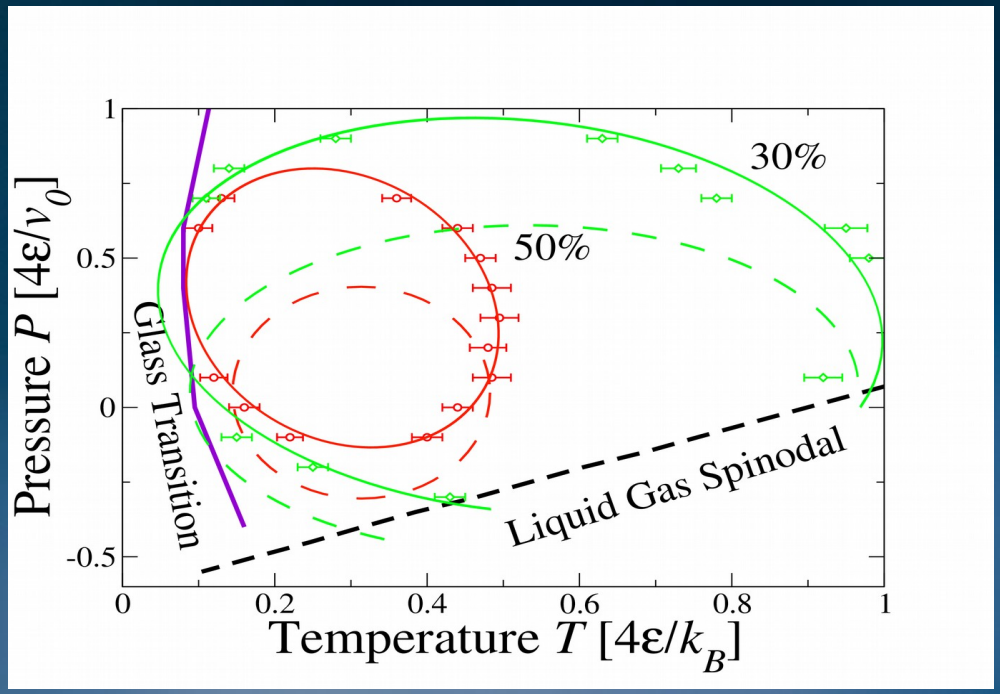


Tune of the Model Parameters

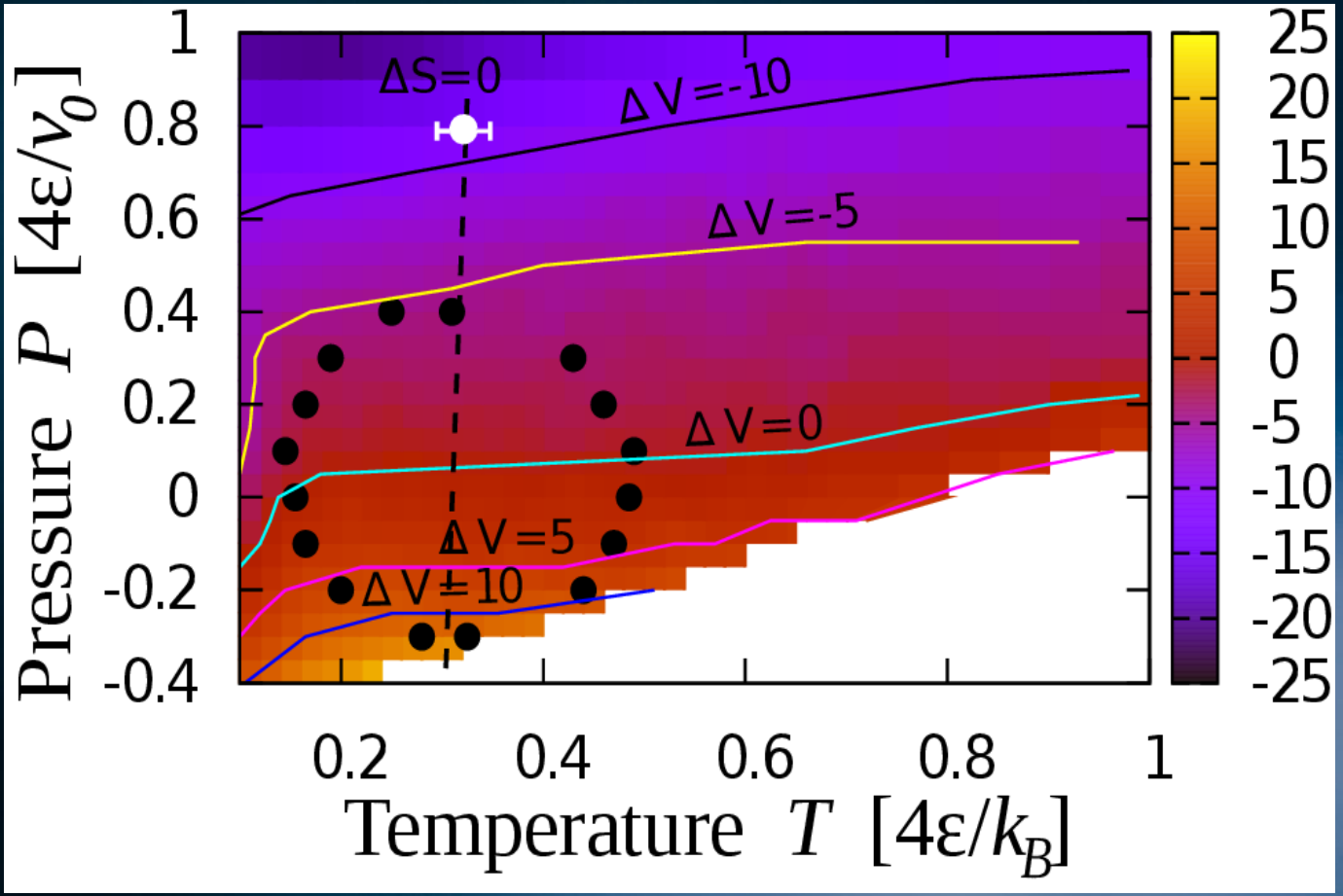
Decrease of the v_HB at P=0



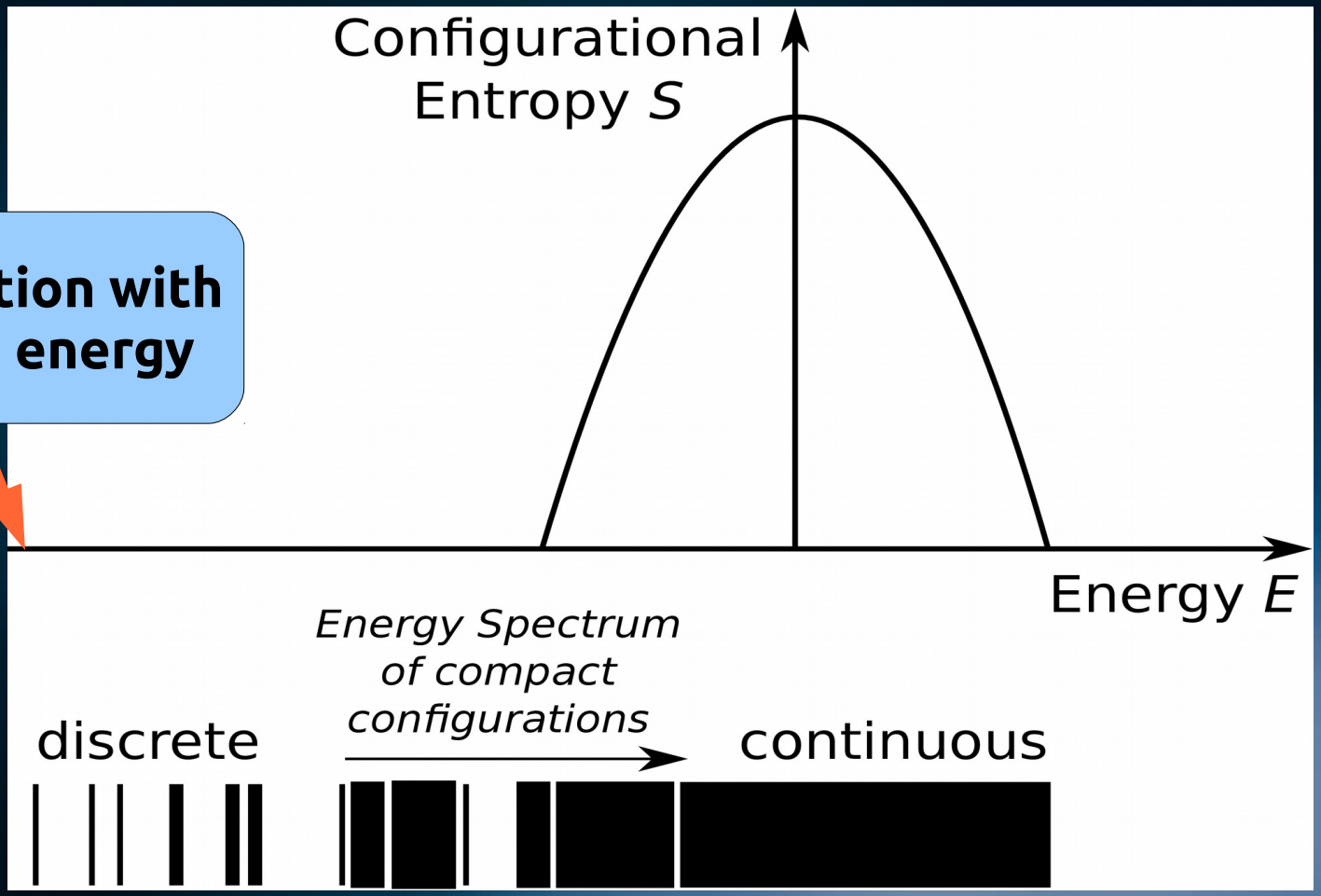
Increase of the v_HB at P=0



Entropy and Volume variation upon denaturation



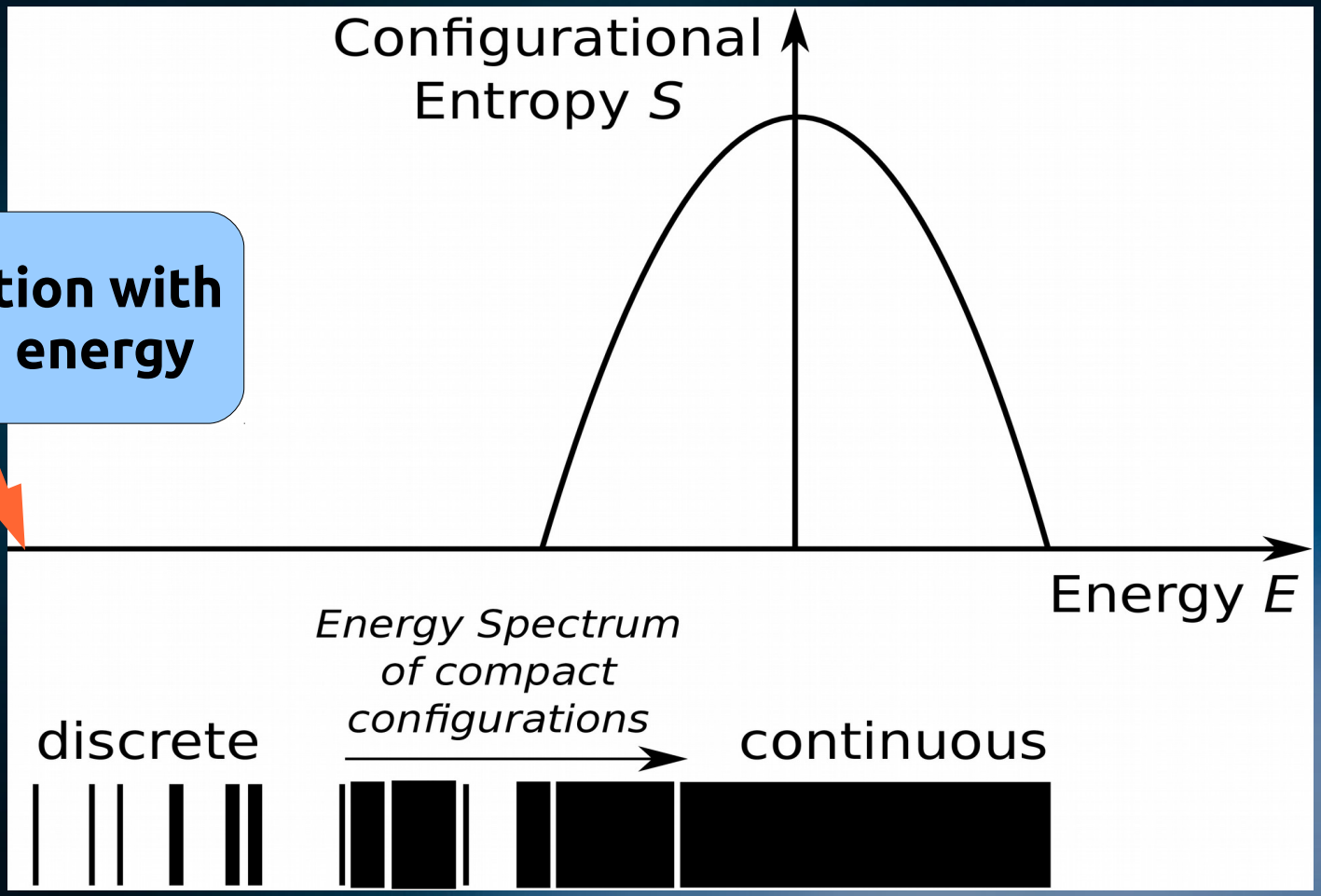
RANDOM ENERGY MODEL



Configuration with minimum energy

Pande et al, Biophys J, 1997

RANDOM ENERGY MODEL



Configuration with minimum energy

Pande et al, Biophys J, 1997