Transferable Coarse-grained potential model for quantitative protein folding and design

Ivan Coluzza

universität wien

De Novo

~~Transferable Coarse-grained potential model for quantitative~~ protein folding and design

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What allows proteins to fold ?

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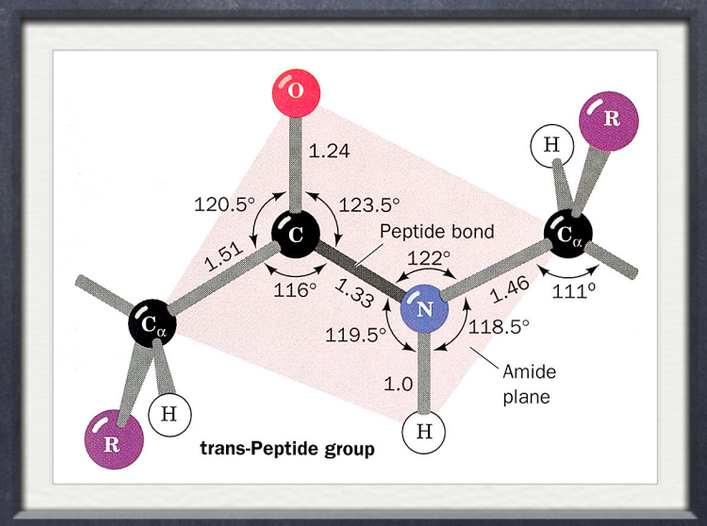
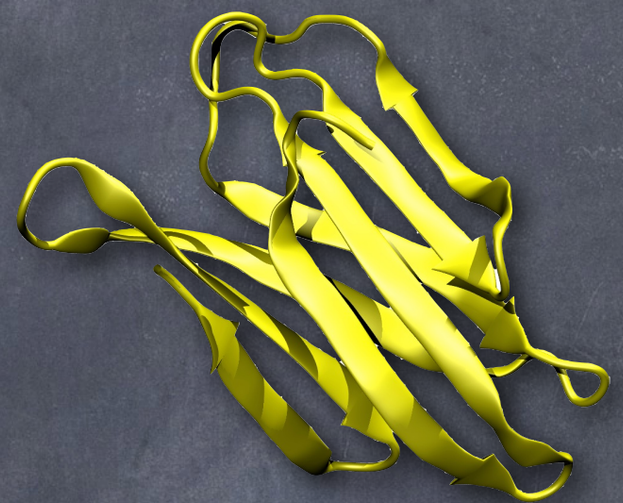
- Proteins
- Made from ~20 different types of amino acids



http://xray.bmc.uu.se/~kurs/BiostrukfunkX2/practicals/practical_1/figs/peptide_bond.jpg

What allows proteins to fold ?

- Proteins
- Made from ~20 different types of amino acids
- Natural sequences fold to thermodynamically stable structures



3MX7 AND 600 MORE

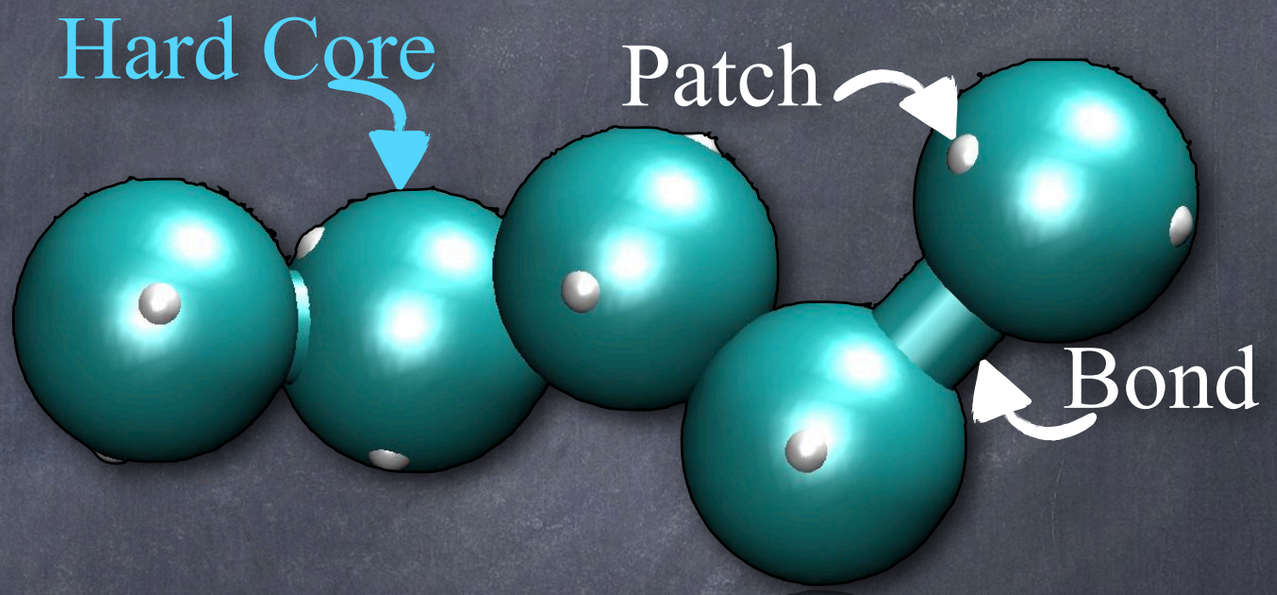
What allows proteins to fold ?

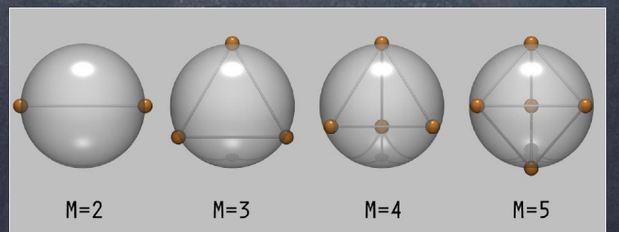
- Proteins
- Made from ~20 different types of amino acids
- Natural sequences fold to thermodynamically stable structures

1GAB and 105 more...

What allows proteins to fold ?

- Proteins
  - Made from ~20 different types of amino acids
  - Natural sequences fold to thermodynamically stable structures
  - Constraints are key to understand proteins





Bianchi et al. Phys. Rev. Lett. (2006) vol. 97 (16) pp. 4

Coluzza, I., & Dellago, C. (2012).. *Journal of Physics: Condensed Matter*, *24*(28), 284111

Coluzza, I., Van Oostrum, P. D. J., Capone, B., Reimhult, E., & Dellago, C. (2012). *Soft Matter*, *DOI*, 10.1039/2sm26967h.

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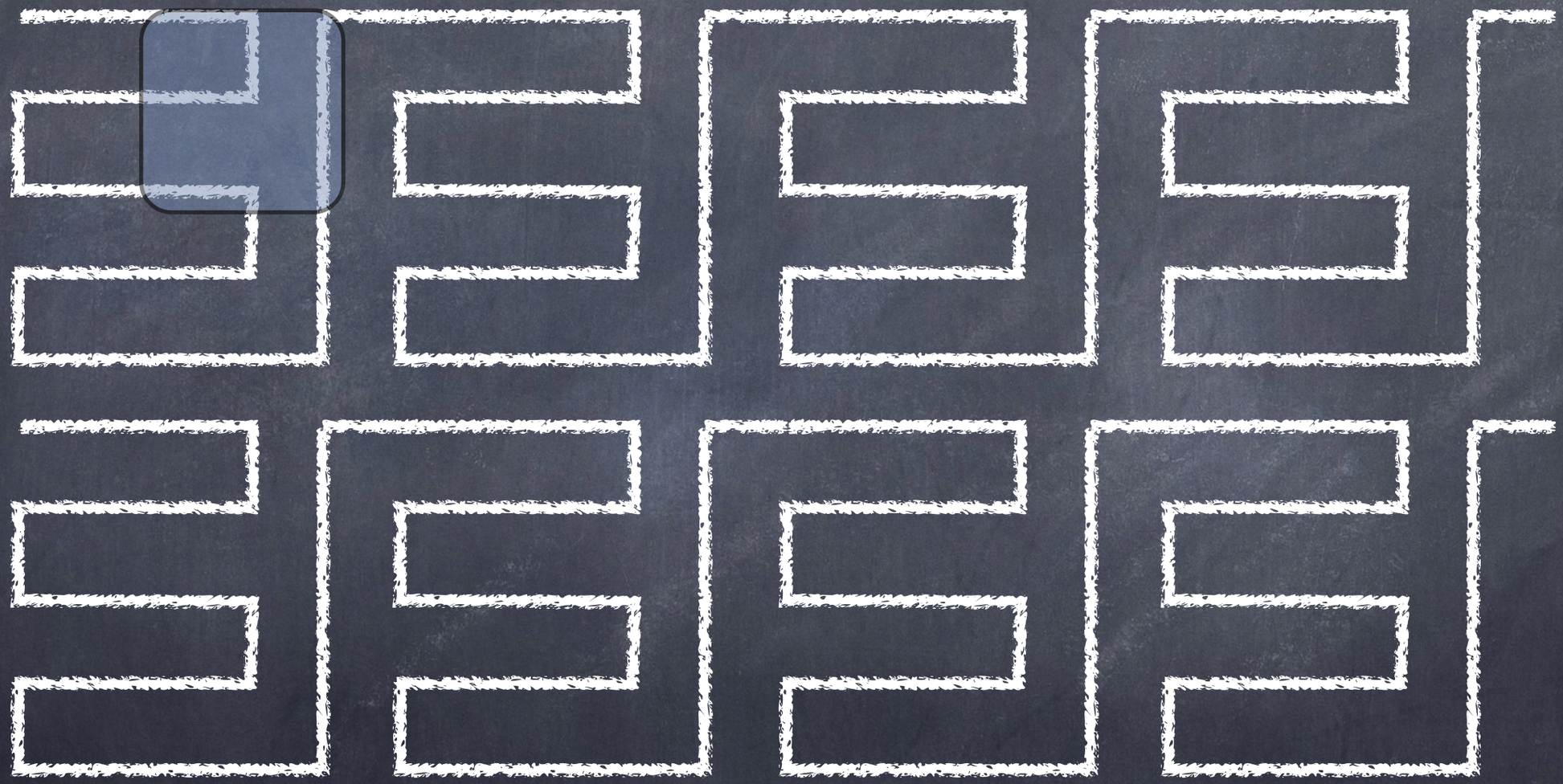
Mean field theory

Random Energy Model



Derrida. ***Phys Rev B*** (1981) vol. 24 (5) pp. 2613-2626
Bryngelson and **Wolynes**. ***P Natl Acad Sci Usa*** (1987) vol. 84 (21) pp. 7524-7528

Mean field theory

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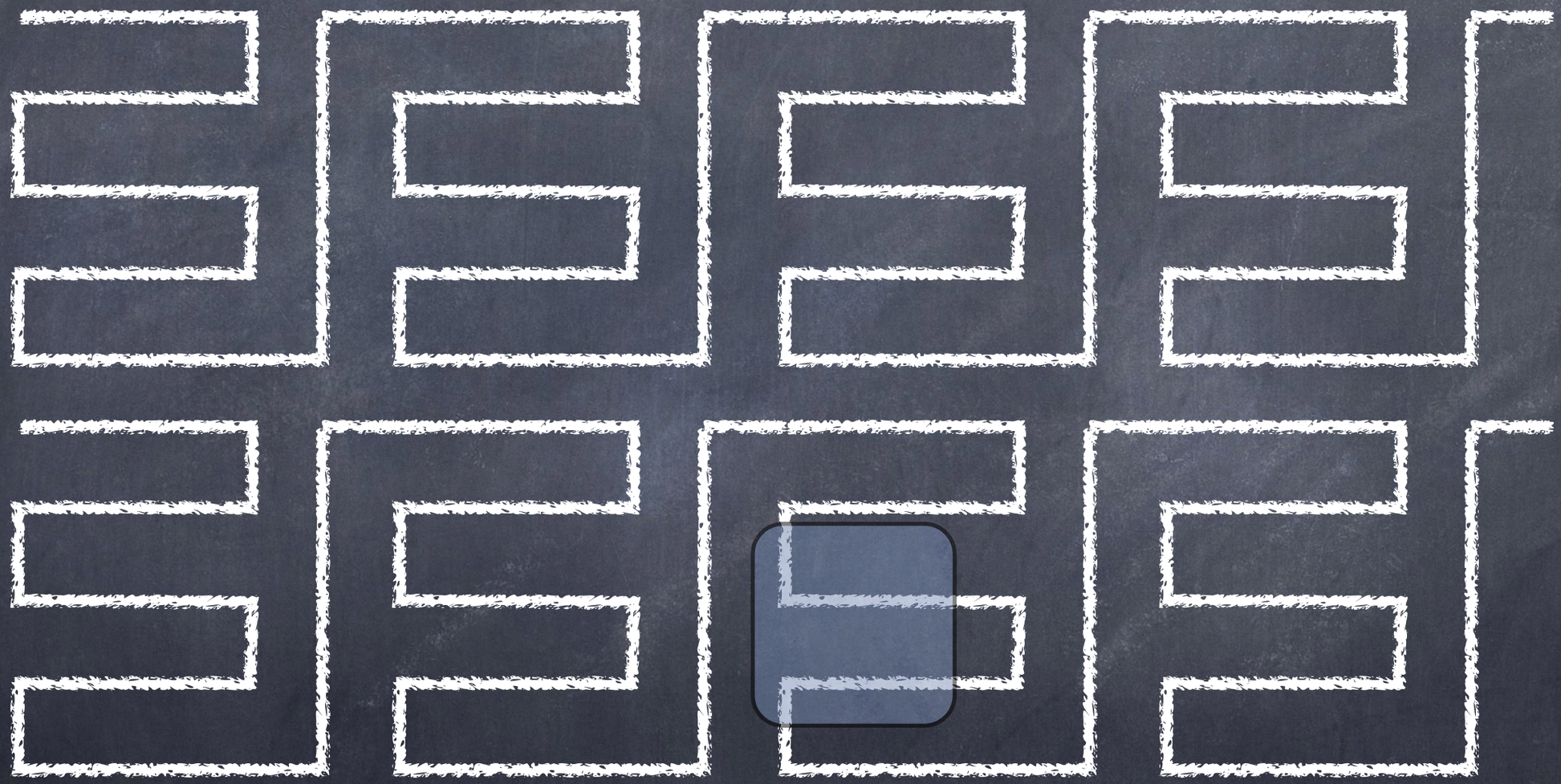

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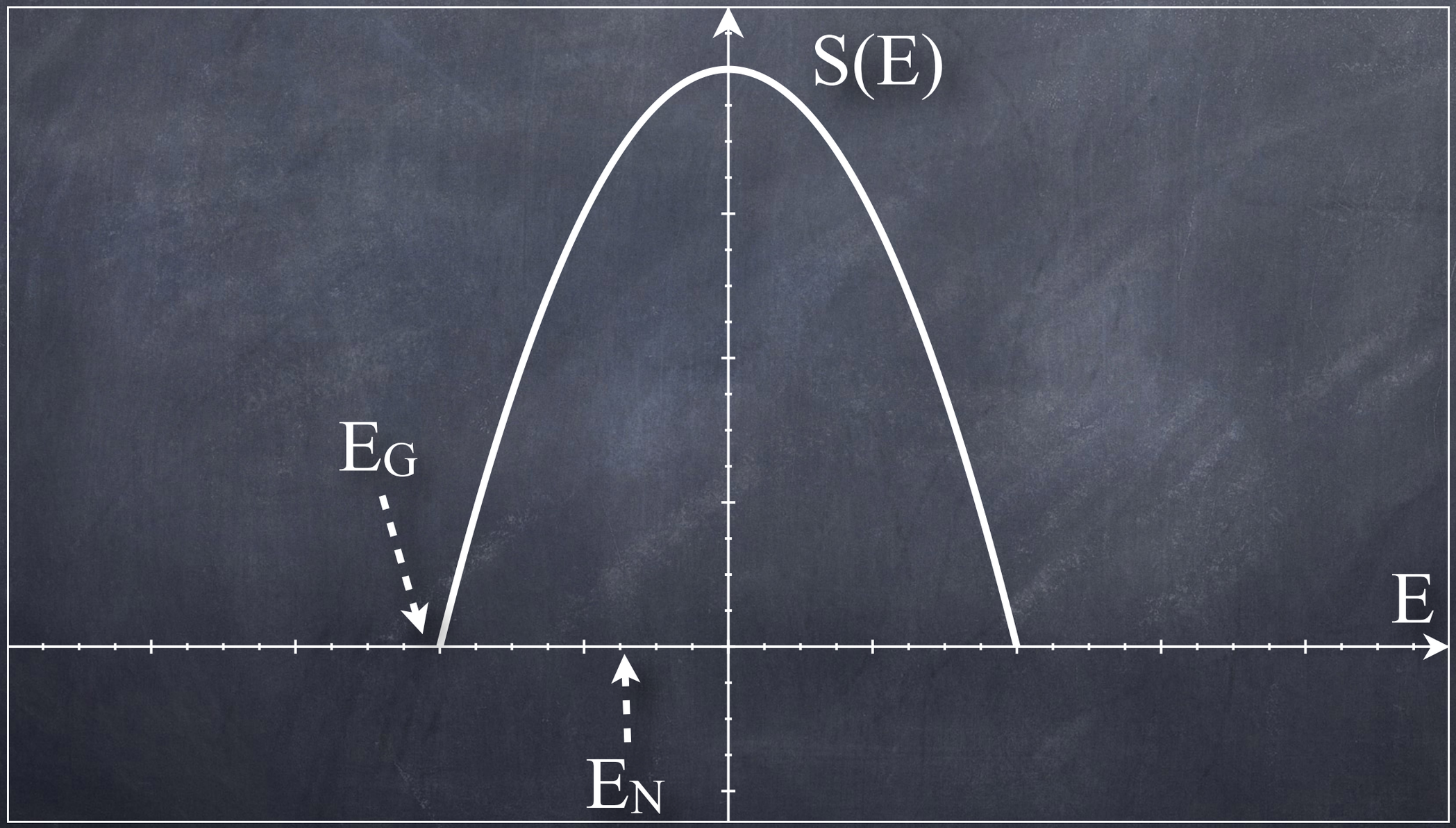
Mean field theory of design



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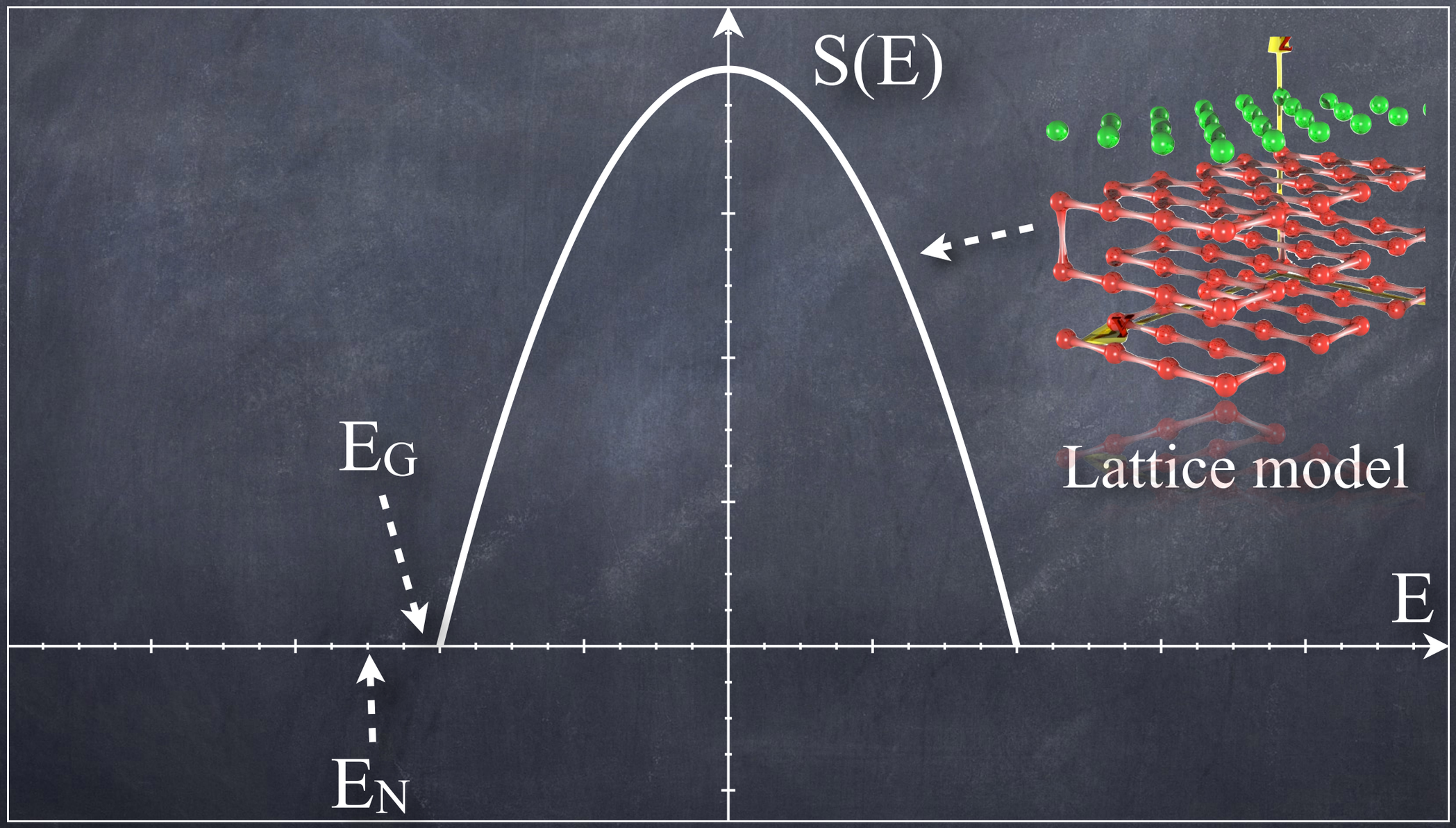

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Folding vs Design

$$E = \sum_{ij} C_{ij} S_{ij}$$

Folding

$$E = \sum_{ij} C_{ij} \bar{S_{ij}}$$

Design

$$E = \sum_{ij} \bar{C_{ij}} S_{ij}$$

ADSVGCA.....

$$E_N = \sum_{ij} \bar{C_{ij}} \bar{S_{ij}}$$

S(E)

E_N

Shakhnovich, E. and Gutin, A. **Protein Engin. 6, 793 (1993).**
Coluzza, I. Muller, H. and Frenkel D. **Phys.Rev.E 68(4), 046703 (2003).**

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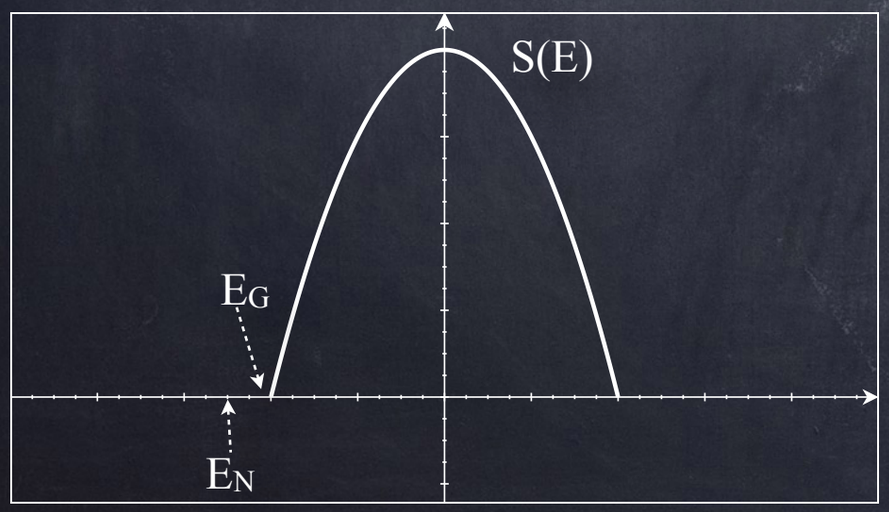

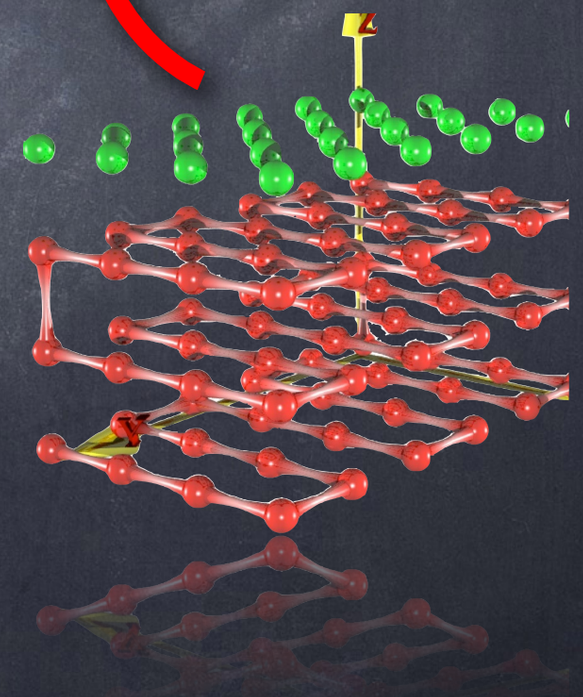

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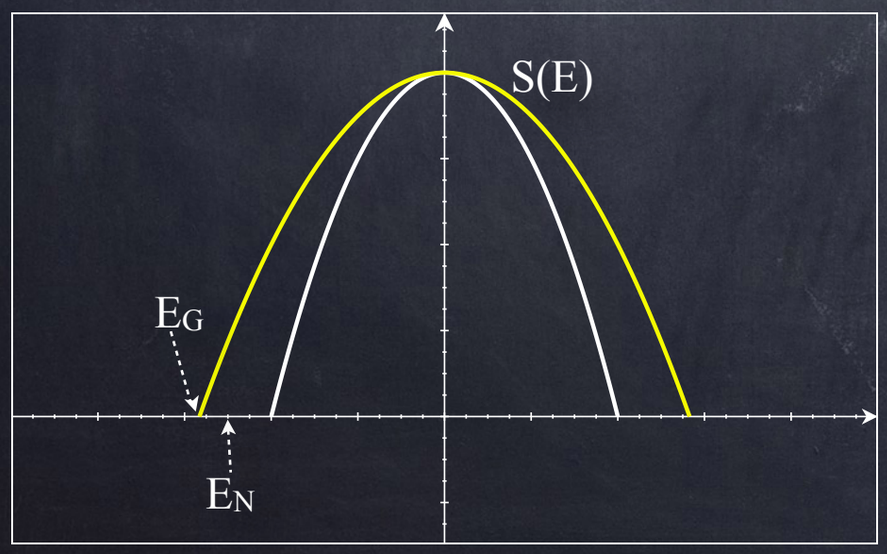

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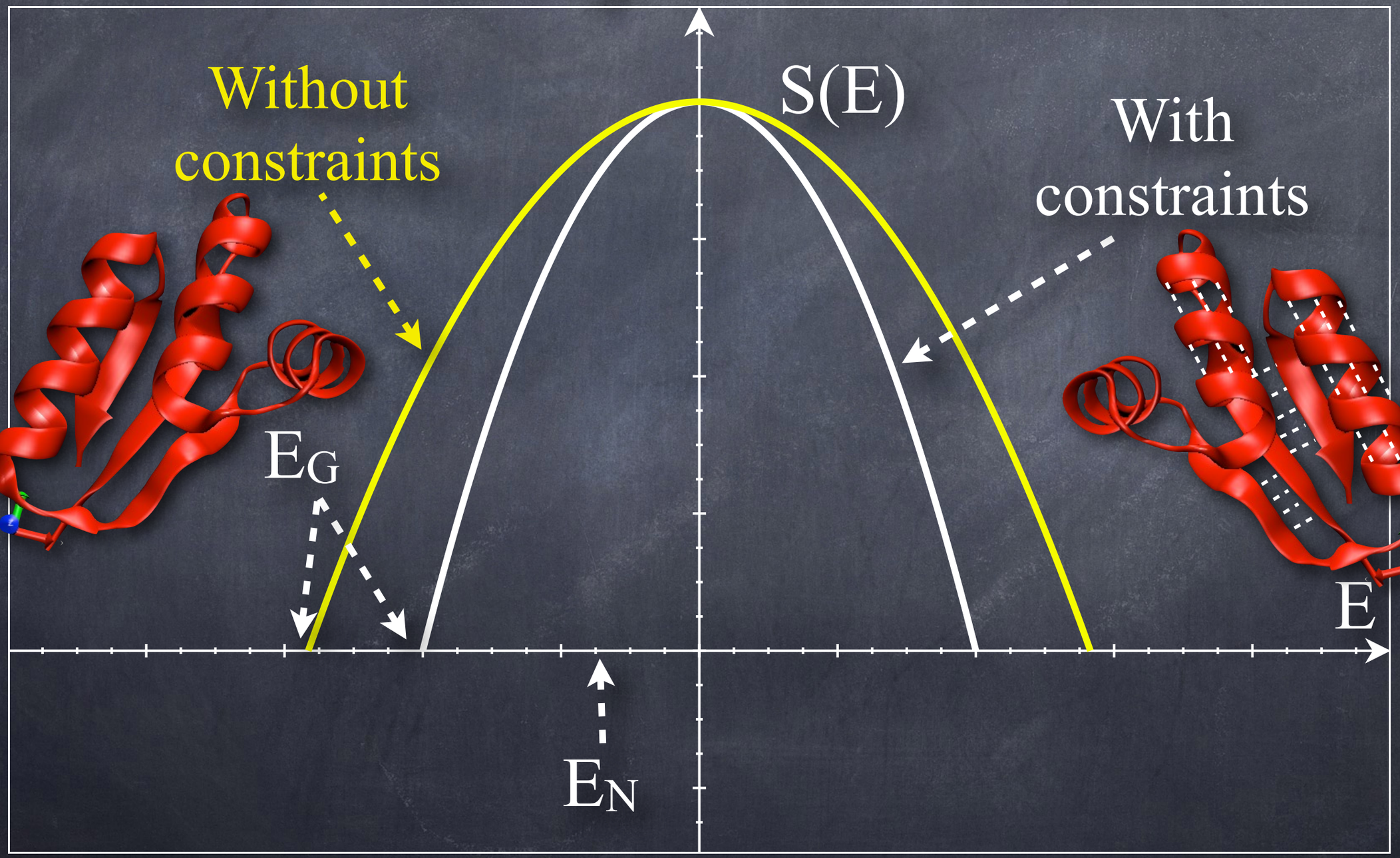
Minimum Constraint Principle (MCP)



Coluzza I., **Plos ONE 10.1371/journal.pone.0020853 (2011)**

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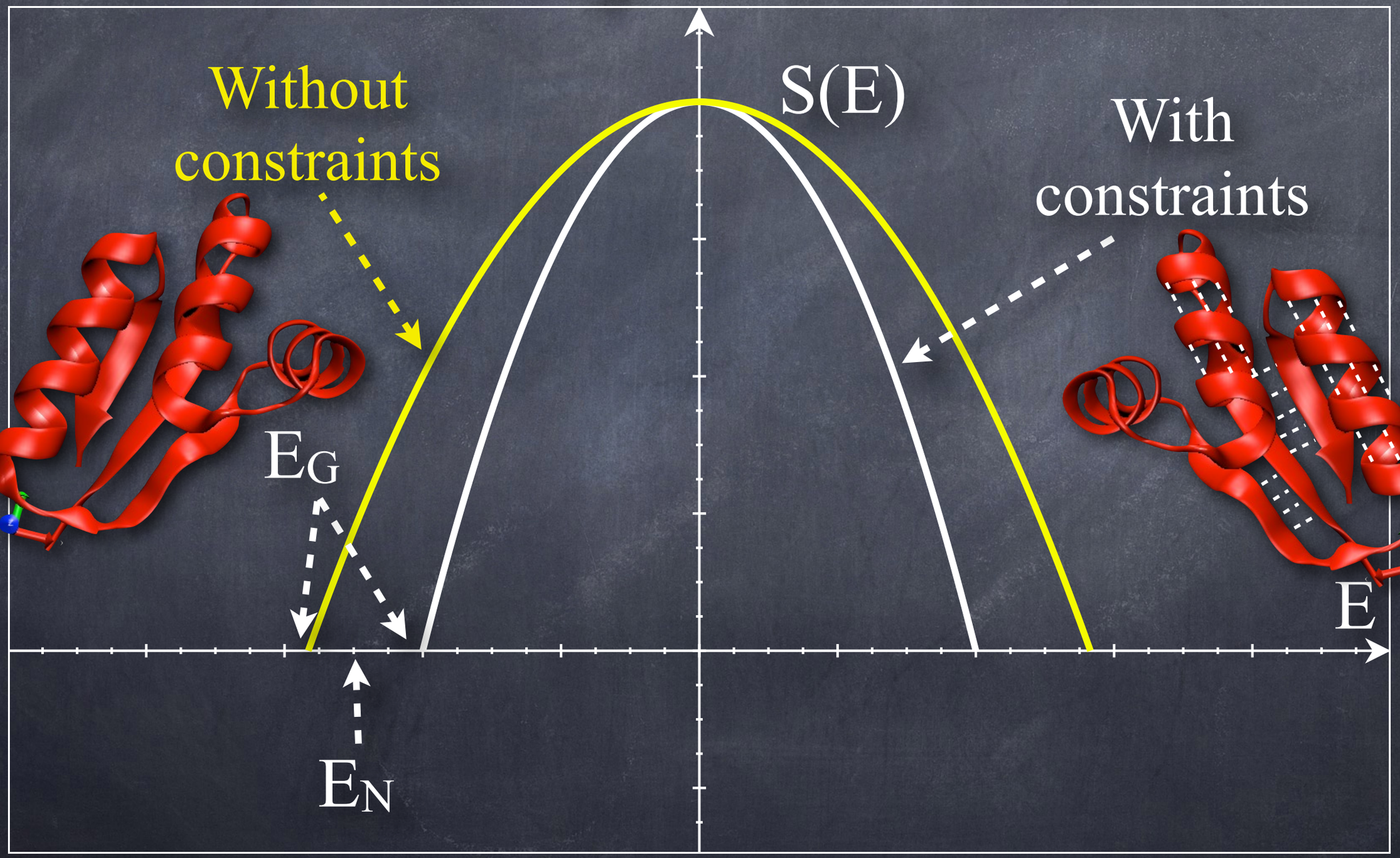

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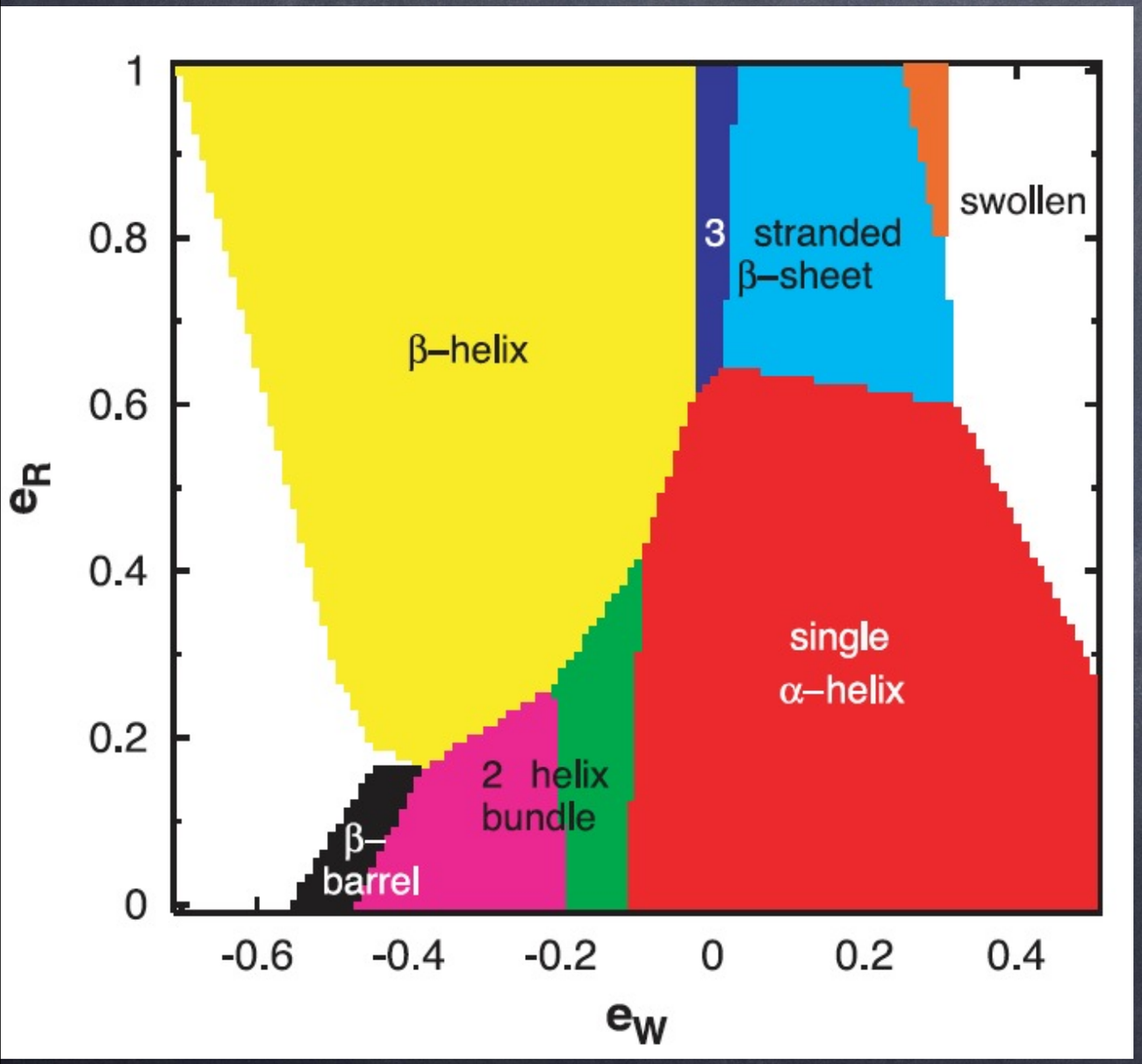
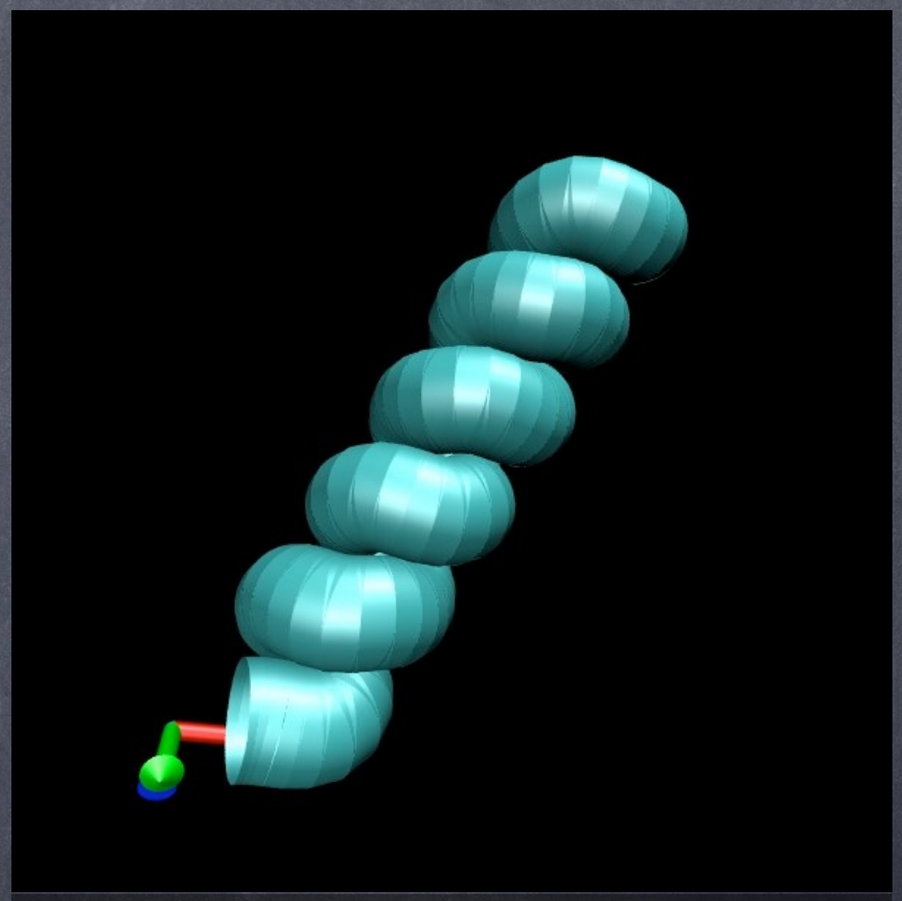
Tube model

The phase space is defined by geometrical constraints





- Fixed tube radius of 2.5 Å
- e_R Local Bending rigidity
- e_W Local Hydrophobic interactions

Hoang et al. Proc. Nat. Acc. Sci. (2004) vol. 101 pp. 7960-7964

Caterpillar model

Side chains Interactions

Self avoiding core

C_α

N

C

ϕ_1

ϕ_2

2.0 Å

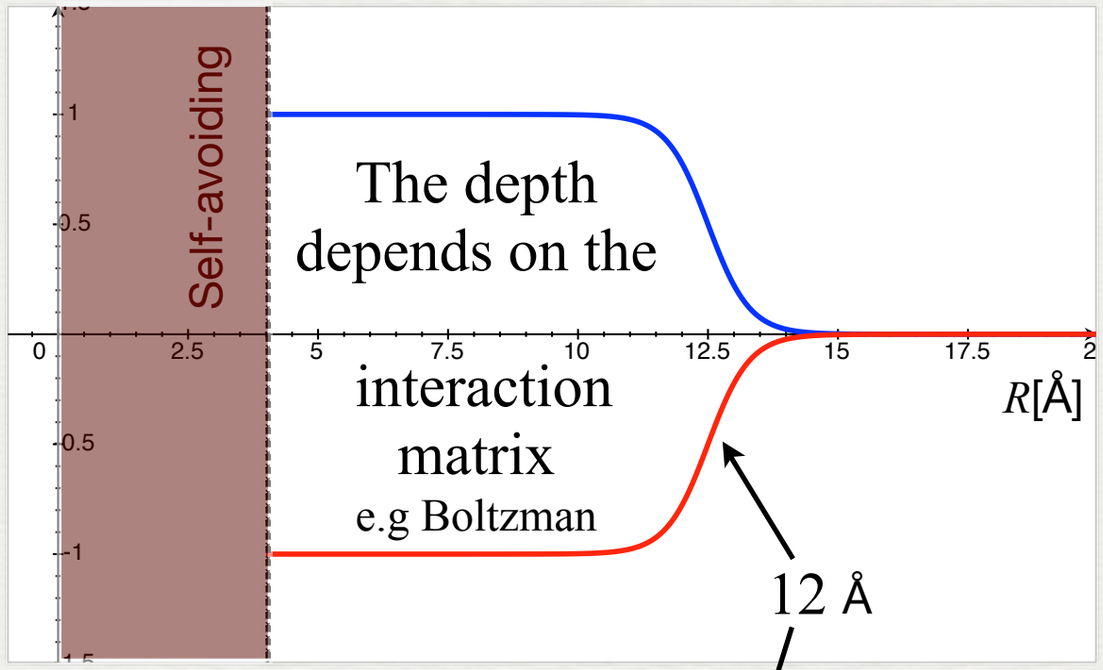
Hydrogen bonds

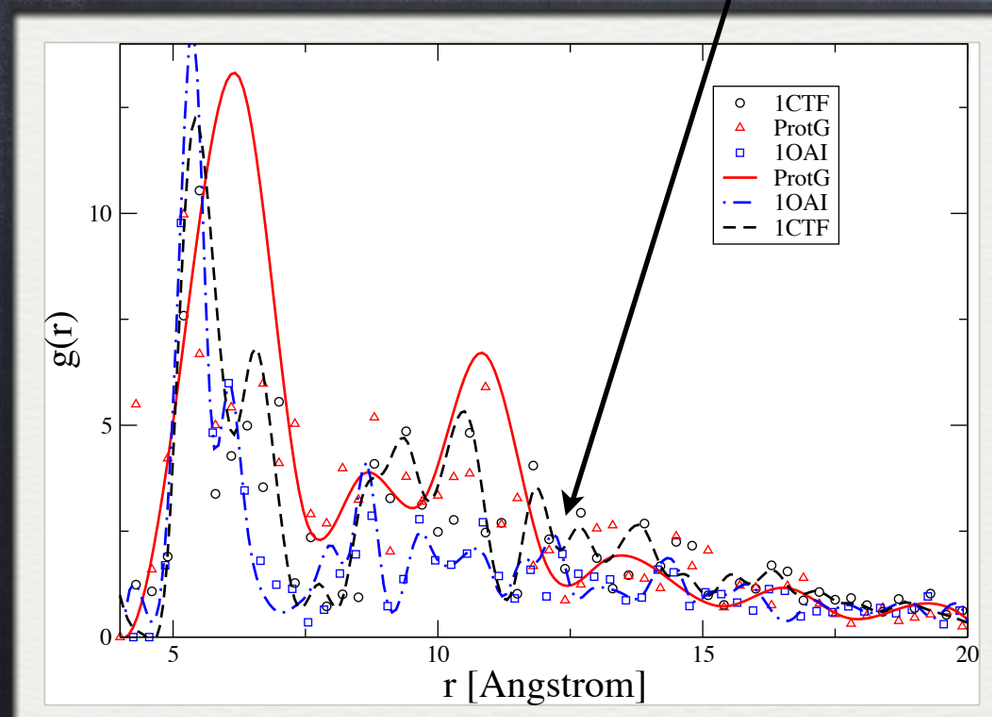
Chain rigidity

Coluzza I., **Plos ONE 10.1371/journal.pone.0020853 (2011)**

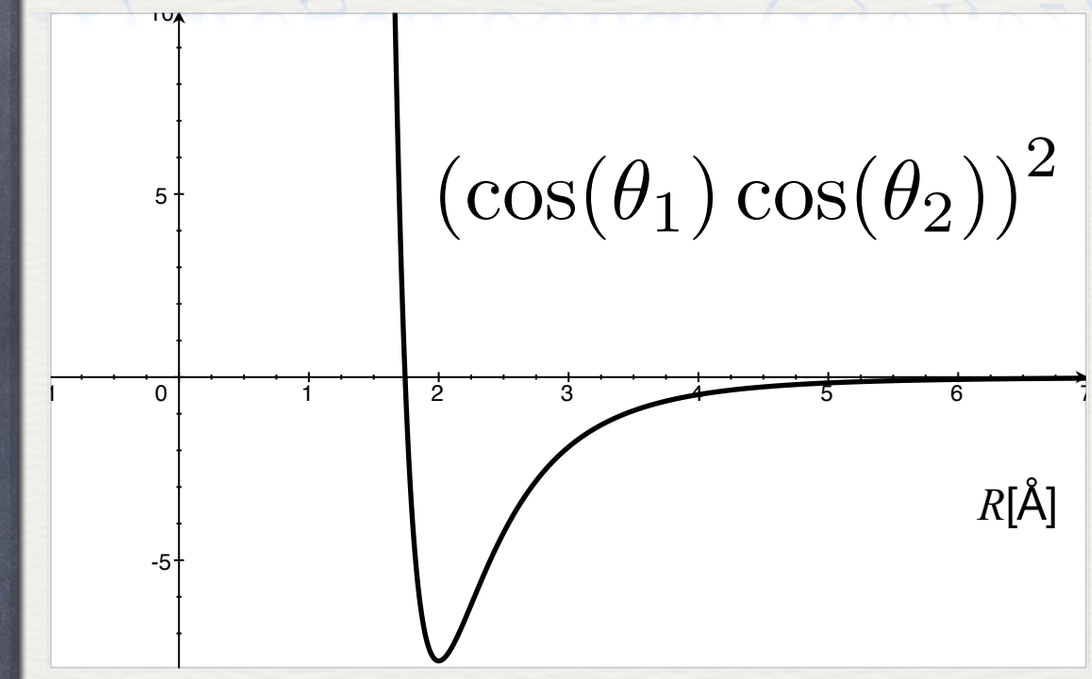
Interaction Potentials

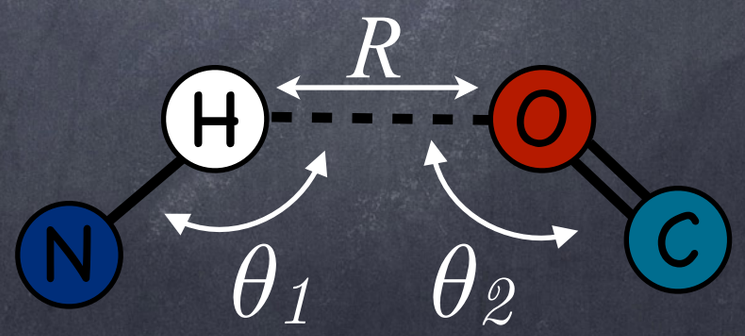
Side chains Interactions (R)





Hydrogen bonds (R, θ_1, θ_2)



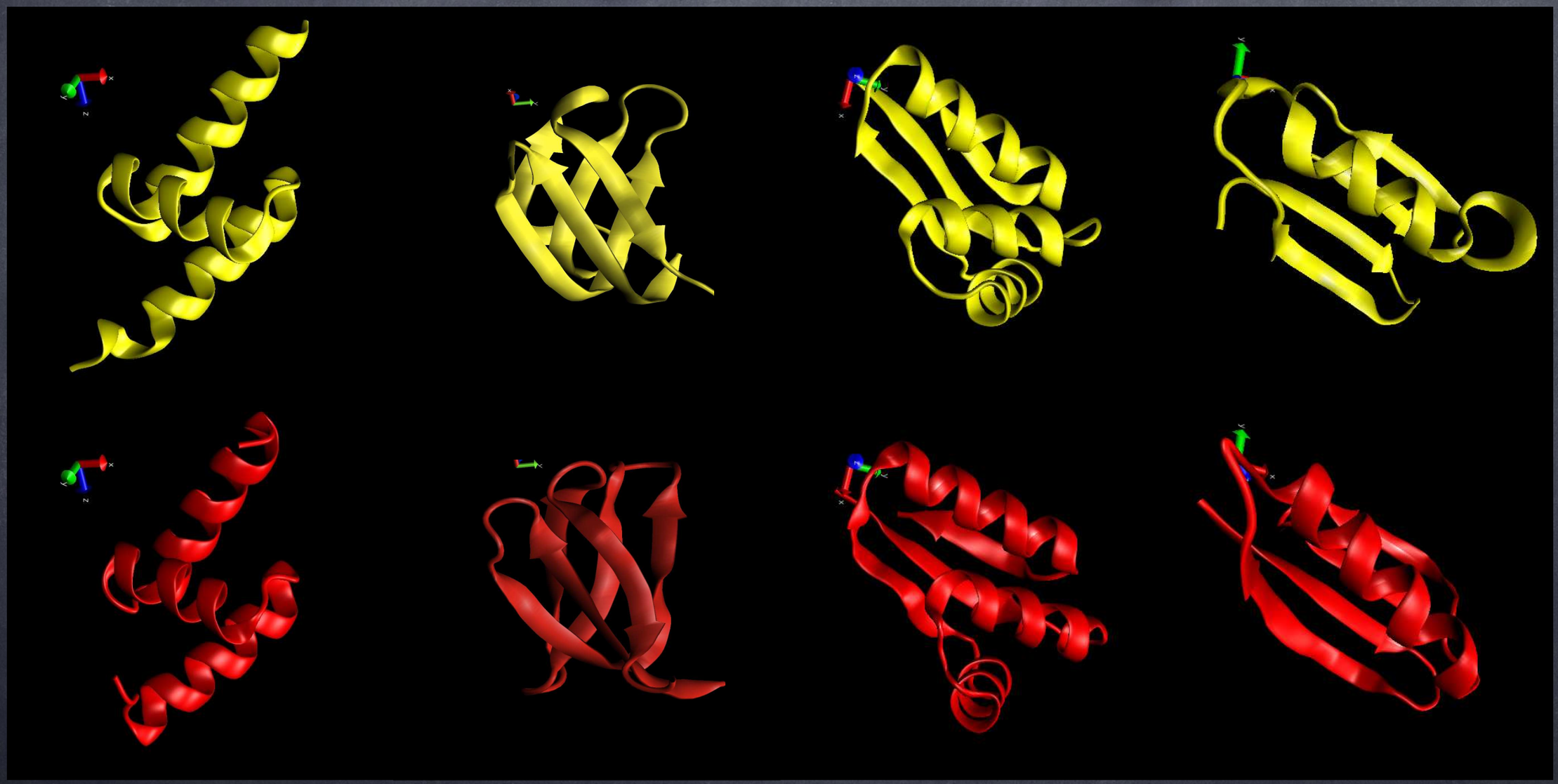


Miyazawa, S., & Jernigan, R. L, **Macromolecules, 18(3), 534–552 (1985).**

Favrin et al. **J Chem Phys 114 (18) pp. 8154-8158 (2001)**

Coluzza I., **Plos ONE 10.1371/journal.pone.0020853 (2011)**

Examples of caterpillar design - folding



Nuclear RNA export factor (1OAI)

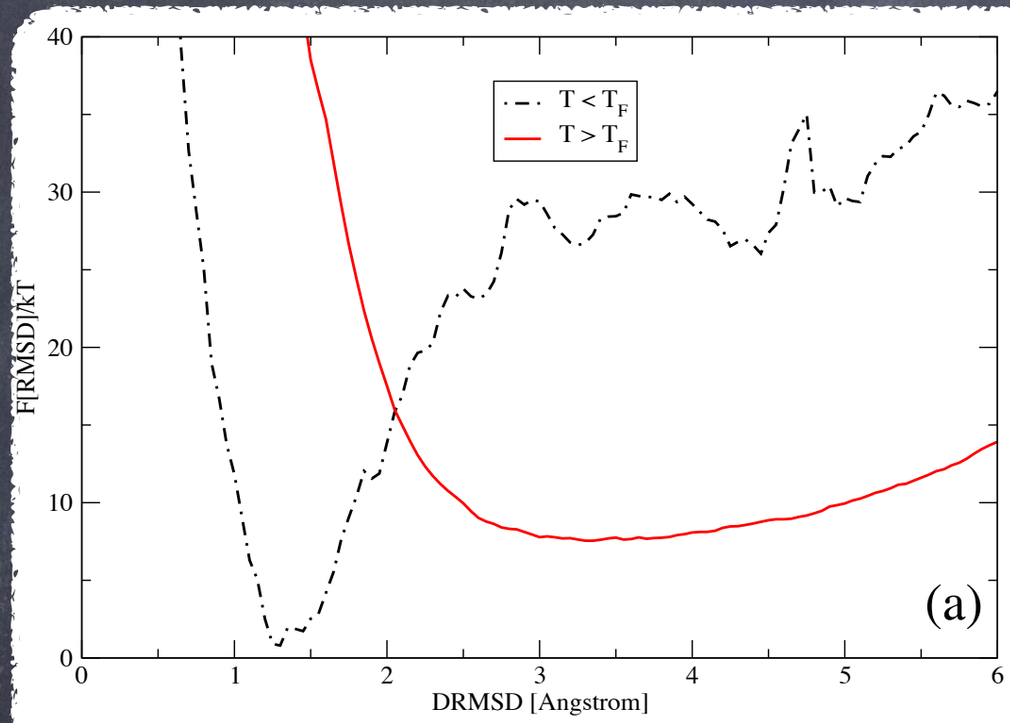
Lipoprotein (2K57)

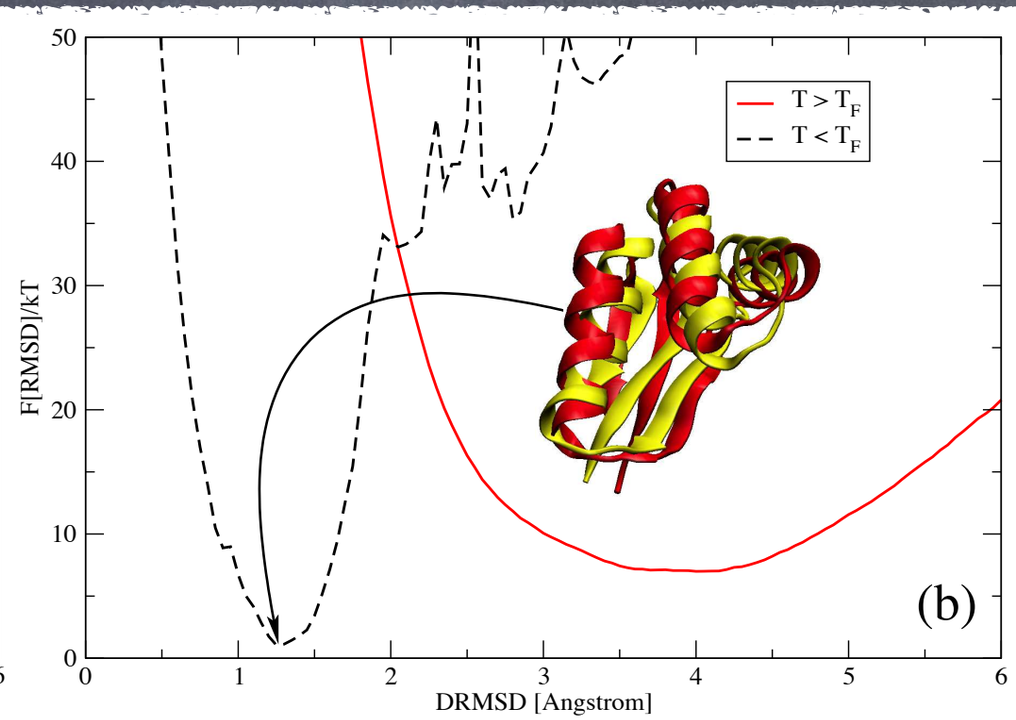
C-Terminal domain of the Ribosomal Protein (1CTF)

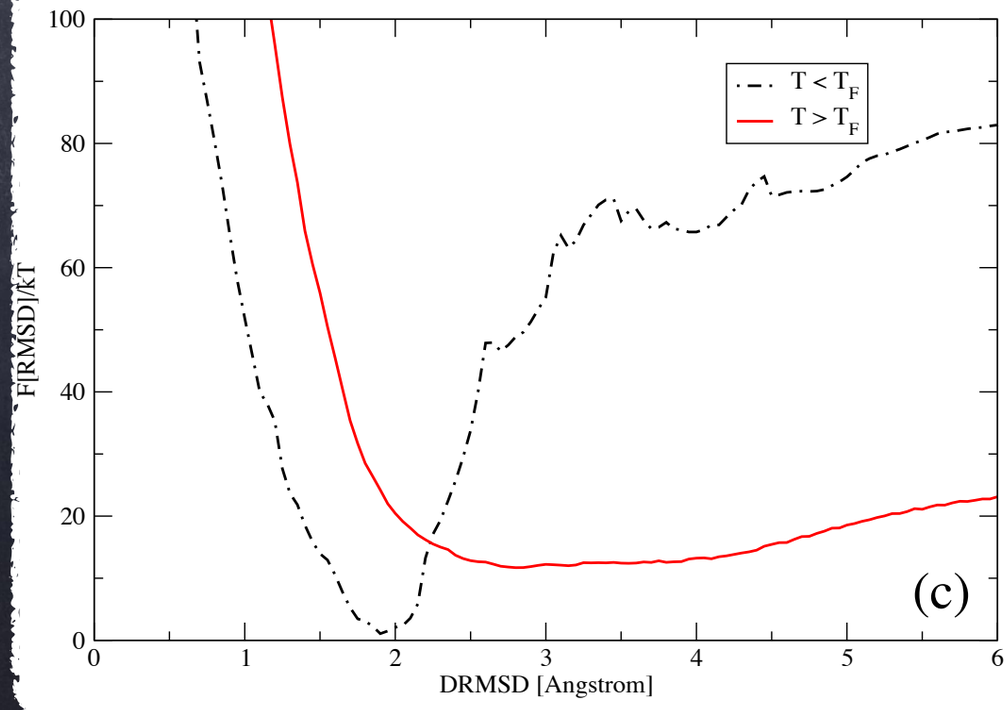
Protein G (1PGB)

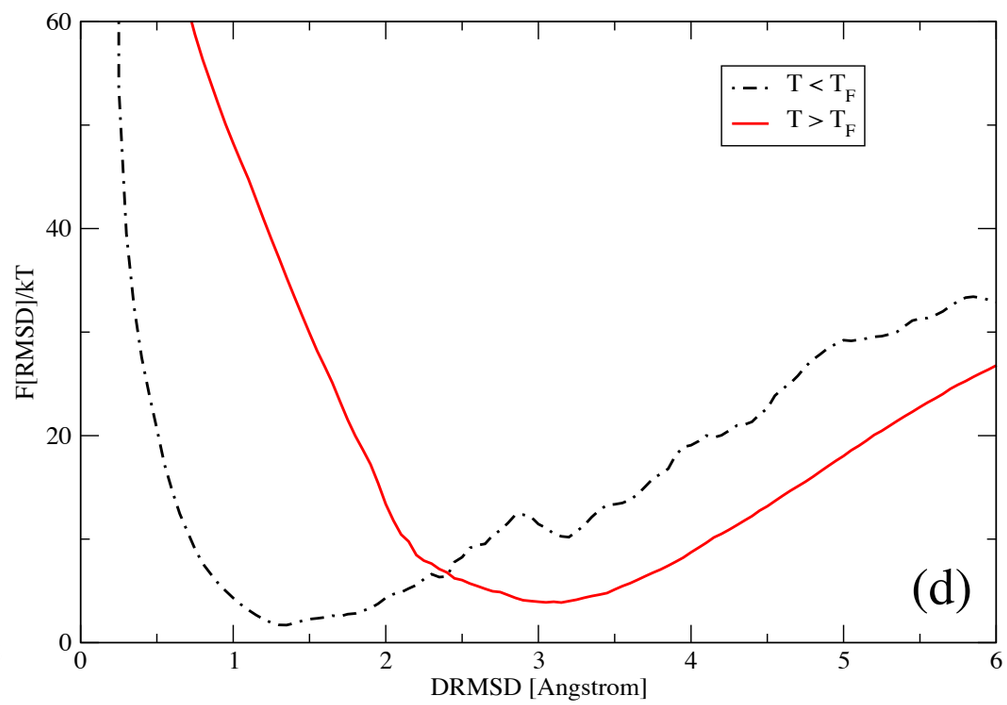
Coluzza I., **Plos ONE 10.1371/journal.pone.0020853 (2011)**

Folding Free energy of designed proteins









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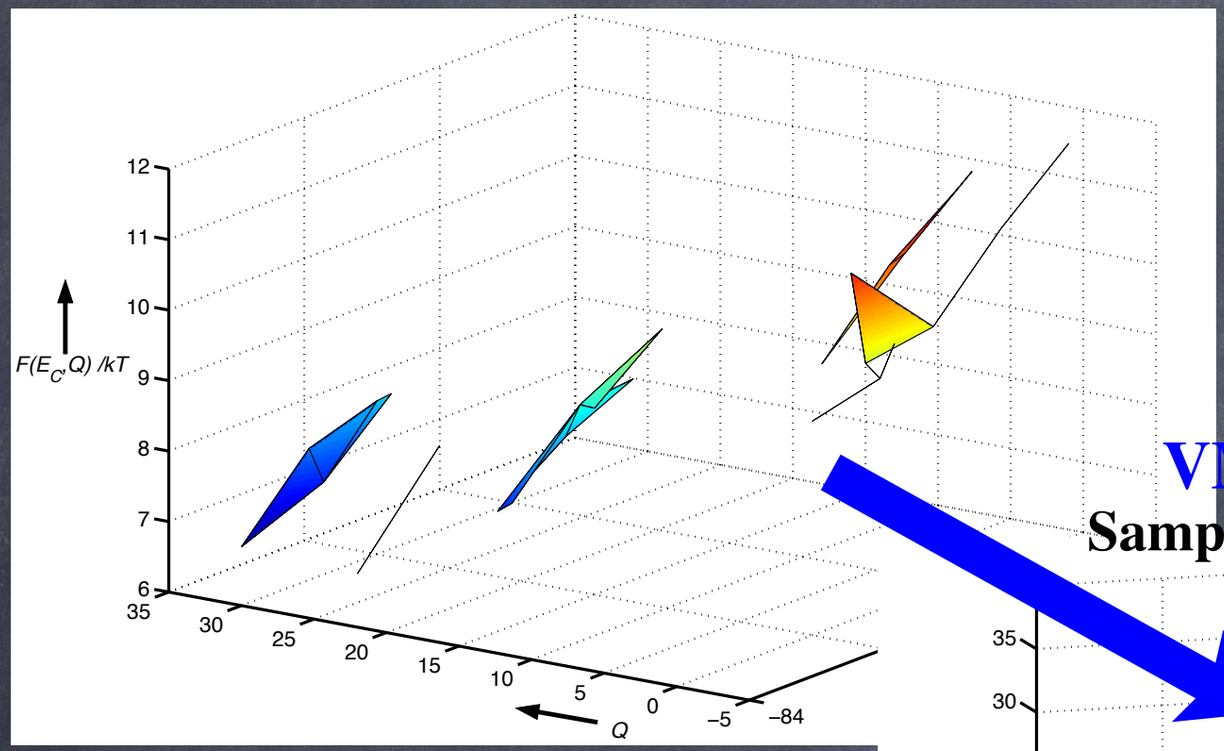
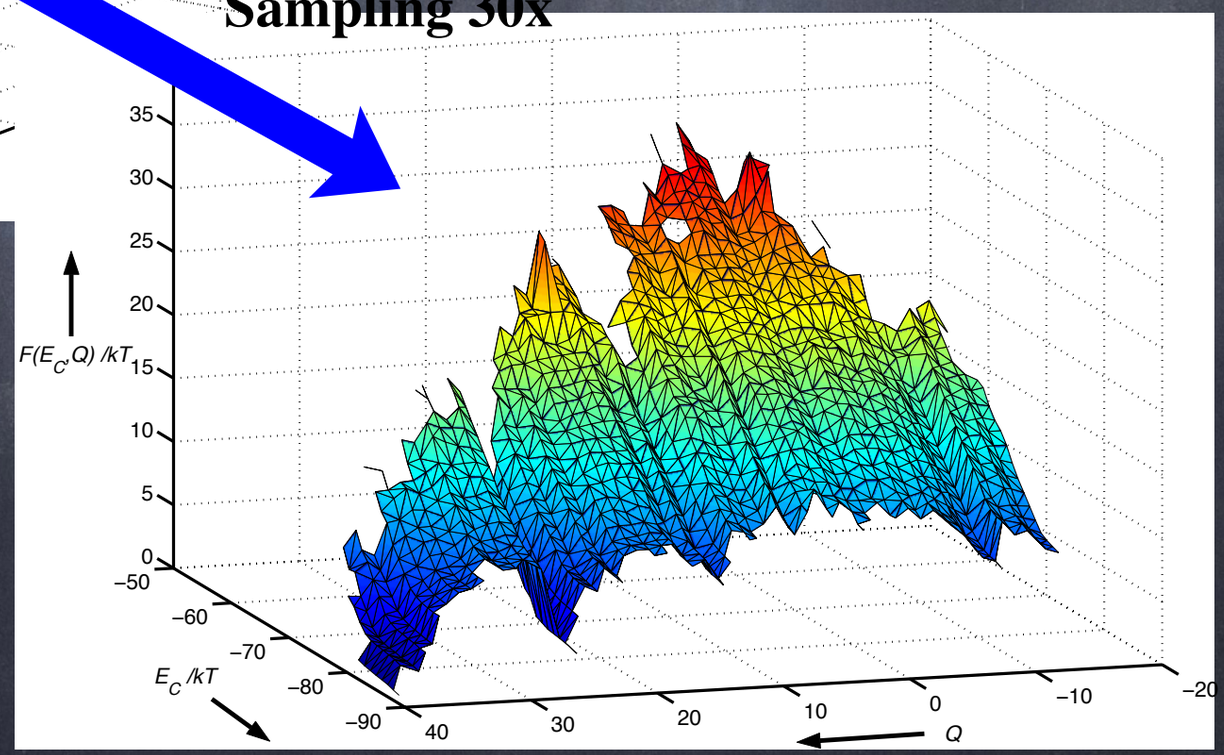


VMPT

Sampling 30x



Coluzza, I., & Frenkel, D. **Chem.Phys.Chem., 6(9), 1779–83 (2005).**

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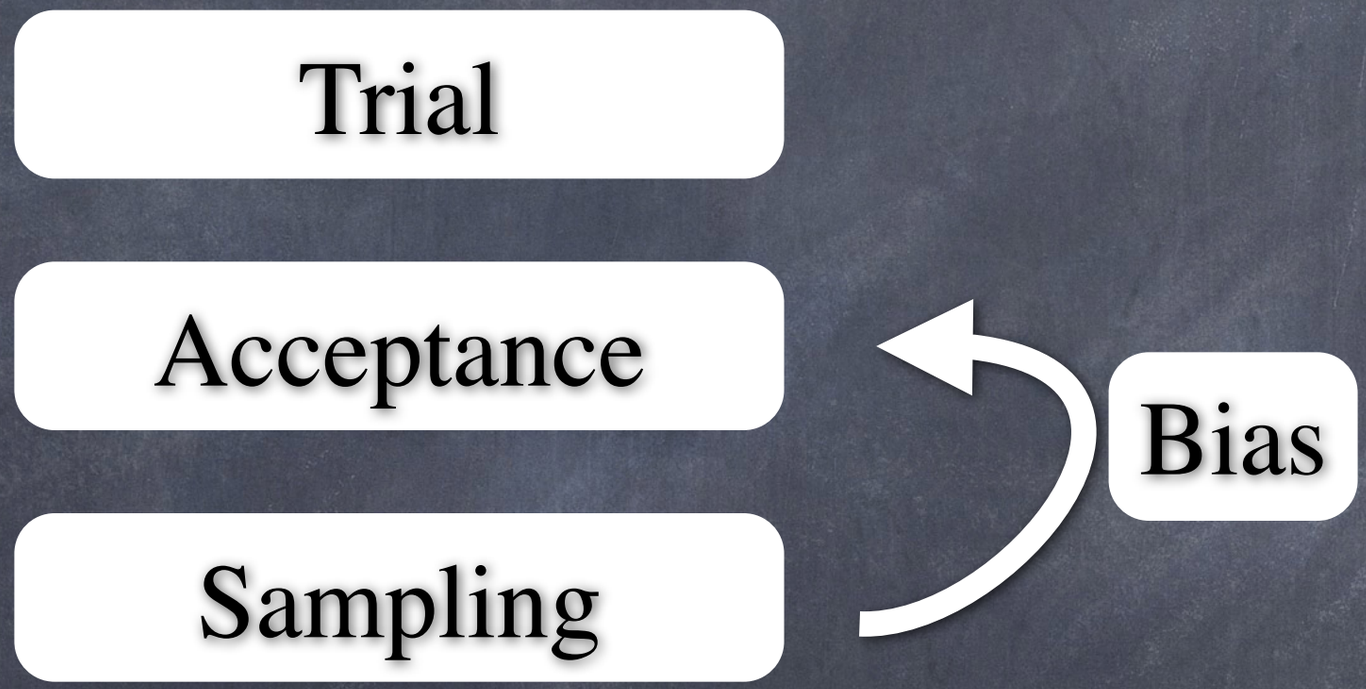
Virtual Move Parallel Tempering



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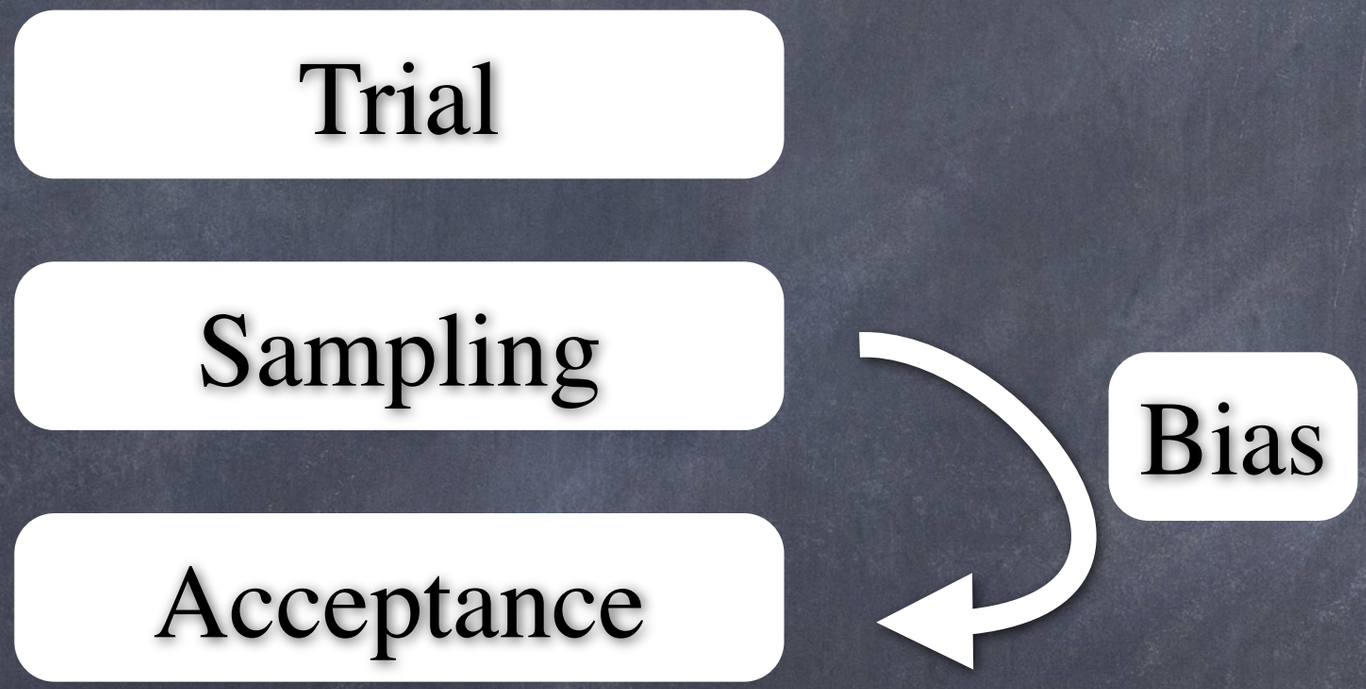

Frenkel, D. **PNAS 101(51), 17571–5 (2004).**

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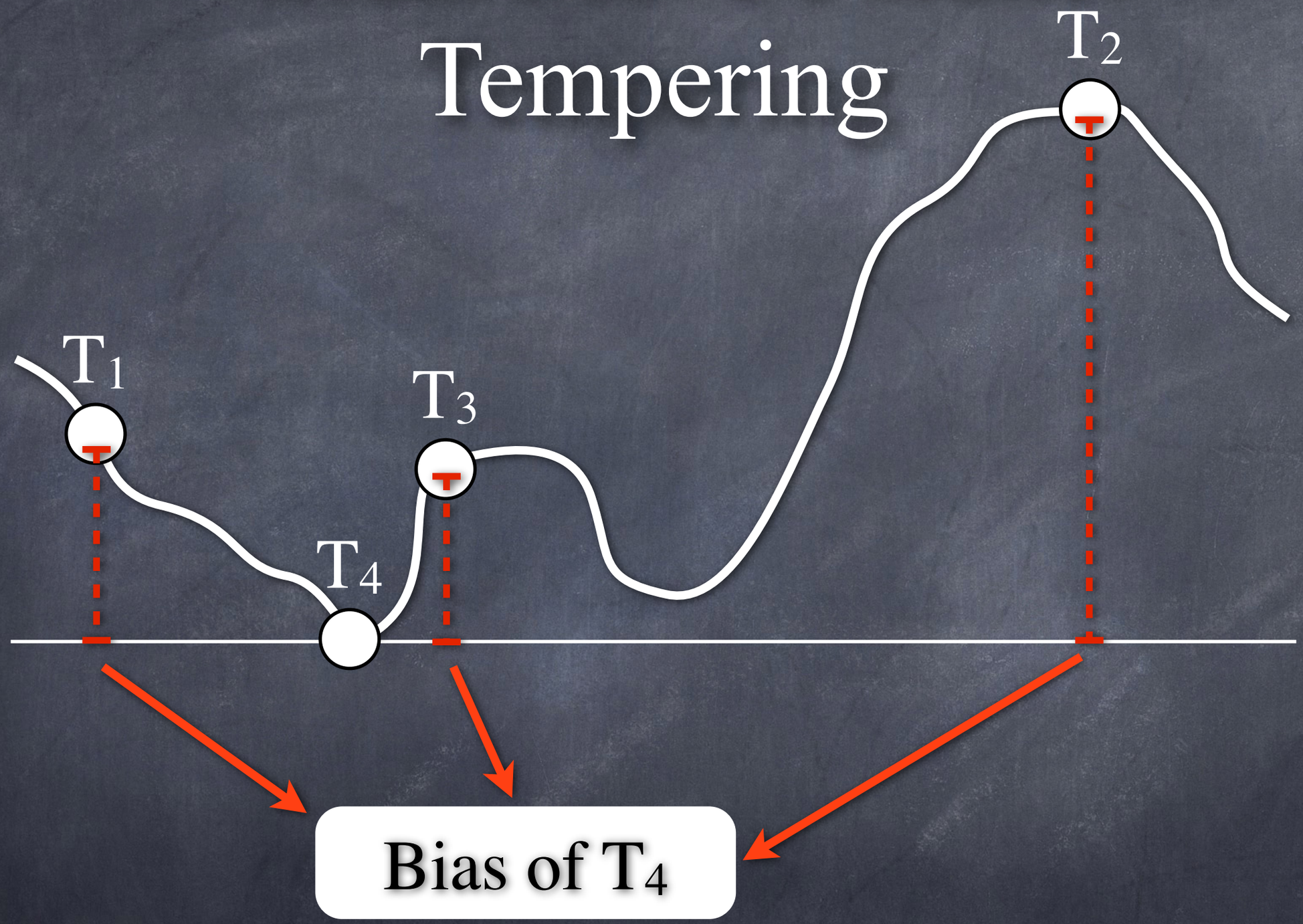
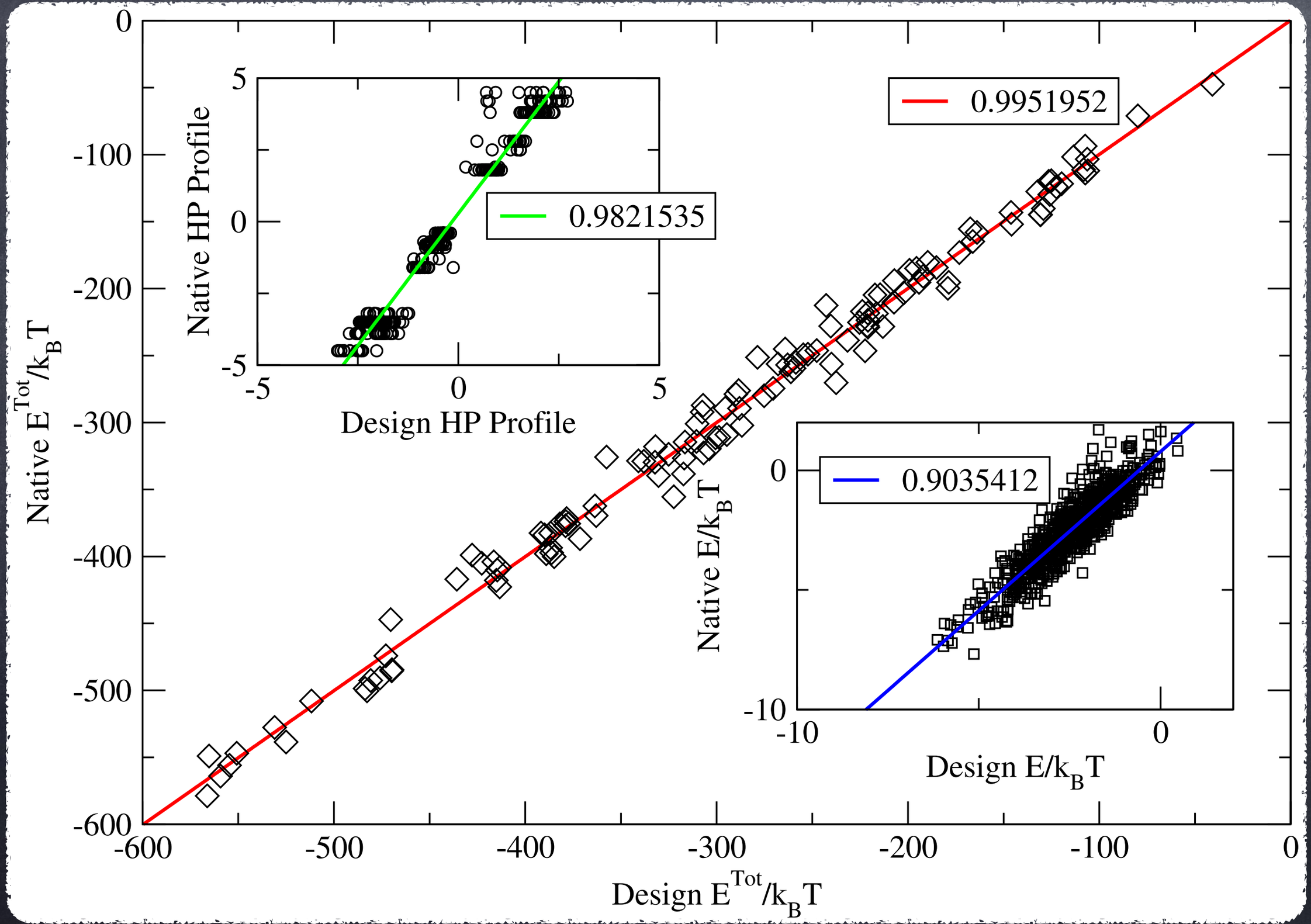
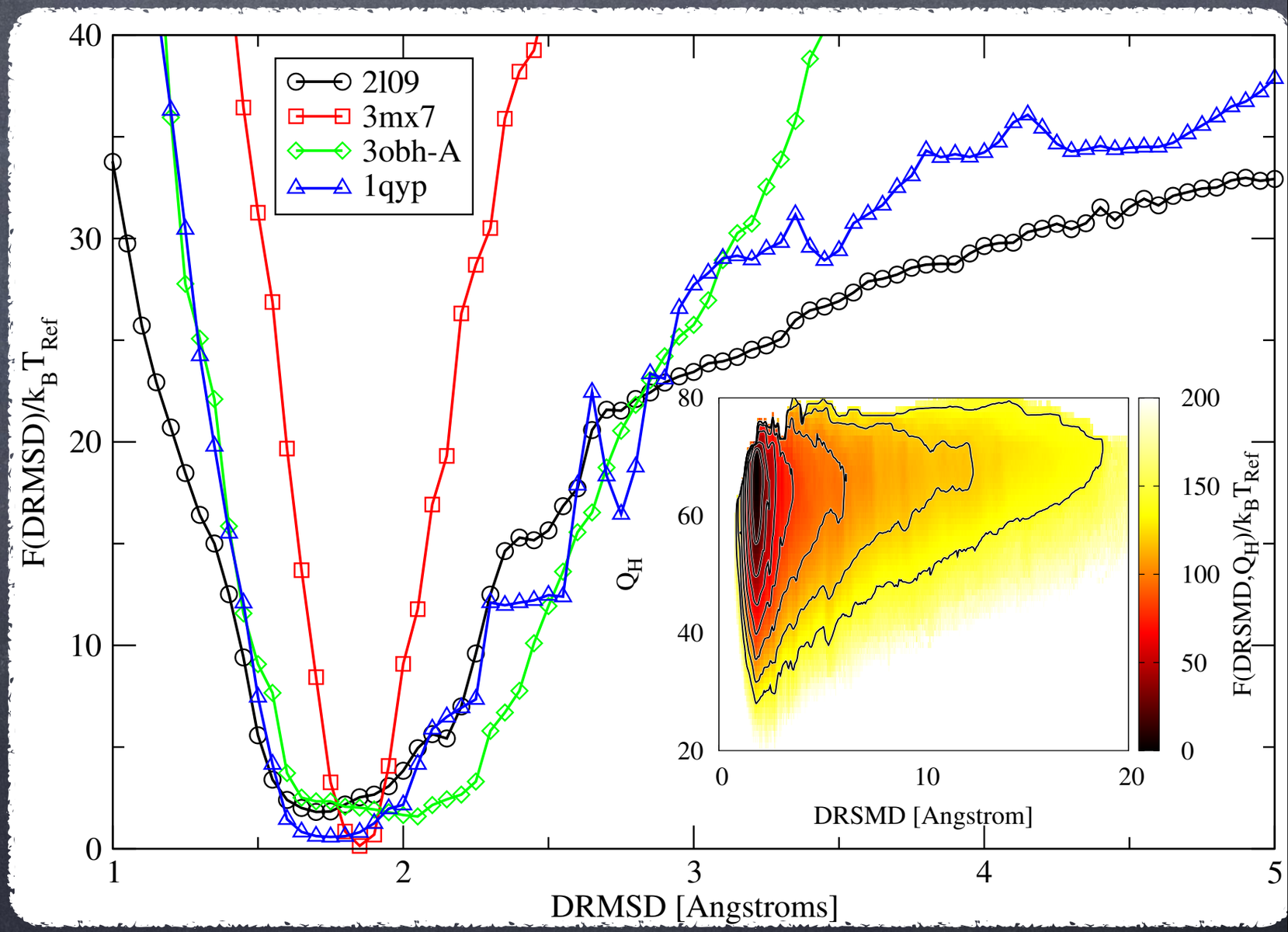


Optimized potential over 120 proteins



Folding Free energy of designed proteins with optimized potential



Coluzza I., **Submitted (2013)**

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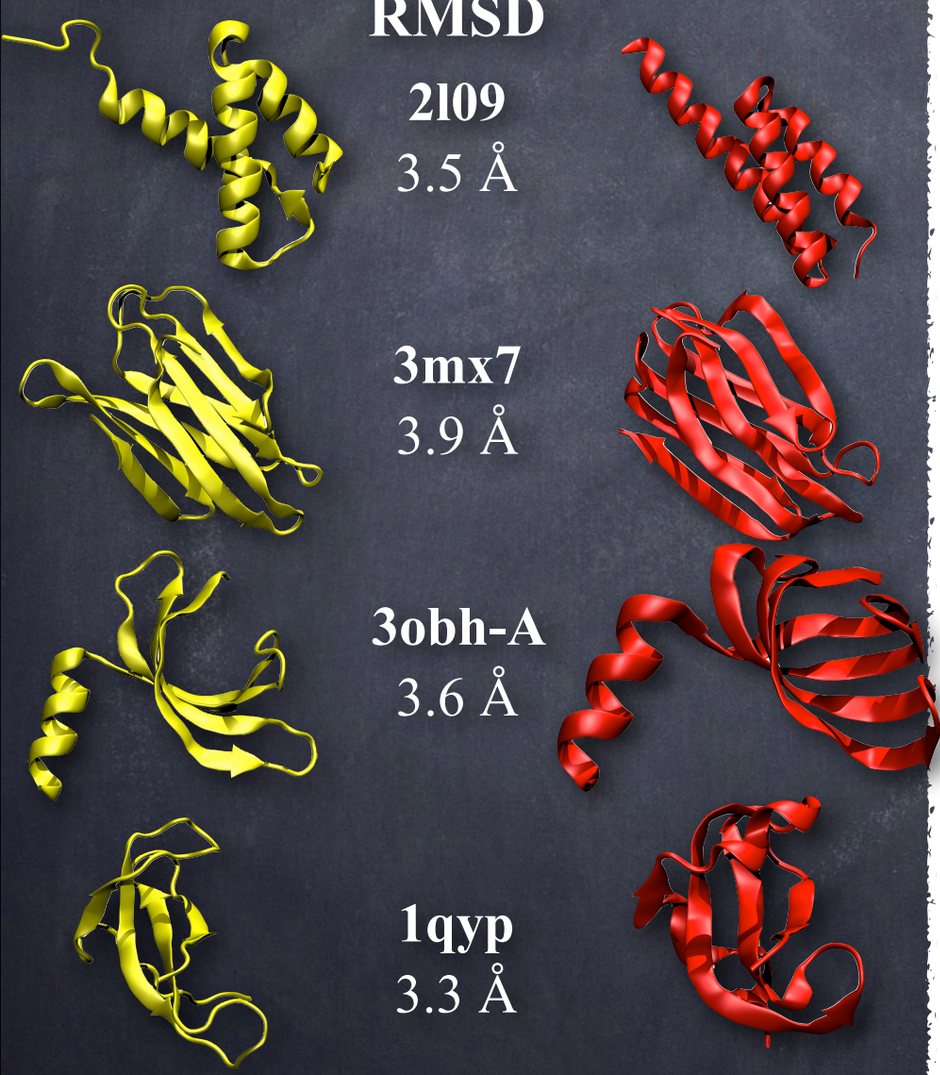

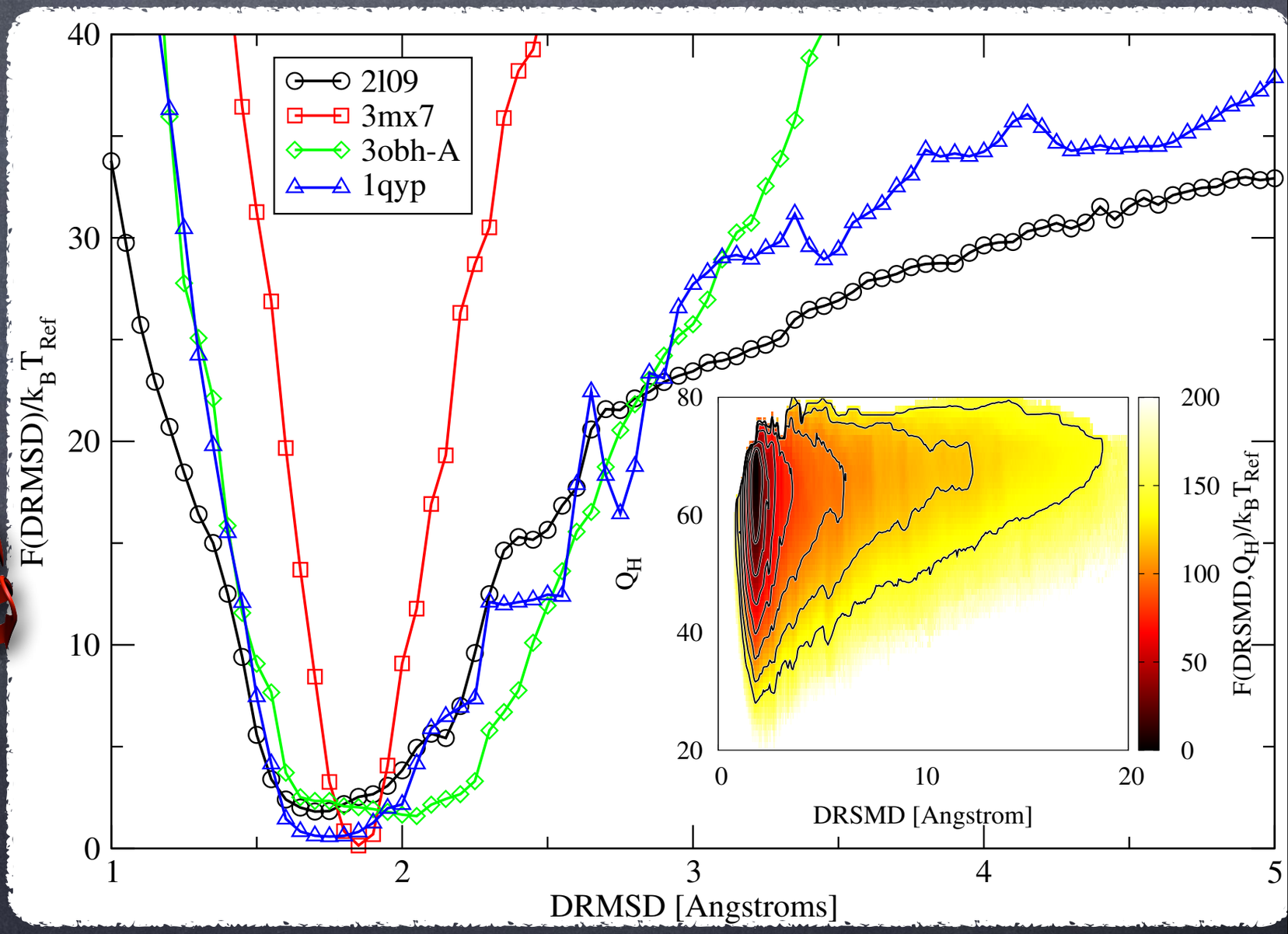

Coluzza I., **Submitted (2013)**

Folding 14 natural proteins not in the set

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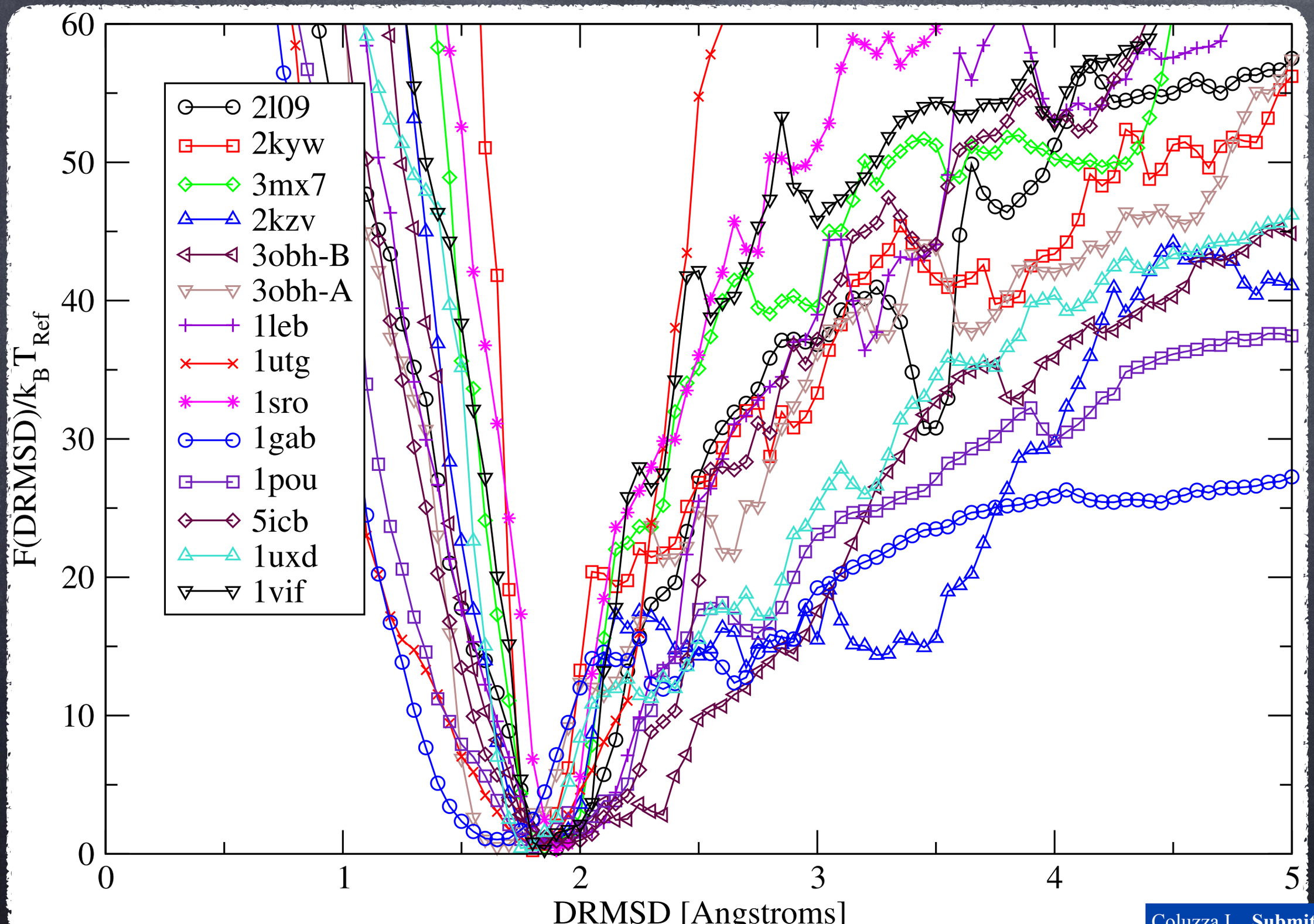

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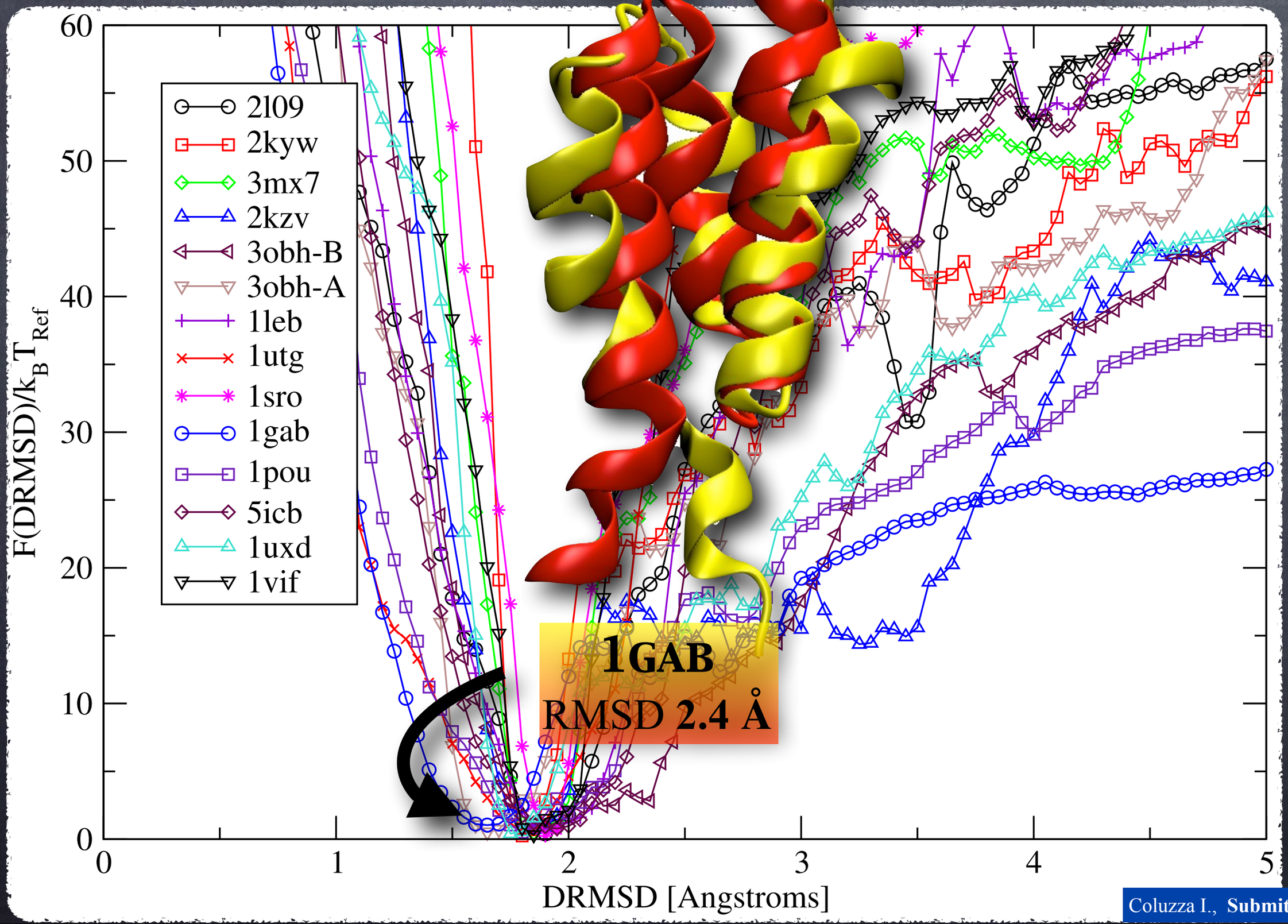

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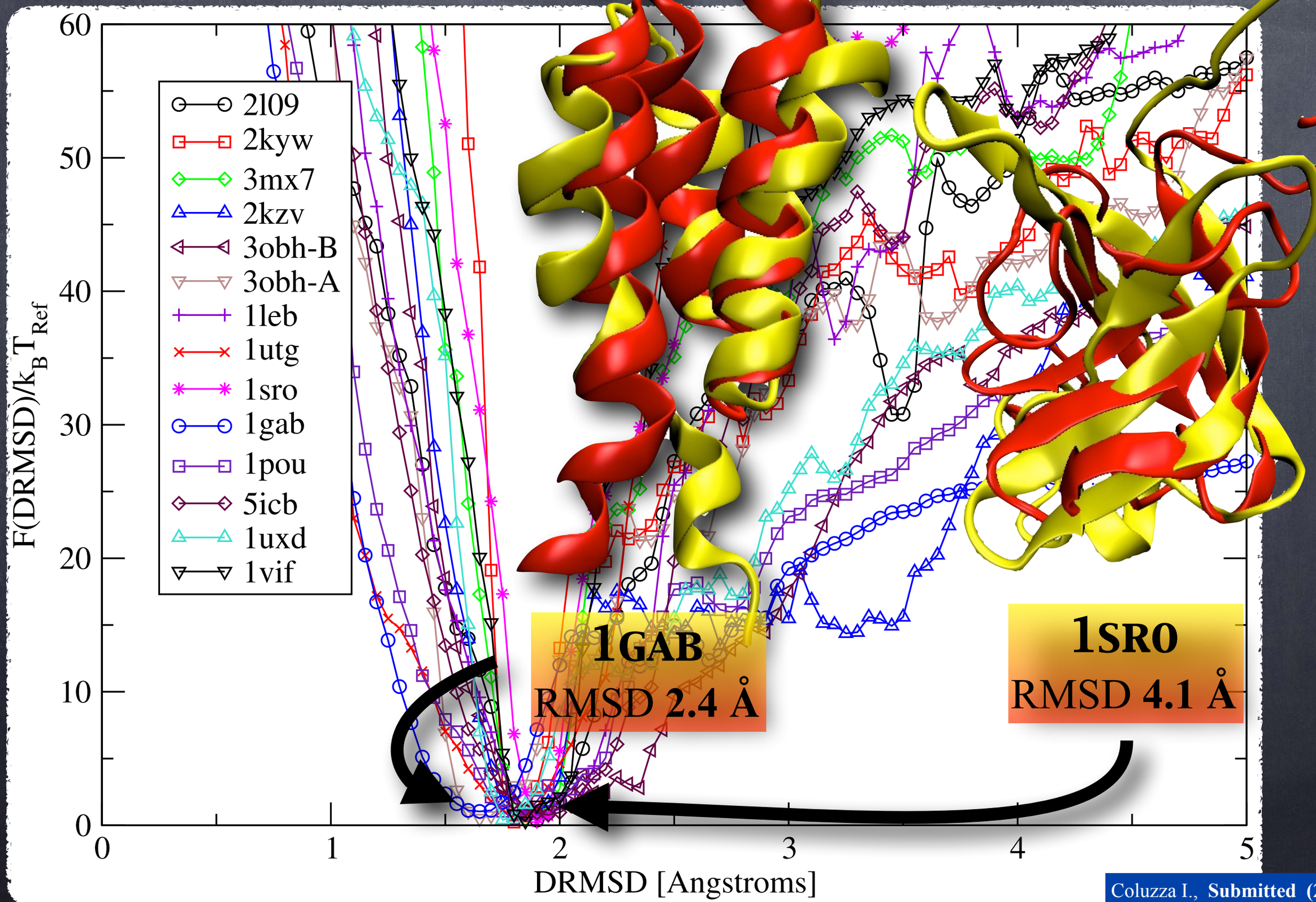
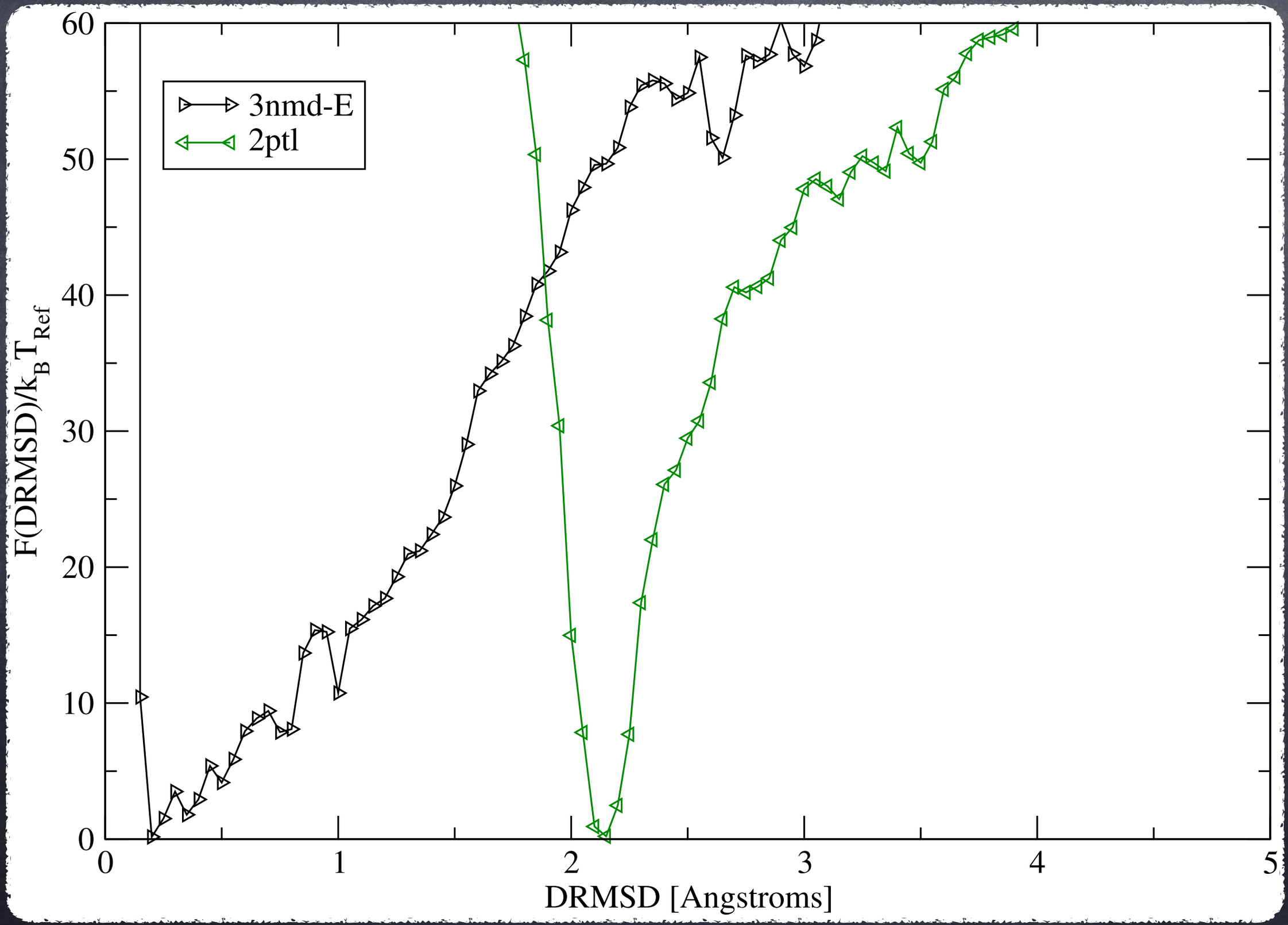


Coluzza I., **Submitted (2013)**

...2 extreme cases



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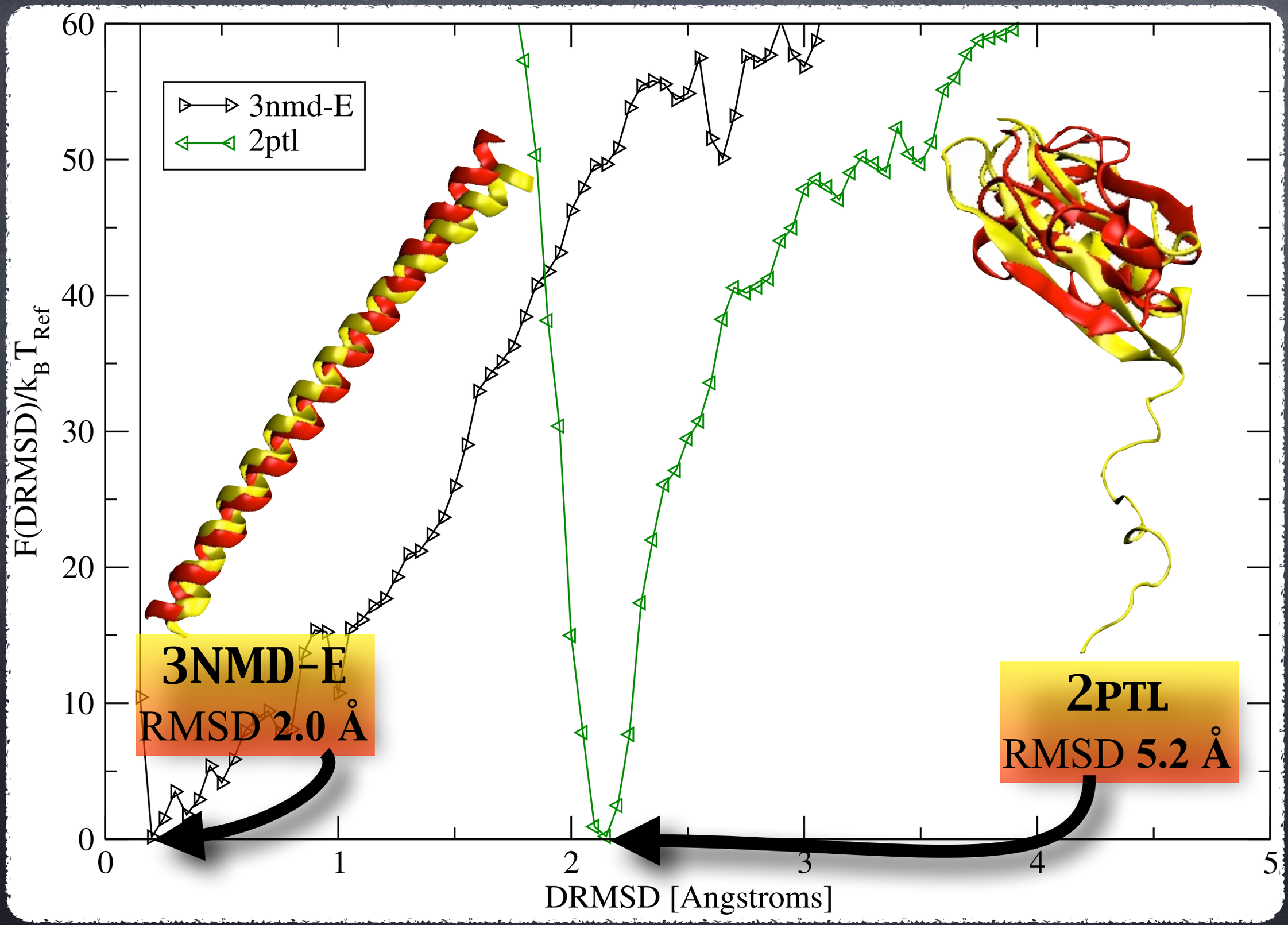
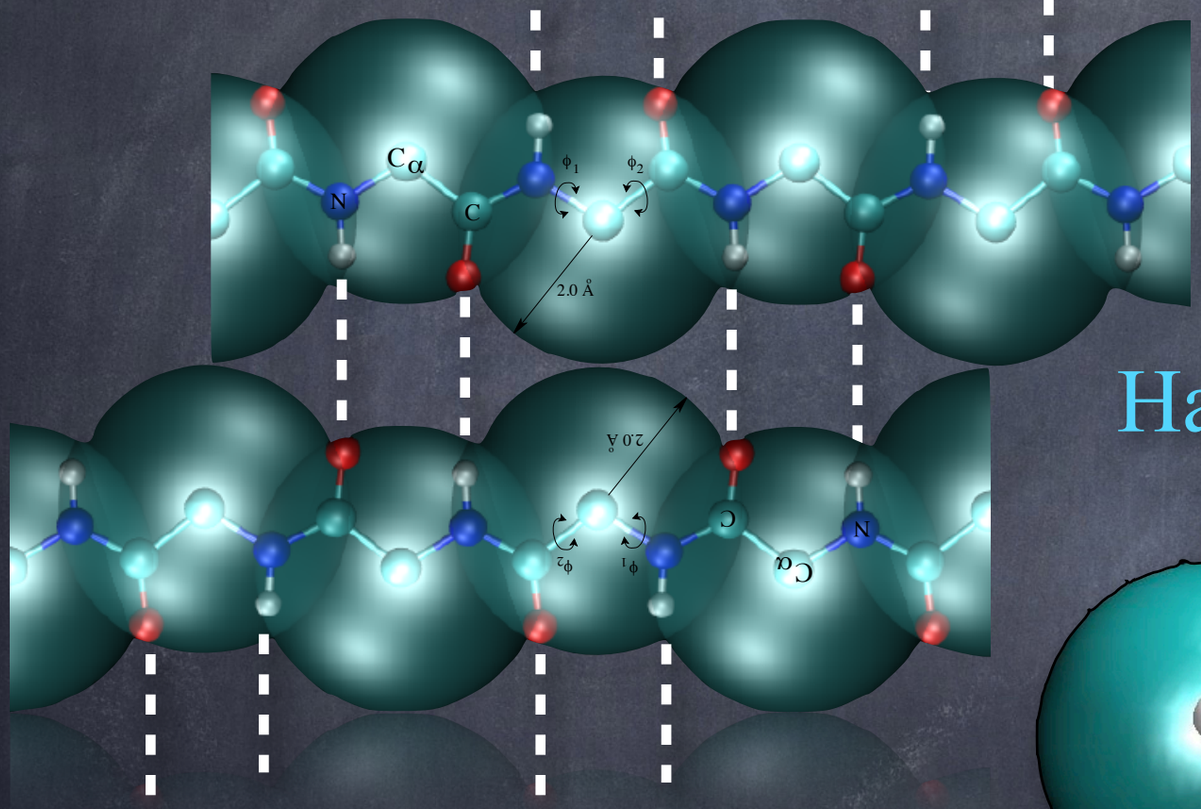
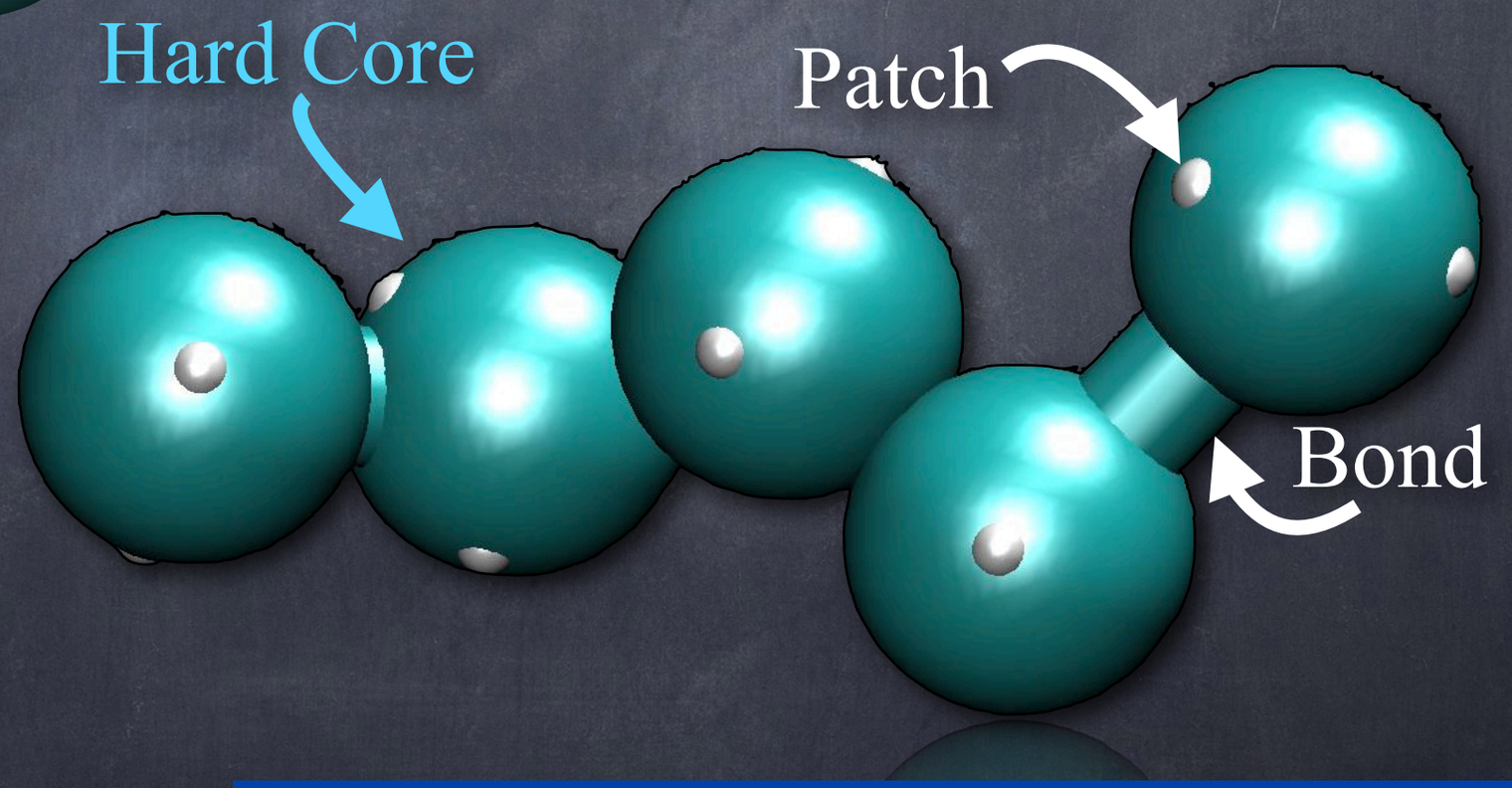


Artificial Protein

Hydrogen Bonds



Patchy-Particles



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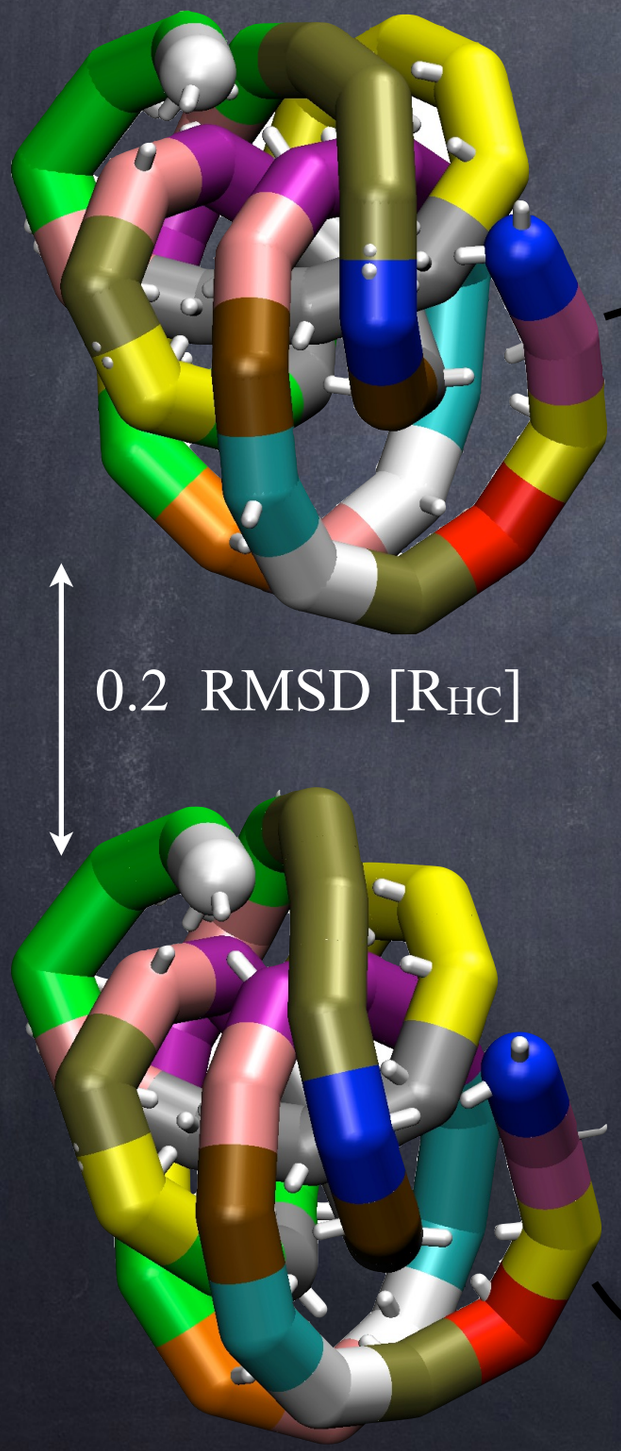
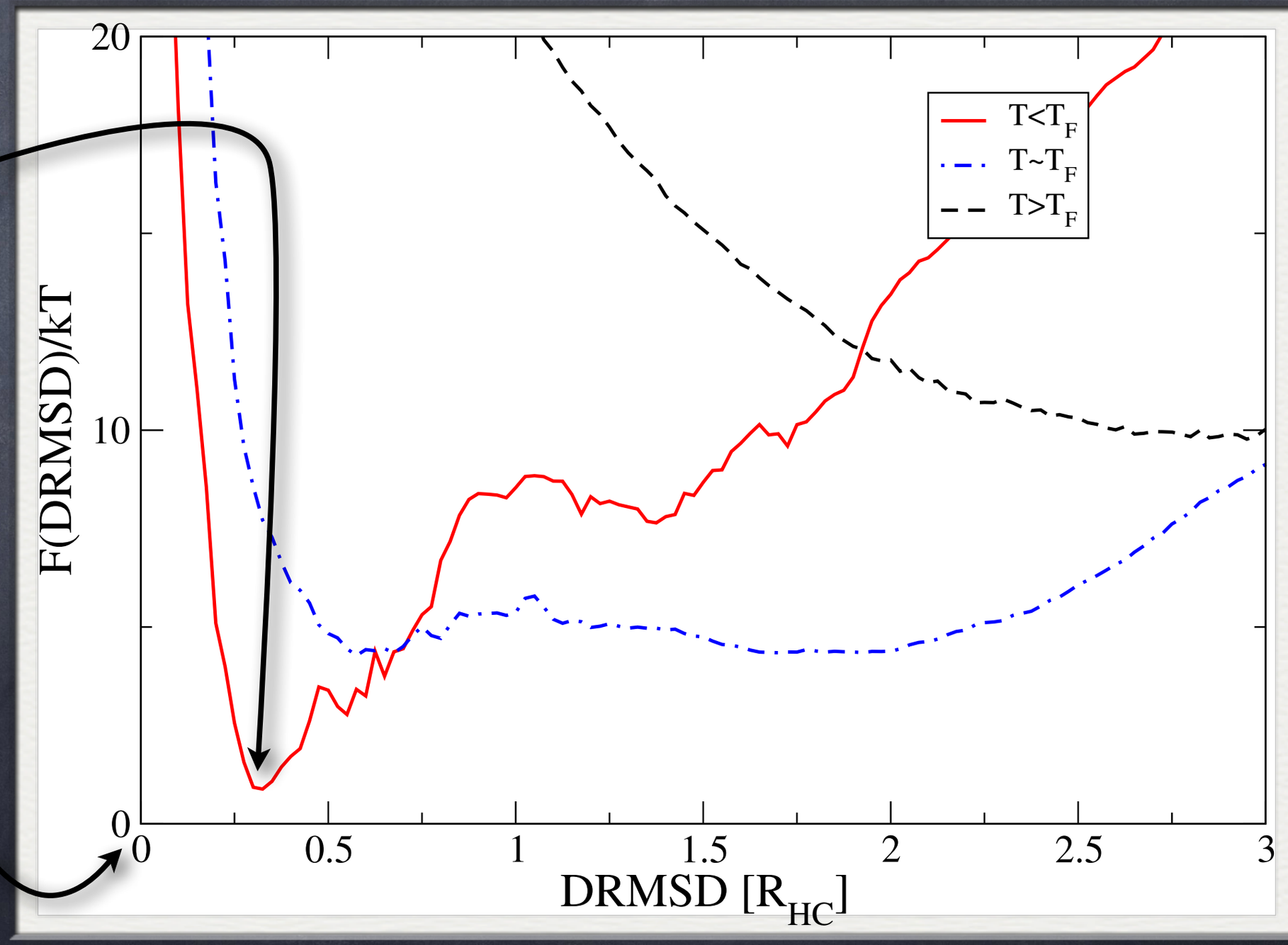
•Coluzza, I., Van Oostrum, P. D. J., Capone, B., Reimhult, E., & Dellago, C. (2013). Physical Review Letters, 110(7), 075501.

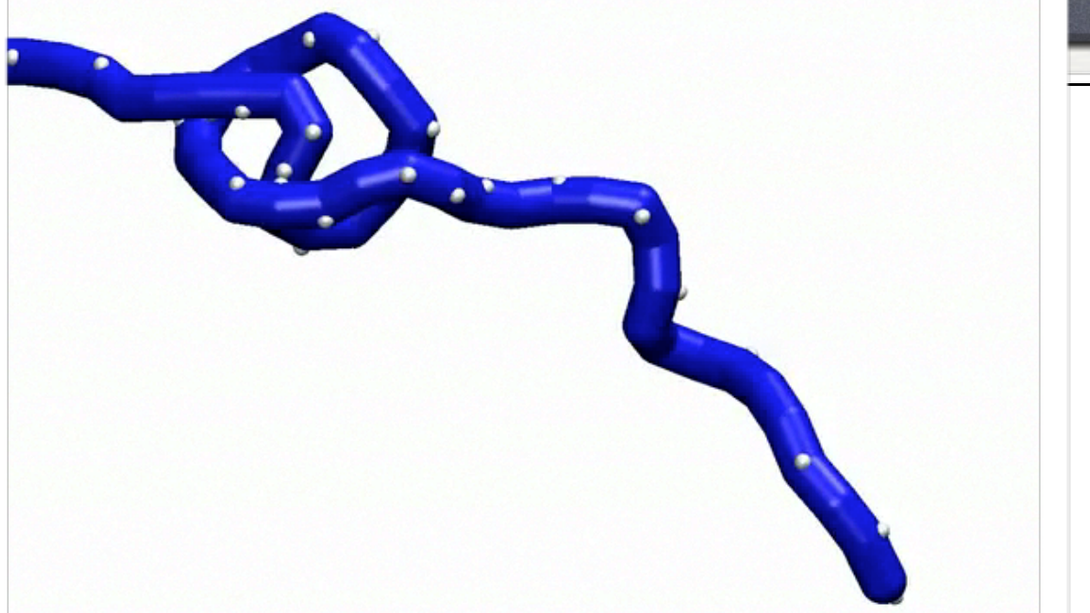
Designed self-knotting patchy polymer

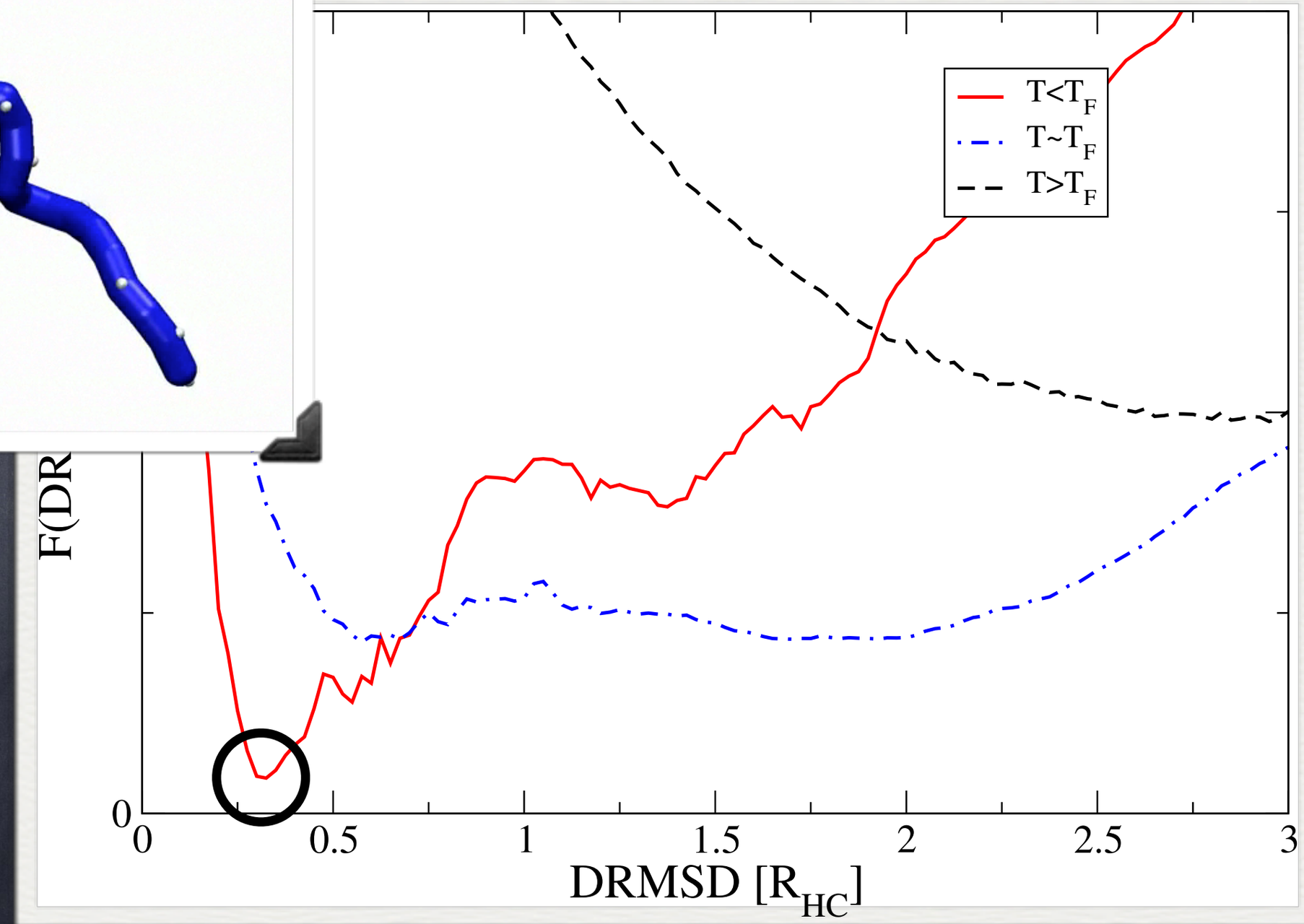




•Coluzza, I., Van Oostrum, P. D. J., Capone, B., Reimhult, E., & Dellago, C. (2013). Physical Review Letters, 110(7), 075501.

Designed self-knotting patchy polymer





•Coluzza, I., Van Oostrum, P. D. J., Capone, B., Reimhult, E., & Dellago, C. (2013). Physical Review Letters, 110(7), 075501.

Conclusions

- A simple model of a protein can be designed and correctly folded
- The folding is dominated by the interplay between heterogeneous isotropic interactions and the directionality of hydrogen bonds
- The model predicts the correct native structures for a wide range of proteins
- Constraining the configurational space is a universal principle for design of self-folding systems

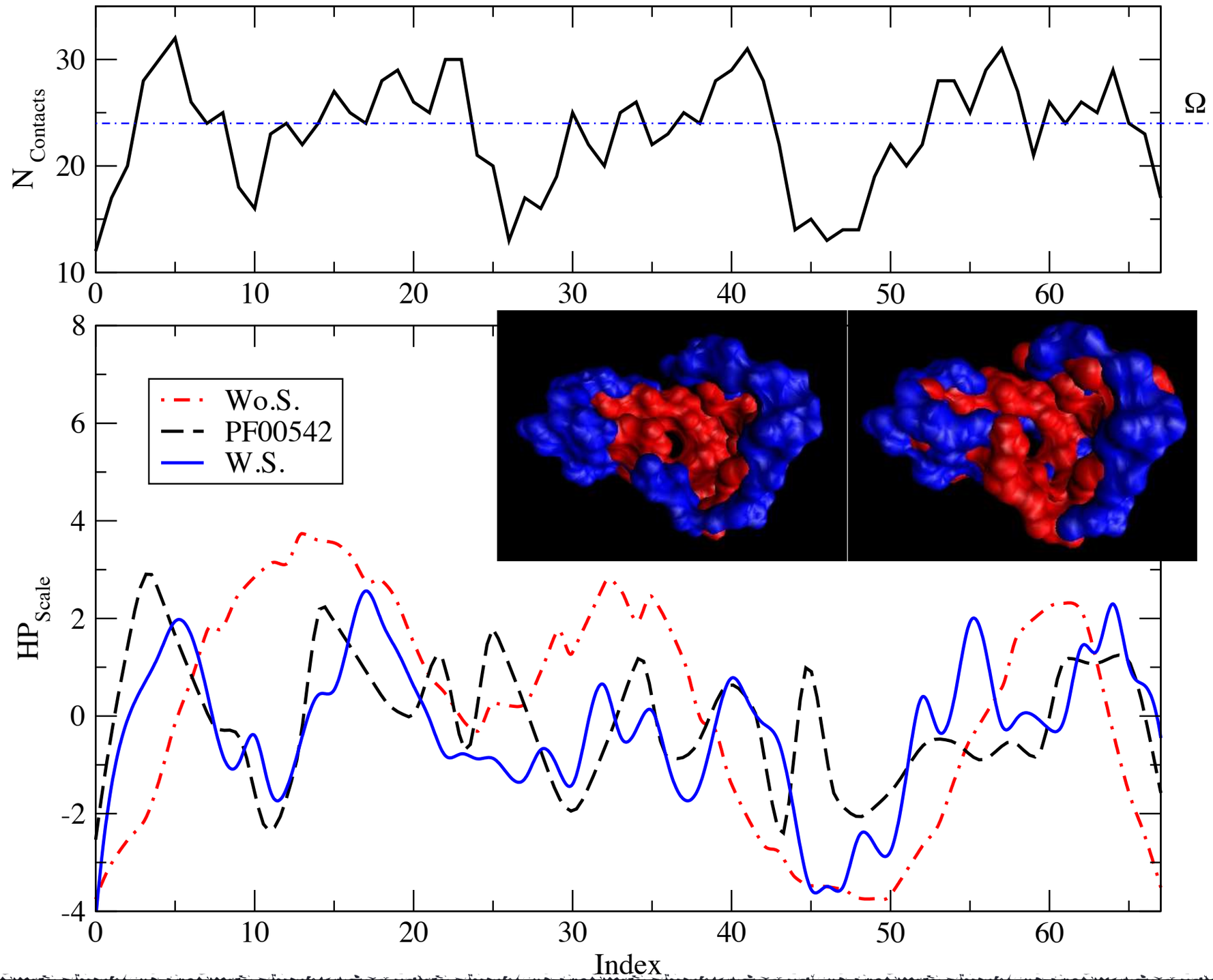
Nobel Prize in Chemistry 2013

Today the computer is just as important a tool for chemists as the test tube. Simulations are so realistic that they predict the outcome of traditional experiments

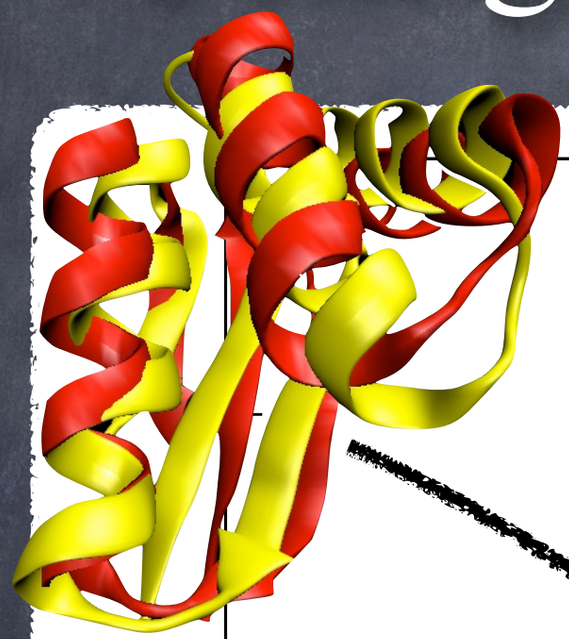
Acknowledgements

- Christoph Dellago
- Barbara Capone
- Peter van Oostrum
- Ronald Zirbs
- Erik Reimhult
- Mark Miller
- Daan Frenkel
- Angelo Cacciuto

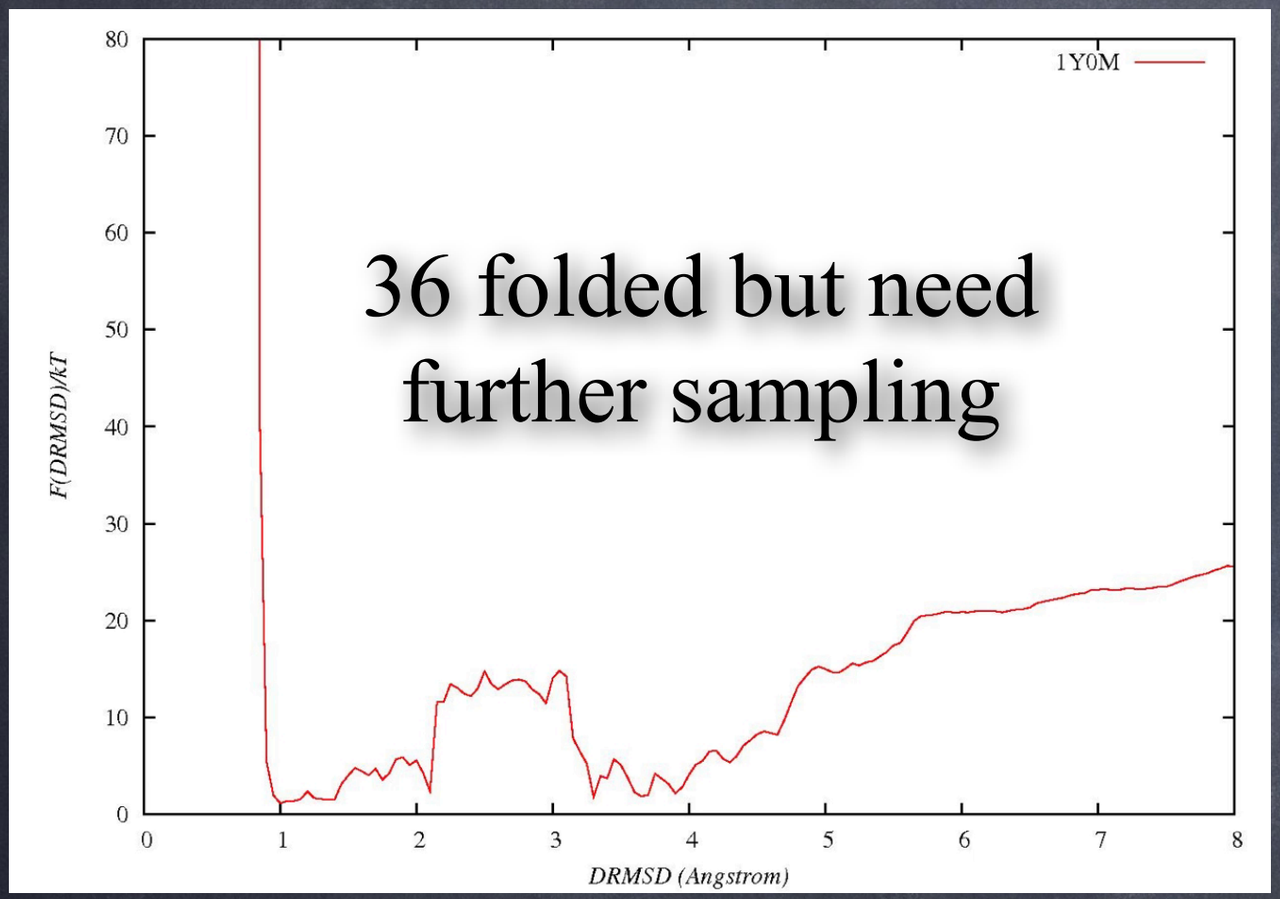
Designed HP-Profile

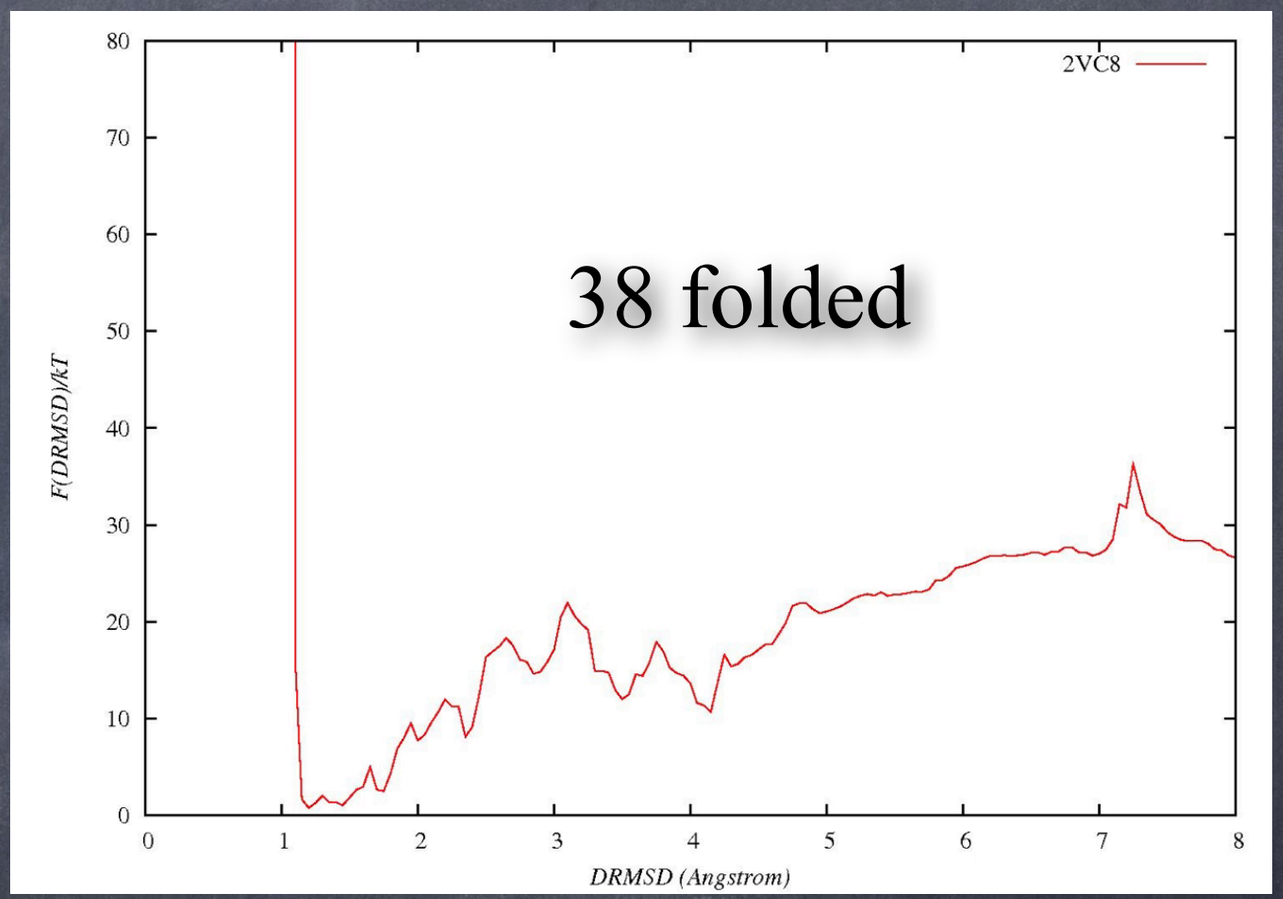


Configurational Free energy



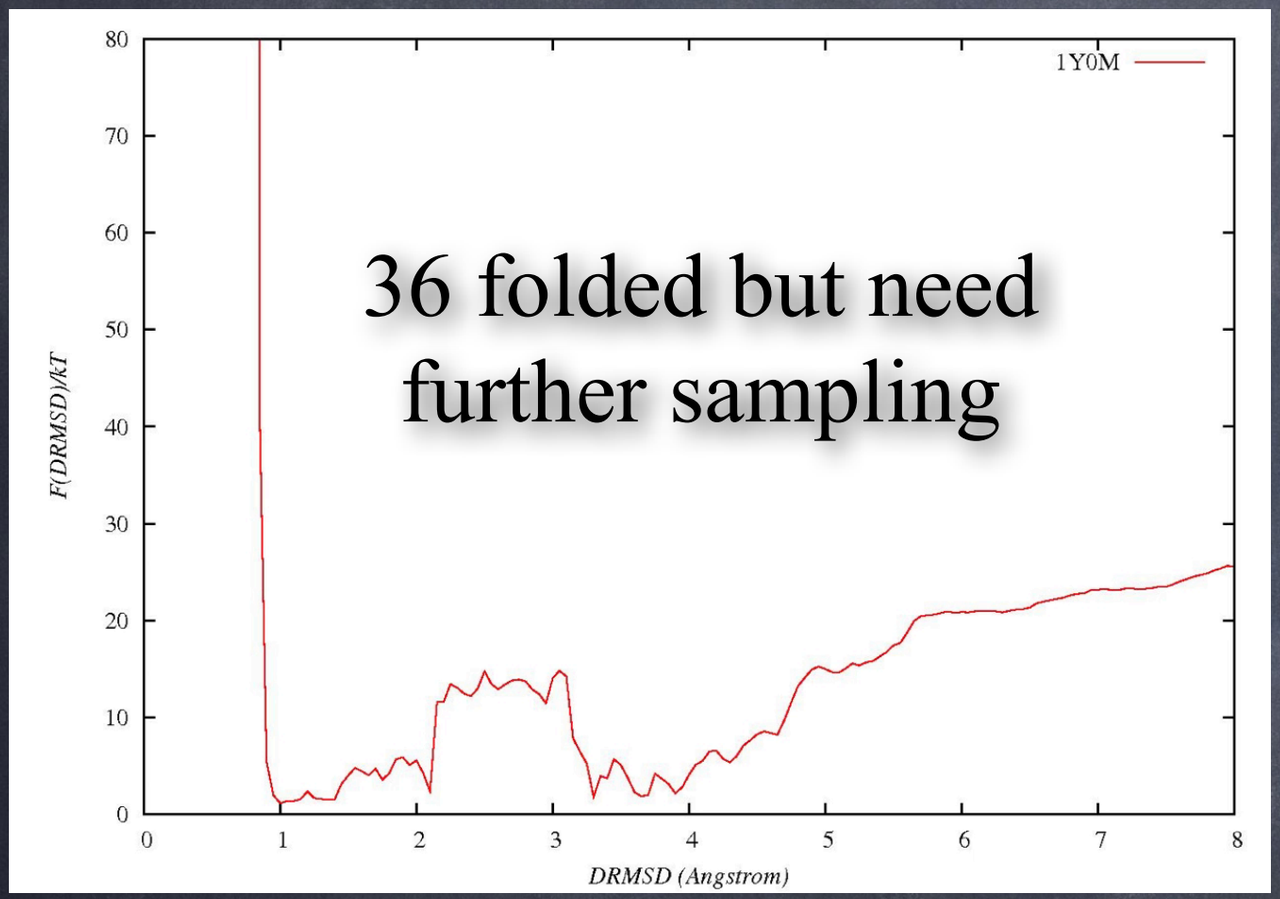
Folding the training set
132 targets

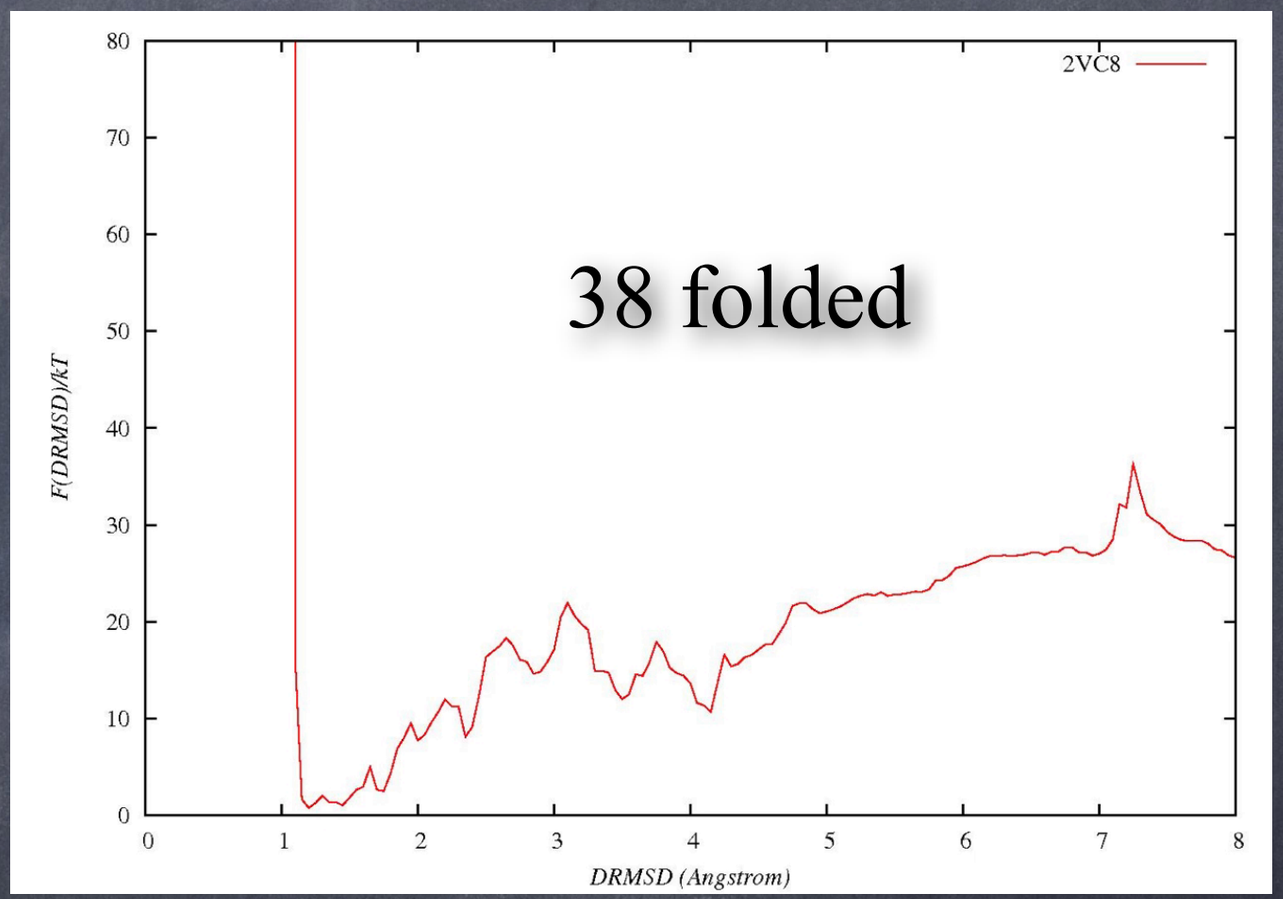




54 have not sampled
the folded state yet.

Folding the training set
132 targets

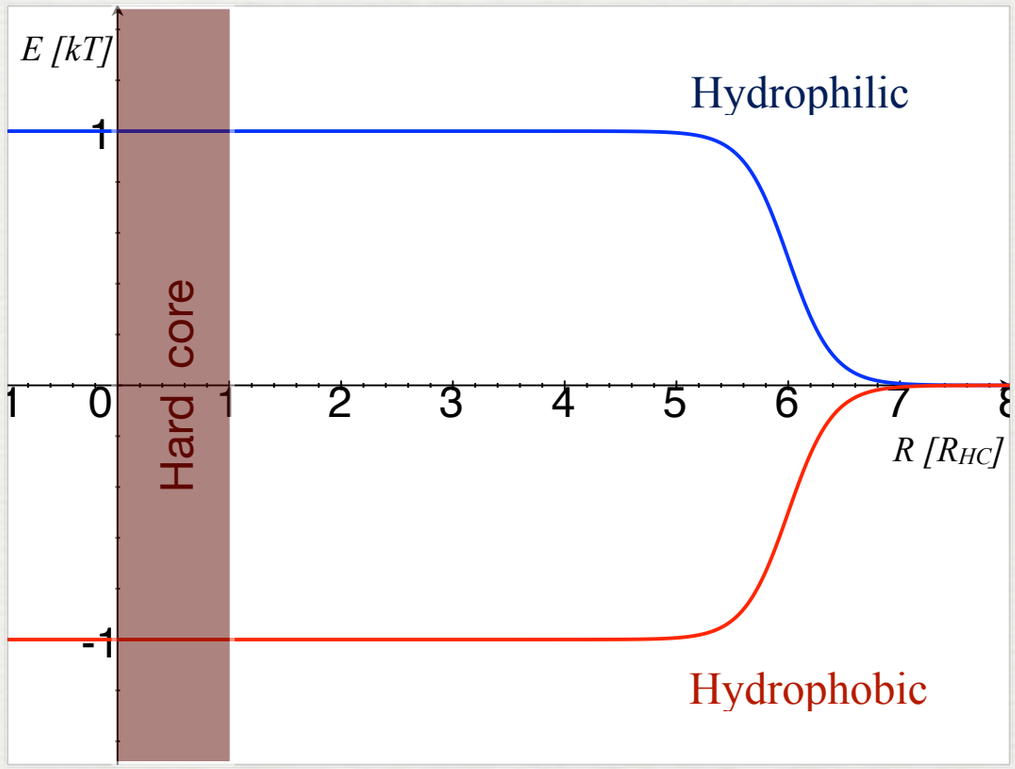


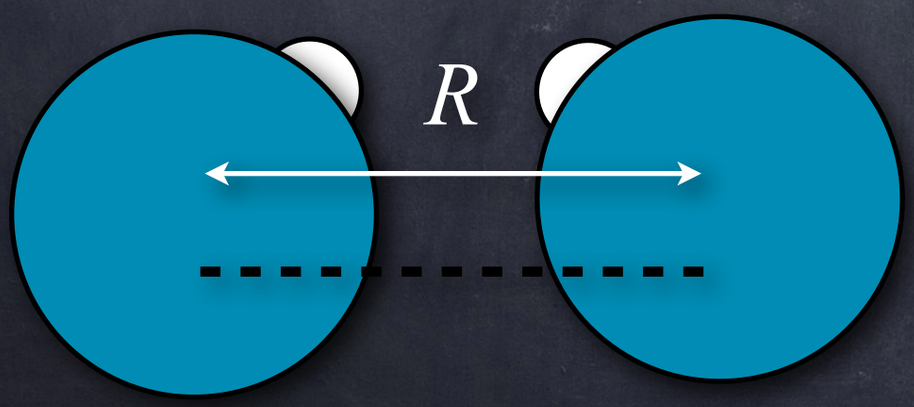


54 have not sampled
the folded state yet.

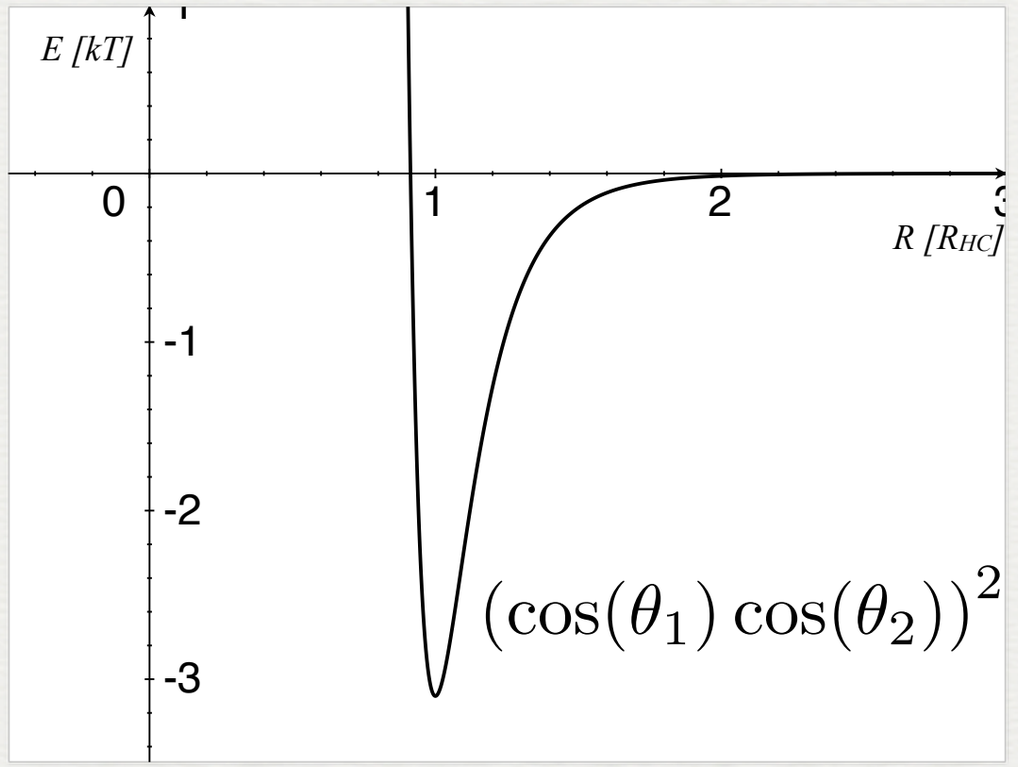
Interaction Potentials

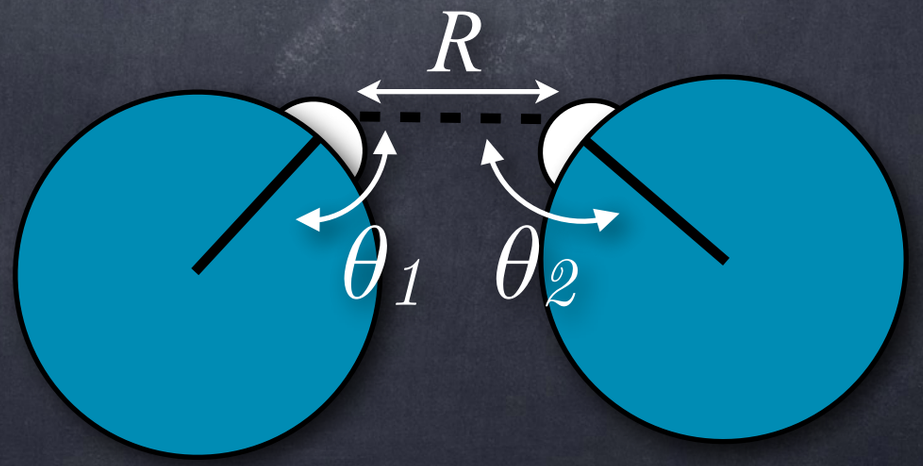
Isotropic Interactions (R)





Patch -Patch Int.(R,θ_1,θ_2)





Patchy-Polymer structure space

1 Patch

2 Patches

Patch

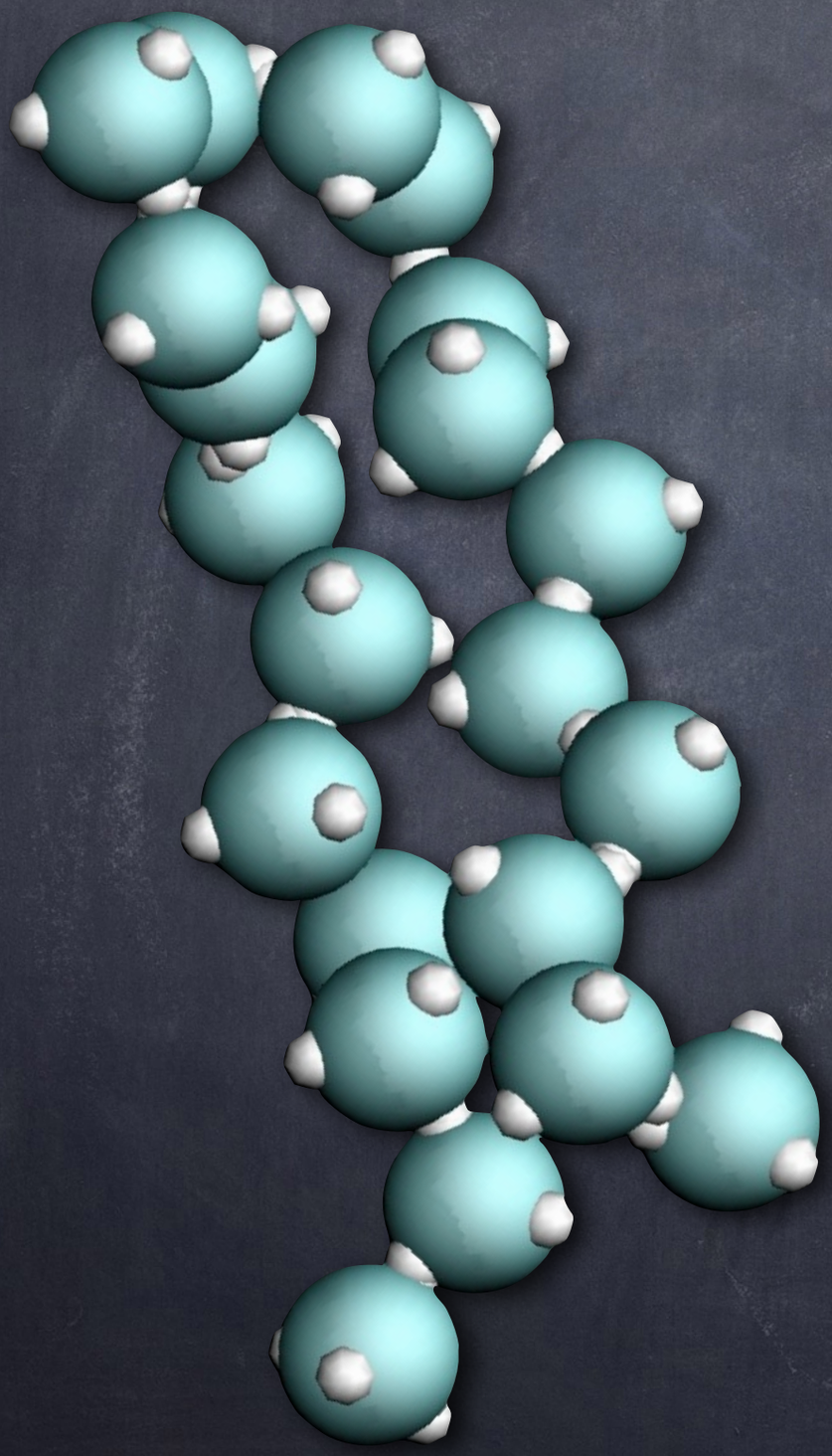
a

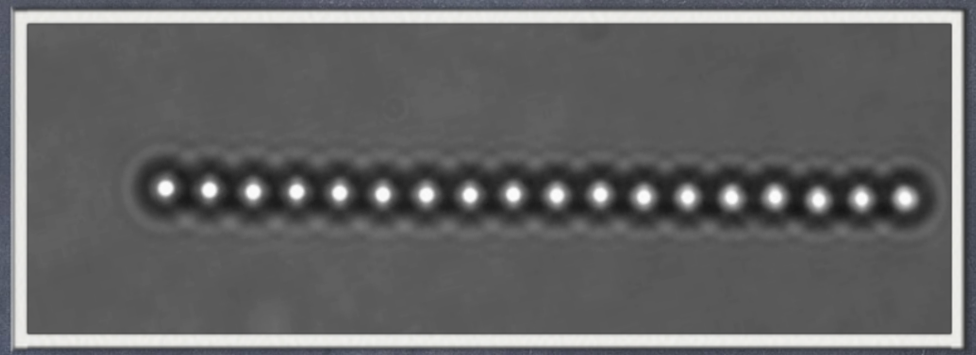
b

Increasing interaction strength

Coluzza, I., & Dellago, C. (2012).. *Journal of Physics: Condensed Matter*, *24*(28), 284111

Experiments





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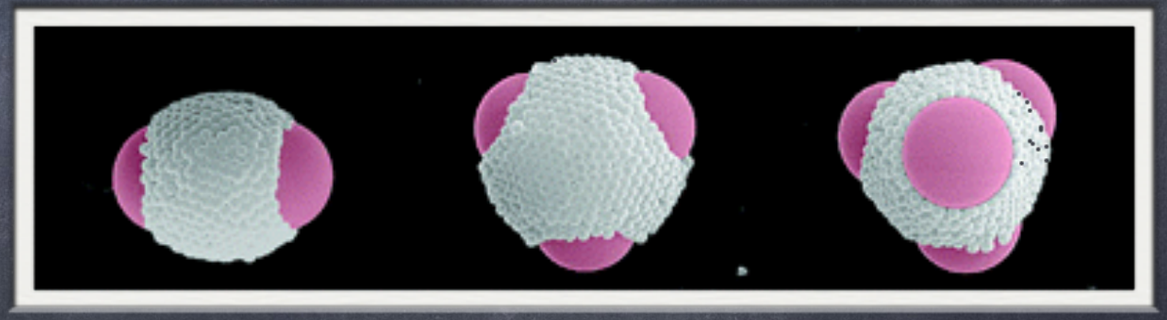
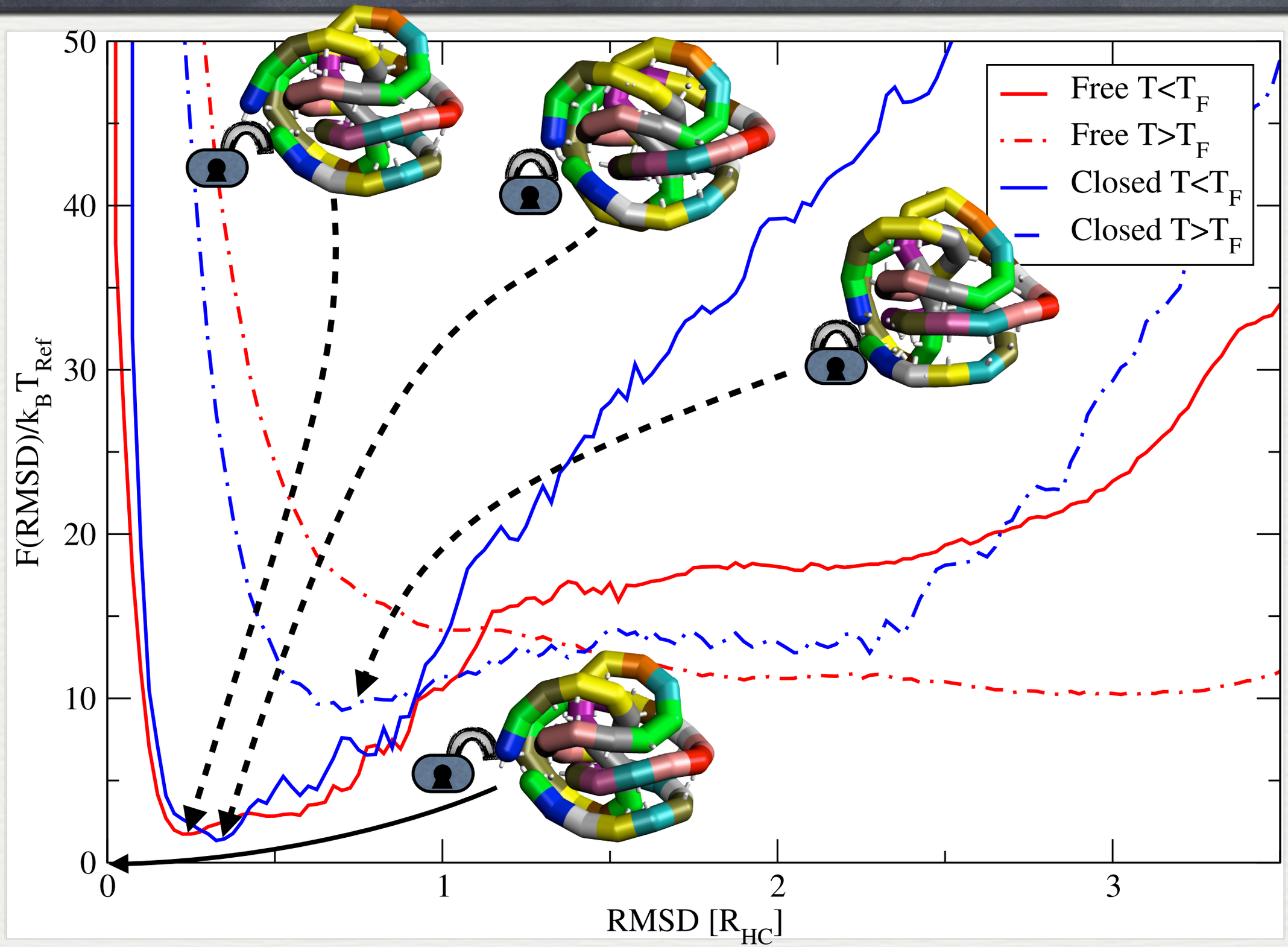


David Pine's group web page

Built-in locking mechanism



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