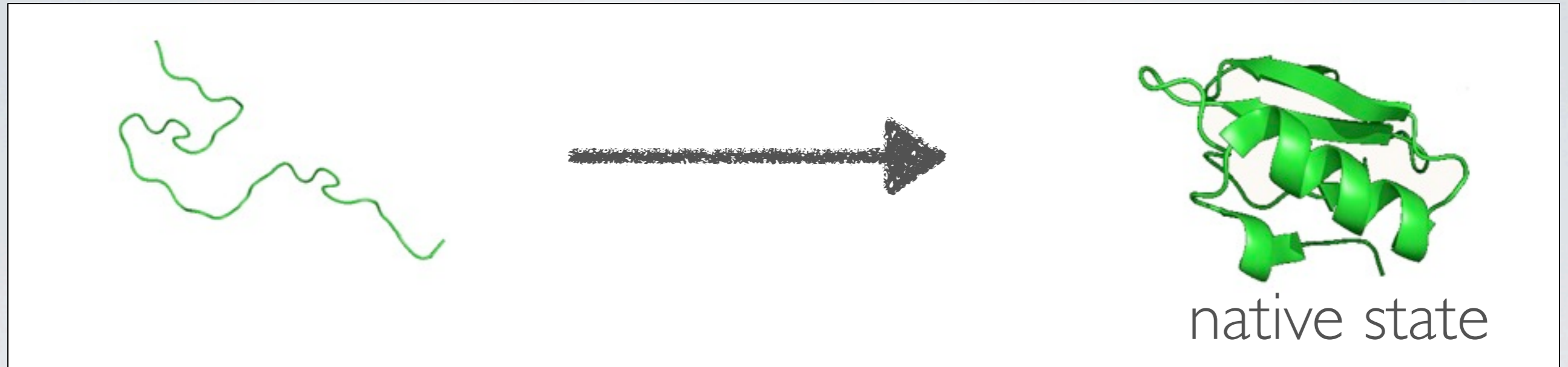


Monte Carlo simulation of proteins: from folding to “nonfolding” to interactions

ATP Colloquium
Nov 2, 2011

Stefan Wallin

Protein folding

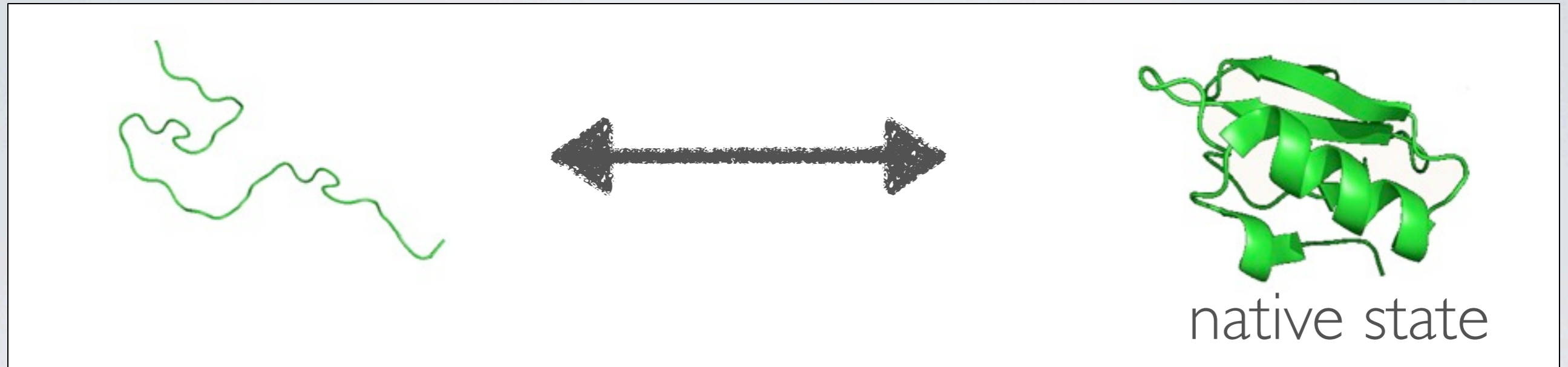


Given the amino acid sequence, what is the 3-dimensional structure of the protein?



Christian B. Anfinsen

Protein folding



Given the amino acid sequence, what is the 3-dimensional structure of the protein?



Christian B. Anfinsen

How does the protein chain find the native state?

153 amino acids

```
GLSDGEWQLVLNVWGKVEADIPGHGQEV LIRLFKGH PETLE  
KFDKFKHLKSEDEMKASEDLKKHGATVLTALGGILKKKGHHE  
AEIKPLAQSHATKHKIPVKYLEFISECIIQVLQSKHPGDFGADA  
QGAMNKALELFRKDMASNYKELGFQG
```

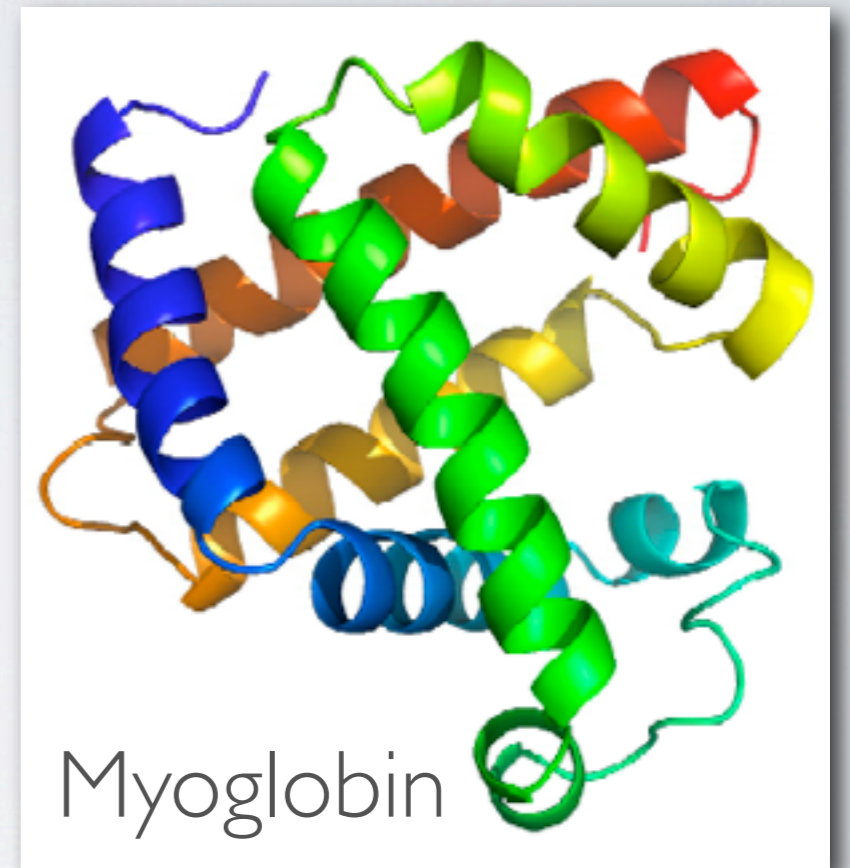
Number of possible conformations:

$$3^{153} = 3.7 \times 10^{71}$$

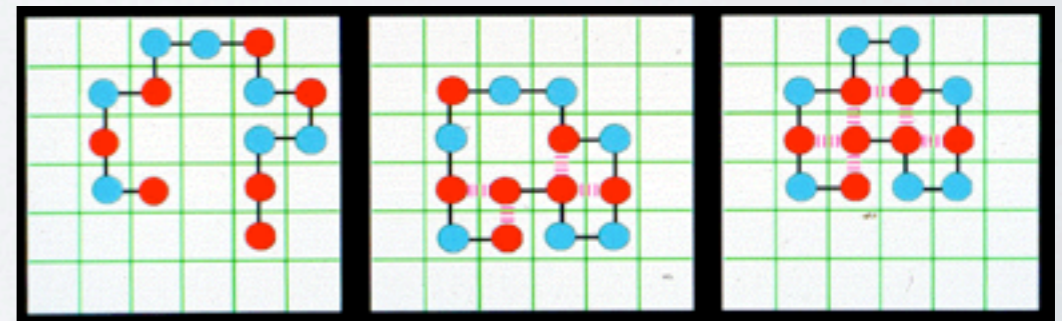
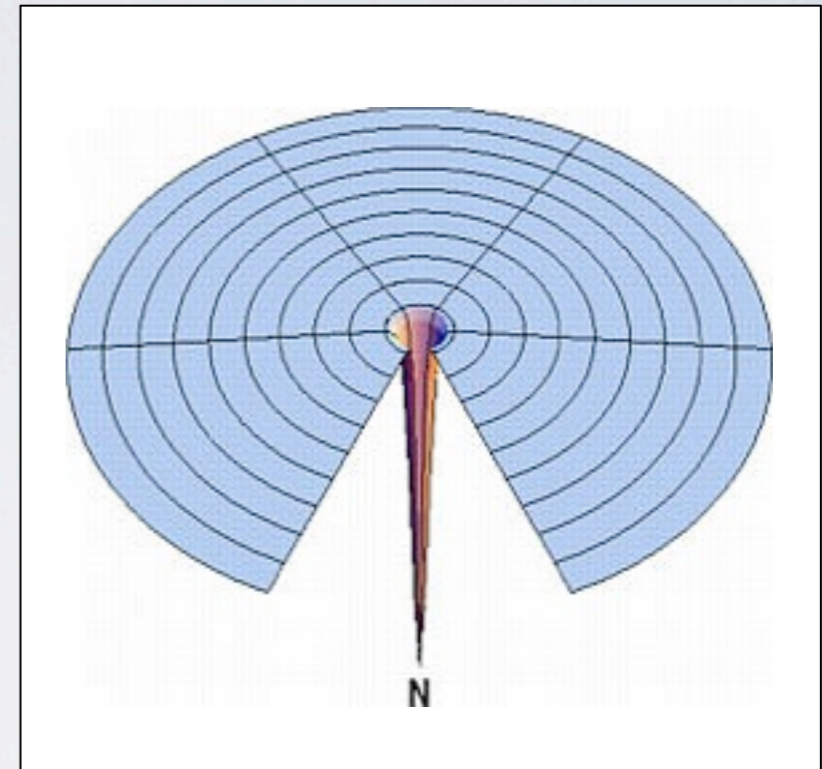
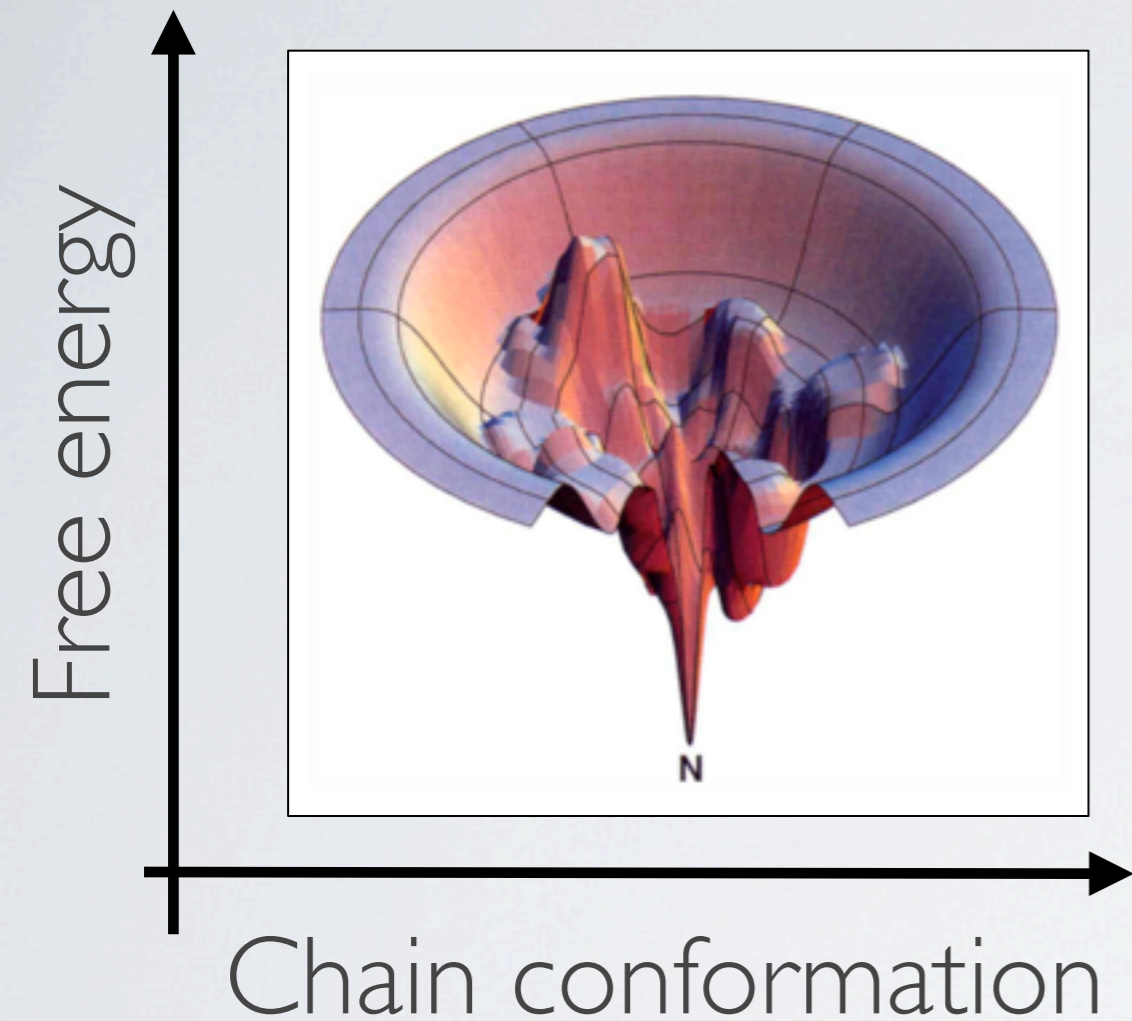
1 ps per conformation:

$$3.7 \times 10^{56} \text{ s}$$

“Levinthal’s paradox” (1969)

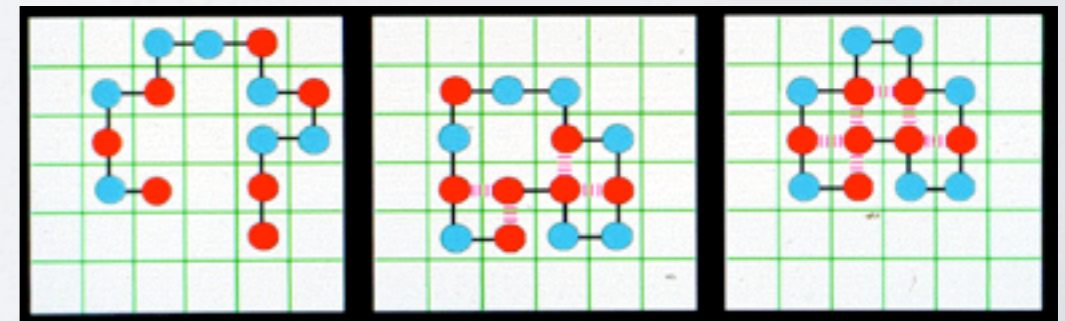
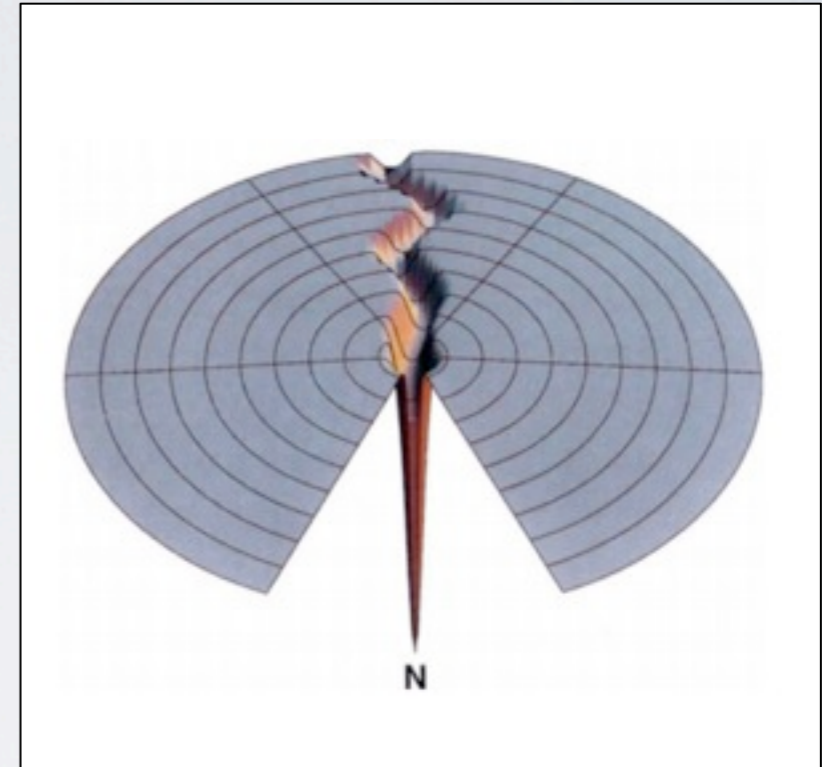
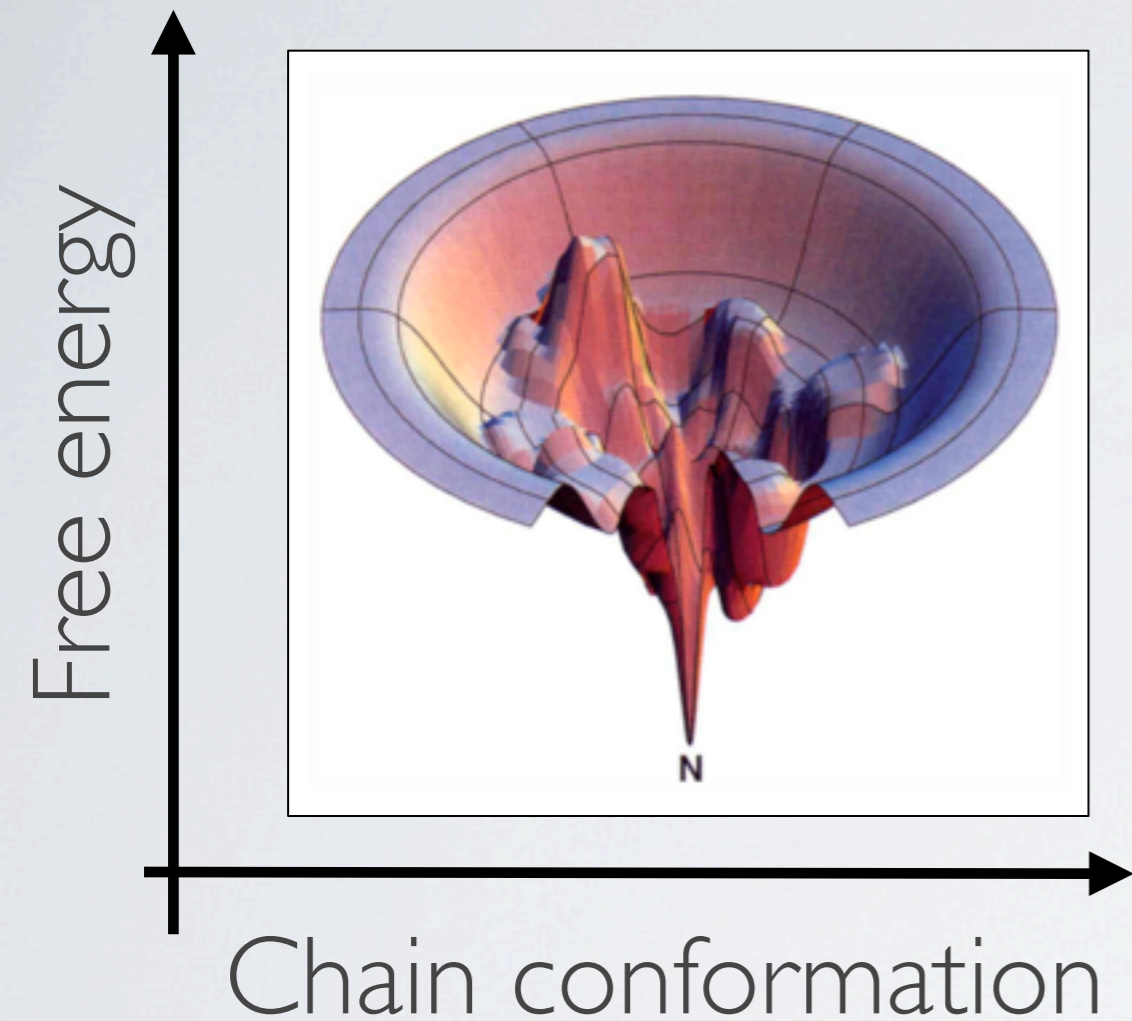


Energy landscape view

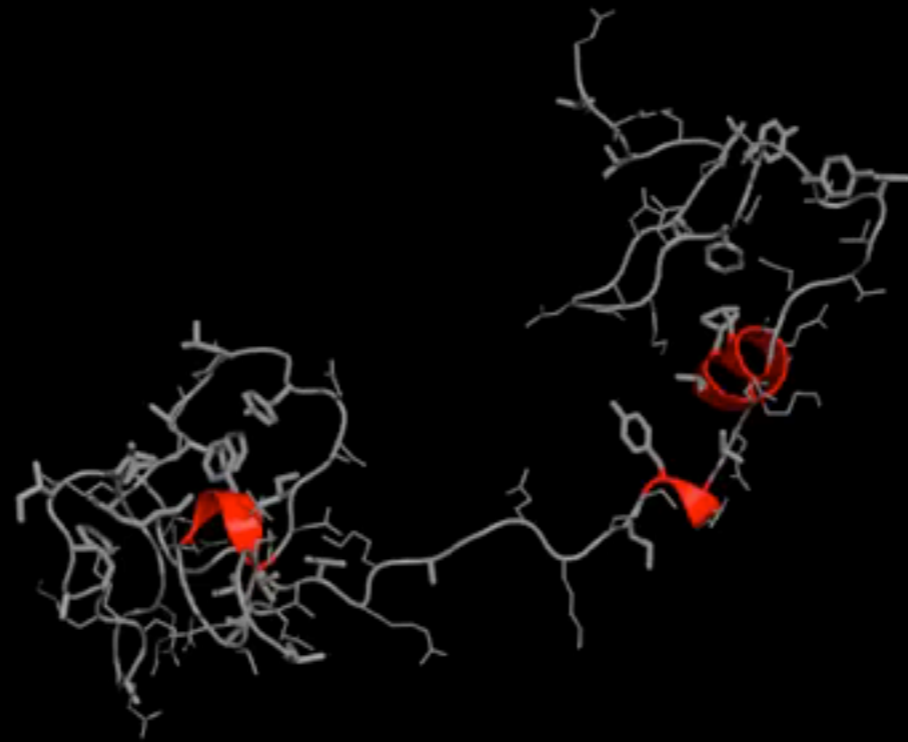


HP model (Lau and Dill, 1989)

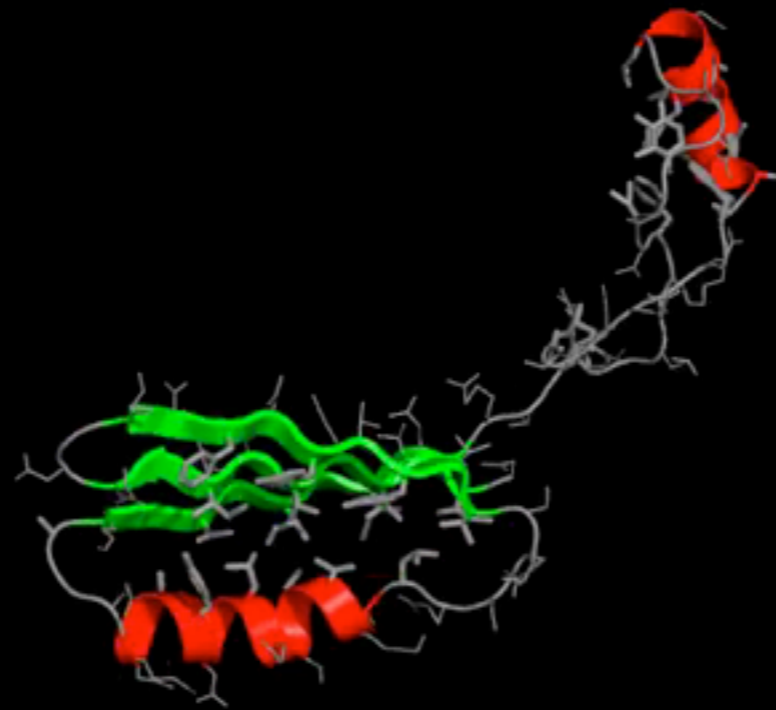
Energy landscape view



HP model (Lau and Dill, 1989)



Credit: Sandipan Mohanty, Jülich
Supercomputing Centre



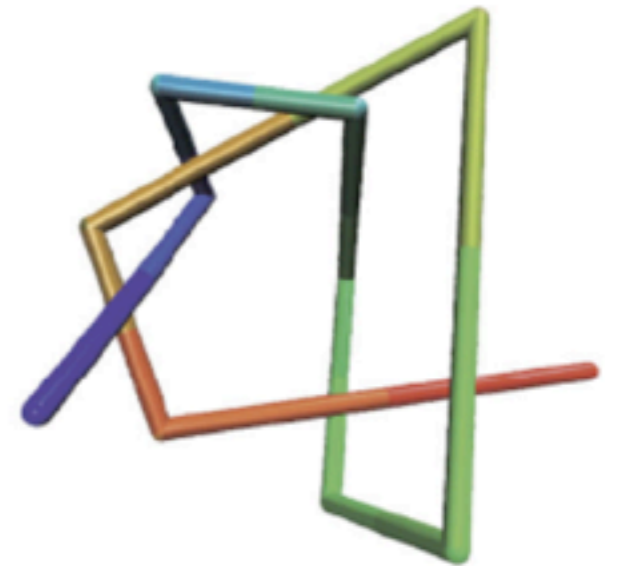
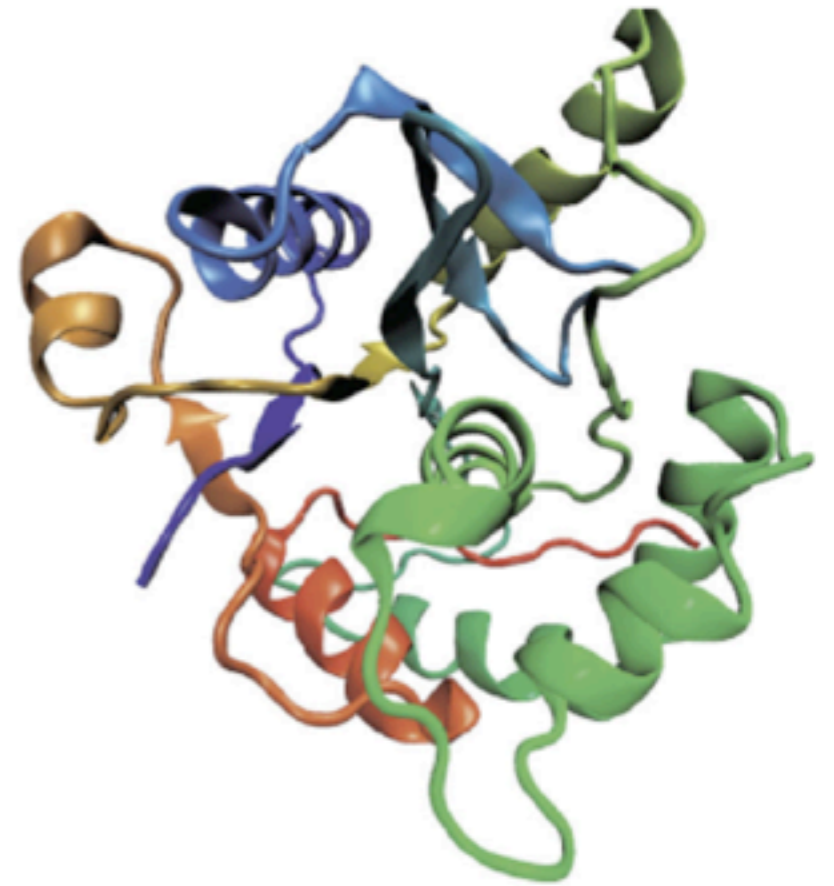
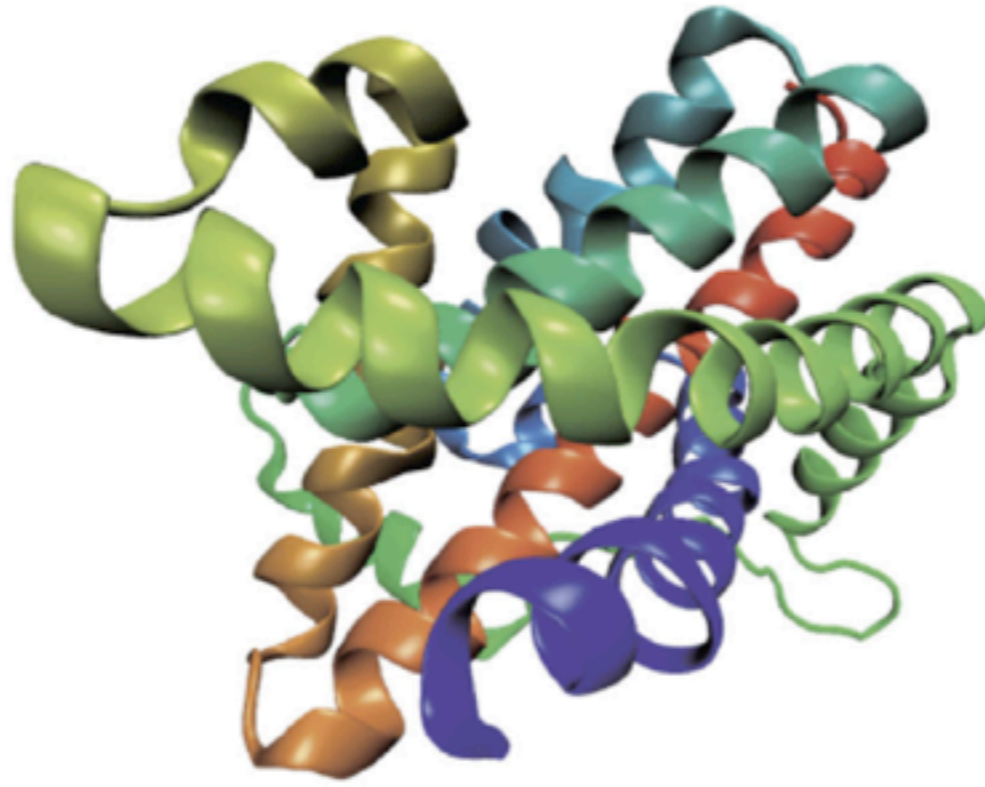
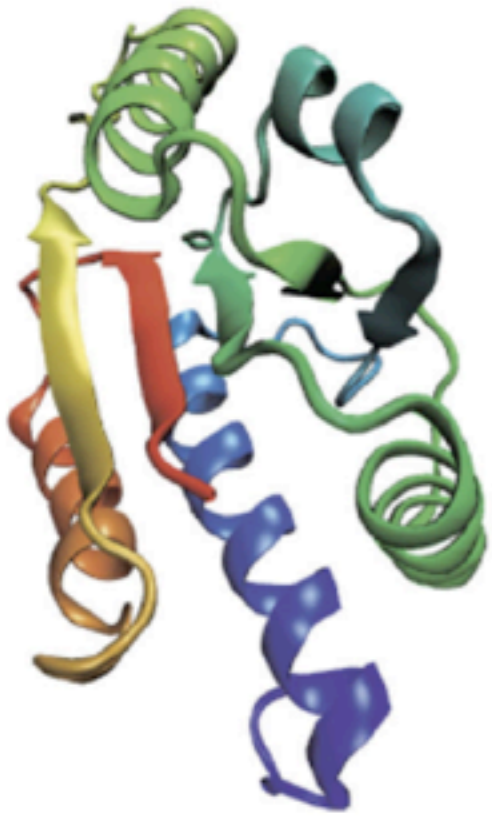
Credit: Sandipan Mohanty, Jülich
Supercomputing Centre

A new challenge in protein folding

Methyltransferase

Reductoisomerase

Ubiquitin hydrolase



Trefoil (3_1)

Figure-of-eight (4_1)

(5_2)

Spontaneous knotting of an agitated string

Dortan M. Raymer* and Douglas L. Smith*

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Edited by Lee P. Kadanoff, University of Chicago, Chicago, IL, and approved July 10, 2007 (received for review December 21, 2006)

It is well known that a jostled string tends to become knotted, yet the factors governing the “spontaneous” formation of various knots are unclear. We performed experiments in which a string was tumbled inside a box and found that complex knots often form within seconds. We used mathematical knot theory to analyze the knots. Above a critical string length, the probability P of knotting at first increased sharply with length but then saturated below 100%. This behavior differs from that of mathematical self-avoiding random walks, where P has been proven to approach 100%. Knot agitation time and geometry of the string due to its stiffness result in lower probability, but P approaches 100% with long flexible strings. We analyzed the knots by calculating their Jones polynomials via computer analysis of digital photos of the string. Remarkably, almost all were identified as prime knots (32 different types, having minimum crossing numbers up to 11, were observed in 2,475 trials. All prime knots with up to seven crossings were observed. The relative probability of forming a knot decreased exponentially with minimum crossing number and Milnor energy, mathematical measure of knot complexity. Based on the observation that long, stiff strings tend to form a coiled structure when confined, we propose a simple model to describe the knot formation based on random “local moves” of the string end. Our model can quantitatively account for the observed distribution of knots and dependence on agitation time and string length.

ions: polynomials; knot energy; knot theory; random walk; statistical physics

Knots have been a subject of scientific study since as early as 1867, when Lord Kelvin proposed that atoms might be described as knots of swirling vortices (1). Although this theory fell into disfavor, it stimulated interest in the subject, and knots currently play a role in many scientific fields, including polymer physics, statistical mechanics, quantum field theory, and DNA biotechnology (2, 3). Knotting and unknotting of DNA molecules occurs in living cells and viruses and has been extensively studied by molecular biologists (4–6). In physics, spontaneous knotting and unknotting of vibrated ball-chains have recently been studied (7–9). In mathematics, knot theory has been an active field of research for more than a century (3).

Formation of knots in mathematical self-avoiding random walks has been extensively studied (10–15). In the 1960s, Frisch and Wasserman (10) and Debrack (11) conjectured that the probability of finding a knot would approach 100% with an increasing walk length. In 1988, Sumson and Whittington (12) proved this conjecture rigorously by showing that exponentially few sites would remain unknotted as the length tends to infinity. Numerical studies of finite-length random walks find that the probability of knotting and the average complexity of knots increase sharply with the number of steps (16).

Here, we describe a simple physical experiment on knot formation. A string was placed in a cubic box and the box was rotated at constant angular velocity about a principle axis perpendicular to gravity, causing the string to tumble. We investigated the probability of knotting, the type of knots formed, and the dependence on string length. Before tumbling, the string was held vertically above the center of the box and dropped in, creating a quasirandom initial conformation. After tumbling, the box was opened and the ends of the string were

held directly upward and joined to form a closed loop. A digital photo was taken whenever a complex knot was formed. The experiment was repeated hundreds of times with each string length to collect statistics.

Results

Most of the measurements were carried out with a string having a diameter of 3.2 mm, a density of 0.04 g/cm³, and a flexural rigidity of 3.1×10^7 dynes/cm², tumbling in a $0.30 \times 0.30 \times 0.30$ -m box rotated at one revolution per second for 10 sec (see Materials and Methods). Photos of the string taken before and after tumbling are shown in Fig. 1, and movies of the tumbling are provided as supporting information (SI) Movies 1–5. The measured dependence of knotting probability P on string length L is shown in Fig. 2. No knots were obtained for $L < 0.86$ m, where SI Movie 1 shows that the confinement and tumbling did not induce sufficient bending to allow knot formation. As L was increased from 0.86 to 1.5 m, P increased sharply. However, as L was increased from 1.5 to 6 m, P saturated at $\sim 50\%$. The photos and movies show that when the string is confined in the box, the finite stiffness of the string results in its tending to form a coil (not perfectly, but to some degree) with a radius similar to the box width. During and after tumbling, this coiled structure is preserved, often with some compression of its radius perpendicular to the rotation axis (Fig. 2 and SI Movie 2).

A series of additional experiments were done to investigate the effect of changing the experimental parameters, as summarized in Table 1. Doubling the agitation time caused a substantial increase in P , indicating that the knotting is kinetically limited. Decreasing the rotation rate by 3-fold while keeping the same number of rotations caused little change in P . SI Movie 3 shows that effective agitation still occurs because the string is periodically carried upward along the box wall. A 3-fold increase in the rotation rate, on the other hand, caused a sharp decrease in P . SI Movie 4 shows that in this case, the string tends to lie flat against the walls of the box by centrifugal force, resulting in less tumbling motion.

Doubling the box width increased P slightly, but decreasing it by 33% caused P to drop sharply. SI Movie 5 shows that the tumbling motion was reduced because the finite stiffness of the coiled string tends to wedge it more firmly against the walls of the box. We also did measurements with a stiffer string (see Materials and Methods) in the 0.15-m box and observed a substantial drop in P . Observations again revealed that the tumbling motion was reduced due to wedging of the string against the walls of the box. Conversely, measurements with a more flexible string found a substantial increase in P . With the longest length studied of this string (4.6 m), P reached 85%.

Author contributions: D.M.R. and D.L.S. designed research, performed research, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

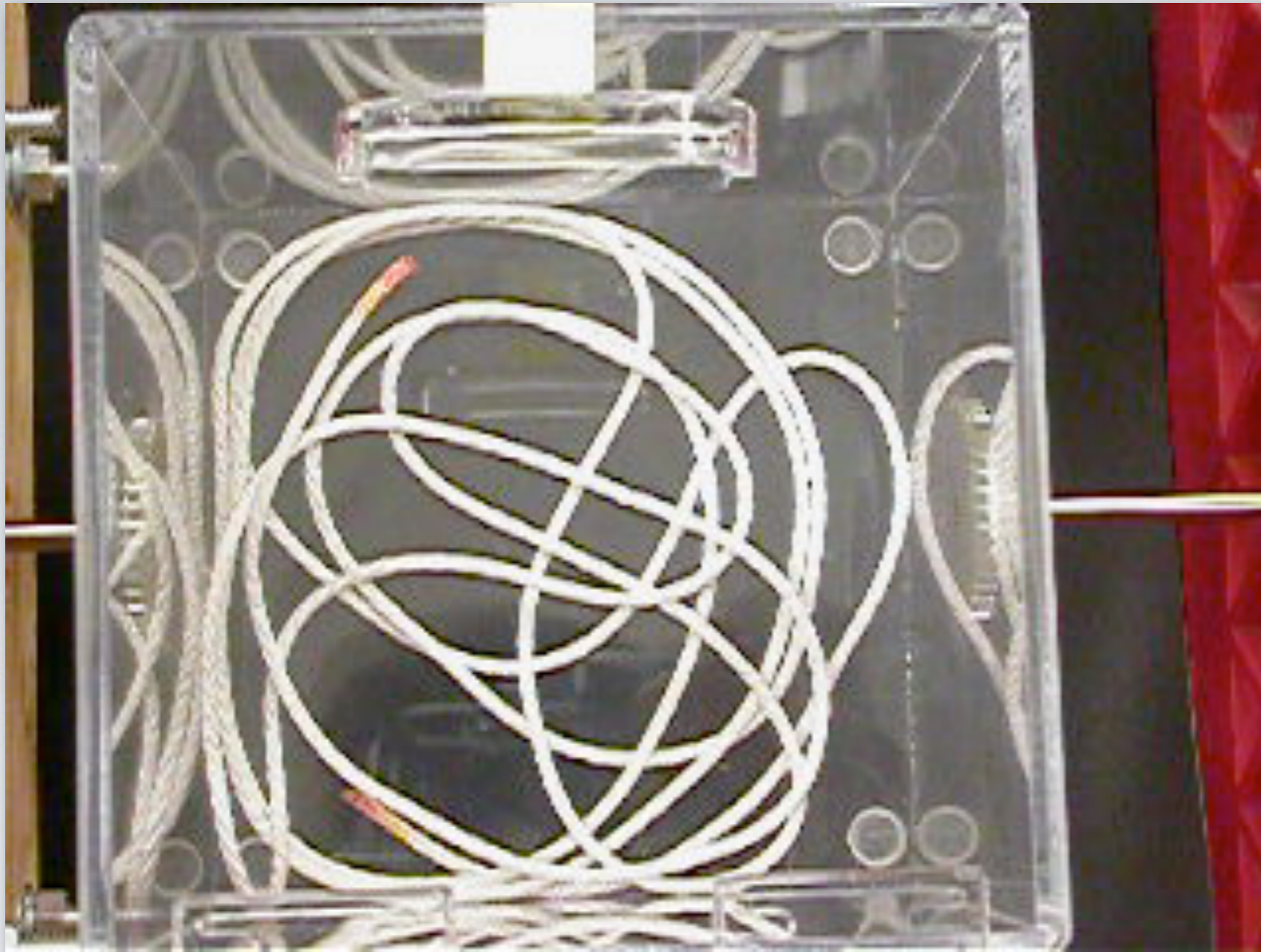
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*To whom correspondence may be addressed. E-mail: dsm@physics.ucsd.edu or draymer@ucsd.edu.

See article comments supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.0710270104.

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“Spontaneous knotting of an agitated string”, *Proceedings of the National Academy of Sciences USA*, D Raymer and D Smith (2007).



Spontaneous knotting of an agitated string

Dorfan M. Raymer* and Douglas E. Smith*

Department of Physics, University of California at San Diego, 9500 Gilman Drive, Mail Code 0276, La Jolla, CA 92093

Contributed by Lee F. Katavoft, University of Chicago, Chicago, IL, and approved July 10, 2007 (received for review December 21, 2006)

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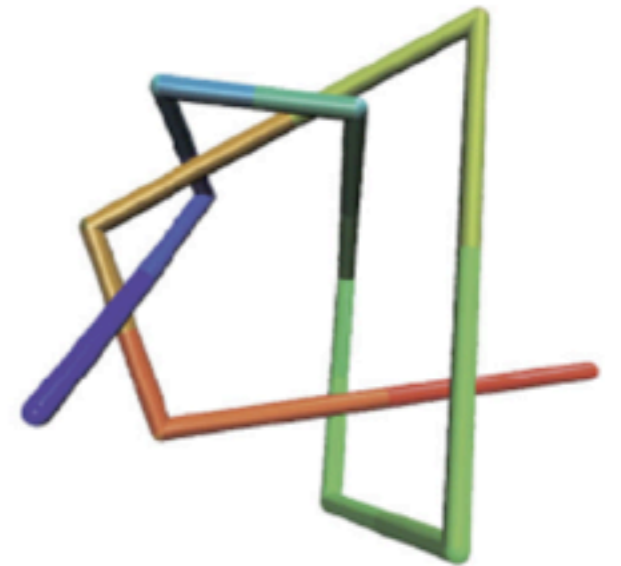
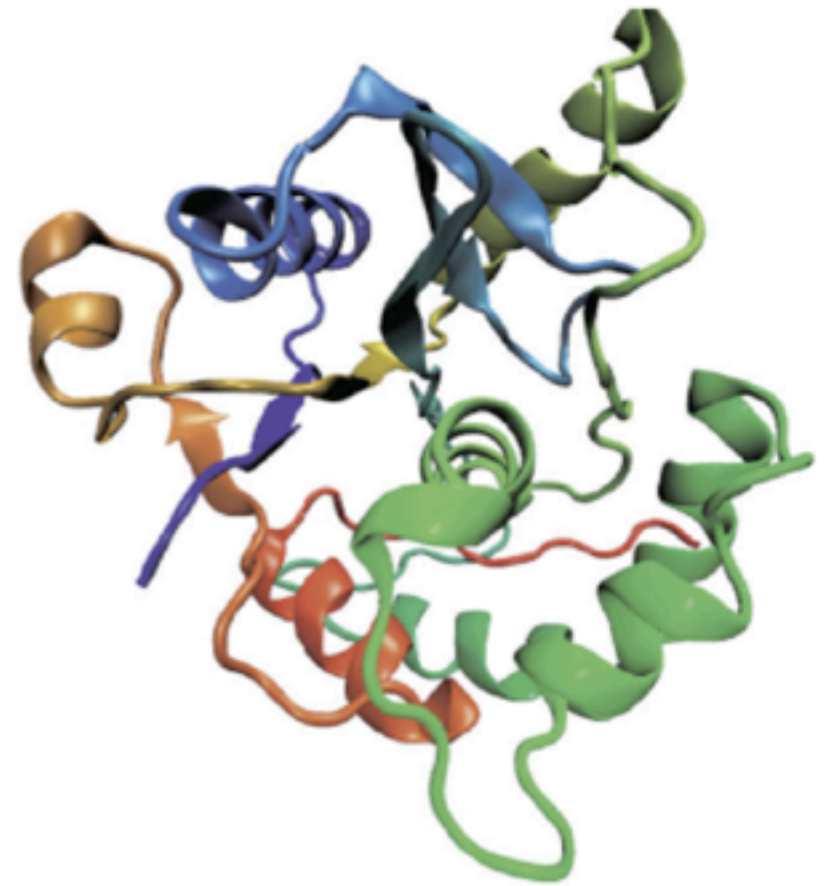
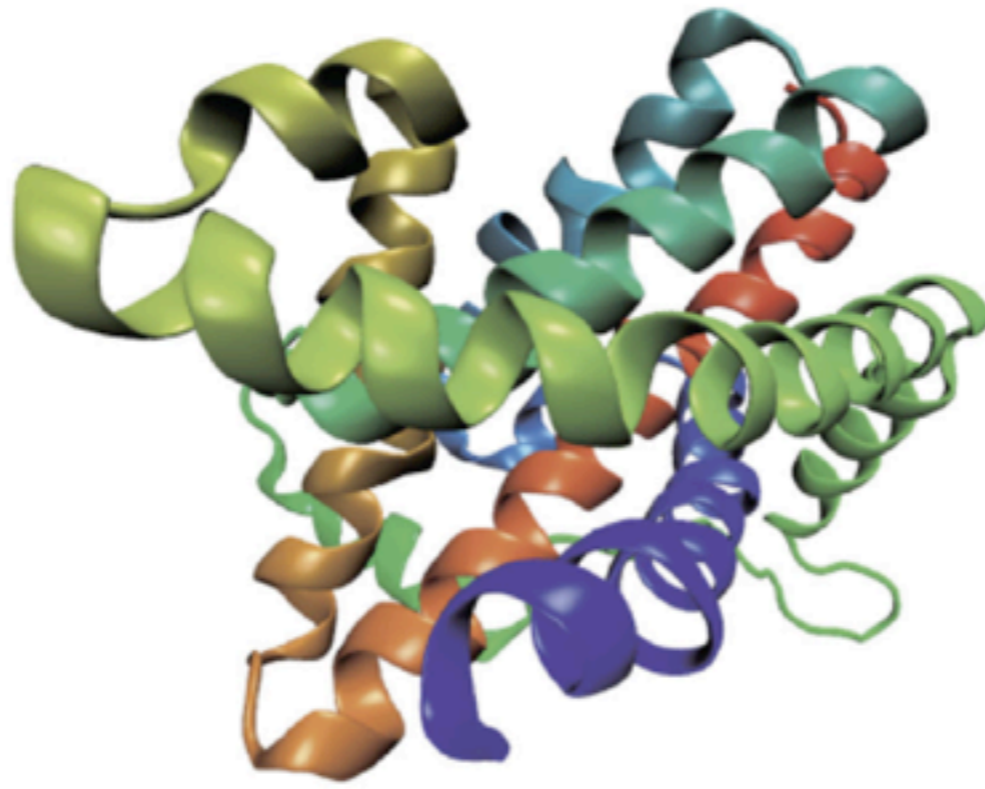
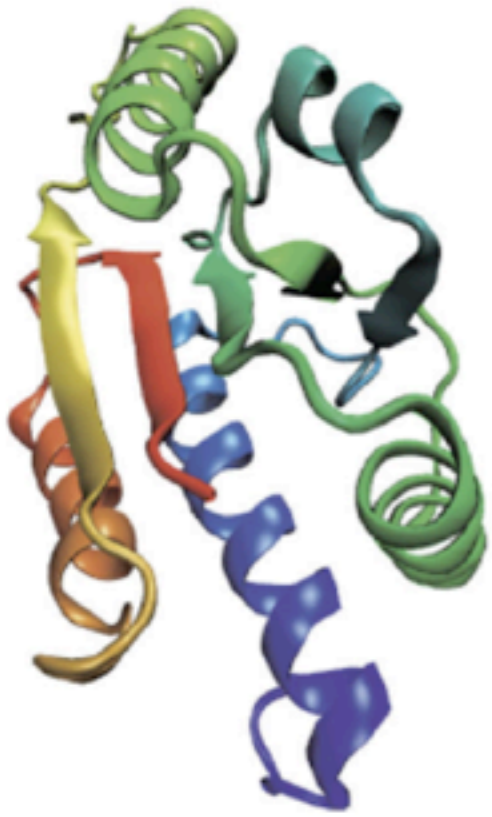
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“Spontaneous knotting of an agitated string”, *Proceedings of the National Academy of Sciences USA*, D Raymer and D Smith (2007).

Methyltransferase

Reductoisomerase

Ubiquitin hydrolase

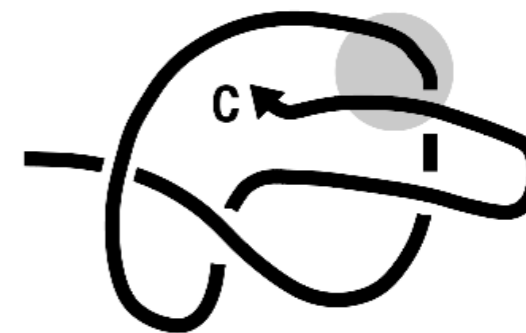
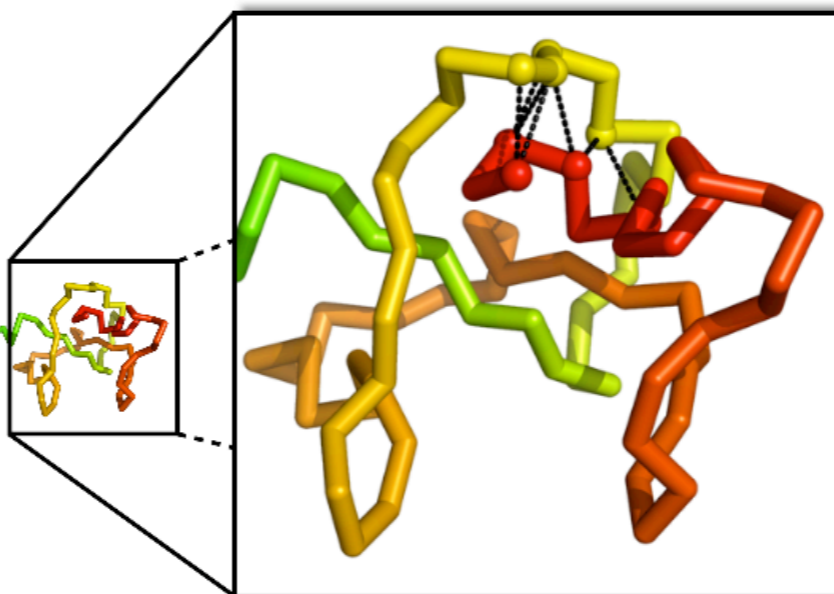
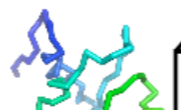
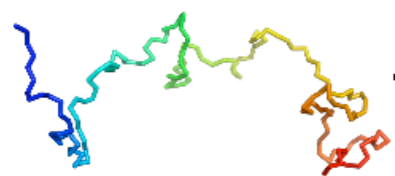


Trefoil (3_1)

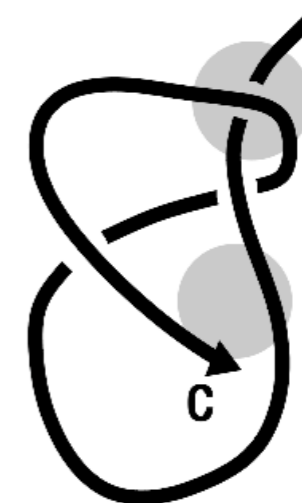
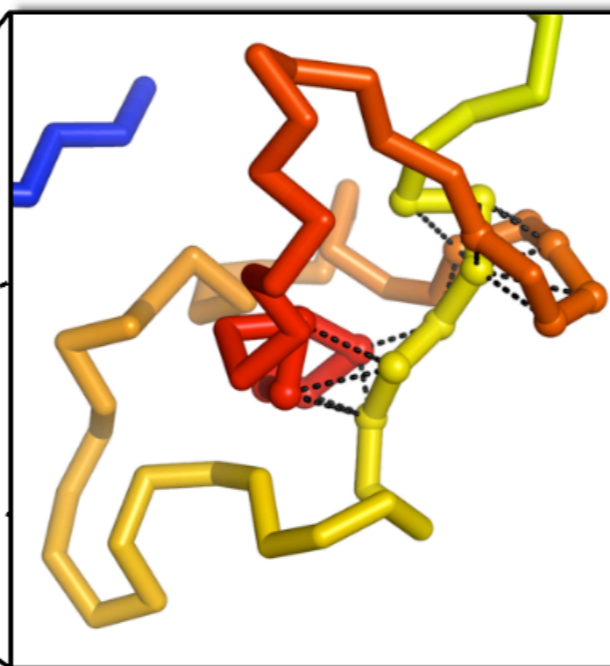
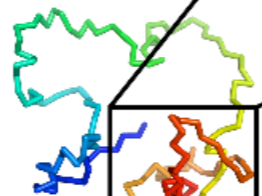
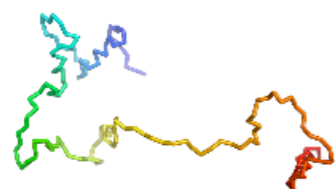
Figure-of-eight (4_1)

(5_2)

(c)



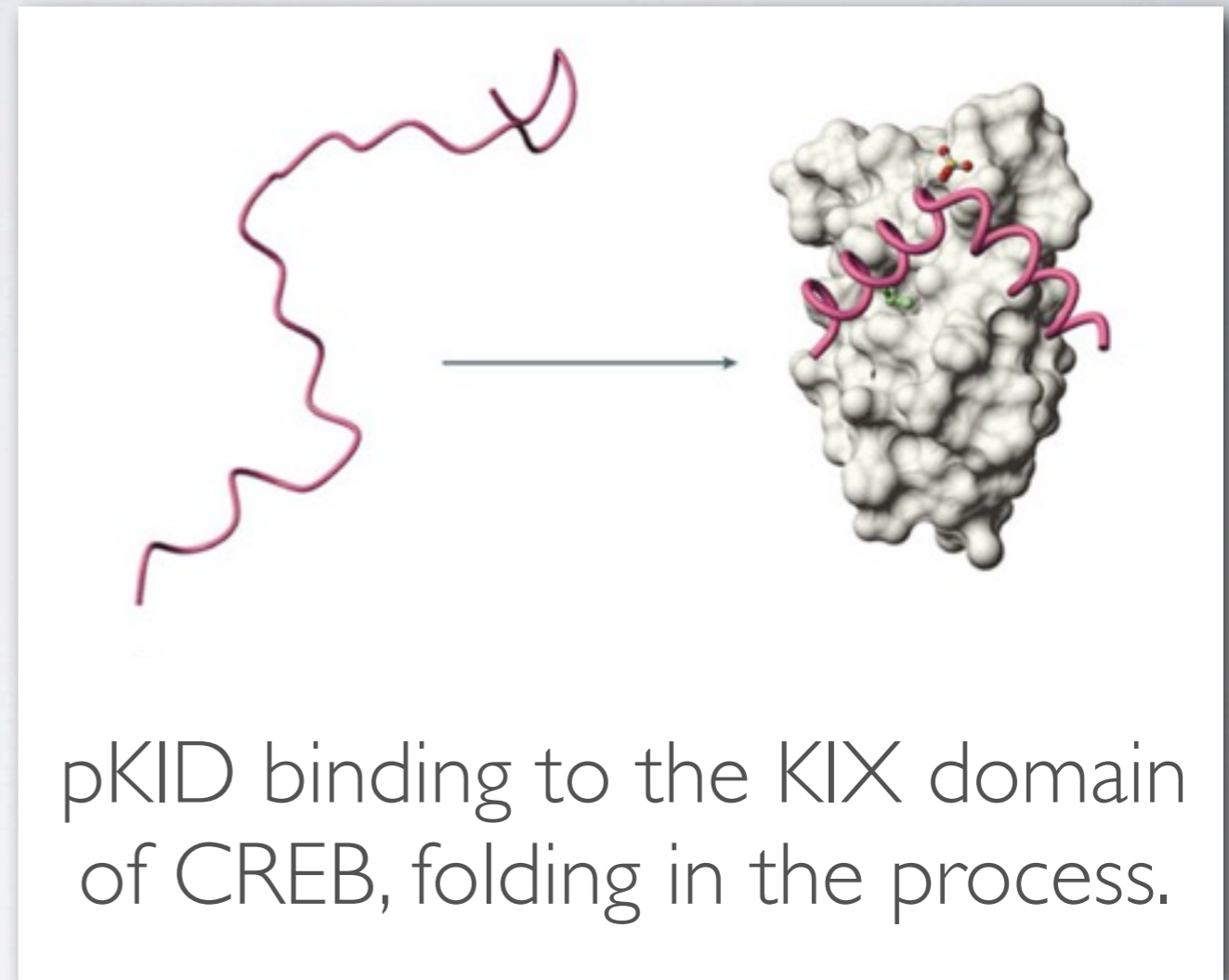
(d)



Sequence → Structure → Function

Intrinsically disordered proteins

- No stable native state, yet fully functional
- Coupled folding-binding



Protein-protein interaction networks:

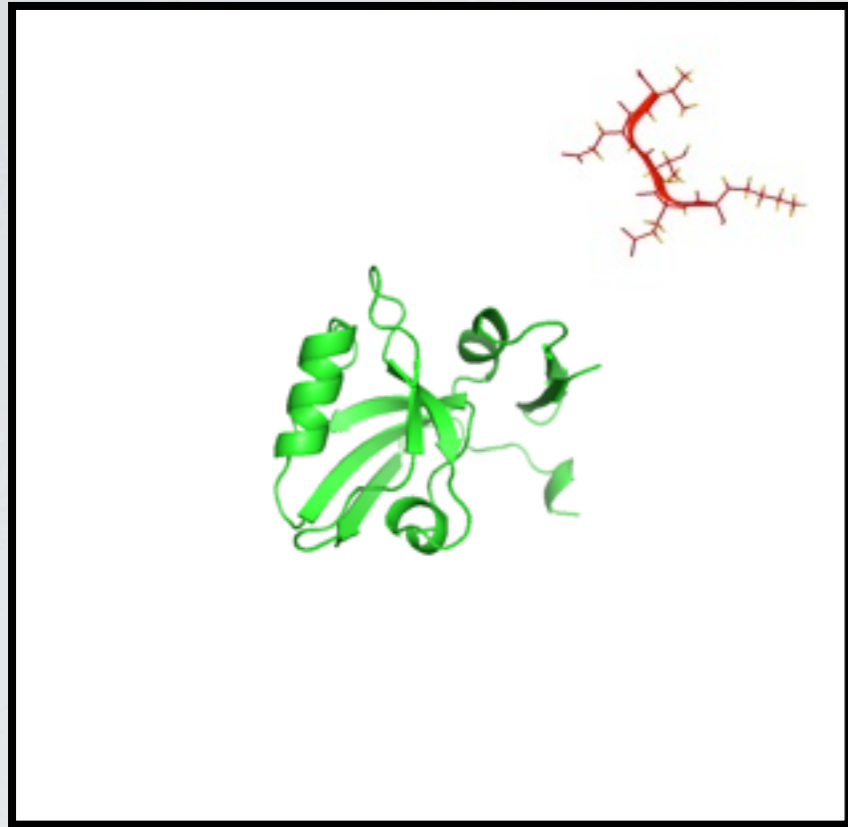
up to 15-40% of all interactions due to protein-peptide binding

An unsolved problem



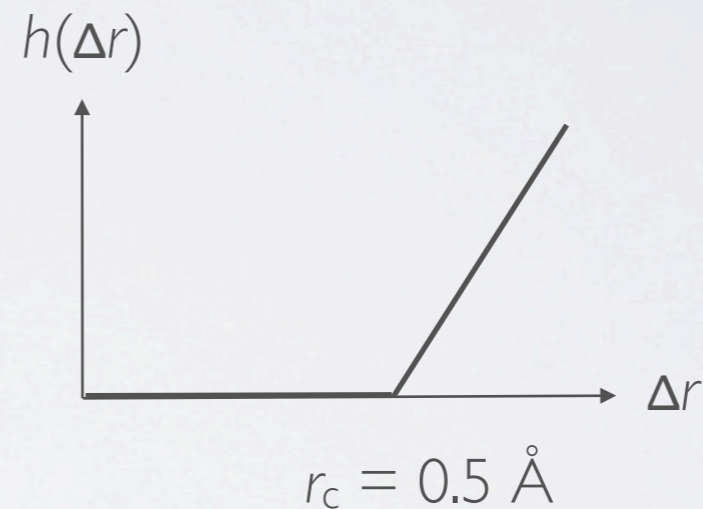
Given a protein structure and a peptide sequence, predict *whether* and *how* the protein can bind the peptide.

Our approach



Protein in native state:

$$E_{\text{fix}} = k_{\text{fix}} \sum_{C_{\alpha}} h(|\mathbf{r}_i^{\text{PDB}} - \mathbf{r}_i|)$$

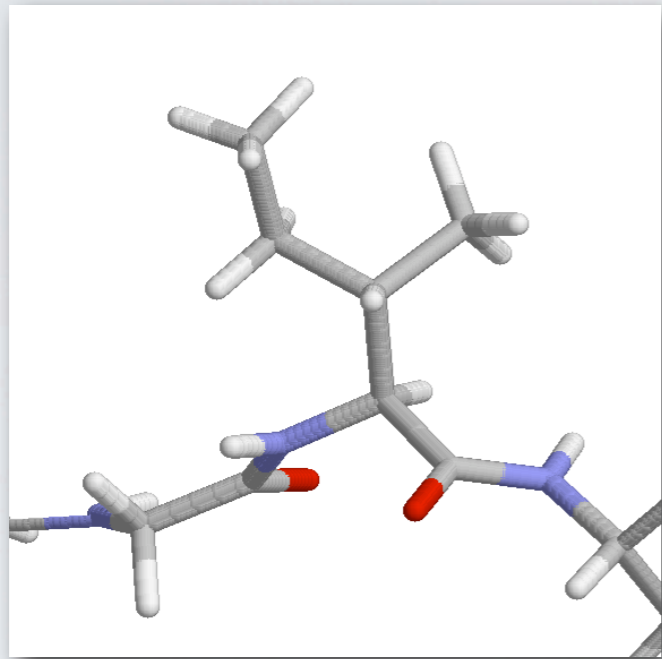


Peptide: no added constraints (full chain flexibility)

Box with periodic boundary conditions

Computational model

All protein atoms represented
but no explicit water



Effective energy function:

- excluded volume
- hydrogen bonding
- hydrophobic attraction
- electrostatic attractions

Sampling method:

- Monte Carlo
- Molecular Dynamics

“makes things as simple as possible, but not simpler”

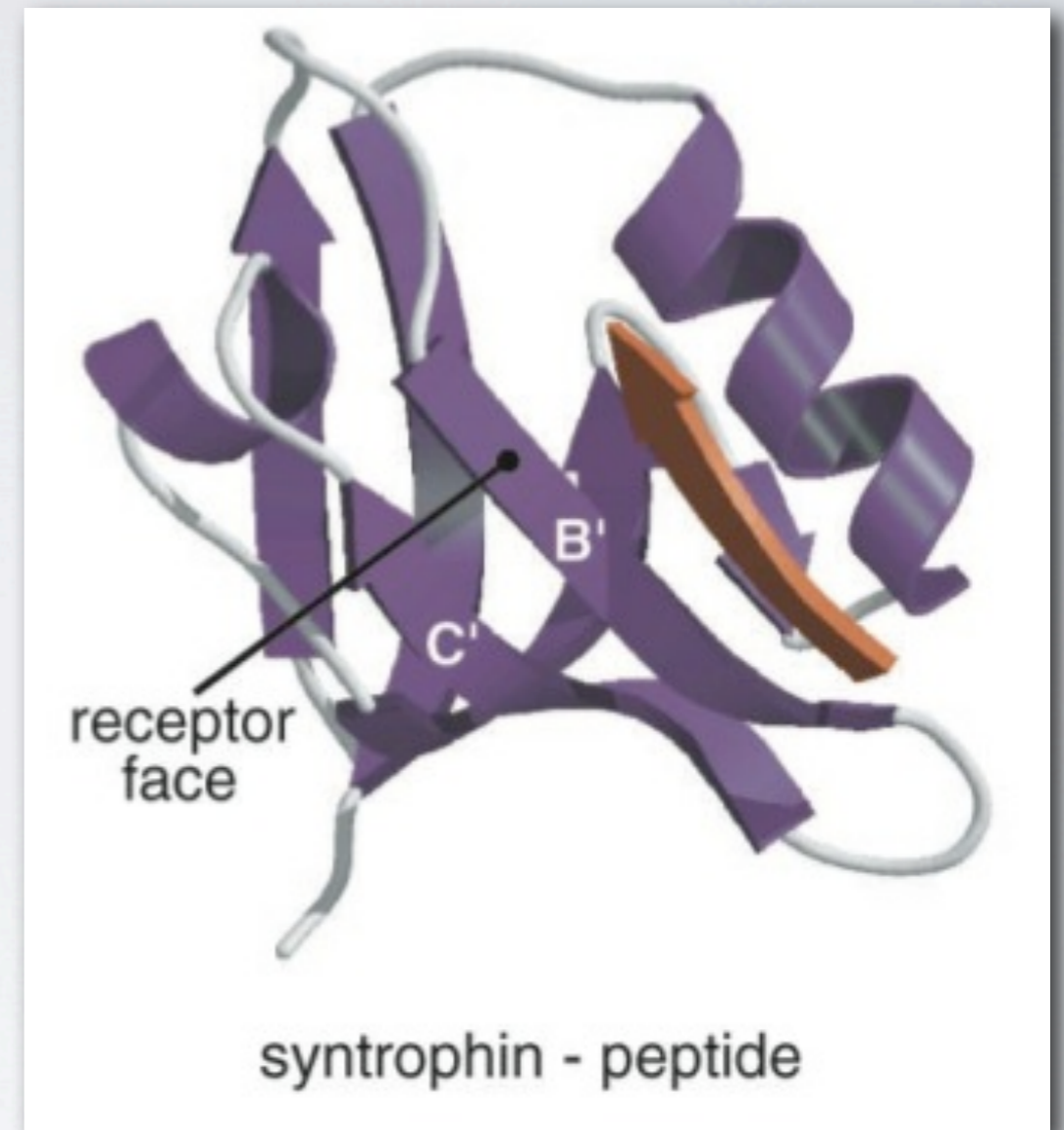
PDZ domains

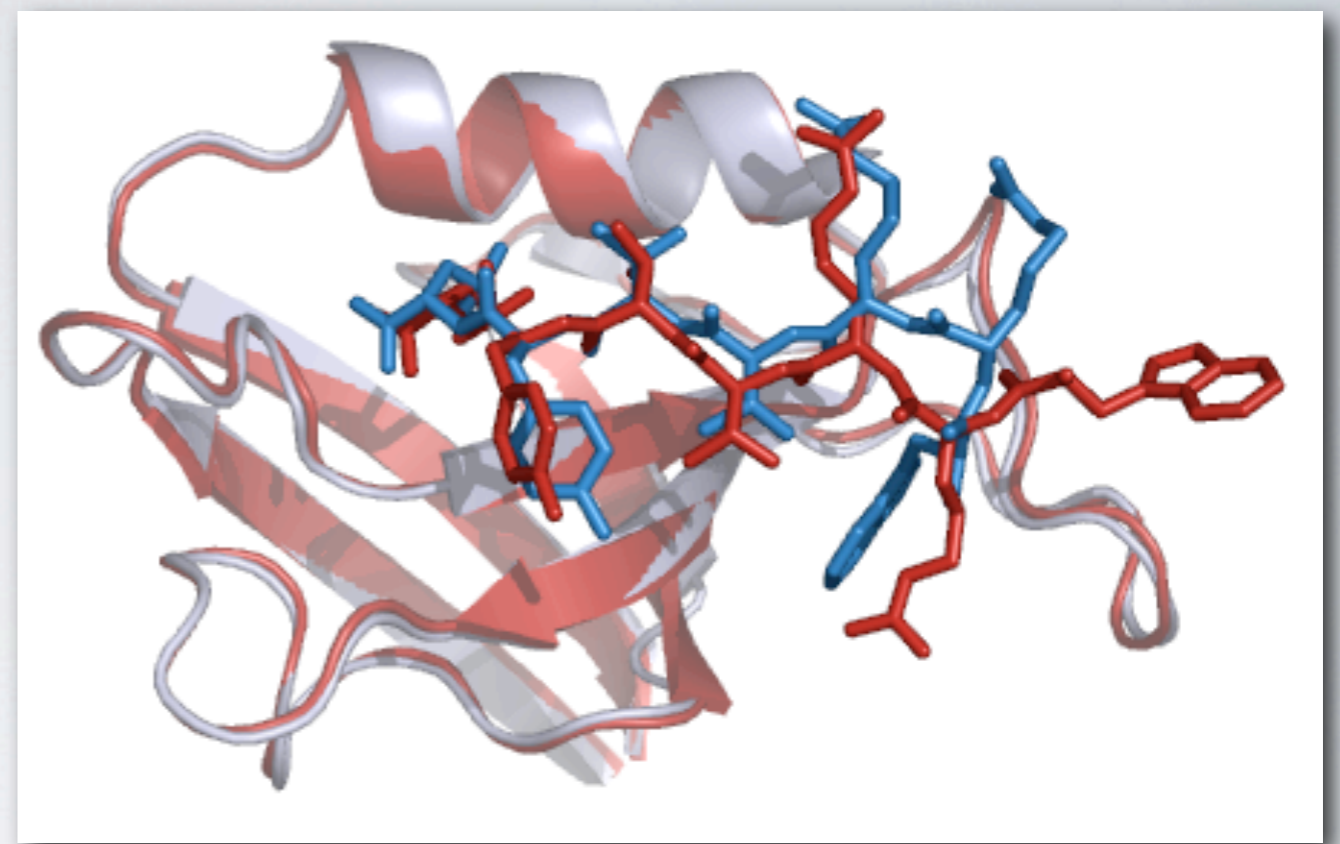
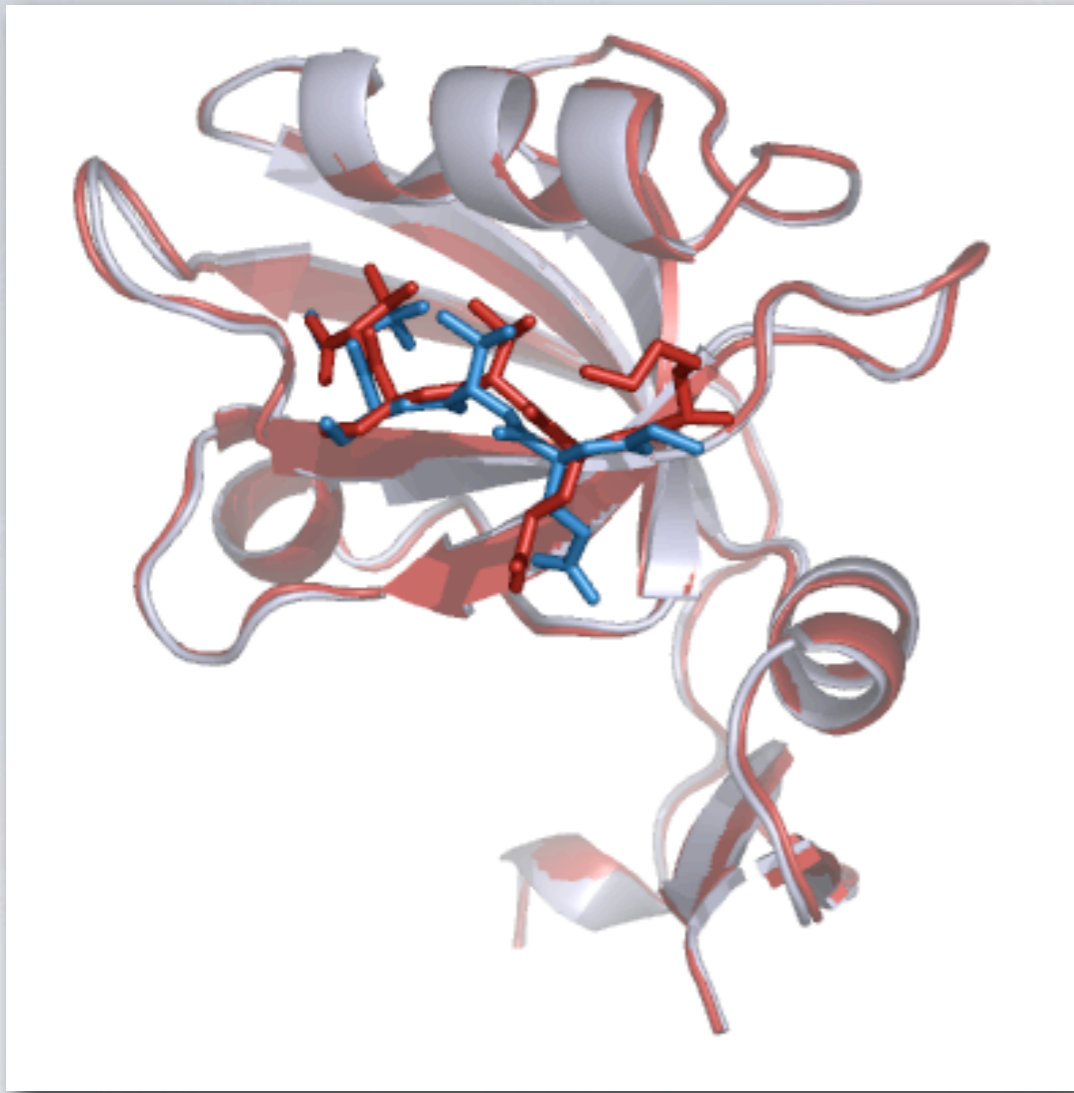
~70-90 amino acid domains

Domain	<i>Homo sapiens</i>	<i>Mus musculus</i>
PDZ	918	771
PTB	141	115
SH2	352	323
SH3	894	738

Peptide-binding groove
- binds C-terminal peptides

Common in signaling and regulatory processes





Minimum-energy conformation
X-ray structure

→ *binding mechanism*

→ *binding specificity and promiscuity*

→ *character of the bound state*

conformational changes in domain (allostery)

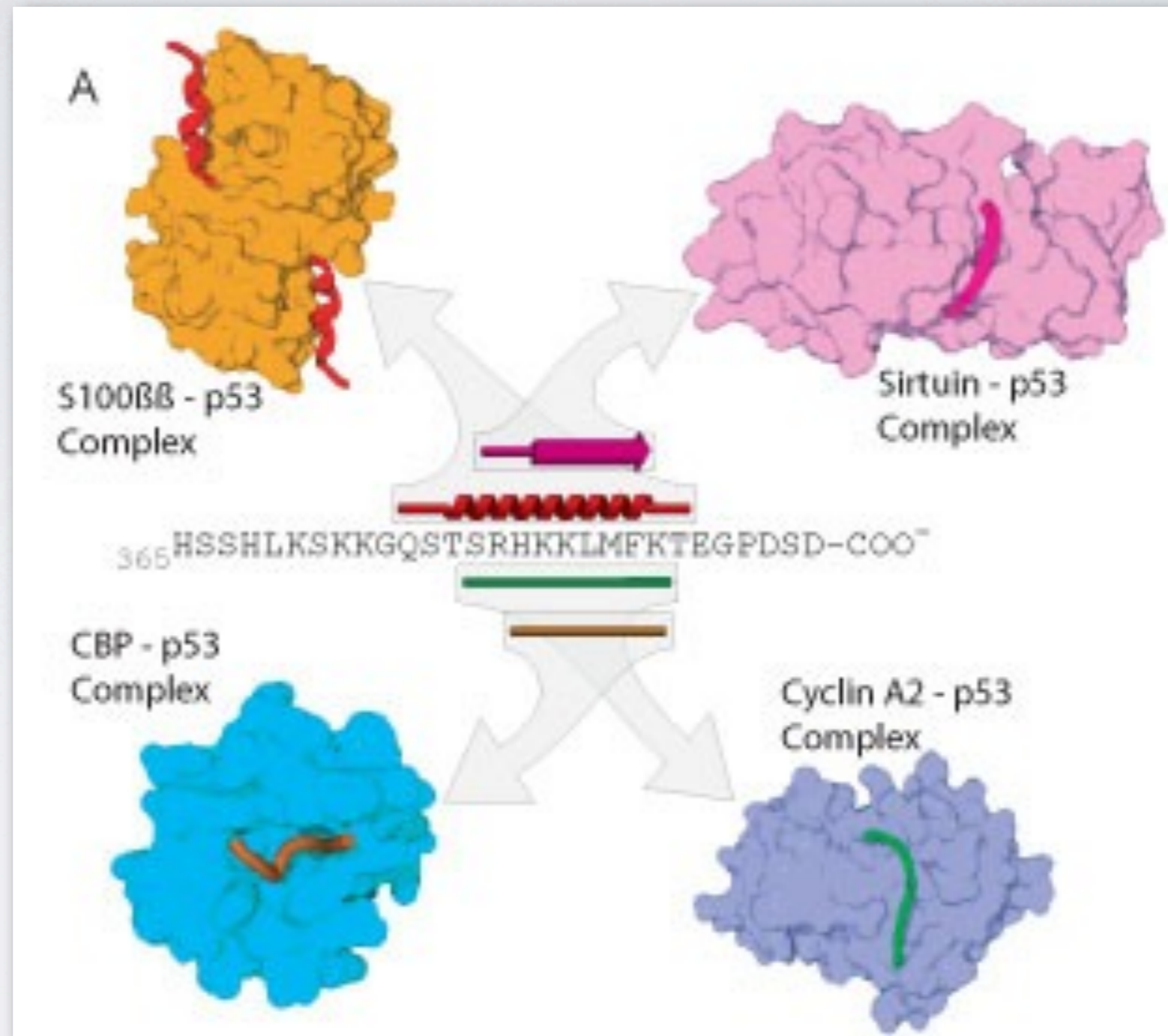
An unsolved problem



Given a protein structure, predict *whether* and *how* a peptide sequence can bind to the protein.

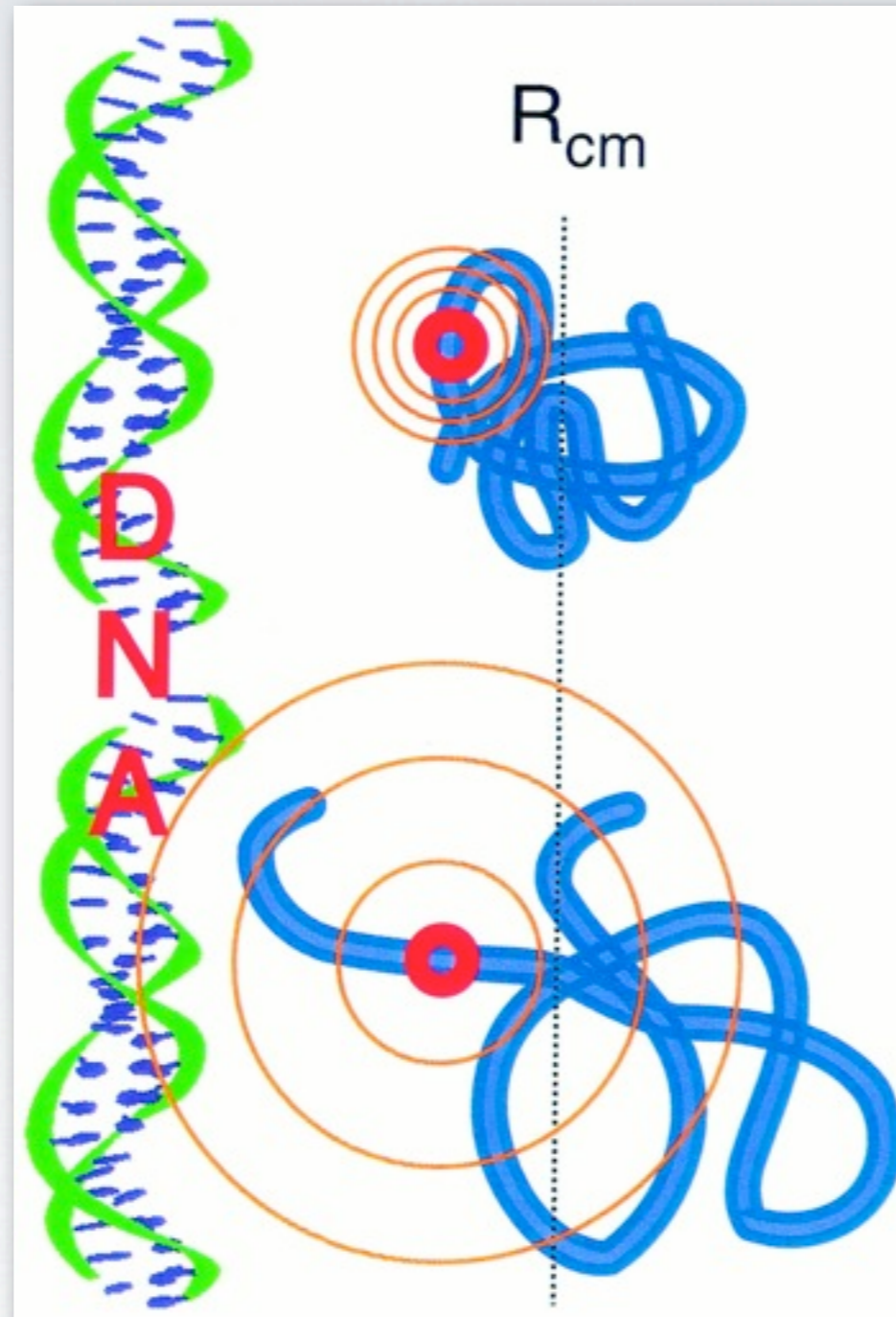
Biological advantages of intrinsic disorder

“Multi-specificity” of a p53 peptide



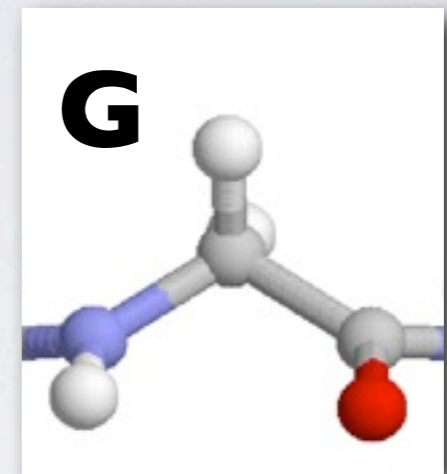
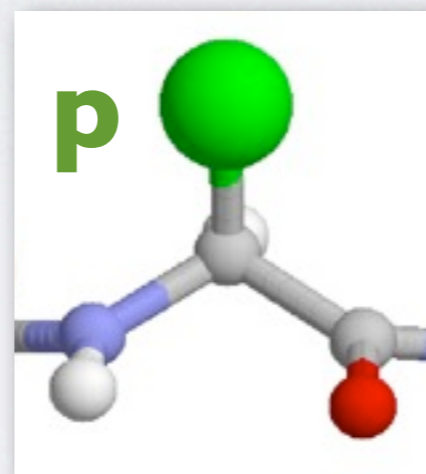
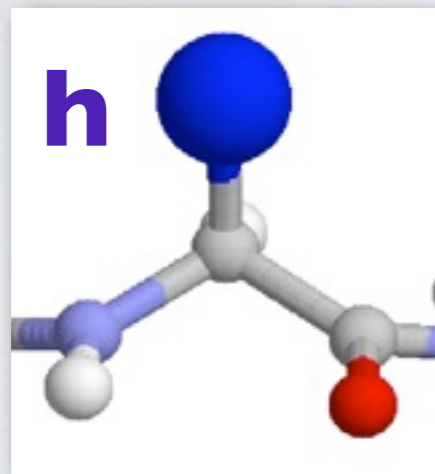
[Iskra Staneva, collaboration with Peking University]

A fly-casting mechanism?



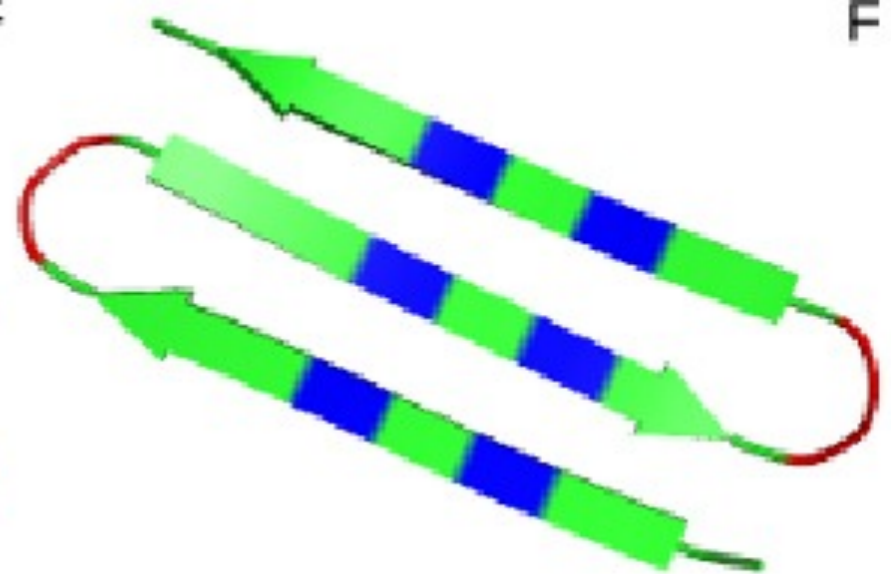
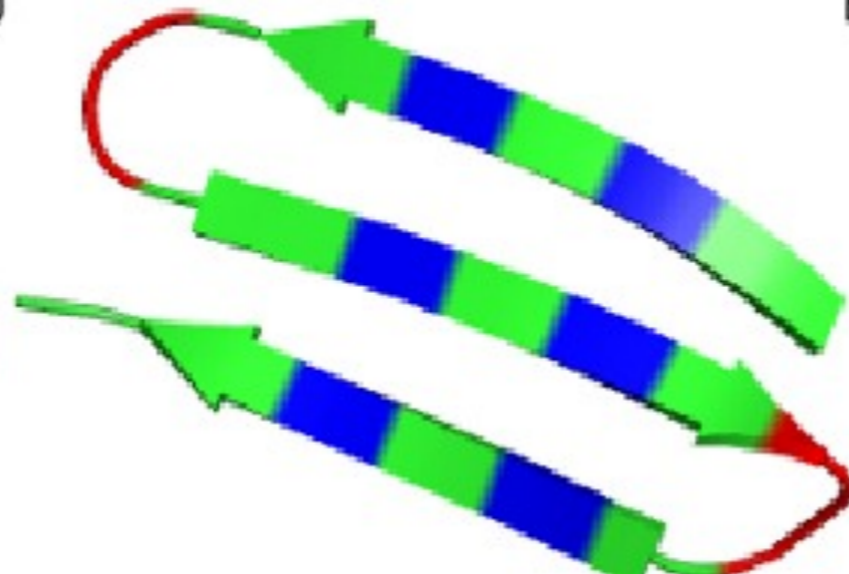
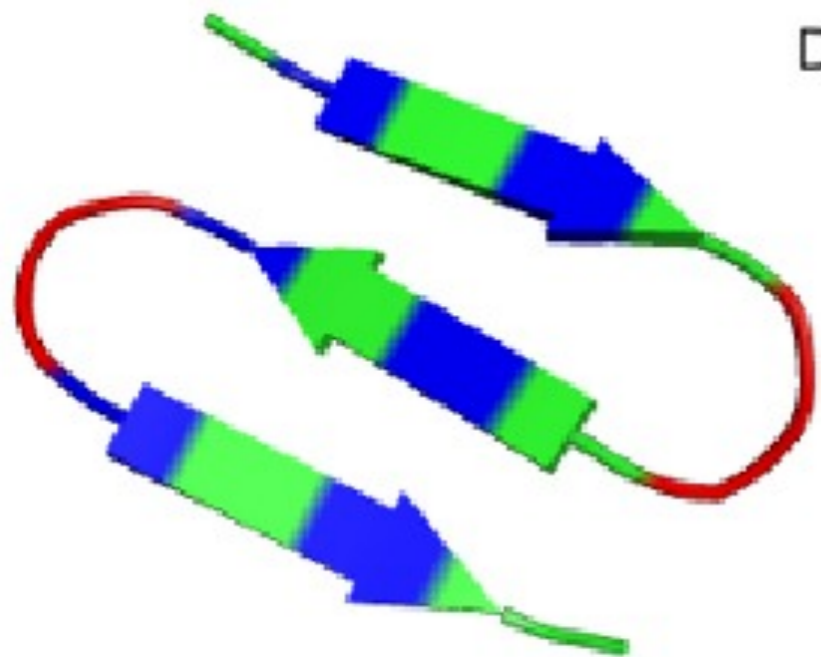
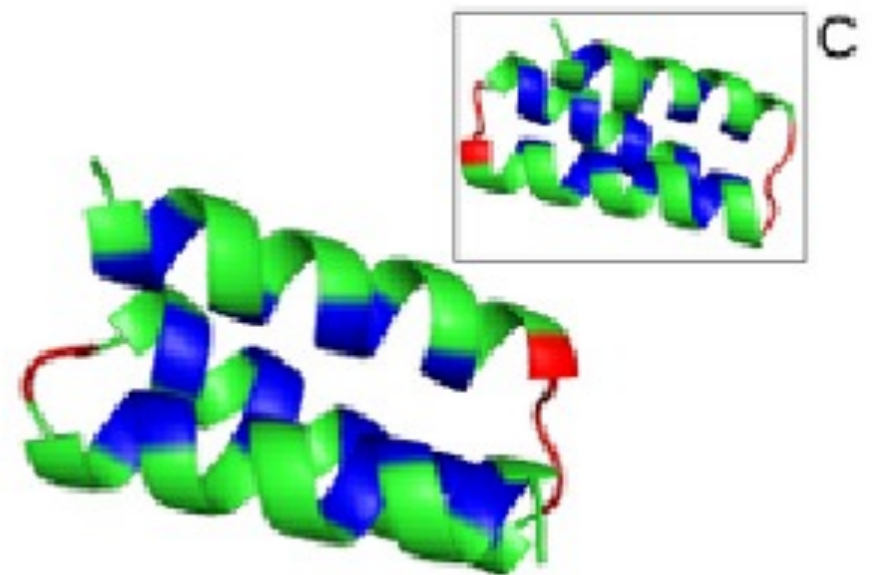
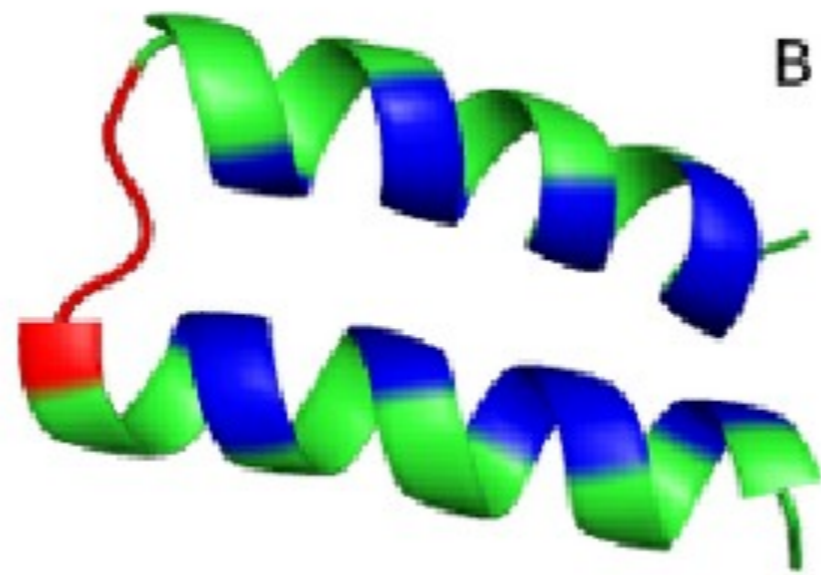
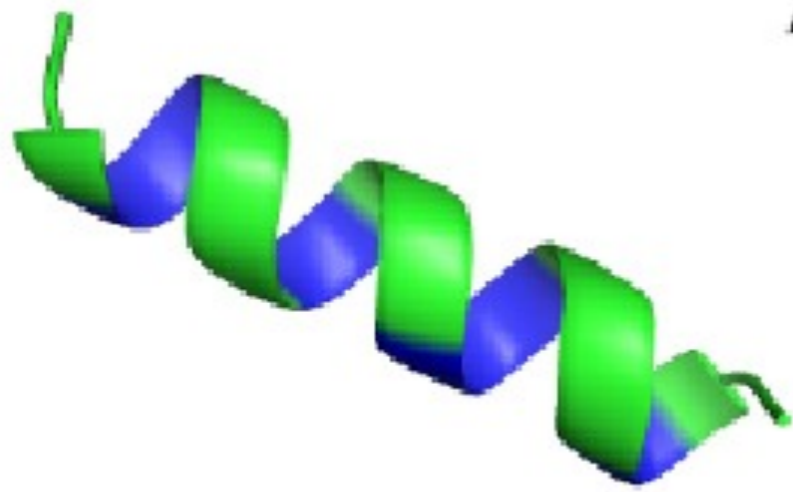
Shoemaker, Portman, & Wolynes *PNAS* **97**, 2000.

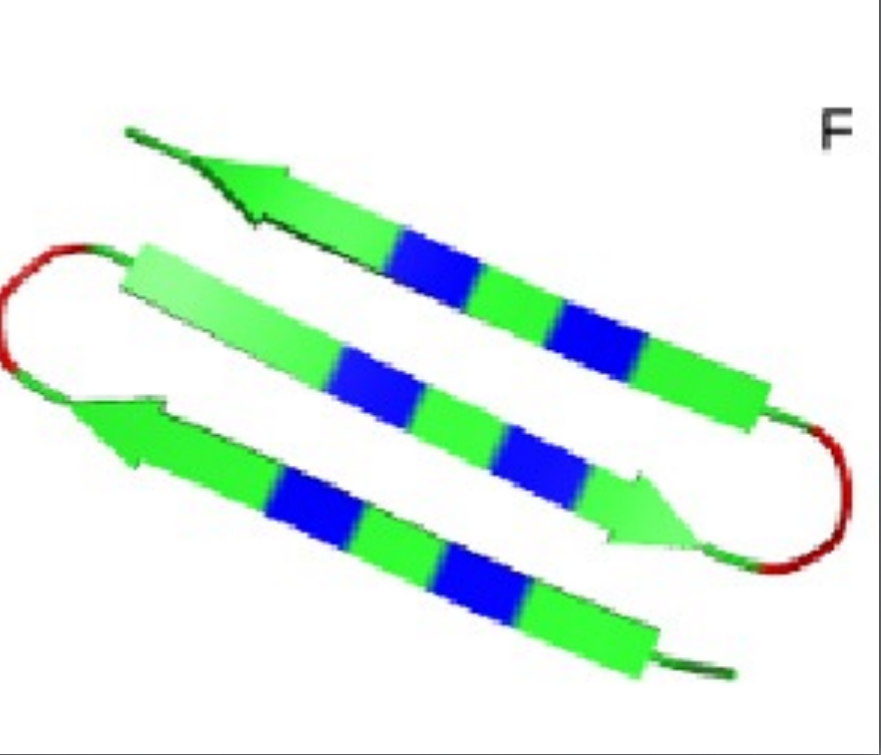
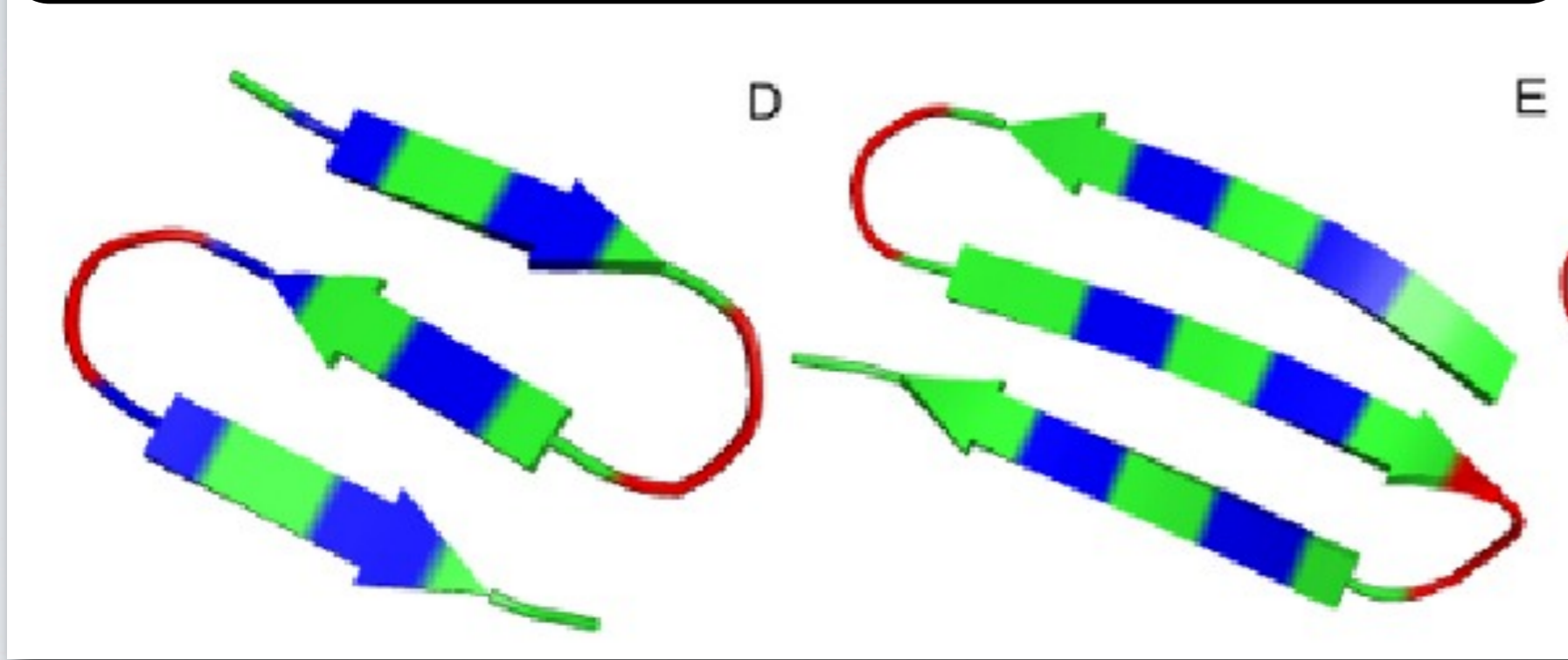
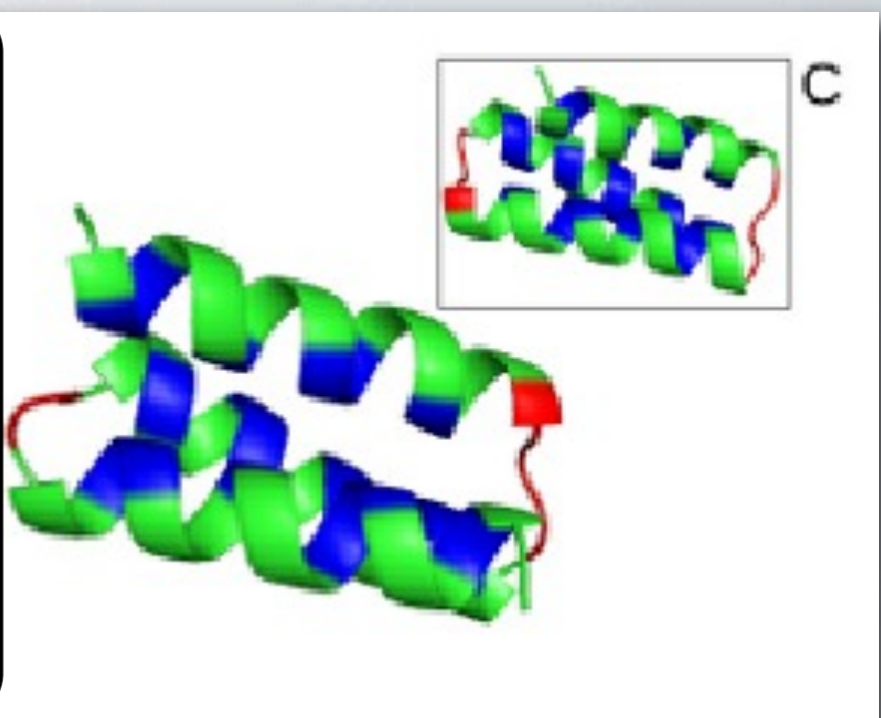
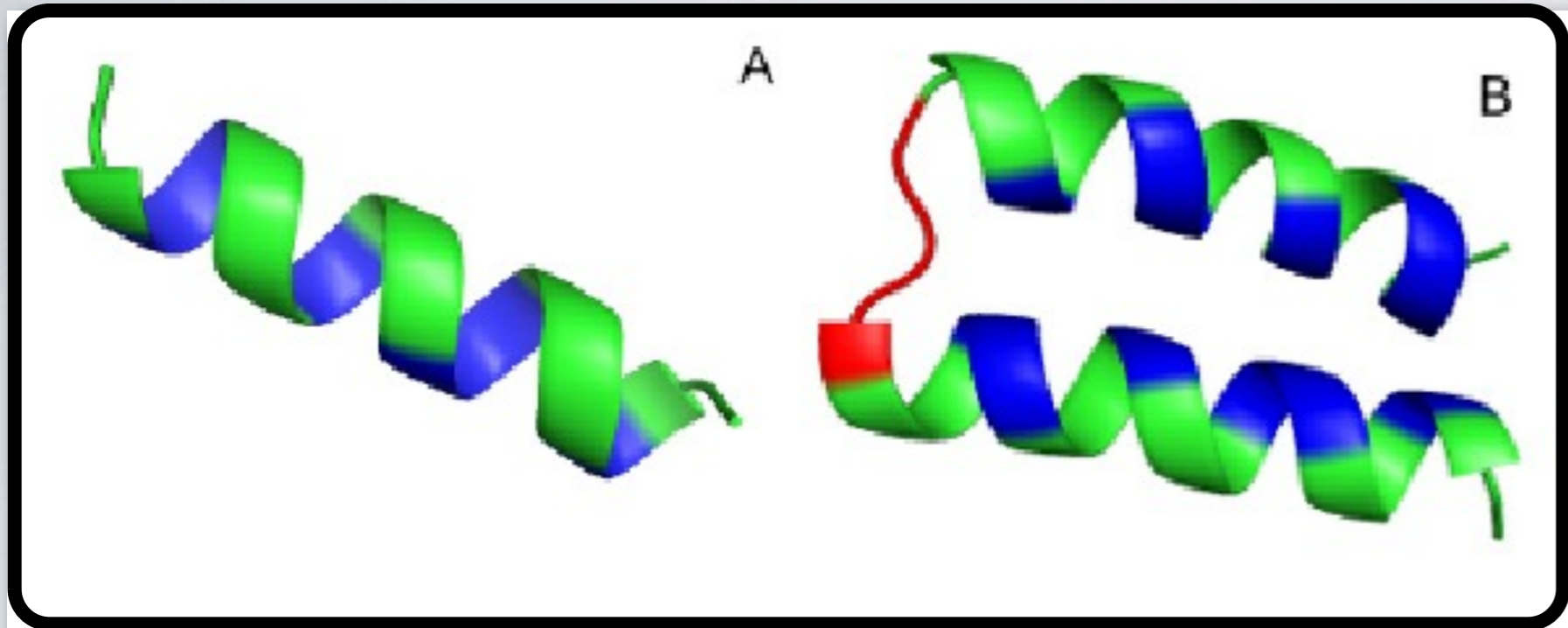
Continuous hydrophobic/ polar model



- Excluded-volume
- Hydrogen bonding (secondary structure)
- Hydrophobic attraction: **h ... h**

[*Arnab Bhattacharjee*]







Thank you!