Complexity Workshop : Key Experiments Using Sources of Hard X-rays Advanced Photon Source, Argonne National Laboratory October 11-13, 2010

Abstract on potential *Key Experiments* for discussion in the Focus Panel 4: Controlling Biological Functions: Understanding Energy Utilization and Fluctuations in Biological Systems

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Suggestions for experimental work concerning the case study 5.4.2 on protein folding

Protein folding has been shown to often involve highly non-equilibrium thermodynamics. Maynard Smith and Szathmary [1] discuss the folding of proteins once they have formed initially as a string of amino acids coded for by the genes in the DNA. In their discussion of pattern formation they draw an analogy with a picture made by an ink-jet printer. They state "..a protein molecule is made in a way analogous to such an image. Thus, there is a one-to-one correspondence between amino acids in the protein and base triplets in the gene that coded for it. Change one base and you will change one amino acid. This is not the whole story: the gene specifies the sequence of bases in the protein, but the string must then fold up to produce the three-dimensional form. In most cases, the string will fold up on its own: folding is a self-organised dynamic process, depending on the laws of physics, which do not need to be programmed. Maynard Smith and Szathmary show that the folding of proteins is self-organised – it is obeying the laws of physics which will ensure a particular folding pattern.

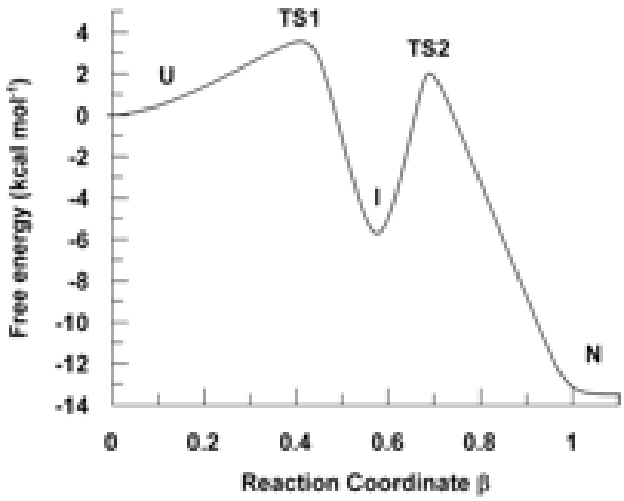

Figure 1 Free energy path for folding of proteins

However it is important to realize that the self-organising principle is already within the system to begin with. In the book *The Ten Most Wanted Solutions in Protein Bioinformatics* [2] by Anna Tramontano, chapter 4 specifically deals with the problem of protein structure prediction. This work very carefully shows that the shape of proteins, though following the laws of physics (Maynard Smith and Szathmary), is in fact a function of a free energy path (see Figure 1), and yet 'the biochemical function of a protein is determined largely by its three-dimensional structure' [2]. Thus, it is evident that the very folding path of the proteins demonstrates in reality another vital piece of intelligent machinery which has itself been pre-programmed – thus what this exposes is that there is a deeper level of information carrying ability within the DNA–RNA–Ribosome–protein communication system which is a layer beneath the already immensely sophisticated coding part of the DNA.

Experiments proposed

It is proposed that x-rays be passed through the proteins and DNA molecules to ascertain the energy bonds as the protein is folded. What are the changes in the free energy available?

Are there different energy paths that could be followed in the folding process?, It should be possible to work out the steepest descent in the phase space of possible energy bonding. The important deduction will be to ascertain what the energy bonds are as the folding and unfolding takes place.

References

[1] Maynard Smith, J. & Szathmary, E., *The Origins of Life*, Oxford University Press: Oxford, New York, 1999.
[2] Tramontano, A., Problem 4 protein structure prediction (Chapter 4). *The Ten Most Wanted Solutions in Protein Bioinformatics*, Chapman and Hall, pp. 69–88, 2005.