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Thermodynamic Analysis of Biological Systems

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The laws of thermodynamics traditionally describe the physical quantities (energy, entropy, temperature, volume, etc) of a thermodynamic system and the relationship between heat and work. Given that these laws are universal and represent the epitome of physical sciences, it is somewhat disconcerting to note that biologists have not always had a comfortable relationship with thermodynamics! This discomfort originates in the seemingly irreconcilable differences between the physical (simple) processes described by thermodynamics and the biological (complex) processes. As we all know, thermodynamic system tend to equilibrium, which for an isolated system implies a state of maximum disorder or maximum entropy. However, almost all biological systems do not ever reach equilibrium and seem to "evolve" to states of higher order, rather than disorder. Clearly, this discrepancy can be explained by simply noting that biological (living) systems are not isolated and are not in equilibrium with their surroundings. But this only explains why biological systems can be ordered but it does not explain how they came to be so. Of all the innumerable processes that increase entropy in the universe why does nature choose to create order in a few of its subsystems? Simply, put why does life create order out of disorder?

This question was originally taken up by Schrodinger in his classic treatise "What is Life", published in 1944 (http://whatislife.stanford.edu/LoCo_files/What-is-Life.pdf). Schrödinger proposed that biological systems feed on negative entropy which they import from their surroundings. For example, the absorption of photons by photosynthesis provides the motive for plant life (and subsequently, all other forms of life) on earth. The efficiency of the transfer of energy from plants to animals through the food cycle is high because the energy is maintained in the form of chemical energy, i.e., it doesn't generate much unrecoverable thermal energy. At the cellular (microscopic) level it is highly probable that all processes in the cell evolve towards equilibrium but that variations in external conditions keep shifting the equilibrium condition to some other state. Thus, resulting in a seemingly non-equilibrium system. For example, the folded configuration of a protein may be the lowest free energy state at a given pH but as the pH is changed, the protein will evolve to a new configuration or its new equilibrium state, which may be the unfolded state. It should be noted that the lifetime of most protein molecules is typically much shorter than that of the organism (with a few interesting exceptions like the eye lens crystallines).

Although, biological systems are non-equilibrium systems, equilibrium thermodynamics has been extensively utilized by biochemists. In the well accepted reductionistic approach, biologists have isolated specific processes and studied them *in vitro* under equilibrium conditions. This approach has two advantages: one the experimental measurements are much easier under equilibrium conditions and two the resulting experimental data can be analyzed using well established equilibrium thermodynamic laws. One example of a process that has been subjected to detailed biophysical characterization is protein folding, i.e., what causes linear amino acid sequences to fold into complex three-dimensional structures, structures which are vital to the function of the protein within a living system. Anfinsen in the 1950's proposed that the amino acid sequence itself determined the three-dimensional structure of the protein; specifically that ribonuclease A folds spontaneously to its native state *in vitro*. Thus, this protein folding theory has one of its central tenets, the primary sequence of a protein. Anfinsen theory relating structure to composition (or amino acid sequence) has been found to apply to a greater or larger degree in a variety of small proteins. Larger proteins, however, require the assistance of other "chaperone" proteins to carry out the folding process.

From a thermodynamic perspective, protein stability depends on the free energy change between the folded and unfolded states which is expressed by the following: "RT ln K = ΔG = ΔH " TΔS where R represents the Avogadro's number (6.0221415 x 1023), T, the absolute temperature, K, the equilibrium constant, ΔG, is the Gibb's free energy change between folded and unfolded, ΔH, the enthalpy change and ΔS, the entropy change from folded to unfolded. The enthalpy change, ΔH, corresponds to the binding energy (dispersion forces, electrostatic interactions, van der Waals potentials and hydrogen bonding) while hydrophobic interactions are described by the entropy term, ΔS. Measured by free energy, the maximum occurs when ΔS=0, while that measured by the equilibrium constant occurs when ΔH=0. These maximum stabilities can occur at quite different temperatures and both are used in different situations. Regardless of which one is used, however, the stability of the folded state decreases as temperature is either increased or decreased from normo-thermic temperature. While we can speak of discrete ground and excited states in simple systems such as atoms and nuclear particles, the description of complex systems like proteins requires more than such simplistic models, the ground state of the folded protein is very degenerate and as such, we use the Energy Landscape to describe it more adequately, where the energy of a protein is a function of the topological arrangement of the atoms. It is found that the thermodynamics of protein stability is modeled quite well by the Energy landscape theory.

I have used protein folding as the example to illustrate the microscopic analysis of macroscopic thermodynamic data. This is, of course, only one area, albeit an important one, where thermodynamics can be used to study elementary biological process. Another area that is justifiably receiving considerable attention is the process of binding

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between macromolecules or between a macromolecule and a ligand. Many more complex events occur in the living cell; they include protein translocation through membranes, large conformational changes, active diffusion, DNA unwinding, vesicle budding, membrane fusion, and virus assembly. At an even larger scale, there are processes like cell division, cell differentiation, development, growth, and aging. The role of thermodynamics is to provide an approach for understanding the driving forces responsible for all these processes and for rationalizing the observed pathways. The Journal of Thermodynamics and Catalysis is ideally placed to take advantage of this ongoing revolution in our thermodynamic understanding of biological systems and to be the primary conduit and forum for dispersion of such advances.