THERMODYNAMICS AND BIOLOGICAL SYSTEMS

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Contents

Summary

This chapter explores the involvement of thermodynamics in living systems. Thermodynamics is an exact science of energy analysis with its first and second laws. Energy analysis is the main connection point between thermodynamics and living systems. Therefore, the scope of the chapter is the thermodynamics analysis of energy production, usage, conversion, storage, and coupling in biological systems.

States in nature exist at global equilibrium, near equilibrium, and far from equilibrium. Classical thermodynamics views ‘nature’ as decaying toward global equilibrium and reaching maximum entropy in a closed system in accordance with the second law of thermodynamics. Biological systems operate far from equilibrium, resist decay to equilibrium, and increase complexity, specialization, and organization in time. They can

create "*order from order*" including synthesized proteins by inherited information in genes and "*order from disorder*", which links biology into thermodynamics. For instance, plants generate highly ordered structures from atoms and molecules, such as carbon, oxygen, hydrogen, nitrogen, found in atmospheric gases, water, and soils. Living systems go through a constant reproduction cycle, preserving information about the past. This leads to information databases about the growth and development strategies that are successful and creates the connection between the *order from order* and *order from disorder* efforts.

As Schrödinger proposed, the study of living systems from a nonequilibrium perspective would reconcile biological self-organization and thermodynamics. The study of nonequilibrium systems with information processing ability is unifying the efforts from biology and thermodynamics fields to understand, describe, and predict the behavior of biological systems. Biological systems are subjected to gradients related to material, energy, information, and move away from equilibrium. To oppose further movement from equilibrium they would utilize all options to counter these gradients effectively by developing more complex pathways and ordered states supported by autocatalytic positive feedback cycles. This leads to dissipative and self-organized systems with coherent behavior under specific kinetics and transport processes. This is in line with the second law of thermodynamics, which states that a finite amount of organization may be obtained at the expense of a greater amount of disorganization in a series of interrelated (coupled) spontaneous changes. For example, living systems combine catabolism with anabolism that are mutually coupled through the intracellular phosphate potential. Catabolism pathways generate energy and carbon dioxide from the growth-supporting energy source of large biomolecules. Anabolism pathways, in turn, utilize this energy for synthesizing macromolecules and biomass from low-molecular-weight substrates in bio-energetic pathways. Regulation and synchronization of bioenergetics within an open nonequilibrium system ensures resilience and may be explained by thermodynamics.

1. Introduction

1.1. Basic Thermodynamics

In open systems mass and energy can pass across the boundary, while only mass is exchanged through the boundary in closed systems. *Energy* is the capacity to do work and comes in various forms, such as motion, heat, light, electrical, chemical, nuclear energy, and gravitational. The *total energy* of a system consists of the *kinetic, potential, and internal energies*. The *internal energy* (U) of a system consists of sensible, latent, chemical, and nuclear energies. For a closed system, the total change in internal energy (ΔU) is:

$$\Delta U = q + W, \qquad (1)$$

where q is the heat, and W is the work, which may have many forms, including mechanical work and chemical work. Chemical work proceeds with changes in internal energy due to changes in the chemical composition (mass action). Heat absorbed by a system increases its internal energy and performs work. Energy is conserved and may

be converted from one form to another and transferred as heat or work through the boundary of a system. If an amount of energy is exchanged because of temperature difference between a system and its surroundings, this energy appears as *heat*; otherwise, it appears as *work*. With an average heat capacity ($C_{\mathrm{p,av}}$) and a mass of *m*, the amount of heat changed when the temperature increases from T_1 to T_2 is estimated by: $q = mC_{\mathrm{p,av}}(T_2 - T_1)$ and the local entropy change is determined by:

$$dS = \delta q_{\mathrm{rev}} / T \,, \tag{2}$$

where δq_{rev} is the reversible heat flow. The rate of change of internal energy with entropy at fixed volume in thermodynamic equilibrium defines temperature: $T = dU / dS\big|_V$. Every system is associated with energy and entropy. When a system changes from one state to another, the total energy remains constant, while the entropy is not conserved.

The change of entropy depends on external $d_{\mathrm{e}}S$ and internal $d_{\mathrm{i}}S$ contributions:

$$dS = d_{\mathrm{e}}S + d_{\mathrm{i}}S \,, \tag{3}$$

where $d_{\mathrm{e}}S$ represents the change through the boundary. For a closed system which exchanges heat only with k number of surrounding elements at temperature T_k, we have: $d_{\mathrm{e}}S = \sum_k \delta q_k / T_k$. $d_{\mathrm{i}}S$ measures the internal irreversibility called the entropy source strength σ, which is estimated by the product of flows or fluxes (J_i) and thermodynamic forces, in the form of gradients, (X_i) regardless the distance from the global equilibrium:

$$\sigma = \sum_i J_i X_i \geq 0 \,, \tag{4}$$

which is positive for irreversible and zero for reversible changes according to the second law of thermodynamics. The dissipation function (Ψ), in the units of power, is obtained as:

$$\Psi = T\sigma = T\sum_i J_i X_i \geq 0 \,, \tag{5}$$

where T is the temperature. If there are no physical and chemical internal mechanisms to change the properties, a system reaches *equilibrium,* in which entropy reaches its maximum value and energy reaches its minimum value.

From a statistical point of view, Boltzmann entropy (*S*) is defined as:

$$S = k_{\mathrm{B}} \ln \Omega \,, \tag{6}$$

and states that the entropy of a macroscopic state is proportional to the number of configurations (Ω) of microscopic states of a system where all microstates are equiprobable. Gibbs extension to a probability (p_j) distribution of the microstates (j) leads to the Gibbs entropy:

$$S = -k_B \sum_j p_j \ln p_j \,. \tag{7}$$

The total changes of enthalpy H and Gibbs energy G are:

$$\Delta H = \Delta U + P\Delta V\,, \tag{8}$$

$$\Delta G = \Delta H - T\Delta S\,, \tag{9}$$

where U is the internal energy, P is the pressure, and V is the volume of the system. The PV term represents the energy. The chemical potential is the partial derivative of thermodynamic potentials, such as Gibbs energy and internal energy, over the number of moles of the species in a mixture. It is defined relative to a reference state. For an ideal gas, the chemical potential is expressed by:

$$\mu_j = \mu_j^0(T_0, P_0) + RT \ln x_j\,, \tag{10}$$

where T_0 and P_0 are the reference temperature and pressure, R is the universal gas constant, and x_j is the mole fraction of species. In the presence of electric field, we get the electrochemical potential $\tilde{\mu}_j$:

$$\tilde{\mu}_j = \mu_j^0(T_0, P_0) + RT \ln x_j + Fz_j\psi\,, \tag{11}$$

where F is the Faraday constant ($F = 96500$ coulombs/mol), z_j is the valence of the species j, and ψ is the electric potential.

Not only amount but also the quality is important for energy. The maximum amount of energy that is available under reversible condition is known as ‘exergy.’ The first law of thermodynamics shows the interactions between internal energy, heat and work, and states that energy is conserved, while the second law of thermodynamics states that during any chemical or physical process ‘exergy’ will degrade. The quality of energy in a system varies because of internal irreversibility. The combination of the first and second laws of thermodynamics leads to the Gibbs equation:

$$dU = TdS + \delta W\,. \tag{12}$$

1.2. Biological Systems

Biological systems include two types of organisms that are eukaryotic and prokaryotic. Eukaryotes include animals, plants, fungi, protists, and have membrane-bound

organelles including nucleus, while prokaryotic cells are unicellular and include bacteria or archaea and have no nucleus. The distinct characteristics of living systems include diversity and adaptation, complexity, and homochiral character. Component biology focuses on enzyme kinetics and fluctuations, while systems biology focuses on the complex biological organization and processes interacting over time and space. Biology converges with many concepts of chemistry, mathematics, thermodynamics, and molecular biology. Alignment often occurs in response to the anisotropy of the cells' environment resulting in the migration of cells along a specific direction driven by both biochemical and entropy related processes. Fluctuations occurring far from equilibrium can lead to self-organized dissipative structures as a part of collective efforts to devise a cyclic flow of optimal energy degradation rate by increasing the entropy in their environments. At each bifurcation point of their evolution path, where the values of gradients exceed a critical value, the biological systems move to a more complex and stable form of order.

Biological systems are non-equilibrium open systems with many interrelated biochemical pathways and transport processes controlled by material, energy, and information flows. Biochemical pathways can create and maintain self-organized dissipative systems by consuming free energy received, hence increasing the net entropy of their environment, while their internal entropy decreases at the same time. Self-organized systems are in line with the second law of thermodynamics, which states that a finite amount of organization may be obtained at the expense of a greater amount of disorganization in a series of interrelated spontaneous changes. Living systems oppose the decay into thermal equilibrium by exporting entropy and increasing in size and complexity in time. The source of energy is the adenosine triphosphate (ATP), which is utilized in biochemical cycles, transport processes, protein synthesis, reproduction, and performing other chemiosmotic work. The processes in molecular and cellular biological systems are stochastic in nature varying in spatial and time scales. However, they are bounded with conservation laws, kinetic laws, and thermodynamic constraints that help describe the energy conversions, self-organizations, and regulations in energy metabolism.

The human genome project revealed that understanding the biological structures, a comprehensive description of deoxyribonucleic acid (DNA), protein and their functions is needed. The genes are transcribed by ribonucleic acid (RNA) polymerases into messenger ribonucleic acid (mRNA) strands under specific conditions and the transcripts are translated into proteins by ribosomes. Proteins are polymers with a precise sequence of amino acids and capability to fold up into multi-dimensional shapes and conformations. Folding may be a mechanism of transporting heat (entropy) away from the protein structure as it moves to a more ordered form at minimum Gibbs free energy. Strong chemical bonds lead to stable protein structures that can interact with each other and balance internal tensions between the counteracting tendencies for order. The analysis of the large-scale biological data sets generated by the human genome project requires expertise from biologists, chemists, physicists, mathematicians, engineers, computer scientists, and others.

Regions of the protein surface generally provide binding sites for different ligands, allowing the protein's activity to be specific and regulated. Proteins reversibly change

their shapes when ligands bind to their surfaces. One ligand may affect the binding of another ligand, and metabolic pathways are controlled by feedback regulations in which some ligands inhibit while others activate enzymes early in a pathway. The binding affinities and Gibbs free energy of formations may change with the biochemical reaction cycles that either release or require energy. The ability to bind to other molecules enables proteins to act as catalysts, signal receptors, information processors, switches, motors, and pumps. For example, proteins perform chemiosmotic work by coupling one of the conformational changes with the hydrolysis of an ATP molecule bound to a protein.

Metabolites like lactate and pyruvate and macromolecules like enzymes, protein complexes, and DNA interact with each other and with an aqueous thermal bath. They may act as inhibitors, activators, and products. Macromolecules are modeled as open systems subject to an external energy supply. They are also in contact with the thermal bath to dissipate the excess energy. Temperature gradients between organelles and between macromolecules and the thermal bath could lead to a cellular regulatory mechanism. The larger number of arrangements exists within the thermal bath known as the *hydrophobic effect* or *entropy stabilization* and may be due to the set of hydrophobic amino acids in proteins. The cell has a compartmental structure surrounded by a semi-permeable lipid membrane housing interacting metabolites and micro-processes.

2. Biochemical Reactions

Biochemical reactions take place in pathways consisting of various types of reactions including esterification, hydroxylation, carboxylation, carboxylation, isomerization, and others. These reactions are catalyzed by specific enzymes and take place in aqueous phase. In a reaction pathway involving oxidation reactions, electrons are lost and in reduction reactions electrons are gained. For example, foods are oxidized, and electrons are released to electron transport chain as a part of energy production pathway where the ATP is produced. Pathways also include acids as proton (H^+) donors and bases as protons acceptors. Consider the representative ATP production reaction below:

$$\mathrm{ADP + P_i = ATP \;\; ADP + P_i = ATP,} \tag{13}$$

where ADP is the adenosine diphosphate and P_i is the inorganic phosphate. The Gibbs free energy change (ΔG_r) of the reaction is related to the concentrations of substrates as reactants and products, as well as to the change of the standard Gibbs free energy of the reaction (ΔG_r^0) at pH = 7:

$$\Delta G_r = \Delta G_r^0 + RT \ln\left(\frac{[\mathrm{ATP}]}{[\mathrm{ADP}]\,[\mathrm{P_i}]}\right), \tag{14}$$

The Gibbs free energy is a state function hence its change between two states does not depend on the path. The speed of a biochemical reaction depends on the enzyme, while the direction of the reaction depends on the change of Gibbs energy. Some reactions proceed at near equilibrium and their directions can be changed by the concentrations of

the substrates, while for reaction proceeding at far from equilibrium, allosteric factors can control the activity of enzymes to change the flow of products in the biochemical pathways.

Only when ΔG_r is negative, the reaction takes place spontaneously and reaches equilibrium when $\Delta G_r = 0$ where forward and backward reaction rates become equal. Equilibrium constant of the reaction becomes:

$$K_{eq} = \left(\frac{[ATP]}{[ADP]\,[P_i]} \right)_{eq}, \tag{15}$$

where all the concentrations are at equilibrium and K_{eq} is related to ΔG_r^0 by:

$$\Delta G_r^0 = -RT \ln K_{eq}. \tag{16}$$

Based on the enthalpy of reaction (ΔH_r), reactions are classified as either *exothermic* ($\Delta H_r < 0$) releasing energy or *endothermic* ($\Delta H_r > 0$) requiring energy to proceed. Reactions can also be classified as *exergonic* ($\Delta G_r < 0$) decreasing free energy or *endergonic* ($\Delta G_r > 0$) increasing free energy during the reaction. The enthalpy of reaction (ΔH_r) can be calculated from the Gibbs-Helmholtz equation:

$$-T^2 \left(\frac{\partial (\Delta G_r / T)}{\partial T} \right)_P = \Delta H_r. \tag{17}$$

where the standard enthalpy of reaction (ΔH_r^0) and the standard Gibbs energy of reaction (ΔG_r^0) can also be obtained from the standard enthalpy of formation of species i (ΔH_{fi}^0) and the standard Gibbs energy of formation of species i (ΔG_{fi}^0).

Dissociation constant K_w of water molecule is:

$$K_w = \left[H^+ \right][OH^-] = 1 \times 10^{-14}. \tag{18}$$

For pure water, the dissociation is weak, and the amount of water remains constant. This leads to distributions of protons (H^+) and hydroxyl ions (OH^-): $\left[H^+ \right] = [OH^-] = 1 \times 10^{-7}$

For an acid (HA) with a weak dissociation of conjugate base of (A^-), we have the dissociation constant (K) as:

$$K = \frac{[H^+]\,[A^-]}{[HA]}. \tag{19}$$

which is related to the pH, assuming that the activity is equal to concentration, by:

$$\mathrm{pH} = \mathrm{pK} + \log_{10}\left(\frac{\mathrm{A}^-}{\mathrm{HA}}\right), \tag{20}$$

where $\mathrm{pH} = -\log_{10}\left[\mathrm{H}^+\right]$ and $\mathrm{pK} = -\log_{10}\mathrm{K}$. Buffers consist of solutions of acid and base conjugate pairs such as acetic acid and acetate.

The rate of many enzyme-catalyzed biochemical reactions can be described by the *Michaelis-Menten* equation. Michaelis and Menten assumed that the enzyme (E) and substrate (S) react reversibly to form a substrate-enzyme complex (ES). Later, the complex releases the free enzyme and product (P):

$$\mathrm{E+S} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{ES} \xrightarrow{k_3} \mathrm{E+P}. \tag{21}$$

The total concentration of the enzyme is constant. If the substrate concentration is larger than that of enzyme ($\mathrm{S} >> \mathrm{E}$) in the stationary state, we have the *Michaelis-Menten* equation*:*

$$J_\mathrm{r} = J_{\mathrm{r,max}} \frac{\mathrm{S}}{K_\mathrm{M} + \mathrm{S}}, \tag{22}$$

where the Michaelis constant (K_M) is defined by: $K_\mathrm{M} = (k_2 + k_3)/k_1$. The reaction rate reaches a maximum value: $J_{\mathrm{r,max}} = k_3\mathrm{ES}$, when the complex contains all the enzyme. This represents zero order kinetic behavior with respect to the complex (ES), and we have: $J_\mathrm{r} = J_{\mathrm{r,max}}/2$. The linear form of Michaelis-Menten equation is called the *Lineweaver-Burk* equation:

$$\frac{1}{J_\mathrm{r}} = \frac{1}{J_{\mathrm{r,max}}} + \frac{K_\mathrm{M}}{J_{\mathrm{r,max}}}\frac{1}{S}, \tag{23}$$

This equation can be used to estimate the value of K_M, which is equal to the substrate concentration at $J_\mathrm{r} = J_{\mathrm{r,max}}/2$. Inhibitors compete for the active site of the enzyme to form an enzyme-inhibitor complex for decreasing the activity of the enzyme. Enzymes are selective for their substrates to produce specific products. Enzyme catalyst increases the rate of biochemical cycles by reducing the energy of activation for reactions to sustain life. Under stable conditions, some substrates remain uniform, and the overall reaction remains close to global equilibrium with a deviation of less than 15%.

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Bibliography

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