The Consistency Between the Second Law of Thermodynamics and the Evolution of Complex Biochemical Systems

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Abstract

According to the three laws of thermodynamics, energy cannot be created nor destroyed, only transformed into a different energy form; entropy, or disorder, of an isolated system is always increasing, thus making many reactions more spontaneous by containing a lower Gibbs Free Energy; and as the temperature approaches absolute zero, the entropy becomes constant and no change occurs. If the entropy of the universe, an isolated system, is supposed to always be increasing, how can evolution occur where these simple molecules join together to create complex molecules, cells, tissues, and organisms if all these seem to be very organized and ordered, thus demonstrating a decrease in disorder, or entropy, in the system? Through the conduction of literature research and various real-life biochemical examples, the explanation of how the cells and other ordered structures were able to be created as well as the analysis of evolution and creation of life will both be able to explain how despite being seemingly unlikely to be created, the life that emerged approximately 3.7 billion years ago not only occurred spontaneously but will continue to grow and evolve. Depending on how one defines the system and its surroundings, different understandings and explanations of this apparent improbable development will be reached and expounded upon in this paper.

1. Introduction

1.1 Basic Terms and their Definitions

In the natural sciences, the universe, which includes all space, matter, and energy, has two components: the system and the surroundings. The system is the body that one is focusing on, whereas the surroundings is everything else in the universe aside from the system. These definitions work together and enable the observations of the transferring of matter and energies and the quantification of many variables as discussed further on. If the system can exchange both matter and energy with its surroundings, it is considered an open system. If the system can exchange energy but not matter, it is labelled as a closed system. Lastly, if the system cannot exchange neither energy nor matter, it is an isolated system.

Energy is the ability to do work and transfer heat. Work (denoted as w) is described as the process of the "transfer[ing] of energy that makes use of organized motion", while heat (q) is the process of the "transfer[ing] of energy that makes use of disorderly molecular motion" (Atkins and De Paula 29). Furthermore, an endothermic reaction occurs when the energy of a system is absorbed from the surroundings as heat. In contrast, an exothermic reaction occurs when the energy is released from a system into its surroundings as heat.

Enthalpy (H) is the energy transferred as heat in constant pressure conditions ($Eqn.$ 1), however the general equation that defines enthalpy is the sum of internal energy and the product of pressure and volume ($Eqn.$ 2).

$$\Delta H = q_p \quad (Eqn. 1)$$

$$\Delta H = \Delta U + P\Delta V \quad (Eqn. 2)$$

Additionally, entropy (*S*) is defined as the dispersal of energy during a process and allows us to see whether a reaction from one state to another is spontaneous or not. Using both enthalpy and entropy, one can use the equation to find the Gibbs free Energy (*G*), as follows,

$$\Delta G = \Delta H - T\Delta S \ \ (Eqn. 3)$$

where the change in Gibbs free energy is equal to the difference of the change in enthalpy and the product of the temperature and change of entropy (*Eqn.* 3). A reaction is spontaneous when the Gibbs free energy is less than zero ($\Delta G < 0$) and is more spontaneous as the value gets more negative. When both enthalpy and entropy are negative, then the reaction is spontaneous at low temperatures; however, when they're both positive, the reaction is spontaneous at high temperatures. When the enthalpy is negative and the entropy is positive, the reaction is always spontaneous; when enthalpy is positive and entropy is negative, the reaction is never spontaneous. Once the change in Gibbs free energy is zero ($\Delta G = 0$), the reaction has reached equilibrium, a state where the concentrations of the reactants and products will have no net change. In other words, the forward reaction will take the same amount of time as the reverse reaction.

Derived from the Greek roots of '*en*' and '*trop*', 'within' and 'change', the word entropy put together is the "change within (a closed system)" ("Entropy"). One definition of the change of entropy is the antiderivative of the quotient of the heat of a reversible reaction and the constant temperature in units of Kelvin (*Eqn.* 4),

$$\Delta S = \int_i^f \frac{dq_{rev}}{T} \ \ (Eqn. 4)$$

thus, giving the value of entropy the units of energy divided by units of temperature, such as J/K, which demonstrates how energy would be distributed (Atkins and De Paula 78). When heat flows out of the system ($q < 0$), the entropy is negative; although when heat is absorbed into the system ($q > 0$), the entropy increases. Because entropy is a state function, each set of values of pressure, temperature and volume, allows only one value for entropy. For example, when a system has P_1, V_1, and T_1, it would contain a different value of entropy than a system with P_2, V_2, and T_2 (assuming at least one of the values is different).

An additional definition of entropy proposed by Ludwig Boltzmann is the product of the Boltzmann's constant and the natural logarithm of the number of microstates ($Eqn.$ 5),

$$S = k \ln W \quad (Eqn. 5)$$

where the Boltzmann's constant is $k = 1.381 \times 10^{-23}$ J K^{-1}. Microstates is the number of possible molecular arrangements in a system in constant energy conditions (Atkins and De Paula 81). When the number of microstates increases, the value of entropy increases; with only one possible arrangement of molecules in a system, the number of microstates is 1 and will thus yield an entropy value of zero.

1.2 Laws of Thermodynamics

In order to study the transformations of energy between systems and the effects of its movements, the study of thermodynamics was created. From the Greek words of '*therme*' and '*dynamis*,' 'heat' and 'power' respectively, the study of thermodynamics falls under the study of both the fields of chemistry and physics (Voet et al. 11). All systems, biotic and abiotic, generally require an exchange of energy and thermodynamics allows the tracking of the energy input and output in all different types of conditions of variable temperatures, pressures, volumes, and amounts of substances.

The study of thermodynamics typically revolves around four laws that define the thermal equilibrium, energy conservation, the spontaneity with regards to increase in disorder, and the inverse relationship with the amount of disorder and temperature. The First Law of thermodynamics states that the internal energy of an isolated system must remain constant. If the heat is increased, the work must decrease, or vice versa. The following equation summarizes the first law,

$$\Delta U = q + w \quad (Eqn. 6)$$

where the change in internal energy of a system (ΔU) is the sum of heat and work ($Eqn.$ 6); the change must equal zero in a closed system. Thus, energy is neither created nor destroyed. (Atkins and De Paula 32-33)

The second law of thermodynamics is expressed differently by various scientists, however for our purpose, the following expression will be used: the entropy of an isolated system will always be increasing. A common way of expressing the second law is the sum of the changes of entropies of the system and surroundings is equal to the sum of the entropy of the universe, which is always greater than zero ($Eqn.$ 7).

$$\Delta S_{sys} + \Delta S_{surr} = \Delta S_{univ} > 0 \quad (Eqn. 7)$$

Therefore, the universe's dispersal of energy will always be increasing (Atkins and De Paula 78). Using the values of entropy, enthalpy, and temperature also allows for the determination of whether the reactions are spontaneous or not using $Eqn.$ 3.

Both the third and zeroth laws of thermodynamics involve different effects on the system regarding the change of temperature. The third law of thermodynamics states that at absolute zero, or -273 ˚C, the constituents of a perfect crystal —atoms or ions— are placed uniformly and will have no thermal motion and thus, no thermal energy (Atkins and De Paula 93). With this, the entropy of the system is zero due to the ordered crystal and lack of thermal motion. While the Zeroth Law of thermodynamics states that if systems A and B are in thermal equilibrium and systems B and C are in thermal equilibrium, then systems A and C are in thermal equilibrium (Atkins and De Paula 6).

All four laws allow the determination and quantification of the reaction spontaneities, energy transfers, and the physical and chemical conditions of the system. These laws highlight the relationships between numerous variables and are applicable in all of the natural sciences.

1.3 Origins of Life and Evolution

Nearly 4.6 billion years ago, the Earth was created, and life only appeared over one billion years later. The oldest fossils on Earth were found in a 3.5 billion year old Western Australian rock (Voet et al. 2), thus these microscopic fossils are "the earliest direct evidence of life on Earth" ("Oldest"). Scientists throughout history have tried to formulate the possible ways that living organisms could have come to being from an abiotic era during the one-billion-year period between the Earth's formation and the earliest fossil evidence. During the prebiotic period, the Earth's atmosphere was primarily composed of water (H_2O), nitrogen gas (N_2), carbon dioxide (CO_2) and partially of methane (CH_4) and ammonia (NH_3). At one point this transitioned into what is described as the primordial soup, an environment with conditions and components that resulted in the origin of life (Voet et al. 2).

While proposed by both Russian biochemist Alex Oparin and British biochemist J.B.S Haldane independently, 'primordial soup' was coined by Haldane. They both suggested that ultraviolet radiation from either the sun or lightning led to the formation of simple organic compounds from the initial inorganic atmospheric contents. Using their proposals later, Stanley Miller and Harold Urey worked together to imitate the same conditions on Earth by having electric emissions applied to a mixture of water, carbon dioxide, methane, hydrogen gas, and ammonia for approximately a week. After a week, a concoction of hydrophilic "organic compounds,…and other biochemically significant" molecules were found in the resulting solution (Voet et al. 2). Initially, Miller only found five amino acids (aspartic acid, glycine, alpha-amino-butyric acid, and two alanine forms); however, using the vials from his original experiments, scientists have found that there were 22 amino acids and many of them had reactive hydroxyl substituents, therefore raising the possibility of new molecule formations. The difference in the experimental analyses is that contemporary scientists have more methods to fully analyze the solutions as compared to Miller's times of research ("NASA").

An additional and popular theory of the origin of life is that the first biological molecules were created at the bottom of the ocean near hydrothermal vents, narrow openings in the ocean floor that release metal sulfides at incredibly high temperatures. These high temperatures are said to give the proper conditions to form amino acids and other organic molecules from the simpler inorganic reactants in the seawater (Voet et al. 2-3).

An alternative theory proposed by scientists is that life was formed inland near fresh hot water springs 4.1 billion years ago during the Hadean era. The cell membranes would not be able to self-assemble in the seawater conditions due to the presence of metals, such as calcium and magnesium. After inserting a vial with lipids and RNA monomers into the acidic hot spring water with consecutive wet-and-dry cycles, polymerization occurred. These resultant molecules would diffuse to other areas and pools, thus allowing the mixture of various molecules ("Where").

Regardless of the method of the creation of these simple biochemical compounds, they would undergo condensation reactions to form polymers and eventually macromolecules. These repeated condensation reactions were most probably enabled by the presence of minerals in the prebiotic solutions that separated the polymerization products from the water in the solution. With this, the hydrolysis reactions would occur at a lower rate and would enable the condensation reactions to remain dominant. Similarly, when the simpler organic molecules join, the diversity in the chemical molecules increases greatly and so too the reactivity of the molecules. Additionally, if two functional groups have a complementary relationship within a molecule, then the replication of the macromolecule is possible due to the specific pairing of the chemical groups (Voet et al. 3).

The primitive molecules and compounds formed were random, however, "natural selection, the competitive process by which reproductive preference is given to the better adapted, would have favored molecules that made more accurate copies of themselves" (Voet et al. 5). After the introduction of compartmentalization and thus the first cells on Earth, the environment within the compartments were very specific and would provide the protection of the necessary components for life-sustaining processes. Due to the narrowly available molecules within the primordial soup, only specific molecules were consistently formed and eventually gave rise to the metabolic pathways that supported the early organisms (Voet et al. 6).

As discussed earlier, all systems, including living organisms, need energy to run different reactions; therefore, the primary selection of the processes that would produce rather than consume energy gave rise to the energy needed to run the unfavorable energy-consuming processes. One example is the use of the sun as an energy source via the process of photosynthesis where carbon dioxide and water form a glucose molecule and diatomic oxygen ($Eqn.$ 8).

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2 \quad (Eqn. 8)$$

As a result of this consistent reaction process nearly 1.5 billion years ago, oxygen was released into the oxygen-deficient atmosphere and gave the anaerobic organisms a new environment to adapt to. Eventually the oxygen was used in other regulatory processes, thus making the metabolic pathways much more efficient and gave rise to aerobic organisms; thus, an explosion of biodiversity emerged and provided the foundation for multiple cells to work together to form more complicated life forms: multicellular organisms (Voet at al. 7).

1.4 Apparent Violation of the Second Law of Thermodynamics

As mentioned earlier, the entropy of the system is the heat divided by the system's temperature at the time the heat was released. Similarly, the entropy is directly proportional to the number of microstates. Therefore, for any macromolecule or organism, the possible arrangements of the molecules of their constituents is very low and is quite ordered comparative to its disordered monomeric constituents. With a decreasing number of microstates, entropy decreases logarithmically.

Functional macromolecules, such as proteins or DNA, must be joined with a certain arrangement of molecules in order to maintain the life-sustaining processes properly. The necessity for a specific arrangement in these molecules leads to a low-entropy state according to *Eqn*. 5. However, according to the Second Law of thermodynamics, the entropy of the universe, an isolated system, must increase for the process to be spontaneous. Therefore, there seems to be a violation in the Second Law of thermodynamics when it comes to biotic molecules and organisms, especially as evolution is occurring, leading to even more complex and ordered life forms which accompanies a decrease in entropy in the system.

2. Does the Origin of Life & Evolution Violate the Second Law of Thermodynamics?

2.1 Approach to Determining the Observance of the Second Law of Thermodynamics

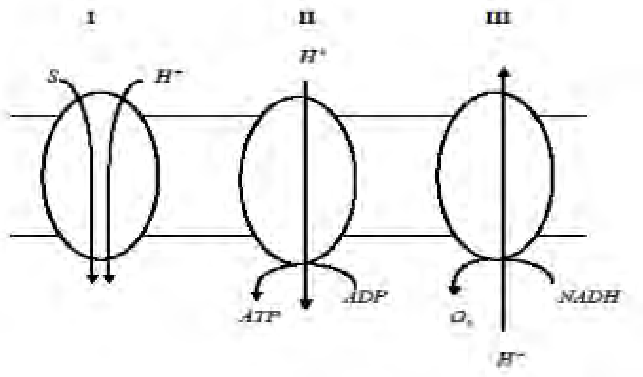
Prior to any calculations, one must assign the different components of the universe, such as the system and the surroundings, and categorize the type of system to see its range of interactions. Furthermore, one must follow the direction of energy from the different components in the system and surroundings to determine the reaction types.

Depending on one's objective, anything can be named as the system or the surroundings. For our purpose, the Earth would be the system and the outer space would be considered the surroundings. Earth is not considered an isolated system; however, the Earth is considered a closed system and takes in energy from space and generally does *not* take in matter. Earth takes in energy in the form of sun light and eventually radiates the energy back into space.

While the Second Law states that the total entropy of a closed or isolated system must always increase when a spontaneous reaction happens, it does not mean that some subsystems cannot decrease in entropy. Rather, some subsystems may increase in entropy while others may decrease in entropy. Despite the number of microstates being very low in a low-entropy state, it is still possible to have overall higher-entropy states for the universe aside from the local areas of lower probability. One of the fundamental thermodynamic principles is the increase in entropy once heat flows into a system, whereas the system that the heat left from, decreased in entropy ("The Second").

A common phenomenon seen in biochemical reactions is the coupling of an unfavorable endergonic (positive Gibbs free energy) reaction to a favorable exergonic (negative Gibbs free energy) reaction. Therefore, seemingly impossible reactions can occur in the cell, such as the

Figure 1 – An illustration of the three types of energy coupled reactions in the cells: chemiosmotic (III – when ion is transferred along with exergonic reaction), osmochemical (II – i.e. the formation of ATP with the favorable reaction of the proton transport), and osmosmotic coupling (I – coupled reaction between an exergonic chemical reaction and active transport of ions) (Ricard 103).



maintaining of the electrochemical gradient of protons in the intermembrane space of the mitochondria during the electron transport chain. In this case, the favorable passing of electrons to the different proteins and the usage of electron carriers enables the protons to continue to build up on the other side and later be used to form ATP via ATP synthase. This process does *not* violate the laws of thermodynamics, despite one part of the system not strictly following the principles.

Three different types of reaction couplings occur in the cell: chemiosmotic, osmochemical, and osmosmotic coupling. Chemiosmotic coupling occurs when the unfavorable transport of ions is coupled with an exergonic reaction, such as with the proton transport as a result of the oxidation of the electron carriers. Osmochemical coupling is the coupling of a favorable transport of ions and an unfavorable endergonic reaction, for instance with the spontaneous transport of protons through the ATP synthase and the endergonic formation of ATP. Lastly, osmosmotic coupling involves the exchanging of different ions through the membrane. When each of these nonspontaneous reactions are coupled with a spontaneous reaction, the overall reaction is favorable (Ricard 103).

2.2 Earth's Observance of the Second Law of Thermodynamics

To describe the quantity of lost energy from a system, the term entropy surfaced. While the system tends to increase in disorder, some areas within the system may not have a higher-entropy state. In an isolated system, the number of possible states must increase, as discussed earlier; however, in life, seemingly unfavorable formations are in fact overall spontaneous. Based on the definitions set earlier, Earth and all its components are the system and everything else is the surroundings. As mentioned above, Earth is not an isolated system and is considered a closed system.

In Alexander Schreiber and Steven Gimbel's article in the journal of *Evolution: Education and Outreach*, they focused on three points that highlight the reasons why evolution is thermodynamically favorable and obeys the Second Law of thermodynamics, thus opposing the anti-evolutionists. Firstly, living organisms have lower-entropy states than their surroundings and the cell membrane regulates the entire process of inputted free energy and outputted entropy. Secondly, while the entropy decreases within subsystems, if the overall total entropy (S_{tot}) increases over time, then complexity of life can develop. The sun is the ultimate energy reservoir that provides low-entropy light to photosynthetic organisms, thus allowing the process of evolution to occur. Thirdly, mutations in organisms are beneficial because they enable the organism to release energy to surrounding environments more efficiently and thus organisms can be seen as energy transfer systems from the thermodynamic perspective (Schreiber and Gimbel 101).

Almost all unicellular or multicellular organisms have different internal conditions than their surroundings and thus use outside energy derived from their fuel sources (e.g. food) for the regulatory metabolism processes. Organisms and their cellular constituents are typically classified as open systems because of the exchange of energy and matter between themselves and their surroundings. Furthermore, these organisms maintain their lower-entropy state via taking in energy from food and then output entropy via waste and heat (Schreiber and Gimbel 102). These waste and heat products have high entropy values compared to the low-entropy structures of the food and fuel sources that were initially taken in (Figure 2).

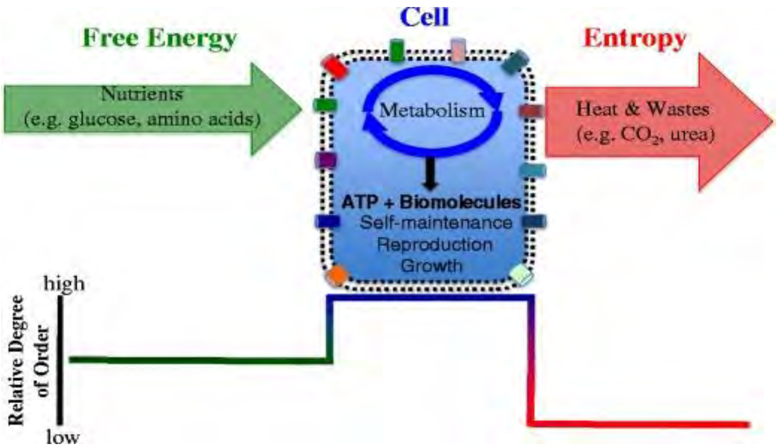


Figure 2 – Organisms can maintain a low-entropy state by (a.) taking in nutrients, (b.) metabolizing within the cell and converting the nutrients into usable energy, (c.) and releasing the heat and waste. The overall process goes from a medium degree of order (nutrients) to a higher degree of order (biomolecules/ATP) to a low degree of order (heat and wastes). This is thus initially decreasing in entropy but then increases after metabolism. (Schreiber and Gimbel 102)

The semi-permeable plasma membrane of the cell has an incredibly important biochemical feature of biotic organisms due to their roles in separating the exterior and interior. It is also the mediator for what can enter and exit the cell. Only specific nutrients and molecules may be brought into the cell and converted to a usable form of energy, such as ATP or other molecules. This usable energy can then be utilized in life-sustaining processes in the cell, such as reproduction, structural support, and protein synthesis. Along with the formation and utilization of the usable forms of energy, waste products and heat are also formed as byproducts; in order to maintain the proper cellular environment, these toxic byproducts must be disposed of to allow the cell to run properly and preserve homeostasis. These byproducts are the disordered waste that are exported from the cell via the plasma membrane, along with heat, as high-entropy products (Schreiber and Gimbel 102).

If there is a greater net entropy, organismal complexity and evolution is possible where a low-entropy state is formed through a favorable and spontaneous reaction. While natural selection did provide many species evolutionary adaptive mutations, evolution is not always synonymous with the ‘creation of more complex organisms’; instead, the complexity that may occur would only occur via an overall spontaneous reaction. For that to occur, one subsystem would have to increase in entropy and become less complex, thus enabling a subsystem to become more complex and ordered. In other words, the overall ΔS_{univ} must be greater than zero (Schreiber and Gimbel 103).

Using planet Earth as the system and the space as the surroundings, the sun (a body within the surroundings) directs high-intensity electromagnetic waves (e.g. ultraviolet light) towards Earth. These low-entropy waves get taken in and are emitted from Earth into space as high-entropy photons. The re-radiated light falls within the infrared category and has higher entropy due to the photons’ scattering into many different directions, adding to the cosmic microwave background (Styler 2). The total energy is conserved, however, fewer high-energy photons were directed

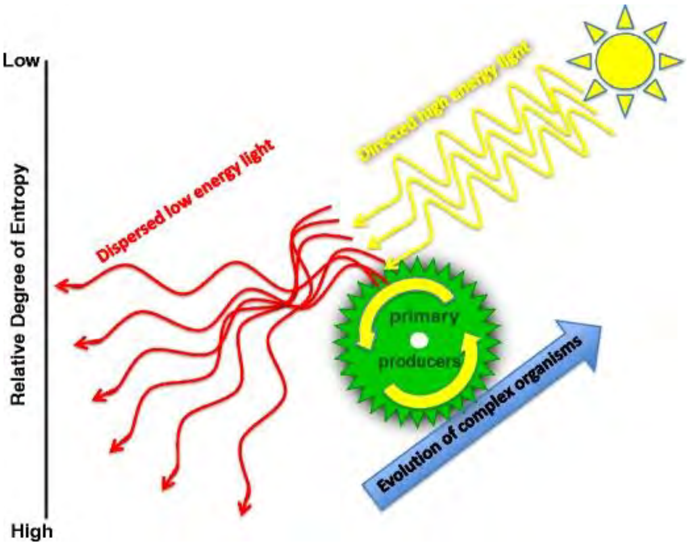


Figure 3 – The sun directs high-intensity light (UV light waves) towards Earth and many plants utilize this light for photosynthesis. Also, many low-intensity waves (infrared light) are radiated from Earth and scatters in many directions. The number of waves increased in the latter step, thus increasing the number of microstates and thus the value of entropy. (Schreiber and Gimbel 104)

towards Earth compared to the greater number of low-energy photons emitted into space (Schreiber and Gimbel 104). Thus, there is an overall increase in ΔS_{univ} (Figure 3).

According to American physicist Daniel F. Styler in his article "Entropy and Evolution", he calculated both the entropy change involved in the evolution of a rough estimate of the organisms on Earth and the entropy changes that Earth itself goes through. Using the Boltzmann's formula (*Eqn*. 5), he stipulated that the newer organisms' microstates are 1000 times less probable than those of the organisms a century ago. Taking the number of all existing organisms today, the value of the decreasing entropy that Styler calculated was one trillion times less than the entropy increase within the cosmic microwave background in outer space. Therefore, the overall significant increase in entropy makes the decrease in entropy from the evolving biotic matter negligible and is the driving force of evolution (Styler 2-3).

Similarly, evolution generally produces the most evolutionary adaptive organisms via natural selection. One specific adaptation that is favored is the type of genetic mutations that enable the maximum amount of entropy and disorder as a result. The cycle that allows the increase in entropy for many organisms is the following: the organism takes in food, converts it into usable energy, and then expels the waste (also the entropy). Once the organism dies, the breakdown of the organism's structure and form leads to the ultimate increase in entropy (paralleling the expulsion of waste products for living organisms). (Pascal et al.; Boojari 3)

As described in both chemistry and physical fields, systems tend to naturally go towards equilibrium. Equilibrium is generally considered to be the most entropically favorable. In the case of biotic matter, organisms utilize energy to withstand this tendency and maintain homeostasis and thus their specific and necessary environments. These same organisms must continuously obtain and consume nutrients from high enthalpy and low entropy sources to get the energy needed and then release the low-enthalpy and high-entropy waste products near equilibrium (Figure 4) (Boojari 3). When this process does not continue, the organism will approach equilibrium and die; organisms are considered open systems, as said earlier, and can never survive at a state of equilibrium (Pascal et al.; Voet et al.; Boojari 3). Death, in other words, is thermodynamically favorable.

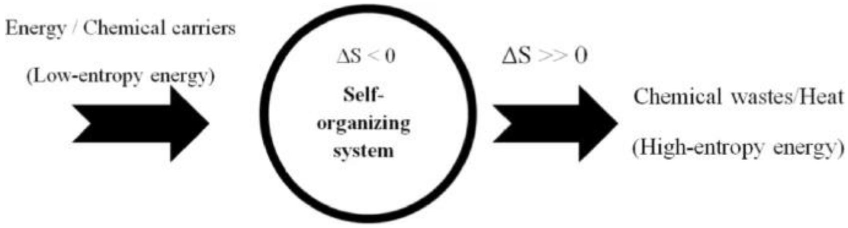


Figure 4 – Similar to *Figure 2*, where initially have low-entropy and then taken up by the system and high-entropy is released from the system. There is an overall increase in entropy, thus the Second Law of Thermodynamics is obeyed (Boojari 3).

Furthermore, the only way equilibrium can be achieved in an open system is if the cessation of matter and energy exchange between the system and its surroundings occurs. With the continuous exchanging of both, the system will never reach equilibrium, which is defined as the maximal state of dispersal of energy and matter. To keep the unfavorable reactions going forward, the addition of the reactants and removal of the products shifts the reaction to the right, according to Le Chatelier's principle. Therefore, the change in Gibbs free energy (ΔG) remains below zero, the range of values corresponding to spontaneous reactions, and does not approach zero unless it approaches equilibrium. From here, one can see the direct correlation between the value of ΔG

and the distance from equilibrium. As stated earlier, organisms at equilibrium cannot survive and will start to breakdown to ensure an increase in entropy. Organisms must maintain homeostasis, or a steady-state, and not an equilibrium state; this is done by utilizing the Le Chatelier's principle. For example, an important source of free energy in organisms comes from the hydrolysis of ATP and once equilibrium is reached, then ATP is primarily hydrolyzed into ADP or AMP and the cell has died from lack of energy (Alberts, et al., "Biological").

3. Significant Examples of Biochemical Molecules and Organisms

ATP, adenosine triphosphate, is the cell's energy currency. All living organisms utilize ATP in order to perform all housekeeping and regulation processes in the cells. In this section, several examples of biochemical systems that use ATP for reproductive and regulatory processes, such as cells, proteins, and DNA, demonstrate the observance of the Second Law of thermodynamics despite their ordered methods and structures.

3.1 Cells

As mentioned before, cells must take in energy in order to maintain their characteristic ordered structure and to grow and survive. Photosynthesis produces the reactants for aerobic respiration, which creates usable energy for the cell to use. Glucose is formed as a result of the

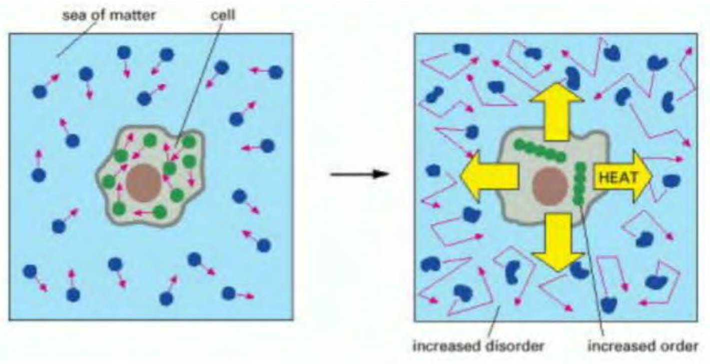


Figure 5 – Left: Disordered universe with a biological cell. The cell being the system and the sea of matter being the surroundings. Disorder is seen in both the system and surroundings. Right: The cell took in nutrients and in turn, released heat. This heat then caused more disorder in the environment *around* the cell. (Alberts, et al., "Biological")

photosynthesis process where the electromagnetic radiation from the sunlight propels the formation of this organic molecule. After aerobic respiration produces carbon dioxide and water from glucose and oxygen, the primary waste product is heat (Alberts, et al., “The Synthesis”). Cells generally undergo constant oxidation of the organic molecules that serve as their fuel sources, in this case, glucose; thus, ATP is produced for all necessary cellular processes along with the waste products. However, not all organisms utilize the sun or glucose as their fuel source. Rather, some organisms are chemosynthetic and use inorganic molecules as their primary source of fuel (Alberts, et al., “Biological”). These organisms also convert these molecules into their usable energy, in which they need to create order within the cells, while simultaneously releasing heat into the environment. This release of heat, regardless of the fuel source, is what makes the S_{tot} to have an overall increase and the thermal motion of its surroundings also increase, due to the random molecular motions from the heat (Figure 5). Lastly, this heat cannot be converted or utilized in any cellular process aside from increasing the overall entropy of the universe and enabling the creation of cellular order (Alberts, et al., “Biological”).

The hydrolysis of ATP is very favorable and is what allows most naturally unfavorable reactions to occur. Due to the repulsive forces from the concentrated negative charges on the ATP’s phosphates, the inorganic phosphate that breaks off accompanies a release of energy, the driving force of many biochemical reactions. In some cases, ATP hydrolysis leads to the phosphorylation of intermediate molecules, as is common in polymerization reactions to form macromolecules. Alternatively, other functional groups are transferred to form intermediate molecules for the same effect and function. Two such examples of forming more reactive intermediates would be the transferring of a hydride ion from the electron carrier NADPH or an acetyl group via acetyl CoA. (Alberts, et al., “The Synthesis”)

The overcoming of the energetic barrier through ATP hydrolysis is what provides the cell with free energy, which allows all sorts of activities. For instance, the separation of the DNA strands for DNA replication and transcription requires an input of energy due to their complementarity (Alberts, et al., "Life"). Also, during the hydrolysis reaction of ATP at physiological pH, the inorganic phosphate that is released only has one hydrogen ion from the water attached, therefore leaving a hydrogen ion in the solution. In this case, the following reaction lists the reactants and products,

$$ATP^{4-} + H_2O \rightarrow ADP^{3-} + HPO_4^{2-} + H^+ \quad (Eqn. 9)$$

where the reaction has two reactants and three products (*Eqn*. 9), thus an increase in entropy and a decrease in Gibbs free energy occurs (*Eqn*. 3). ATP is very reactive and has a higher Gibbs free energy than ADP and systems tend to go towards lower energy levels; consequently, reactions go towards the formation of ADP, a lower energy molecule (Libretexts).

In Araceli Venegas-Gomez's article, she highlights that one can compare cells of an organism with thermal engines, such as a Carnot engine, however there are differences: cells contain catalysts which form the cellular enzymes through the catalytic reactions and these catalysts also drive forward the cellular growth in volume from the synthesis of the membrane from the pieces of the nutrients. The cell is considered an open system and through the reactions with the catalysts, energy is exchanged, which is the main difference from the ideal Carnot engine that is equilibrated with the environment. Also, she explicitly says that a decrease in an open system's entropy obeys the Second Law due to the exchanging of matter and energy with the surrounding environment (Venegas-Gomez 4-6).

Because of the constant changes of the system through the different chemical reactions, one can view entropy as the system's energy flow rather than the typical view of dispersal of energy and matter. The energy flow can be understood as the force of approaching the natural tendency of a variable (i.e. variable gradient). With this understanding of energy flow and the idea that interactions between atoms and molecules occur locally, irreversible thermodynamics emerges from these two assumptions. Irreversible thermodynamics typically describes the transition of the system from a non-equilibrium state to an equilibrium state. Furthermore, the cell undergoes similar processes where entropy is produced. Researchers use models to quantify the entropy production of a cell and see the chemical processes that result in this entropy production. One such model is a protocell which is described as a "'self-producing' system" and is "self-organized, endogenously ordered, [and has a] spherical collection of lipids," which can also be called the plasma membrane with its phospholipid components (Venegas-Gomez 7-8).

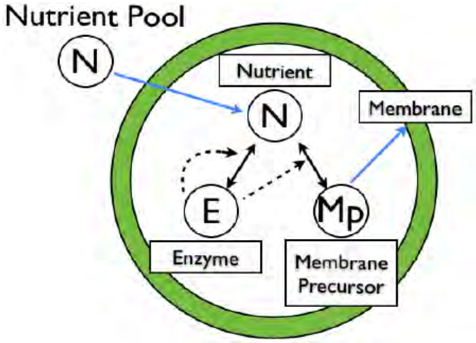


Figure 6 – This simple illustration depicts the protocell and the two-component system, the first approach suggested by Venegas-Gomez, with the concentration of the enzyme and membrane precursors (Venegas-Gomez 9).

Three approaches were proposed to evaluate the entropy production: a protocell solely dependent on two variables [the concentrations of the membrane precursors and the enzyme] (Figure 6), similar protocell however the material flow is also considered, and lastly a multi-component model. Firstly, the entropy produced while the cell grew as a result of a chemical reaction was at a minimum when the nutrients uptake rate was limited. When catalysis was present, the nutrients from outside the cell and the membrane precursors were far from equilibrium (non-equilibrium state). The entropy production was directly proportional to the nutrient uptake rate up until a point, and then the relationship became inversely proportional (decreasing of nutrient uptake) due to cellular growth. The growth of a cell reduces the surface area to volume ratio; thus, the nutrient uptake is not as high as before due to the new, bigger size. If one sets aside the nutrient uptake and focuses on the concentration of the enzyme, the overall entropy increases because of the increase in cell volume. In an equilibrium state, the cell's free energy stays constant and so too does the entropy; the environment, however, has increasing entropy and decreasing free energy. Alternatively, when looking at the flow, the cell's entropy and free energy increases and decreases, respectively, whereas both values remain constant in the environment. This shows that the cell is very different from the thermal engines because the latter has minimal entropy production (Venegas-Gomez 9-10).

In the second model, the flow of matter into the cell also contributes to the increase in entropy, as opposed to only the chemical reactions contributing to the entropy production. When the system has non-equilibrium chemical flow, not as much entropy is produced, thus the first model's conclusions still stand. The third and last model considers multiple variables, especially the abundance of molecules in the system and using a complex equation derived in her article, the conclusion that not as much entropy is produced with the non-zero nutrient concentration conditions. Depending on the level of nutrient uptake, the value of entropy production per unit cell volume growth varies; when the cell grew a lot, the value of the entropy produced increases due to the enzyme driving the non-equilibrium system to an equilibrium state. This also happened due to the synthesis of these enzyme and the growth of the plasma membrane and thus the increase in cellular volume (Venegas-Gomez 10-11).

While these models differ greatly from the typical cell and its biochemical complexities, one can utilize them to demonstrate conceptually how the cell grows with respect to the nutrient intake and the corresponding entropy that is produced (Figure 7) (Venegas-Gomez 13).

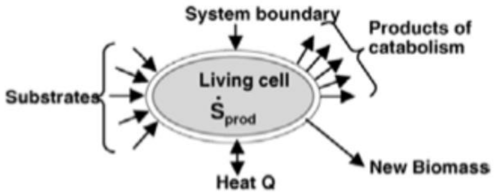


Figure 7 – A simplified illustration of the inputs and outputs of a growing cell and the balance of entropy. Nutrients are taken up, broken down and utilized to drive the cellular reactions, and lastly the heat and waste products are released, thus the entropy is balanced (Venegas-Gomez 12).

3.2 Proteins

Proteins are one of the four most biochemically significant classes of macromolecules and have wide-ranging functions within cells and biological organisms. To form the protein macromolecule, amino acid monomer subunits must undergo energetically favorable condensation reactions to form the polymer (Alberts, et al., “The Synthesis”). Based on the primary structure, or the order of the amino acid subunits, the structure of the protein will vary, making each protein specific for the role in which it will serve in the cells of the organism. When the protein is in its native state, the entropy of the protein is very low due to its specific conformation and structure. When denatured and unfolded, the number of possible protein structures increase, thus increasing the value of entropy. The more the protein is unfolded, the higher the value of entropy, as can be demonstrated by *Eqn*. 5 (Udgaonkar 3-4).

The entropy decreases as the protein becomes more folded; therefore, to make it energetically favorable, a greater negative value for enthalpy is required to ensure a negative value of Gibbs free energy, or to make it a spontaneous reaction. Proteins form via different types of bonds: both covalent bonds and non-covalent bonds, such as hydrogen bonding and London dispersion forces. When these bonds form, energy is released and is generally enough to allow the folding of the protein (Udgaonkar 4).

However, this favorable process is limited based on its environmental conditions. One such example of this would be the changing of solvents where the protein is a solute. Suppose the protein is in a polar solvent, such as water. Any nonpolar amino acids in the folded polypeptide would remain in the interior of the protein to reduce the interactions with water. On the other hand, if the polypeptide is unfolded, the water would form an intricate structure surrounding the hydrophobic polypeptide regions because they would disrupt the water's hydrogen bonding network. This new network structure of water that forms as a result to being exposed to the hydrophobic subunits makes the solution less disordered and occupies a low-entropy state. Once the protein is folded, the typical hydrogen bonding network of water returns due to the interior concentration of the hydrophobic amino acids within the folded protein and the solution occupies a higher-entropy state. Additionally, according to *Eqn.* 4, a greater increase of entropy would be observed when the reaction occurs at a lower temperature. With regards to proteins, there would be a greater increase in entropy when the protein is folded in a lower temperature solution compared to a higher temperature solution (Udgaonkar 4-5).

Further, enzymes are biological catalysts that accelerate reactions by lowering the Gibbs free energy of activation to reach the transition state and are typically made of proteins. These biochemically significant structures enable life-sustaining reactions to occur at the necessary rates. The slow nature of the reactions without a catalyst is due to the cost in entropy when the reactants are brought close to each other and must interact, especially if they form fewer molecules than the starting number of reactant molecules. However, there is a release of energy when the enzyme and the substrate bind together and that helps overcome the entropy decrease and reduces the loss of entropy.

3.3 DNA

The genetic material of an organism is composed of nucleic acids, one of the four significant classes of macromolecules, and is generally either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). A strand of nucleic acids is composed of nucleoside triphosphates, such as ATP, TTP (or UTP for RNA), GTP, and CTP, all of which are high-energy molecules. The phosphates in the nucleotides enable the polymerization of these monomers through their inherent high-energy state: the energy localized in the second and third phosphates of the pyrophosphate group that was released from the deoxyribonucleoside triphosphates (dNTPs). The synthesis of a DNA molecules starts with a phosphodiester bond being formed using the energy from the bond broken between the phosphates. As mentioned above, the hydrolysis of ATP (and other dNTPs) produces the energy for DNA replication. This reaction will repeat itself over and over again, forming the bonds between the growing strand and the new nucleotides (Cooper, “The Fidelity”).

This reaction occurs via the hydrolysis of the 5’ triphosphate group of the incoming nucleotide and is added to the 3’ hydroxyl group (OH^-) of the growing chain (Figure 8). The reaction cannot occur from the 3’ to 5’ due to the following situation: if the hydrolysis of the triphosphate group of the last nucleotide in the DNA would be the one that provided the energy, the DNA polymerase would not be able to proofread the strand. The lack of proofreading ability happens when the wrongly placed nucleotide is removed which leads to the 5’ triphosphate group also being removed. Since the DNA polymerase can only add from the 5’ to the 3’ direction, the strand will no longer be able to be lengthened. (Cooper, “The Fidelity”)

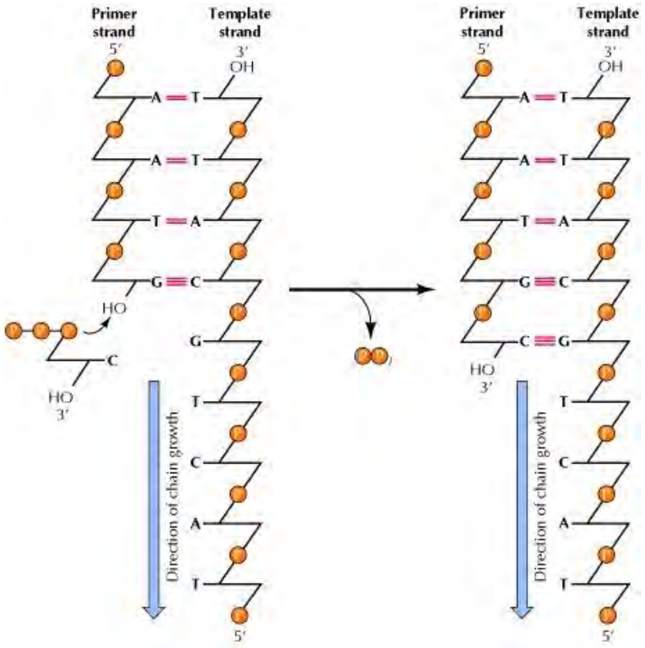


Figure 8 – An illustration of a growing DNA strand and the release of the pyrophosphate from the 5’ triphosphate group when added to the 3’ hydroxyl group is visible (Cooper, “DNA Polymerase”).

DNA has practically infinite possible ways the bases can be organized, and it requires an input of energy to prevent the tendency towards maximal dispersal or a higher state of entropy. One solution that was evolutionary adaptive was the utilization of the double-helix template with complementary strands that not only controls what is added but also serves as the blueprint of all life processes (Peterson 2). Organisms take in food that fuels their cells and in turn enables the proper running of the cells, which includes the essential task of DNA and the importance of its replication: holding genetic instructions for the organism’s life and the proper replication is needed to ensure the safety and protection of the organism. The intake of energy reduced the cost of entropy in the DNA that is associated with a specific order of base pairs, the double helix, and the tight packing of the DNA in the nucleus.

3.4 Aging and Disease

The ‘death of an organism’ used as a synonym with ‘equilibrium’ was and is a generally accepted notion. Along the same lines, the increasing of entropy, or the approach to the equilibrium state, is associated with aging and disease. Thus, the maintaining of a lower entropy state would possibly lead to different benefits, such as longevity and good health (Wang 1). However, if the organism is overall supposed to approach equilibrium throughout life and increase in entropy, how can this natural tendency stop in its track and reverse to maintain the desired low-entropy state of the system?

Firstly, the entropy can be reduced under certain conditions, such as when the organism has enough sustenance, proper metabolism, strong immune system, and strong ‘self-healing capabilities.’ Life is generally associated with order whereas death is associated with maximal state of equilibrium and dispersal; therefore, when the entropy starts to decrease or increase, it is associated simply with health and disease, respectively. When the molecules and cells of the body get disordered and lose its structures, then disease will be the result, whether it’s a type of cancer, metabolic disease, etc. Disease can be understood as the increasing of disorder of anything, whether cellular, genomic, proteomic, or other (Wang 1).

In Zhiguo Wang’s “The entropy perspective on human illness and aging,” there were four ways that the entropy of humans can be reduced. Every human has the following four things when they are born that allow the entropy to be reduced: “self-organizing, self-defense, self-healing, and anti-wear-and-tear capabilities” (Wang 2).

The self-organizing system can be defined as the ability of the cell to maintain complex and ordered structures throughout the body from an initially disordered state. Many cellular structures are morphologically significant and if the formation or upkeeping process is interrupted, the order and complexities of the structures might be compromised and harmful for the organism. Self-organization depends on how much fuel can be taken in and how much energy can be produced for all the cellular life processes, along with the excretion of heat and waste. The food is broken down from complex structures to simpler molecules, thus increasing the entropy (Wang 2-3).

The self-defense system is made up of different ways humans can be protected from pathogenic organisms, some of which are autophagy, apoptosis, immunity, and so on. For example, the immune system is famous for protecting the body by fighting pathogens via the innate and adaptive immune systems. When an individual is sick, the immune system spreads many different molecules all over the body, thus the entropy was very high. Another example is during an inflammatory episode where the cytokine concentration is too high and thus may cause an adverse reaction and damage the surrounding tissues and cells, a high-entropy situation (Wang 3-4).

The third way was through the self-healing system of the body that comprises of three levels: the renewal and regeneration of cells and tissues, DNA-repair machinery for any damaged or mutated genes, and the ability to make new cells to replace the damaged cells and tissues. All three methods involve the preservation of a lower state of entropy (Wang 4). The last way to reduce entropy was through the ‘anti-wear-and-tear’ system, the effects of constant stress on the body that may cause severe damage to the tissues. While it is difficult for the ‘wear-and-tear’ effect to become a reality without specific circumstances, the body typically tries to fix itself and maintain order. However, during those specific cases in which the body is worn down enough, the different tissues and organs of the body may be damaged, and the entropy will start to increase as the health of the individual declines (Wang 4-5).

Ultimately, when any of the four safety mechanisms of the body are compromised, the entropy will start to increase. The only way one can achieve an overall low-entropy state is by consistently following healthy lifestyle choices, which will in turn build up the four entropy-reducing systems of the body (Wang 5).

4. Conclusion

Through the literature review of articles, excerpts from textbooks, and blog posts on the fields of biology, chemistry, engineering, and physics, one can delve into the true scientific and mathematic definitions of key principles of nature. With superficial understandings of these principles, such as the laws of thermodynamics, different systems in nature would seem as though they violate these principles. However, a more careful analysis shows that these laws are still observed. As scientific research progresses, more and more connections between these fundamental topics to other fields of research and careers will be drawn. With deeper understandings of the laws of thermodynamics, one can draw connections between seemingly unrelated topics; for instance, between physical and chemical topics, such as entropy, and clinical topics, such as diseases and aging.

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