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Self-organization and entropy reduction in a living cell

Paul C.W. Davies [a], Elisabeth Rieper [b], Jack A. Tuszynski [c,*]

[a] Beyond Center for Fundamental Concepts in Science, Arizona State University, Tempe, AZ 85287-1504, USA
[b] Centre for Quantum Technologies, National University of Singapore, Block S15, 3 Science Drive 2, Singapore 117543, Singapore
[c] Department of Physics, University of Alberta, Edmonton, Alberta T6G 2E1, Canada

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ABSTRACT

In this paper we discuss the entropy and information aspects of a living cell. Particular attention is paid to the information gain on assembling and maintaining a living state. Numerical estimates of the information and entropy reduction are given and discussed in the context of the cell's metabolic activity. We discuss a solution to an apparent paradox that there is less information content in DNA than in the proteins that are assembled based on the genetic code encrypted in DNA. When energy input required for protein synthesis is accounted for, the paradox is clearly resolved. Finally, differences between biological information and instruction are discussed.

1. Introduction

Over the past century relatively little attention has been paid to the physical basis of embryology. With the discovery through the space program that the very important cytoskeletal proteins, such as microtubules, are differentially sensitive to gravity (Portet et al., 2003), it is clear that the fundamental conceptual basis of embryology cannot be developed merely by employing a classical molecular genetic framework. In addition to gravity, other physical forces such as surface tension due to intercellular adhesion (Goel et al., 1970, 1975; Gordon et al., 1972, 1975; Steinberg, 1996; Trinkaus, 1984a), the mechanical forces exerted during cell division (Rappaport, 1996), and physical waves of cytoskeletal expansion and contraction that traverse embryos (Gordon, 1999) all provide important non-chemical contributions to morphogenesis of embryos. Moreover, cell differentiation leading to morphological differences between cells in various tissues and organs are extreme examples of what appears to be an entropy reduction process, i.e. self-organization. This apparent contradiction of the second law of thermodynamics drew attention of many physicists beginning with Schrödinger (1967). At the macroscopic level, living systems are thermodynamically open and far-from-equilibrium systems, hence the balance of entropy at this level must necessarily involve metabolic energy production as well as heat and waste product dissipation into the external environment. A more subtle question arises at the level of a single cell, especially an embryonal cell, that undergoes rapid self-organization, all the while being sensitive to physical forces acting on it from the environment. Houliston et al. (1993) have shown by means of time-lapse video recordings that a wave of cytoplasmic reorganization, involving displacement of perinuclear organelles and movements of the surface relative to the underlying layer of cytoplasm, occurs prior to first cleavage. This wave requires dynamic microtubules in association with the organelles. Precleavage waves have also been described, progressing in the same direction (Yoneda et al., 1982). In many species rearrangements of the cytoplasm directed by external cues may introduce new axes of cleavage (Driesch and Morgan, 1895; Speksnijder et al., 1990). Thus, there appears to be a relationship between microtubules and rearrangements of cytoplasmic components induced by precleavage waves, but the correlation between them is unknown. It is, therefore, important to understand the entropy reduction contributions arising from internal self-organization, information storage and transfer, at a single cell level, as the only way to reconcile this with laws of thermodynamics is by balancing these free energy changes with metabolic energy expenditures. We will discuss these processes in some detail in this paper. This paper is largely aimed at providing an overview of the problem of linking biological organization with information and entropy.

Living cells perform numerous complicated, synchronized and very specific tasks in order to maintain their biological functions. These complex tasks require information input (e.g. a chemical gradient), information processing (signals sent into the cell from membrane receptors), and instruction (e.g. reorganization of the actin cytoskeleton for motility) as the output of the underlying

* Corresponding author at: 3-336 Cross Cancer Institute, 11560, University Avenue, Edmonton, Alberta T6G 1Z2, Canada. Tel.: +1 780 432 8906.
E-mail addresses: jackt@ualberta.ca, jack.tuszynski@gmail.com (J.A. Tuszynski).

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computations. In order to function, a living cell, similarly to a man-made machine, requires specific components to be interconnected in an intelligent fashion so they can perform the desired tasks. In addition, a steady supply of energy must be provided to be converted, with some level of efficiency, into useful work and to keep the organism at a constant physiological temperature. However, it should be noted that living organisms cannot simply be reduced to machines as demonstrated by Rosen (1991). In fact, organisms are different from machines because they are characterized as being closed to efficient cause which means that the catalysts needed for its operation must be generated internally. As Rosen stated it "A material system is an organism if, and only if, it is closed to efficient causation". The closure of the relational diagram he showed establishes a category of objects called organisms that are clearly distinguishable from machines. This distinction arose from a procedure which did not reduce the system to its material parts, nor did it explicitly invoke dynamics. Also, the concept of replication in this context means that what is replicated is a functional component, not a material part as such. Thus while organisms are complex, not all complex objects are organisms. An organism possesses the kind of *unity* invoked when discussing autopoietic systems (Maturana and Varela, 1980). It is necessary and useful to recognize functional components as making up separate tangible aspects of the system. Biological cells are constructed from yet smaller machine-like entities called organelles. Cell organelles include mitochondria, Golgi complexes, endoplasmic reticulum, and the protein filaments of the cytoskeleton such as microtubules and actin filaments (microfilaments). Even below this level there are machine-like parts of the cell, namely motor proteins and enzymes, that perform specific functions involving energy input and power output, e.g. transport, motility and cell division (Alberts et al., 1994). A critically important macromolecule is ATP (and its relative GTP), which serves as the primary energy currency of the cell. ATP is used to build complex molecules, provide energy for nearly all living processes in order to power virtually every activity of the cell. While organic components of nutrients contain numerous low-energy covalent bonds, they are not directly useful to do most type of work in the cell. Thus, low energy bonds must be translated into high-energy bonds using ATP energy by removing one of the phosphate-oxygen groups, turning ATP into ADP. Subsequently, ADP is usually immediately recycled in the mitochondria where it is recharged and re-emerges again as ATP. ATP synthesis in a mitochondrion requires approximately 60 kJ/mol of energy delivered through complex and well-tuned electron transport reactions. ATP hydrolysis releases approximately 30.5 kJ/mol of free energy (dependent on the concentration and pH values), which can be viewed as a biological energy unit. The human body requires the production of its weight in ATP every day in order to function, which translates into 10^{21} ATP molecules per second. Since there are on the order of 3.5×10^{13} cells in the human body and each cell has on the order of 10^3 mitochondria, there are approximately 3×10^4 ATP production events per mitochondrion per second. This process involves a complex set of biochemical reactions called oxidative phosphorylation whose net effect is a conversion of one molecule of glucose into 38 molecules ATP. At any instant each cell contains about one billion ATP molecules. Because the amount of energy released in ATP hydrolysis is very close to that needed by most biological reactions, little energy is wasted in the process. Generally, ATP is coupled to another reaction such that the two reactions occur nearby utilizing the same enzyme complex. Release of phosphate from ATP is exothermic while the coupled reaction is endothermic. The terminal phosphate group is then transferred by hydrolysis to another compound, via a process called phosphorylation, producing ADP, phosphate (Pi) and energy. Phosphorylation often takes place in cascades becoming an important signaling mechanism within the cell. Importantly, ATP is not excessively unstable, but it is designed so that its hydrolysis is slow in the absence of a catalyst. This insures that its stored energy is released only in the presence of an appropriate enzyme. The mitochondrion, where ATP is produced, itself functions to produce an electro-chemical gradient – similar to a battery – by accumulating hydrogen ions between the inner and outer membrane. This electro-chemical energy comes from the estimated 10,000 enzyme chains in the membranous sacks on the mitochondrial walls. As the charge builds up, it provides an electrical potential that releases its energy by causing a flow of hydrogen ions across the inner membrane into the inner chamber. The energy causes an enzyme to be attached to ADP, which catalyzes the addition of a third phosphorus to form ATP. Energy production and utilization is essential to life and is also part of the information processing equation as will be discussed later in the paper.

2. Probability, entropy and information

From the point of view of information processing, the description of both a complex system with a large number of degrees of freedom and a system with a small number of degrees of freedom that is unstable, practically requires an infinite number of bits of information. Biological systems fall into this category and require a statistical description of their behavior. Statistical physics (Penrose, 1979) offers a simple method to circumvent the problem with incomplete knowledge of the system's initial state. Instead of a single system, it concerns itself with an ensemble of many identical copies of the same system (called replicas) that only differ in the choice of their initial state. The state of an ensemble with a uniform distribution of states over the available domain in phase space of the individual system is referred to as thermodynamic equilibrium. Given the volume of the available domain **S** in the phase space we assign the meaning of probability $P(\mathbf{A})$ to the volume of an arbitrary subset **A** of **S**. If domain **S** is not covered uniformly by its states, then we introduce the probability density $\rho(s)$ determined for all states s in **S**. The probability that a state belongs to a given subset **A** of the available state space **S**, is

$$P(\mathbf{A}) = \int_A ds\, \rho(s). \tag{1}$$

The probability density is normalized to unity, so that

$$\int_S ds\, \rho(s) = 1. \tag{2}$$

If the probability $P(\mathbf{A})$ is known, then as a result of finding that the state indeed belongs to the set **A** the observer has gained a certain amount of information about the system under consideration and what was initially a probability $P(\mathbf{A})$ has now become a certainty. The smaller the probability $P(\mathbf{A})$, the greater the information gain. Conversely, if $P(\mathbf{A})$ was large, the information gain is small. Hence, the information gain I is a decreasing function of P. The amount of information about two independent events whose probability is the product of individual probabilities is the sum of the information values for each of the events separately. A function of probability P that has both these properties can be defined as

$$I(A) = -k \log_b P(\mathbf{A}), \tag{3}$$

where k and b are constants. Since the logarithm of unity is zero, the outcome of an event **A** that was certain before the observation took place, $P(\mathbf{A}) = 1$, and no new information is gained, $I = 0$. Eq. (3) was first derived in a famous paper on information theory (Shannon, 1948). The coefficients k and b determine the units of information. For $k = 1$ and $b = 2$ we obtain the unit of information called one bit. One bit is the amount of information gained as a result of an