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Growth of stable order in eukaryotes from environmental energy

Robert A. Gatenby¹ and B. Roy Frieden²

¹Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida, United States of America

²College of Optical Sciences, University of Arizona, Tucson, Arizona, United States of America

Abstract

Living cells are spatially bounded, but open, low entropy systems that, although far from thermodynamic equilibrium, remain stable over time. Schrodinger, Prigogine and others explored the physical principles of living systems primarily in terms of the thermodynamics of order, energy and entropy. This provided valuable insights, but not a comprehensive model. We propose that the first principles of living systems must include: 1. Information dynamics, which permits the synthesis of specific and reproducible, structurally-ordered components within the system; and 2. Non-equilibrium thermodynamics, which provides a feedback mechanism that generate optimizing Darwinian forces.

The information in living system encodes structural order with high specificity that forms well-defined spatial boundaries and self replicates by efficiently converting environmental energy into order. This is a feed-forward loop that permits increasing order – a process observed in other order-forming system such as crystals or planets. . This is, however, subject to environmental perturbations that could increase entropy (decrease order), perhaps fatally.

Critically, living systems are fundamentally unstable because they exist far from thermodynamic equilibrium, which allows three potential outcomes: (1) Stability as environmental perturbations that result in loss of order also generate information that flows to the nucleus and initiates a corresponding response *to restore* baseline state(2) Death due to a return to thermodynamic equilibrium in systems that cannot maintain order in the context of local conditions and perturbations. This rapidly eliminates failed systems. (3) Mitosis in response to attaining order that is too high to be sustainable by environmental energy. Each daughter cell has a much smaller energy requirement, thereby avoiding the instability and returning to a baseline state. These outcomes that result from non-equilibrium thermodynamics permit Darwinian forces which optimize system dynamics, conferring robustness sufficient to have maintained living systems over billions of years.

Introduction

What is order? Consider a system of finite extension L specified by a continuous probability density law $p(\mathbf{x})$, $\mathbf{x}=(x,y,z)$ the usual rectangular coordinates. Suppose that the density $p(\mathbf{x})$ exhibits “structure” in the form of oscillations of some general nature. How much “complexity” or “order” R exists in this structure? That is, how is R related to $p(\mathbf{x})$?

Derivation

It is reasonable for the relation to have the property that R must decrease or stay the same if the system is “coarse grained,” i.e. if $p(\mathbf{x})$ is perturbed such that it loses some of its finer structure. Thus, algebraically, we require

$$\delta R \leq 0 \text{ for } \delta t > 0 \quad (1)$$

after a coarse graining. On this sole basis, R was found [1],[2] to obey

$$R = 8^{-1} L^2 I, \text{ with } I = 4 \int d\mathbf{x} \nabla q^* \cdot \nabla q, \quad q = q(\mathbf{x}) \propto p^{1/2}(\mathbf{x}). \quad (2)$$

Quantity I is the Fisher information of the system. Notation ∇ means the usual gradient, and the asterisk means complex conjugate.

The function $q(\mathbf{x})$ is defined in (2) as the amplitude law for the density $p(\mathbf{x})$. Thus, I generally depends upon both the magnitude and phase of function of $q(\mathbf{x})$. Also, it increases with the level of roughness, i.e. of structure, in $q(\mathbf{x})$. In this sense it is also the “morphological” information in the system (G. Chaitin, ref. below). The length L is by definition the longest chord connecting two surface points of the system. We note that this expression for order R assumes that L is finite, i.e. the system has a well-defined surface. However, the system is not assumed to be “closed” in the thermodynamic sense: energy may enter from the environment.

We note in passing that, by comparison with form (2) for the order of a continuous system $p(\mathbf{x})$, the order of a discrete system --characterized by discrete probabilities P_i , $i=1, \dots, N$ -- is instead measured by its negentropy $R_H = -\sum_i P_i \log P_i$. See [3] for a survey of its properties. It has been common for past workers on order and complexity to use the negentropy rather than the Fisher order (2); see, e.g., [3],[4].

We will be dealing with growing cells. Assume a time at which the cell is a sphere of extension (diameter) L . Then its surface area $A_{CM} = 4\pi(L/2)^2 = \pi L^2$, so that by (2)

$$R = (A_{CM}/8\pi) I. \quad (3)$$

Mathematical Properties of the Order

Among the useful properties obeyed by representation (2) for the order R are the following [1],[2]: It is unitless, invariant to uniform system stretch and, for a K -dimensional system consisting of n sinusoidal oscillations in each direction, increases as $K^2 n^2$. Thus, R does not depend upon the extension of the system. It simply depends upon the system dimension and the *total number* of isolated, regularly spaced details in each direction. In this sense it resembles the Kolmogoroff-Chaitin measure of complexity [5], which likewise measures the total number of “details” in the system (whether they be nodes in a circuit or statements in a computer program).

Eq. (2) holds for any continuous system, living or nonliving, with specified properties L , I , R . In particular, a hypothesis that $I = \max$ was found to derive [6–8] many laws of science governing nonliving systems. Here our emphasis is upon its application to a living, eukaryotic cell, whose mass distribution function $p(\mathbf{x})$ is assumed to grow and develop according to classical physics, with continuous coordinates $\mathbf{x} = (x, y, z)$. For simplicity the cell is modeled as a sphere with an outer, cell membrane CM of diameter L and a nucleus of diameter a . We are generally interested in determining how such a cell develops and grows out of energy inputs at the CM. Will the hypothesis $I = \max$ hold here as well? It will instead be found that, more generally, the information per unit surface area I/A_{CM} is a maximum, where A_{CM} is the surface area of the cell membrane.

Historical Aspects

The unique role of living systems in nature has been contemplated by a number of physical scientists over many decades. In particular, the need to overcome the 2nd law of thermodynamics to maintain order was investigated by Schrodinger, in his classic book “What is life?” [3]. He proposed that living systems may require previously unknown physical principles to maintain order over time. It is interesting that Schrodinger [9] proposed that living systems “eat” order, i.e. import it from the outside. In reality, of course, cells typically import small molecules and construct their own order, using input energy and internal information to convert these precursors into larger macromolecules with a specific structure and order. Prigogine [10] emphasized the need for symmetry breaking in biochemical reactions in the cell. He famously stated “The point is that in a non-isolated [open] system there exists a possibility for formation of ordered, low-entropy structures at sufficiently low temperatures. This ordering principle is responsible for the appearance of ordered structures such as crystals as well as for the phenomena of phase transitions. Unfortunately this principle *cannot explain* the formation of biological structures.” (our italics.) Thus, neither researcher found a specific mechanism for enabling a living system, in particular, to exist stably in a state far from thermodynamic equilibrium.

We find here that the required additional mechanism is that of maximum structural information, in particular that of R.A. Fisher [11]. Fisher was a noted biologist and statistician who did much to quantify Darwin’s theory of natural selection.

Energy Input and Entropy Output

In general, the normal growth in mass of a cell depends strongly upon its level of environmental substrate and energy E [12],[13]. This requires the cell to be a thermodynamically semi-open system, allowing energy to enter and waste entropy to leave. The membrane is “semi -open” because the macromolecules synthesized within the cell are generally too large to escape into the environment across the cell membrane. Thus, in effect the cell membrane forms an order sieve. Uniquely in nature, living systems use environmental energy and internal information to both (i) form and maintain order over time and to (ii) permit system self-replication. The vital role of energy is long known: “In any such transformation [from simple to more complex organic compounds] external energy is necessary, because the reacting bodies, carbon dioxide and water, are fully oxidized and must be reduced with ... uptake of energy in what is called an endothermic reaction.”

(Quote dated 1913 by B. Moore and T.A. Webster in book [14]. The square bracketed remark is added for clarification.)

The byproducts of system metabolism, including heat, entropy and waste products, must pass back out of the cell. The examination of flows of energy and entropy across the cell membrane, and information across the nuclear membrane (in eukaryotes), are found to provide insight into how these quantities act to maintain an ordered, non-equilibrium system that is stable.

Required Role of the Information

It is conventional to describe living systems as stable but operating at far from thermodynamic equilibrium, with input energy used to enforce stability [4]. If the energy flow stops, the system order declines rapidly to equilibrium, and death. This is unlike, for example, crystals that can maintain their order over long periods of time without input. However, the role of information in maintaining the stable state is not often considered. In fact our central theme is the role of input energy in forming cell order R as permitted by the existing cellular information I via Eq. (3). That is, if information flow stops, the cell will also die.

We view the heritable information in a biological system to be stored entirely within its DNA [15]. However, the cell also requires a continuous internal flow of information about internal and external factors. This information flow is carried by messenger molecules (usually, but not always, proteins) to the DNA. In eukaryotes this flow is through nuclear pores in the nuclear membrane, which thus forms a convenient boundary to view information flux. In the nucleus, this continuous flow of information must be constantly decoded, analyzed and integrated and then followed by appropriate responses, which includes altered gene expression and a reciprocal flow of information in the distribution of mRNA traversing the NM back into the cytoplasm. This mRNA then serves as a template for new protein synthesis which effectively carries out the alterations in cellular function directed by the DNA.

As will be shown, these information dynamics are necessary for maintaining a stable state while far from thermodynamic equilibrium, even in the presence of environmental perturbations and degradation of internal order due to the 2nd law of thermodynamics.

Environmental Information I and Flux F across the NM

As noted above, in eukaryotic cells all information must pass through the NM in the form of some messenger molecules. For example, when a ligand binds to a cell membrane receptor, such as Epidermal Growth Factor (EGF) binding to its receptor (EGFR), it generates messenger proteins which enter the nucleus and convey their information by binding to genetic elements which can then initiate a response through transcription of mRNA. Furthermore, events in the cell which decrease order must also generate information (in the form of changes in Ca or AMP concentrations) which must also flow to the nucleus for response. Thus, the NM serves as a boundary to estimate information flux.

Example: Information flow from ligand binding on the cell membrane

Let the NM have area $A_{NM} = A_{NM}(t)$ since the cell is growing. We briefly quantify the level of Fisher information for a messenger molecule on area A_{NM} . Denote as x_0 the *ideal* transverse displacement of the ligand on the cell membrane. This defines the position of a target NPC (nuclear pore complex). However, the actual position of the ligand is $y = x_0 + x$, where x represents a random displacement due to diffusion of the protein as it travels through the cell cytoplasm. Let $p(x)$ denote the density law for such diffusion-based noise values. What is $p(x)$?

This diffusion scenario describes a variant of the random walk problem [19], with the result that $p(x)$ is a member of the exponential family of probability densities. Then information $I = 1/\sigma_x^2$, the latter the variance in x . Also, at each time t let the information per unit area A_{NM} in the actual position y about the ideal position x_0 on the NM be required [16] to obey $I = \max$ [18]. Then the information becomes

$$I = (A_{NM}/(2D))F_{NM}, \text{ with } F_{NM} = \max = \text{const.} \quad (4)$$

All quantities are functions of the time t except the constant value of F_{NM} . Thus, information $I(t)$ increases linearly with instantaneous NM area $A_{NM}(t)$, which is increasing during cell growth. Or, the *information per unit area* is a constant maximum in time,

$$I/A_{NM} = F_{NM}/2D = \text{const.} \quad (5)$$

Diffusion parameter $D = 2.5 \times 10^6 \text{ nm}^2/\text{sec}$ for protein motion through cytoplasm. Function $F_{NM}(t)$ is the messenger protein flux, in proteins/area-time, at the NM, and this is assumed to be fixed at its maximum value, so that by (5) information I is likewise maximized, thereby allowing the protein to quite accurately locate its target NPC and enter it. The maximization in (4) is through choice of the cytoplasm parameters of temperature T , density ρ , diffusion D , etc (see later).

Stability of information I

Suppose 'environmental' parameters T, ρ, D etc. are perturbed by small amounts. Then (4) indicates that both F_{NM} and I will suffer zero perturbation to first order,

$$\delta I(t) = \delta F(t) = 0 \quad (6)$$

The outside equality in particular states that the information I at the NM about ideal protein position x_0 is stable to first-order perturbation of environmental parameters T, ρ, D etc. Then since I measures the information in cell structure, the *cell structure per se is stable to such perturbations*. Finally, by the Cramer-Rao error inequality $e_{\max}^2 = 1/I$ governing the mean-squared error in positions x on the NM (see above), the error in the stable cell is minimized. Such a property expresses the efficiency of natural selection.

Central Role of NM in Creating Order

All eukaryotes, whether in a single cell or multicellular organism, maintain an NM. The central role played by the NM in optimization effects (4) and (5) is noted. This indicates that the NM, while not necessary in, e.g., prokaryotes, plays a critical role in the functioning of eukaryote cells, and is likely necessary for the increased complexity and order that leads to multi-cellularity. One of the vital properties of the NM is its development of a system of pore openings through which the messenger proteins and energy inputs can pass. The high (maximal) flux rate F indicated in (4) is needed. How can this be attained?

The nuclear envelope generates a strong electric field [16] (tens of millions of volts/meter) which contributes greatly to cellular organization by attracting sufficient proteins toward it to promote the high flux rate F that was needed (see above). Thus, the high flux F is highly dependent upon the total energy E within the cell. This, in turn, draws on the ATP and GTP present within the cytoplasm and nucleus. The nuclear envelope also provides pores that are necessary to reduce ionic shielding [13] from a Debye-Huckel distance of nanometers to one of microns; this likewise contributes to the high flux F required. The upshot is that the increased complexity found in a eukaryote is strongly linked to the presence of an NM, for two principal reasons:

- a. The NM surface contains such high-gradient structural detail $\nabla q(\mathbf{x})$ in its pore complexes that this dominates the overall contribution to the total cellular information I defined by Eq. (2).
- b. There is a maximum level of protein flux F_{NM} reaching the NM. For humans $F_{NM} \approx 0.1$ protein/(nm²sec), since this value favors RAS, RAF, MEK and other human protein pathways [16]; other life forms have other constant values of F_{NM} . Since the diameter of an NPC ≈ 9 nm this flux permits about 8 protein/sec to pass into an NPC. By Eq. (2) in the absence of pre-existing *structural* information I there is no life. Hence the level of order R in the cell should be very sensitive to the number and extent of its protein filaments, pores, etc. These are highly dynamic, as they change with time according to the amounts of protein, ATP and mRNA flowing through. Indeed the important role played by the pores and the nuclear pore complex (NPC) has been noted [17]:

“The import of nuclear proteins through the NPC concentrates specific proteins in the nucleus and thereby increases order in the cell. The cell obtains the energy it needs for this process through the hydrolysis of GTP by the monomeric GTPase Ran. Ran is found in both the cytosol and the nucleus, and it is required for both nuclear import and export.”

Likewise by (4) if there is inadequate protein flux F_{NM} there is inadequate structural information I to sustain life.

Consequently we propose that the NM flux F of proteins is vital to maintaining and increasing cellular order -a necessary requirement for the increased complexity found in eukaryotes. Heritable information in the form of DNA in eukaryotic cells is stored in the nucleus, and is necessary for maintaining long term cellular order. The entering energy

(discussed above and below) at the CM induces intra-and extra -cellular perturbation, which are assumed small to first order.

Eqs. (4) and (5) are postulated to hold during any one phase of cell growth. Do they actually hold over all phases?

Information/Area on NM Constant over All Phases of Cell Growth

The information contained by the DNA in the cell chromosomes is actually only “potential,” since it is not transcribed until it is “activated” by proteins that bind to the DNA. Particular proteins activate particular DNA sequences in a process called *transcriptional regulation*. The activation consists of unbinding DNA segments so that they can be transcribed into an active information state. In other words, information coming into the nucleus via messenger proteins directly causes *transition of specific information in the DNA from potential to active information*. (This is somewhat like the transformation of potential into kinetic energy.) This active information then returns to the cell cytoplasm of membrane as mRNA so as to maintain or increase order.

This DNA unbinding process takes place within the NPCs, and is highly accurate. There is about 1 erroneous transcription per 10,000 nucleotides [20] comprising the required DNA or RNA. Hence, it does not effectively add to error x indicated above Eq. (4) and does not reduce the information level I .

The sites that are recognized (and regulated) by any one DNA -binding protein are in general not a unique sequence. Rather, the sites of recognition are a family of similar sequences, many of which do not fall into the protein’s family of recognition sequences [21]. Since the vast majority of the genome comprises non -site DNA sequences, and since site-specific DNA-binding proteins still have a weak affinity for the non -site DNA, the protein *must* display a much higher binding affinity for its own site(s) than for non -site DNA in order for the regulatory system to work. To accomplish this within the cell nucleus *the concentration of DNA is so high that the protein will be bound to DNA, site or non-site, essentially all of the time* [21].

This includes all growth phases from G0 to M of the cell cycle. Then the transcriptional regulation of the DNA by the incident proteins will likewise be constant in time.

This implies that the flux F_{NM} of proteins effectively maintains its maximum value *over all growth phases* of the cell. Then properties (4) and (5) -- the linear growth of information with NM area and the constancy of the information/area -- hold over all phases of cell growth. And by (4), the information grows *linearly* with area $A_{NM}(t)$ over all growth phases. The latter also makes sense on the grounds that the NPCs and chromatin complex of the NM contain the steepest mass gradients ∇q in the cell, and hence contribute most strongly to I in Eq. (2). They also are uniformly distributed over its area A_{NM} . Indeed, experiments [22] measuring optical scatter from the entire cell show nearly all scatter as coming locally from the NM, again indicating high mass gradients ∇q . On this basis as well the larger A_{NM} is the larger the information should be.

It is also important to mention that these results are only possible because the NM pore structure allows both messenger proteins *and inorganic ions* to enter, the latter thereby not acting to form a deleterious ion cloud just outside the NM [16] which would otherwise severely attenuate the needed electric field. Note, however, that not all of this flux F based information I is transformed into mRNA and later cell structure. Some is lost, e.g., as waste heat to outside the cell. The degree of inefficiency is sufficient to satisfy the overall loss of order required of the 2nd law of thermodynamics.

Requirements of Replication and Non-equilibrium

Eukaryotes are stable, ordered systems but these characteristics are not unique in nature since they also describe other structures such as nonliving crystals. However, unlike such structures, eukaryotes are not at thermodynamic equilibrium. That is, they are not at a free energy minimum. Furthermore, such cells are more than just stable e.g. they self-replicate and evolve new mechanisms to increase order even in the face of changing environmental conditions. We propose that these two properties are fundamentally related and that their interactions, mediated through information, are critical for the formation and maintenance of life. In fact, it is clear, at least empirically, that cells in general cannot exist in thermodynamic equilibrium, since the latter represents death for the cell. Thus, non-equilibrium dynamics is a necessary condition for life of the organism because it provides critical feedback of death in its absence. But what are the first principles of this “life” solution? A clue is that a state of thermodynamic nonequilibrium does not imply a state of nonequilibrium of information or order. It will be shown that thermodynamic nonequilibrium implies equilibrium of the information, as the life solution.

Roles of ATP and GTP in Energy to Order Conversion in Cytoplasm and Nucleus

All environmental energy inputs enter the cell through the cell membrane. The conversion from energy to order first requires this entering energy to be converted into ATP. This conversion occurs exclusively in the cytoplasm (whether in the mitochondria or cytosol). Most of the ATP is used in the cytoplasm but some is also used in the nucleus. A related energy resource, GTP (a nucleotide composed of guanine, ribose, and three linked phosphate groups), is also produced in the nucleus. Both ATP and GTP are then used as energy resources for growing order in both the cytoplasm and nucleus. Also, as mentioned above, the ATP and GTP are used to power the high electric field within the cytoplasm that is needed to produce the maximized flux rate F_{NM} indicated in Eq. (4).

After the flux F of messenger proteins enters the nucleus, the latter generates its own information-bearing proteins. Some of these, constituting a fraction of F ; are used to maintain and grow order in the nucleus, drawing on the GTP there. As noted in [23], “molecular switches” of the G-protein family, residing in RAS, are better ordered in the transition-state complex attained there. Another fraction of F is used to generate proteins that flow back out of the NM. These contain mRNA-tRNA molecules. On the basis of kinetic data on ribosome protein synthesis, the mechanical energy for translocation of the mRNA-tRNA complex is thought to be provided by GTP hydrolysis in the cytoplasm [24]. In a small time interval $\Delta t \approx 0.01s$ [16], a fraction of this protein flux F is converted into increased order dR in the organelles of the cytoplasm by drawing on an energy amount dE

from existing ATP and GTP as above. Thus, flux F contributes to the growth of structure *in both the nucleus and cytoplasm*.

Equivalence Principle

We propose that in a stable state, a net energy-order flow across the NM is preserved. That is, in eukaryotes order and energy flow are essentially two different forms of the same thing [see proportionality R/F_{NM} in Eq. (8) below]. Also, the levels of both within the cell remain stable to perturbation over time.

What Cell Properties Are Assumed Perturbed?

The specific cell parameters that are so perturbed are those that define the Debye-Huckel constant k_0 (reciprocal of length l_{DH}) value that maximizes the curve of F (and therefore of information I) vs k_0 ; as plotted in reference [16]. Constant k_0 obeys

$$k_0 = [(\rho q_e^2)/(\epsilon k_B T)]^{1/2} \quad (7)$$

The maximum value of I is therefore attained by certain fixed values of the cell temperature T , protein density ρ , cytoplasmic dielectric constant ϵ , particle charge q_e and k_B , the Boltzmann constant. *Therefore any fluctuations from these values constitute the environmental perturbations addressed by the theory.* For example the density ρ would be perturbed by any fluctuation in the incoming number of proteins; or the temperature by a sudden burn injury; or ϵ or q_e by entering particles with changed electrical parameters.

Methods

Central Result: Relation Connecting Order to Energy and CM Area

Because of the abovementioned strong *contribution* of the *pore complex* to I , in particular the high gradients $\nabla q(\mathbf{x})$ of structural mass that dominate integral (2) for I , we approximate the total cellular I by the amount that occurs on the NM. How does the structural order of the NM grow with time?

Our thesis is that cell order requires energy input. For example, pyruvate – a carbon- based molecule – provides energy of glycolysis in the cytoplasm. Each resulting chain of glucose enters the NM as molecules of pyruvate. Also, the cell obtains the energy it needs for increased order by the hydrolysis of GTP by the monomeric GTPase Ran which is found in both the cytosol and the nucleus, and required for both nuclear *import* and export. Hence we seek to find the order resulting from a given input of energy to the NM.

We found at Eq. (5) that ratio $I(t)/A_{NM}(t)$ is constant over all time and, therefore, *over all phases of cell growth*. By (4), the ratio has fixed value $F_{NM}/2D$. Using (4) in (3) then gives

$$R = (16\pi D)^{-1} A_{CM} A_{NM} F_{NM}. \quad (8)$$

During growth, areas A_{CM} and A_{NM} increase with time, so that order R increases as well. Now in vertebrates the ratio a/L of diameters of NM and CM is about $3/5$. Then (a) the ratio of areas $A_{NM}/A_{CM} = (a/L)^2 \approx 9/25$. Also, let each protein comprising flux F_{NM} carry average total (kinetic plus potential) energy e_0 . Then (b) there is an equivalent energy flux $E_{NM} = e_0 F_{NM}$. Using the preceding equalities (a), (b) in (8) gives

$$R = C(d\epsilon_{NM}/dt)A_{CM}, \text{ where constant } C \equiv (160)^{-1} \quad (9)$$

and $d\epsilon_{NM}/dt \equiv E_{NM}A_{NM}$ is the total energy per unit time entering the NM, as averaged over the NM.

Thus the order at any time t grows linearly with both the total input rate $d\epsilon_{NM}/dt$ of energy to the NM and the cell surface area A_{CM} . This makes sense. The inverse dependence on diffusion constant D is also reasonable, in that the greater the diffusion is the greater is the random scatter of the proteins from their target positions $\mathbf{x}_0$ on the NM (see above Eq. (4)). The positions have corresponding NPCs containing DNA molecules that are to be activated by the proteins so as to increase cell order. Hence increased random scatter inhibits the growth of cell order.

Order Growth, or Loss (latter by Coarse Graining)

The linearity between R and $d\epsilon_{NM}/dt$ in Eq. (9) also implies that a *loss* of energy gives rise to a *loss* of order. That is, once the energy E_{NM} falls below its maximum value order level R starts to fall. This is proposed to occur only during transition to senescence or apoptosis.

As a corollary of the latter, by (1), *senescence or apoptosis are biological coarse graining processes*. These obey, in fact, the *defining effect* $dR = 0$ for order (see [1],[2]).

Mitosis

Eq. (9) indicates that, for a fixed energy input rate $d\epsilon_{NM}/dt$ the order R increases linearly with the surface area A_{CM} , i.e. as the cell grows. However, cells absorb nutrients and release waste through their CM. The larger the cell is, the harder it is for the cell to do this, since the area/volume ratio goes as $L^2/L^3 = 1/L$, which decreases with cell size L . Thus mitosis takes place, with each daughter initially half the size of the mother but with corresponding organelles and interior structure. This gives rise to an immediate gain of a *factor of eight* in total order over that of the mother (see Appendix A). There is also a gain of factor $2^{1/3} = 1.26$ in the total area/volume ratio. Also, even immediately after mitosis each daughter has finite Fisher information I and surface area, so that by (3) their total order advantage over the mother ever grows with time.

Exponential Growth or Reduction of Order

It is now known that during the interphase cell growth in mass is exponential [25]. Then surface area A_{CM} grows exponentially as well, so that its square in Eq. (9) likewise grows exponentially (with twice the exponent). Finally, in (9) energy flux $E_{NM} = \text{const.}$ since $E_{NM} = e_0 F_{NM}$ (see text below Eq. (8)) with particle flux $F_{NM} = \text{const.}$ by (4). Thus, order R grows

exponentially with time. Hence, from the preceding subsection, cell growth, senescence and apoptosis are all approached exponentially in time.

Consequence of Stability

Since flux $F_{NM} = \max$ then likewise by (b) the energy $E_{NM} = \max$. Then directly, and in view of $R \sim E_{NM}$ in (9), to first -order perturbations

$$\delta R = \delta E_{NM} = 0. \quad (10)$$

The energy input rate and the order are both stable. We next show that this stability occurs, in fact, at a state that is far from thermodynamic equilibrium.

Non-equilibrium as a Source of Order

It was shown [16] that the lateral positions x of messenger molecules striking the NM obey a normal law $p(x)$. For this law [19], information $I = 1/\sigma^2$ and entropy $H = \frac{1}{2} + \ln[(2\pi)\sigma]$. Then they are analytically related as

$$H = 2^{-1} [1 + \ln(2\pi) - \ln I]. \quad (11)$$

This shows that H decreases as I increases. In fact by Eq. (4) $I = \max$ for the given area A_{NM} at general time t . Therefore by (11) the cell will operate at a level of H that is *far below* its maximum possible value (the latter defining thermodynamic equilibrium). Hence the cell will have considerable order. Or, as shown by (11), “nonequilibrium becomes a source of order” R[4].

This and the effect (10) accounts for how systems can maintain first-order stability in order R , *despite* operating at far from thermodynamic equilibrium.

Discussion

The first principles that govern the dynamics of systems considered to be “living” remain unresolved. Universally, such systems are viewed as both structurally ordered and far from thermodynamic equilibrium. We propose that an additional property that defines living systems is the central role of the structural information governing this state. Information is deeply integrated into the low entropy structures of the cell, and functions to convert environmental information into order. This is a feed-forward loop that is necessary to maintain a living state. Critically, and unlike other ordered systems like crystals, the dependence of order on information renders the system increasingly unstable as order increases, ultimately requiring self replication. In addition, we propose that loss of order activates a feedback loop that allows self correction. Finally, information permits the instability of non-equilibrium thermodynamics to enforce two system outcomes: death or self-replication. This provides the optimization process that is defined as evolution.

Organisms generally build order until a maximum value is reached. But why is the maximum level of order finite, despite a potentially unending flow of incoming protein flux

and energy E_{CM} ? As discussed, the answer is that every cell eventually becomes either mitotic, senescent or apoptotic. Such a cell thereby stops its contribution R to the total R . The cell also acts to block or waste any new flux increment that would otherwise enter a cell behind it. Hence, with enough such cells present their total loss of order offsets the growth of order due to the mitosis of cells still in growth phase, so that the net system order R saturates. The exponential dependence of the order R upon time allows for a quick transition to such a state.

The maintenance of cellular stability to these perturbations requires conversion of the influxing energy into specific low entropy molecules. These replace molecules that are lost or excreted from the cell in order to satisfy the 2nd law of thermodynamics. Note the critical difference in specificity when compared to other examples of order formation in nature, such as crystal or (even) planet formation. Cells do not convert energy into just any ordered structure. Rather, these are highly specific structures that carry out functions to maintain a specific probability mass density $p(\mathbf{x})$ describing the normal interphase cell. Specifically, cells convert inputs of environmental energy (as above) into order. The added order maintains or increases the “distance” of the cell from thermodynamic equilibrium (Eq. (11)). The necessity for such increased order forces the cell ever-further from its state of thermodynamic equilibrium (death). We find that maximizing the order of the non-equilibrium system can ultimately lead to doubling, or mitosis, of the system into about equal daughter systems. Another benefit of this strategy is the stability of the cell in the sense of attaining a stable level of Fisher I : Its first-order variation due to small environmental perturbations (in cell temperature T , protein density ρ , cytoplasmic diffusion constant D and/or particle charge q_e) obeys $\delta I = 0$ (Eq. 6). In summary of Eqs. (6) and (11): The cell evolves toward a simultaneous state of both thermodynamic *non-equilibrium* and Fisher information *equilibrium*. This is in contrast to other ordered structures in nature, such as crystals, in which order formation achieves a state of minimum free-energy and thermodynamic *equilibrium* (and therefore a non-living state).

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Appendix A

We show that mitosis leads to an increase in order R of a factor of 8. By Eq. (2), for the mother cell $R = 8^{-1}L^2I$, with I the information level I and L the length. The cell breaks into two identical daughters, each a scaled-down version of the mother. Therefore, to preserve mass (and volume) the width of each daughter must be $L_I = 2^{-1/3}L$. Hence the scale-down factor is $m = 2^{-1/3}$. In general, uniformly scaling down by factor m a system that initially has an information level I increases its information level to $I_I = m^{-2}I$. Hence, each daughter's information level is increased to value $I_I = 2^{2/3}I$. Therefore the total information in both is $I_{tot} = 2I_I = 2^{5/3}I \approx 4I$, or nearly 4 times the information of the mother. Is there also a comparable gain in order?

We assume the two-daughter system has a geometry of two just-touching spheres. Therefore, this system has a total extension of $2L_I = 2^{2/3}L$ from before. Thus by Eq. (2) its level of order is $R_I = 8^{-1}(2L_I)^2I_{tot} = 8^{-1}(2^{2/3}L)^2(2^{5/3}I)$ from before. Multiplying out gives $R_I = L^2I$. This is 8 times the order R indicated above for the mother.