



Seeking the foundations of cognition in bacteria: From Schrödinger's negative entropy to latent information

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What was life? No one knew the actual point whence it sprang, where it kindled itself... Between the protean amoeba and the vertebrate the difference was slight, unessential, as compared to that between the simplest organism and that nature which did not even deserve to be called dead, because it was inorganic. For death was only the logical negation of life; but between life and inanimate nature yawned a gulf which research strove in vain to bridge. They tried to close it with hypotheses, which it swallowed down without becoming any less deep or broad. (Thomas Mann, 1924, p. 275) [1]

Abstract

We reexamine Schrödinger's reflections on the fundamental requirements for life in view of new observations about bacterial self-organization and the emerging understanding of gene-network regulation mechanisms and dynamics. Focusing on the energy, matter and thermodynamic imbalances provided by the environment, Schrödinger proposed his consumption of negative entropy requirement for life. We take the criteria further and propose that, besides "negative entropy", organisms extract latent information embedded in the complexity of their environment.

By latent information we refer to the non-arbitrary spatio-temporal patterns of regularities and variations that characterize the environmental dynamics. Hence it can be used to generate

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an internal condensed description (model or usable information) of the environment which guides the organisms functioning.

Accordingly, we propose that Schrödinger's criterion of "consumption of negative entropy" is not sufficient and "consumption of latent information" is an additional fundamental requirement of Life. In other words, all organisms, including bacteria, the most primitive (fundamental) ones, must be able to sense the environment and perform internal information processing for thriving on latent information embedded in the complexity of their environment.

We then propose that by acting together, bacteria can perform this most elementary cognitive function more efficiently as can be illustrated by their cooperative behavior (colonial or inter-cellular self-organization). As a member of a complex superorganism—the colony—each unit (bacteria) must possess the ability to sense and communicate with the other units comprising the collective and perform its task within a distribution of tasks. Bacterial communication thus entails collective sensing and cooperativity. The fundamental (primitive) elements of cognition in such systems include interpretation of (chemical) messages, distinction between internal and external information, and some self vs., non-self distinction (peers and cheaters).

We outline how intra-cellular self-organization together with genome plasticity and membrane dynamics might, in principle, provide the intra-cellular mechanisms needed for these fundamental cognitive functions. In regard to intra-cellular processes, Schrödinger postulated that new physics is needed to explain the conversion of the genetically stored information into a functioning cell. At present, his ontogenetic dilemma is generally perceived to be solved and is attributed to a lack of knowledge when it was proposed. So it is widely accepted that there is no need for some unknown laws of physics to explain cellular ontogenetic development. We take a different view and in Schrödinger's foot steps suggest that yet unknown physics principles of self-organization in open systems are missing for understanding how to assemble the cell's component into an information-based functioning "machine".

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1. Introduction

We begin with a concise review of Schrödinger's "consumption of negative entropy" requirement [1,2]. Focusing on the energy, matter, and thermodynamic imbalances provided by the environment, Schrödinger proposed that life required the consumption of negative entropy, i.e., the use of thermodynamic imbalances in the environment. And in regards to the specific issue of the use of genetic information, he postulated that a new physics beckoned to explain inheritance of cellular functions. At present, his ontogenetic dilemma is generally perceived as solved, and his original postulate attributed to the status of knowledge in the pre-DNA era of molecular biology. But the genome-centered paradigm does not satisfactorily address his original intuitions and we suggest that new understandings about self-organization in open systems, together with new discoveries about

gene-networks dynamics and genome plasticity (e.g. alternative splicing, RNA editing, small RNA, etc.), might lead to revised views about the fundamental requirements for life.

Following Schrödinger, we build upon his original argument and suggest that, despite the developments over the last decade concerning our understanding of self-organization in non-living open systems, we still lack a satisfactory framework of explanation for living systems. In other words, a new physics of self-organization is missing for understanding the basic organizational principles of organisms. We continue with a concise description of the notion of thermodynamic machines and compare them to biotic machines. We explain the special role of ATP as the energy currency—feeding energy in a specific manner, according to stored information, into specific micro-level degrees of freedom. Next, we present the idea that biotic machines are information-driven and should be viewed as analogous to man-made systems composed of a thermodynamic machine and an information processing unit. The former is composed of an engine (that provides work) and a pump (that can reduce the entropy), both regulated by the information processing unit. Moreover, the biotic machine can also generate new information, assign contextual meaning to gathered information and change its structure according to the task it has to perform.

In the subsequent section we discuss organisms' sensing of the environment, using two examples of bacteria "sniffing before eating": (1) Food chemotaxis, in which bacteria perform sequential measurements of concentration of nutrients and regulate their movement in the direction of increasing levels of food. (2) The well-studied case of lactose vs. glucose consumption, in which the available "food source" is sensed to activate the genes that produce the appropriate enzymes needed for opportune "digestion".

The next phase of discussion concerns bacterial cooperative behavior, the advantage of cooperativity, and the communication level required to achieve colonial behavior. We propose that linguistic (semantic and pragmatic) levels of communication are required for communal behavior. We further propose that some modes of behavior might reflect underlying (primitive) elements of biotic cognition. Note, our notions of "biotic cognition" are not to be confused with human symbolic cognition, but rather understood as meaning that the roots of cognition may be traced back to bacteria—the simplest of all organisms.

We then continue with the related question about meaning-based natural intelligence of organisms vs. information-based artificial intelligence. We begin by asking if the two are essentially different, and if so, what are the special features of organisms that afford them capabilities beyond current man-made machines. We hold the view that a difference does exist and it relates to postulated genomic capabilities. Recently, with the sequencing of the human genome and discoveries about intra-cellular "natural bioinformatics" (such as alternative splicing and RNA editing), circumstantial hints suggest that the current view of a static genome should be reexamined.

In light of these novel findings and their plausible interpretation, Schrödinger's ontogenetic dilemma is revisited. We propose that, unlike the widely accepted view,

the current dogma in biology does not provide a satisfactory answer to the ontogenetic dilemma. The rapid progress in the micro-level studies in biology seems to lead to the false perception that a comprehensive understanding of genomic function is available and that only minor details are missing. But from the perspective of physics, basic genomic principles seem missing. Biology lacks a theory of non-equilibrium, which might explain self-organization in open systems. Indeed, contemporary physics calculates the efficiency of a thermodynamic machine if it functions infinitely slowly, but not when it operates at a given finite rate. But we have no idea even how to describe the dynamics of an open system whose composition changes according to internal information, let alone the underlying principles involved.

2. Schrödinger's biotic requirement—consumption of negative entropy

In 1943, a decade before the discovery of DNA's structure, Erwin Schrödinger, one of the founders of quantum mechanics, ventured into a novel speculation about the fundamental character of life processes in what he regarded as a promising new challenge for physics. In a series of lectures, which was soon published as *What is Life?—The Physical Aspects of Living Cells* (1945) [2], Schrödinger postulated that to answer fundamental questions related to “What is Life?” demanded a new research approach. He began modestly enough:

A scientist is supposed to have a complete and thorough knowledge, at first hand, of *some* subjects and, therefore, is usually expected not to write on any topic of which he is not a life master. This is regarded as a matter of *noblesse oblige*. For the present purpose I beg to renounce the *noblesse*, if any, and to be freed of the ensuing obligation. ...some of us should venture to embark on a synthesis of facts and theories, albeit with second-hand and incomplete knowledge of some of them—and at the risk of making fools of ourselves. So much for my apology. (Schrödinger, 1945, p. vii)

But he quickly dispensed with apologies and allowed himself the wonder of life's mysteries. He opined, as true now as then, that despite the vast accumulation of detailed knowledge about the biochemistry and genetics of cellular processes, the physical principles which enable them are still a mystery. It seemed to Schrödinger, and to us, that some fundamental principle(s) is missing which would explain the behavior of open systems not at thermal equilibrium. Schrödinger observed,

Today, thanks to the ingenious work of biologists, mainly of geneticists, during the last 30 or 40 years, enough is known about the actual material structure of organisms and about their functioning to state that, and to tell precisely why present-day physics and chemistry could not possibly account for what happens in space and time within a living organism. (Schrödinger, 1945, p. 2)

It seems that his circumspection still holds, inasmuch as we lack such universal physical principles of function, as well as those that are required to comprehend

self-organization in open biological systems. Following Schrödinger, we too are intrigued by the conceptual challenge he posed, and more to the point, he offered us a fecund approach to these beguiling issues. So let us linger with him a bit longer.

Schrödinger, despite the warning that seeking such principles “*is a rather subtle line of thought, open to misconception in more than one respect*” (Schrödinger, 1945, *ibid.* p.69) began a dissection of the basic character of vital processes, one which avoided the conceptually paradoxical attempts to provide an analytical definition of Life. Instead, he posed the following questions: what are the fundamental requirements for sustained life, the special features associated with living organisms, and to what extent, or can these features, be, shared by non-living systems?

What is the characteristic feature of life? When is a piece of matter said to be alive? When it goes on ‘doing something’, moving, exchanging material with its environment, and so forth, and that for a much longer period than we would expect of an inanimate piece of matter to ‘keep going’ under similar circumstances. (Schrödinger, 1945, p. 70)

To explain how the organism maintains vitality and avoids equilibrium, Schrödinger formulated the basis of life from the point of view of statistical physics. He proposed (from an equilibrium thermodynamic perspective) that to maintain life, it was not sufficient for organisms just to feed on energy, like man-made machines do. Instead, internal metabolism requires that organisms absorb low-entropy energy and exude high-entropy waste products. More specifically, in consistency with the second law of thermodynamics, he noted how all life rests on those organisms which feed on organic materials produced by bacteria or plants [3–7].

Applying the limitations imposed by equilibrium statistical mechanics to living systems, he re-framed the energy flow of the organic food chain of life on earth. The latter is performed by photosynthesizing bacteria or by former bacteria—chloroplasts in amoeba or plant cells. These “biotic machines” operate at room temperature of about 300 K while the typical energy of the photon is about 1 eV. Note, the photon translates to about 40 times higher temperature, and hence the “intaken entropy” is much lower than the “excreted entropy.” In short, these energy-entry-level organisms provide Schrödinger with the key for understanding the unique quality of life in terms of the Second Law of Thermodynamics. It should be kept in mind that the principles of non-equilibrium statistical physics with respect to self-organization of open non-living and living systems [5–7] were only developed a decade later, following Turing’s papers, “The chemical basis of morphogenesis,” “The morphogen theory of phyllotaxis” and “Outline of the development of the daisy” [Appendix A].

Every process, event, happening—call it what you will; in a word, everything that is going on in Nature means an increase of the entropy of the part of the world where it is going on. Thus a living organism continually increases its entropy—or, as you may say, produces positive entropy—and thus tends to approach the dangerous state of maximum entropy, which is death. It can only keep aloof from

it, i.e., alive, by continually drawing from its environment negative entropy... (Schrödinger, 1945, p. 72)

Photosynthesizing organisms (here we will also refer to organelles with their own DNA as organisms) satisfy the requirements for feeding on negative entropy and thus they provide Schrödinger with the conceptual apparatus with which he might explore the unique thermodynamic machinery of metabolism. After all, from the perspective of physics, the consumption of photons can be viewed as a general principle of living on imbalances. In this case, the imbalance employed by biotic machines is more transparent than, for instance, that existing between the sun (the source of the photons) and the colder earth.

How would we express in terms of the statistical theory the marvelous faculty of a living organism, by which it delays the decay into thermodynamic equilibrium (death)? We said before: ‘It feeds upon negative entropy’, attracting, as it was a stream of negative entropy upon itself, to compensate the entropy increase it produces by living and thus to maintain itself on a stationary and fairly low entropy level... Indeed, in the case of higher animals we know the kind of orderliness they feed upon well enough, viz. the extremely well-ordered state of matter in more or less complicated organic compounds, which serve them as foodstuffs. After utilizing it they return it in a very much degraded form—not entirely degraded, however, for plants can still make use of it. (Schrödinger, 1945, pp. 74, 75)

Bacteria use a variety of available sources of energy and entropy imbalances encountered in their different environments, from deep inside the earth crust to nuclear reactors and from freezing icebergs to sulfuric hot springs [8–15]. Using thermodynamic imbalances bacteria are capable of converting myriad substances, from tar to metals, into life sustaining organic molecules. More complex organisms depend on this unique bacterial (and the symbiotic chloroplast) capacity. And, as Schrödinger noted, with all of our scientific knowledge and technological advances, we cannot design man-made machines to mimic the ways in which bacteria solve this fundamental requirement for life.

Both biotic and man-made machines use imbalances for their operation, yet there are some essential differences [7,11–13]. We begin from Schrödinger’s, perspective of equilibrium statistical physics and show that, even on this simplified level, additional requirements are called for to explain bacterial abilities. We then build upon his original argument and suggest that despite the developments over the last decade concerning our understanding of self-organization in non-living open system (Appendix A), we still lack a satisfactory physical theory of explanation. As previously suggested by Ben Jacob et al. [5–7,11–13], new principles connected with the selective exchange of relevant information in evolved open systems might be the crucial missing element in fulfilling Schrödinger’s original attempt.

3. Thermodynamic vs. biotic machines—membrane, internal information and ATP

The second law of equilibrium thermodynamics evolved from a practical quest to improve the efficiency of steam engines. These engines use the temperature imbalances between the higher temperature (T_h) of burning coal and the lower temperature (T_c) of the environment. Simply phrased, according to the second law, even an ideal engine cannot convert the entire amount of heat (energy) δQ_h from the burning coal into useful work, as some amount of heat δQ_c has to be transferred in the process to the colder environment. Therefore, an ideal machine is limited in its ability to generate the amount of work δW with ideal (theoretical) efficiency $\varepsilon \equiv \delta W / \delta Q_h$. This result is derived from the requirement of energy conservation:

$$\delta W = \delta Q_h - \delta Q_c$$

and the requirement that the machine's internal entropy changes $\delta S = 0$, where

$$\delta S = \delta Q_h / T_h - \delta Q_c / T_c.$$

Other thermodynamic machines operate as active pumps and use energy to operate against imbalances. For example, air conditioners use energy to transfer heat against temperature imbalances (say from a cold room into the warmer exterior). Ionic pumps that transfer ions against concentration imbalances represent biotic examples.

Returning to bacteria, from the perspective of a thermodynamic machine, each is a hybridization of two mechanisms. One uses imbalances to extract energy to perform work, while the other uses this energy to act against natural imbalances, e.g. the synthesis of organic substances. Note that the first machine is equivalent to an engine, while the second one functions as a pump that reduces its own entropy. In this fashion, each of the machines performs an open cycle in contrast to the ideal thermodynamic engine that operates on closed cycles, i.e. the system returns to its initial state. In other words, on each individual cycle the machines can return to a state that is close but not equal to the initial state. As a result, the internal state of the cell, itself an open system, changes continuously. At present, we lack a physical theory to describe such situations and can only use equilibrium and close-equilibrium thermodynamics for approximate description over finite time intervals. And even so, we need an additional assumption about the use of internal supply of “negative entropy” that is provided by ATP, as we explain further below.

The coordination of the two machines is regulated by utilizing the contextual information stored in the system and relevant information extracted from the environment during the execution of the cycles (Appendix A). It means that a third information processing machine is coupled to the other two machines. Namely a biotic machine is analogous to hybridization of three man-made machines—a thermodynamic engine, a pump and an information processing system.

Note that in this case the pump represents the internal cellular metabolism of synthesis of the organic materials that is similar to a reduction of entropy. So what we have in mind is a thermodynamic engine that operates between two baths: the external environment that is represented by a higher temperature T_E and the

intra-cellular bath at a colder temperature T_I . Say that in one cycle the amount of work produced by the engine is

$$\delta W = \delta Q_E - \delta Q_I.$$

If the engine returns to its initial state, the increase in entropy of the cell is given by

$$\delta S_I = \delta Q_I/T_I = \delta Q_E/T_E$$

and

$$\delta Q_I = T_I * \delta W / (T_E - T_I).$$

Turning to the pump, if it can use a fraction Γ of the work produced by the engine the amount of heat δQ_P it can pump out from the cell is given by

$$\delta Q_P = T_I * \Gamma * \delta W / (T_E - T_I) = \Gamma * \delta Q_I.$$

Clearly, at best, if $\Gamma = 1$, the pump can take out an equal amount of heat, which implies that the cell just returns to its initial state with no metabolism. These naïve (simplified) considerations led Schrödinger to propose that the engine has to operate on negative entropy. In terms of the above description, it implies that the engine extracts heat from a heat bath at a temperature T_{NE} , so that

$$\delta Q_I = T_I * \delta W / (T_{NE} - T_I)$$

and hence, the reduction of entropy $\delta S_R \equiv (\delta Q_P - \delta Q_I/T_I)$ for an amount of energy received from the high-temperature (negative entropy) source δQ_{NE} is given by

$$\delta S_R = [\delta Q_{NE}/T_{NE}] * [\Gamma * (T_{NE} - T_I) / (T_E - T_I) - 1].$$

Note that if the energy is provided by photons at about 1 eV, even for low values of Γ , the reduction in entropy (the equivalent of synthesis in biological systems) can be quite efficient. However, this is not the case when “negative entropy” is provided by organic molecules that were produced by lower level organisms. Bacteria pose an additional challenge as they can consume inorganic substances.

As we describe below, to increase the efficiency, the biotic machines can maintain a non-equilibrium (evolving) state, where both their internal structure and composition are regulated by internally stored information. In addition, biotic machines possess a membrane which enables them to generate from the external environment large internal imbalances which may be regulated and used when needed. Moreover, the exchange of energy, matter and information across the membrane is actively regulated according to the internal state and stored information of the biotic machine and the surrounding conditions.

Bacteria and chloroplasts share an additional operating principle: low-entropy energy is first stored in transferable packets of usable “currency”—ATP molecules [16–20]. Namely, the photon energy is stored in nano-size coins for ready use. These coins are used in a regulated manner only when and where needed according to the internally stored functional information that reflects the intra-cellular state (including the gene-network state) of the cell. In this fashion, the low-entropy quanta of high energy are fed directly into micro-level degrees of freedom of the system and the process is self-regulated by the very same biotic machine according to

its specific needs and stored knowledge. This is perhaps one of the most essential differences between man-made and biotic machines: a biotic machine should be compared not to a single man-made machine but to a cluster (factory) of man-made machines and information processing systems that regulate the operation and exchange of energy and materials between the machines.

Ordinarily, entropy is produced when ordered energy (say mechanical work) is distributed homogeneously into micro-level degrees of freedom. By using ATP nano-machines, the biotic systems feed low entropy energy into a specific spatio-temporal micro-level distribution. Currently we lack the physical principles to describe such processes. Note that, since energy is fed in a specific manner, the process is essentially far from equilibrium. In addition, we note that the ATP machinery uses the ADP–ATP cycle as a mode of information processing in which the entropy of the functional part of the cell is reduced. In this picture, ATP/ADP transfers latent information from the surrounding, via low-entropy energy coins, into specific sites where they are used for further information processing. The latter could take the form, for example, of generating complex organic molecules or of enzymatic functioning.

4. Sensing the environment — bacteria “sniff” before feeding

In light of the above, feeding and sensing faculties must have evolved side by side. To fulfill energy needs, bacteria first assess the level of energy source at their location and then actively move towards a region with a higher supply of food. This directed motion, chemotaxis [21–26], differs from the usual random walk composed of alternating segments of straight swimming with tumbling actions that end in randomly selected new directions of motion. Bacteria are too short to detect chemical gradients, yet they are still able to sense gradients and bias their movement accordingly. To move towards higher food concentrations, they perform frequent measurements of the local environment as they swim, and if the food concentration increases they delay their tumbling. In other words, the bacteria “sniff” the food before eating it. The net result is a biased random walk (or drift), towards a higher concentration of food.

Bacteria measure the level of food before consuming it. For example, consider how sniffing before eating is used when several food sources are available. To discern the preferred food, bacteria need to perform continuous measurements of the various available ones and perform internal computations [27,28]. For that purpose many bacteria (e.g., *E. coli*) have different sets of genes for digesting (producing metabolic enzymes for) different sugars. The biological problem is how to activate (express) the right set of genes to digest only the preferred sugar glucose (a better source of carbon) when it is present in the medium. When they are not seeking to digest other sugars, say lactose, a specific gene continuously produces a repressor of the *lac* gene (whose product is required for lactose digestion), so under normal conditions the *lac* gene is off. The presence of lactose turns the repressor gene off, but this is not sufficient to turn the *lac* gene on. Other specific genes produce catabolic

activator protein (CAP), which is an activator of the *lac* genes. The glucose enzymes act as repressors for these genes, so in the presence of glucose the expression of the CAP genes is disabled. Hence, the *lac* genes are expressed only if lactose is present and glucose is not.

From the perspective of physics and information theory, in addition to stored genetic information, an efficient operation of such computation-based consumption requires that the ATP coins are injected in a regulated manner according to the execution of the process. Here again we suggest that ATP provides a “sensory system” for the genome, or in another parlance, the “contextual information” required for function.

The *lac* case simply serves to illustrate what we mean by internal information processing and to justify the notion of “sniffing” food as a cognitive act. A similar sniffing mechanism is used in other cases of bacterial taxis. For example, photosynthesizing bacteria “sniff” light and assess its level to perform phototaxis towards higher intensity. In short, bacteria continuously sense their milieu and store the relevant information and thus exhibit “cognition” by their ability to process information and responding accordingly. From those fundamental sensing faculties, bacterial information processing has evolved communication capabilities that allow the creation of cooperative structures among individuals to form super-organisms [4–15]. An illuminating example of collective sensing is provided by the Myxobacteria that can send foraging parties of advantageous bacteria who can move ahead of the colony. Upon detection of food source they send back the information to the colony, which then expands towards the newly detected food source [9,13].

5. Gleaning information and interpreting it

Bacteria are not the solitary, simple organisms as they are usually depicted. Under natural growth conditions, certain bacterial species self-organize into hierarchically complex structured colonies containing 10^9 – 10^{12} organisms (Fig. 1). To coordinate such cooperative ventures, these bacteria have developed and utilized various methods of biochemical communication [29–38], by using a variety of mediators, which range from simple molecules to polymers, peptides, complex proteins, genetic material, and even “cassettes of genetic information” such as plasmids and viruses. The resulting colony patterns reflect cooperative survival strategies. The colony behaves much like a multi-cellular community. It has been proposed [7–15] to view the colony’s capabilities to perform collective sensing, distributed information processing and collective gene-regulation as fundamental cognitive functions. And consequently it can change its spatio-temporal organization (engineered self-organization) for better adaptability to changes in the environment. We emphasize that in addition colonial internal sensing is crucial since the complex patterns emerge through the communication-based interplay between individual bacteria (the micro-level), as well as sensing characteristics of the collective, i.e., the colony (the macro-level).

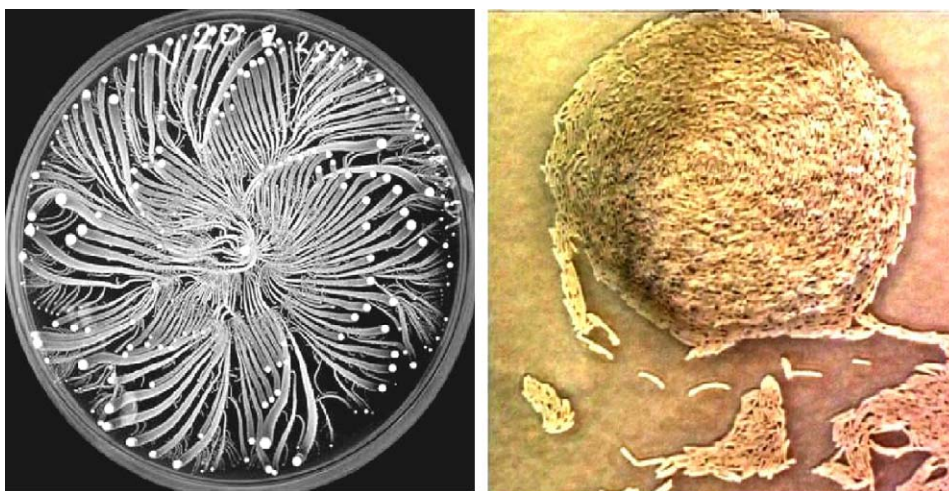


Fig. 1. Hierarchical colony pattern generated by *Paenibacillus vortex* bacteria.

Each vortex (the condensed group of bacteria) is composed of many organisms that swarm collectively around their common center at about $10\ \mu\text{m/s}$. The vortices vary in size from tens to millions of bacteria, according to their location in the colony [13]. Both clockwise and anticlockwise rotating vortices are observed, although the majority has the same handedness. The cells in the vortex replicate, and the vortex expands in size and moves outward as a unit. The bottom picture shows snapshots from a video recording [available from Physicaplus—the online magazine of the Israel Physical Society], taken during formation of new vortices (magnification $\times 500$; the bars are the individual bacteria). Maintaining the integrity of the vortex while it serves as a higher-order building block of the colony requires advanced communication: Each cell in the vortex needs to be informed that its role is now more complex, being a member of both the specific vortex and the whole colony, so it can adjust its activities accordingly. For example, as is explained in Ref. [13], it adjust its motion relative to the rotation rate of the vortex (via attractive chemotaxis signaling emitted by bacteria that are part of the vortex) and is pushed outwards together with the entire vortex by repulsive chemotactic signaling sent by bacteria that are not part of the vortex. Ongoing communication on the colony level is particularly apparent when it comes to the birth of new vortices. New vortices emerge in the trail behind a vortex following initiation signals that cause the bacteria there to produce more lubricating fluid and to move quite rapidly as a turbulent “biofluid”, until an eddy forms and turns into a new vortex.

5.1. Bacterial communication

Quorum sensing [34–38] is a well-studied example of communication-based cooperation using bacterial advanced sensing faculties. Many Gram-negative

bacterial species use quorum-sensing molecules to turn on the expression of a variety of genetic suites (e.g., virulence genes) once the species density exceeds a threshold. A typical case arises in *Vibrio fischeri*, where production of a membrane-permeable homoserine lactone is sensed and turns on luminescence.

Bacterial communication-based cooperation is readily exhibited by colony morphogenesis, which requires coordinated gene expression, regulated cell differentiation and division of tasks [7–14]. Collectively, bacteria can glean relevant latent information from the complex environment and from other organisms, interpret the information in an existential “meaningful” way, develop common knowledge, and learn from past experience.

For that each bacterium has intricate intra-cellular signaling mechanisms involving signal transduction networks [27] and genetic language [28]. These mechanisms are part of the intra-cellular functional complexity which is used to generate intrinsic meaning for contextual interpretations of the chemical messages and for formulating appropriate complex responses. Biochemical messages are also used in bacterial cell–cell talk to exchange meaningful information across colonies of different species, and also with other organisms [38].

One cannot help but notice that linguistic metaphors have begun to penetrate the literature in the description of these and other biological processes, from “protein linguistics” and “language of genes” [28] to “bacterial chemical language” [32–38]. The current usage of “language” with respect to intra- and inter-bacteria communication is mainly in the sense that one would use in, for example, “computer language” or “language of algebra”. Namely, it refers to structural aspects of communication, corresponding to the structural (lexical and syntactic) linguistic motifs [39–46]. Higher linguistic levels—assigning contextual meaning to words and sentences (semantic) and conducting meaningful dialogue (pragmatic)—are typically associated with the cognitive of human and higher primates or social insects [47–51], but regard as well beyond the realm of bacterial communication. This view is now reconsidered as is implied in Refs. [4,7,52–57].

This ability to form cooperative collectives is an evolutionary novelty: New functional features that support the foundation of cognition appear at every level of colonial self-organization—from the internal cellular gel to the growth of the colony as a whole—thus facilitating a high level of functional complexity. To form such multi-cellular super-organisms, the respective units (the individual bacteria) assume newly co-generated traits and faculties that are not explicitly stored in the genetic information of the individuals. For example, bacteria cannot genetically store all the relevant information required for creating the colonial patterns. In the new scenario, they need not, since the required contextual information is cooperatively generated by using internally stored information and information gleaned from the environment. Thus, the bacteria only require genetically stored information on how to produce perceptive faculties and how these capabilities along with the guidelines for using them may be employed to generate new knowledge as required. The bacteria use their intra-cellular flexibility, involving signal transduction networks and genomic plasticity, to collectively create the colony and maintain its integrity by sharing interpretations of chemical cues and exchanging

meaning-bearing chemical messages. The ensuing dialogues are nothing less than meaning-based communication [4,7,13,39–46], which allows the colony purposeful alteration of structure and decision-making. These features represent primordial social intelligence and fundamental (primitive) elements of cognition [47–56].

5.2. *Individual sensing*

In the cooperative setting, bacteria communicate about food sources by employing “chemotactic signaling,” which is a chemotaxis response to chemicals produced by the bacteria themselves. Both attractive and repulsive chemotactic signaling mechanisms are used by the bacteria to shape their colonial structure (Fig. 2). For example, in attractive signaling, bacteria emit food-like molecules to entice other bacteria to move towards them, and in repulsive chemotactic signaling, they emit chemicals which drive the overall colonial growth away from themselves. Doing so, bacteria that detect regions of low food or harmful chemical imbalances can signal to others to stay away. In other settings, when detecting high level of nutrients, they can signal their peers to join the meal.

To self-engineer their colonial structure, these bacteria regulate the balance between attractive and repulsive chemotactic signaling as well as their food chemotaxis [13]. The top panel shows the pattern at higher food levels when attractive chemotactic signaling is activated. The middle panel shows the typical pattern when food chemotaxis dominates the growth at intermediate levels of food depletion. The bottom panel shows the growth for a very low level of food when repulsive chemotactic signaling is intensified. Note that the pattern is organized into narrow straight branches. The above examples of bacterial engineered self-organization provide the colony the ability to make a more efficient use of the available resources while being able to overcome the challenge posed by the hardness of the substrate. For a more detailed discussion we refer the reader to Ref. [5].

The recently identified autoinducer AI-2 in *Vibrio harveyi* seems to be responsible for interspecies message-passing of the type that probably occurs quite regularly in multi-species biofilms [34–38,57]. For instance, there might be some pheromone-based negotiation for the trade of genetic information. Frequently, such contextual information is directly transferred by conjugation following chemical courtship played by the potential partners: bacteria resistant to antibiotics emit chemical signals to announce this fact. Bacteria in need of that information, upon receiving the signal, emit pheromone-like peptides to declare their willingness to mate. Sometimes, the decision to mate is followed by exchange of competence factors (peptides). This pre-conjugation communication modifies the membrane of the partner cell into a penetrable state needed for conjugation.

5.3. *Collective decision-making*

An example of bacterial discourse is illustrated by chemical communication prior to sporulation [52]: when growth conditions become too stressful, bacteria can transform themselves into inert, enduring spores. Sporulation is a process executed

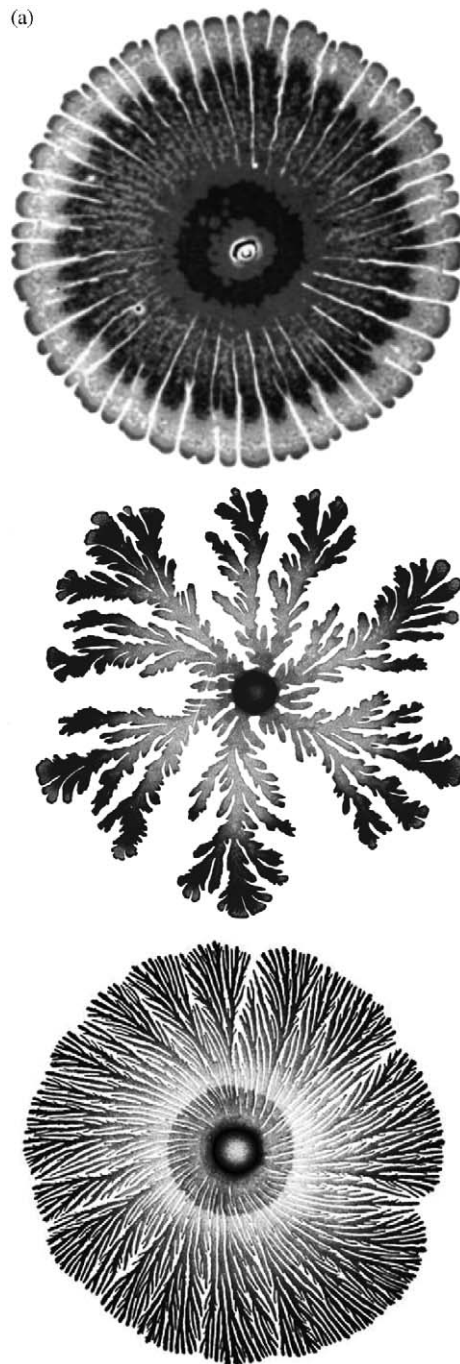


Fig. 2. Examples of different branching patterns formed during colony development of *P. dedritiformis*.

collectively and beginning only after “consultation,” which is an assessment of the colonial stress as a whole determined by the perception of individual bacteria. Simply put, starved cells emit chemical messages to convey their stress. Each of the other bacteria uses the information for contextual interpretation of the state of the colony relative to its own situation. Accordingly, each unit decides to send a message for or against sporulation. Once all the colony members have sent out their decisions and read all the other messages, sporulation occurs if the “majority vote” is in favor.

5.4. Learning from experience

In Fig. 3, we show two different colonial patternings having emerged in response to the non-lethal stress provided by two different kinds of antibiotics: co-trimazole (Septrin), a suppressor of cell reproduction that might enhance communication, and ampicillin, a distorter of cell wall structure that might impair cell communication. In both cases, in a subsequent encounter with the same antibiotic the bacteria can respond more efficiently; yet, this effect is erased if they are exposed to neutral conditions between stress encounters. It seems that the bacteria can generate an erasable, collective inheritable memory, as if they have learned from their past experience [4,7,13,58,59].

The top left panel shows the effects of co-trimazole (Septrin) on a colony of *P. deditiformis*. This antibiotic inhibits the synthesis of folic acid and thus suppresses cell reproduction and growth [4]. In response to Septrin, the bacteria enhance their cooperation by intensifying chemotactic attraction to form larger vortices. This clever strategy protects the bacteria, since the antibiotic is diluted in larger vortices by the lubricating fluid excreted by the bacteria. This occurs provided that the larger vortices also move faster away from the antibiotic stress, and, indeed, the bacteria also elevate repulsive chemotactic substances which drive other bacteria to form large vortices that move away more rapidly than under control conditions. Clearly, during growth on an artificially prepared substrate with a homogenous distribution all over the surface, such strategy has no advantage. However, in the natural environment this is not the case as the concentration of antibiotic which is produced by organisms in the environment is concentrated around their location. Hence, in such cases the strategy helps the bacteria to move away from the locations rich in antibiotic. The bacteria employ this strategy (developed through evolution) when they encounter antibiotic in the Petri dish, as they are “programmed” to do. The top right panel shows disorganized colony development in response to ampicillin, which distorts cell wall structure and thus in most likelihood impairs the exterior mediation required for normal communication-based coordination. Such disruption is seen as a disorganized patterning. The bottom two panels show the effects of growing bacteria that had been pre-exposed to ampicillin and Septrin. In these experiments, bacteria picked from a “proto-colony”—one that had already been exposed to an antibiotic—were then grown under the same conditions, i.e., again exposed to the same antibiotic. The left panel shows the effect of Septrin and the right panel that of Ampicillin. As compared to the upper panels, these colonies are better developed as if the bacteria had “learned” from their past experience and

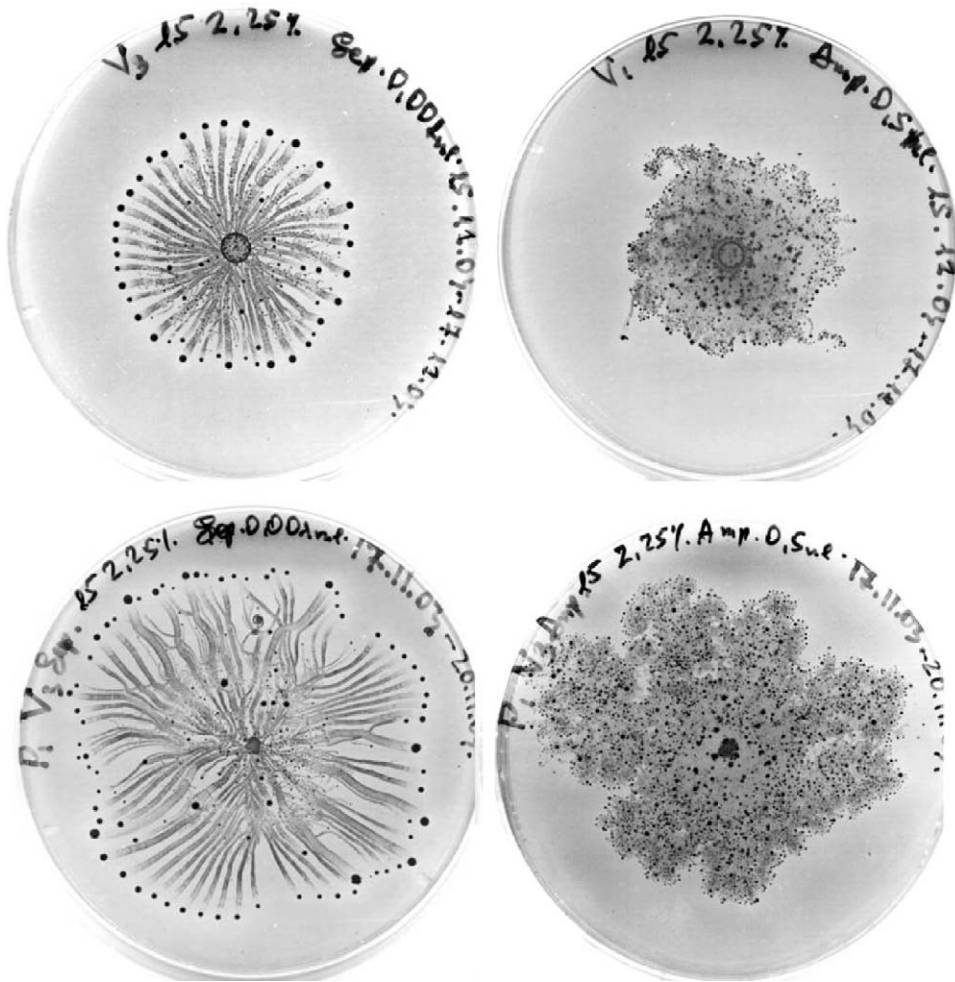


Fig. 3. Effect of antibiotics on colony formation of *P. deitrichiformis*.

compensated accordingly. We note that in other studies we showed that better adapted sequence mutations result in a burst of faster expanding sectors. In other words, during growth in a patterned colony there is automatic segregation into sectors of faster expanding mutants.

5.5. An open riddle

Another example is the no win rock–paper–scissors game played between strains of *Escherichia coli*: strain C produces colicin, which kills the colicin-sensitive strain S that outcompetes the colicin-resistant strain R. The latter closes the circle by

outcompeting strain C [60]. Expectedly, in this game of no prevailing strategy all three strains survive. However, in a recent *in vivo* version played by feeding the strains to different mice, strain C tends to loose over time [61]. The special communication mechanisms behind these observations are yet to be deciphered.

5.6. *Clashes of bacterial intelligence*

Myxobacteria provide an additional illustration that by using linguistic communication, bacteria show collective behavior that might reflect some underlying fundamental elements of cognition. These bacteria can use a variety of sophisticated strategy when their collective behavior is challenged by cheaters—opportunistic individuals who take advantage of the group’s cooperative effort [53–56]. For example, they can single out defectors by collective alteration of their own identity into a new gene expression state. By doing so, the cooperators can generate a new “dialect” which is hard for the defectors to imitate. This ever-ongoing intelligence clash with defectors is beneficial to the group as it helps the bacteria to improve their social skills for better cooperation.

The term “cognition” usually refers to human mental functions associated with capacities such as the use of semantic and pragmatic levels of language, perceiving self vs. non-self, association with group identity and perceiving individual and group goals. It is now realized that bacteria facilitate surprising collective functions. They can develop collective memory, use and generate common knowledge, develop group chemical identity, distinguish the chemical identity of other colonies in their environment or even higher organisms, learn from experience to improve their collective state and more.

These are the bacteria faculties we refer to when using the term fundamental elements of cognition. We emphasize that these features should not be confused with the unique, human level of symbolic cognition. We do not imply that bacteria possess human capabilities but that fundamental elements of cognition can also be found in bacteria. From a practical perspective, this realization can shed light on the evolution of cognition and on the most basic requirement for its facilitation in all organisms.

5.7. *Meaning-based natural intelligence*

By meaning-based natural intelligence we refer to that common trait shared by all organisms, from bacteria to humans, which share some fundamental cognitive functions such as sensing, information processing and contextual interpretation of information (the ability to assign contextual meaning to externally gathered information). By contextual, we refer to how external latent information is placed within a framework in which its relevance (meaning), is derived according to the organism’s external and internal conditions and internally stored information. The ability to assign contextual meaning to externally gathered information is a fundamental semantic function of natural intelligence that every organism must have.

By intelligence we further mean the ability to process gathered external information, which is then coupled to internal information states that in turn may be immediately processed or stored as “knowledge” for later use.

To come to grips with this phenomenology, we draw insights from human linguistics, and the metaphors which have already begun to penetrate the description of bacterial communication. Usually, these metaphors refer to the structural (lexical and syntactic) linguistic motifs. More recently [4], as we have already discussed, bacterial chemical communication also includes assignment of contextual meaning to words and sentences (semantic/syntax functions) and conduction of “dialogue”—the fundamental aspects of linguistic communication [39–44].

We propose that bacterial signaling also involves linguistic communication—the term currently used to describe the meaning-exchange function of language [28,29]. This includes the semantic aspects that are associated with the assignment of context-dependent meaning to words, sentences, and paragraphs [39–44].

Beyond the individual semantic level of linguistics, some linguists identify the dialogue (discourse, or goal-driven conversation), as the pragmatic level of linguistics [4]. This level requires the existence of shared knowledge and common goals. The group usage of a dialogue can vary from activity coordination through collective decision-making to the emergence of a group self-identity.

With regard to bacteria, semantics would imply that each bacterium has some freedom (plasticity) to assign its own interpretation to a chemical signal according to its own specific, intercellular state and external conditions.

It has been proposed [4] that such semantic function requires that a chemical message will not just trigger a specific pre-determined pathway but will also initiate an intra-cellular response that involves internal restructuring—self-organization of the intra-cellular gel and/or the gene-network or even the genome itself.

In other words, semantic function has to involve internal processes that are regulated by some master switch in the gene regulation network capable of producing intra-cellular messages (say transcription-factors or smallRNA) that can modify the expression levels of the self-same genes. In this way an external message can initiate transitions between different operating states of the genome according to the specific (contextual) intra-cellular state of the specific organism under given external conditions.

While it is known that such switches do exist [27,28], future research will have to decipher how the degrees of freedom of the gene network are coupled to the degrees of freedom responsible for the perceptive apparatus of the organism.

To sustain a dialogue based on semantic messages, the bacteria presumably have, in addition, common pre-existing knowledge (collective memory) together with abilities to collectively generate new knowledge that is transferable upon replication. Thus, the ability to conduct a dialogue implies the existence of some mechanisms for collective gene expression, analogous to that of cell differentiation during embryonic development of multi-cellular organisms.

Such a mechanism may take a variety of different forms. The simplest possibility is that bacterial communication and response are determined by ordinary genome regulation—the state of gene expression. More exotic possibilities are “natural

genetic engineering” [77], or “genome cybernetics”, referring to the ability of the genome to perform information processing and alter itself accordingly [79]. Genome cybernetics upon replication has been illustrated in ciliates [87], and more recent work shows that transposable elements can effectively re-program the genome between replications. We also expect that small RNA [85] (that has been shown to play a role in bacterial quorum sensing) might provide new intra-cellular and gene-network mechanisms needed for the fundamental semantic and pragmatic functions.

In summary, we propose that meaning-based natural intelligence is a fundamental requirement of life, and that the roots of cognition can be traced back to bacteria. However, the fundamental semantic and pragmatic cognitive functions are likely to require as yet undefined mechanisms at the genomic level. Based on these predictions and the outline of such a cognitive mechanism, we face the following questions:

- (1) Are we subject to a metaphorical fallacy, namely a convenient but distorting extrapolation from current linguistic theory?
- (2) How can the ontological reality of such a formulation be tested?
- (3) Is the linguistic construction consistent with the current gene-network picture of the neo-Darwinian paradigm?
- (4) How might this formulation be constituted within the constraints of physical causal determinism and time causality?

This last issue, the one with which Schrödinger ended *What is Life?*, focuses our concluding sections. But first, in the next section, we reexamine Schrödinger’s proposed dilemma related to the intra-cellular states.

6. Returning to Schrödinger: the ontogenetic dilemma and the cybernetic genome

In 1943, the year Schrödinger delivered his lectures, Luria and Delbrück performed a cornerstone experiment to prove that random mutation can occur [62–65] (these experiments were a crucial step in the dominance of the current paradigm [66–69]). The observations were in agreement with Schrödinger’s view of the DNA as a non-periodic, one-dimensional crystal. He proposed that random mutations can *in principle* be accounted for by the laws of physics and chemistry, especially those of quantum mechanics and chemical bonding.

But Schrödinger was troubled by other features of Life, postulating that cellular internal self-organization associated with cell development between replications might call for additional fundamental physical principles. In short, Schrödinger proposed that a new physics is missing for the understanding of Life, and we suggest that this missing science is still absent. The following extract describes Schrödinger’s ontogenetic dilemma, which we have cause to reconsider even with our 21st century understanding (Although such related principles emerged in nascent form a decade later following Turing’s seminal work and the elucidation of DNA’s structure):

...I tried to explain that the molecular picture of the gene made it at least conceivable that the miniature code should be in one-to-one correspondence with

a highly complicated and specified plan of development and should somehow contain the means of putting it into operation. Very well then, but how does it do this? How are we going to turn “conceivability” into true understanding?

...No detailed information about the functioning of the genetic mechanism can emerge from a description of its structure so general as has been given above. That is obvious. But, strangely enough, there is just one general conclusion to be obtained from it, and that, I confess, was my only motive for writing this book. From Delbrück’s general picture of the hereditary substance it emerges that living matter, while not eluding the ‘laws of physics’ as established up to date, is likely to involve ‘other laws of physics’ hitherto unknown, which, however, once they have been revealed, will form just as integral a part of this science as the former. (1945, pp. 68, 69)

Schrödinger’s dilemma about the conversion of latent genetic information (embedded in structural coding) into a functioning organism is largely assumed obsolete in light of subsequent experimental findings: At present, according to the central paradigm, cell development can be explained solely (in a complete and self-consistent manner) by the information stored in the genetic material (DNA sequence). Hence, Schrödinger’s dilemma is generally perceived as a mere misconception due to the historical moment he was writing. Accordingly, it is widely accepted there is no need for some unknown laws of physics to explain ontogenetic development, or, for that matter, any other faculties of life.

We take a different stand and propose that, as Schrödinger feared, the current view is itself misconceived, or at least incomplete, and as he pointed out, “*is a rather subtle line of thought, open to misconception in more than one respect*” (p. 69). Certainly, Schrödinger expected that additional information would be discovered and his argument did not rest on such progress. Rather, his dilemma combined two more basic concerns. One is the distinction between accumulations of data and understanding their significance or meaning according to the organism’s internal previously acquired knowledge.

This issue is probably best illustrated by the example of the ATP machinery we presented earlier. The importance of this machinery is widely recognized and consequently much research effort has been devoted to study it in great detail. Yet ATP’s metabolism is not understood in terms we regard as closer to its function within the system-as-a-whole, namely as a mediator of information. In other words, our knowledge of how all the known components of this complex machinery function together remains incomplete. Especially about how proper function requires flow of information from both detected external signals as well as internal sensing of the state of the cell.

Metaphorically speaking, these questions of organization and regulation, based on information retrieval and processing, are equivalent to understanding the workings of a large complex of chemical factories linked together and operated by a power plant. Knowing all the details of the complex itself is not sufficient for our comprehending their function. We also require knowledge about the information received from the market about customer behaviors, as well as the constraints and

cost of the needed raw materials to make the finished products. In addition, for a deeper understanding, we must seek the principles underlying the bridge between contextual information processing and the production of chemical factories. In this metaphor, the monetary values of the products, the manpower hours and associated costs of shipping the goods, the starting raw materials and energy expenses, etc. are the analogues of the information (entropy) associated with the absorbed energy required for the synthesis of organic molecules, the absorption of materials from the surrounding environment, and the transport and eventual assembly of the produced molecules.

Therefore, further descriptive molecular studies are appropriate for what they elucidate, i.e., the details of a biochemical cascade, but what is not provided by such investigations is better insight into understanding the overall organization of the system and its information-based regulation and control.

We emphasize again that, even for man-made machines, the laws of thermodynamics only allow us to deduce the ideal efficiency of machines that operate very close to equilibrium, i.e. infinitely slowly so time does not play a role [70,71]. A physical principle describing the operation of evolving (non-equilibrium) systems, where time does play a role, is still missing. For example, we cannot predict the ideal efficiency of a machine when required to operate at a given rate! We only know that as non-living systems are driven further from equilibrium they show self-organization into hierarchical complex structures [71], and this in turn appears to be based upon self-consistency principles that involves the flow of information between micro- and macro-levels [13,71,72].

Returning to biological systems where operations at regulated rates and flow of information are crucial, we suggest that additional accumulation of ever increasing wealth of details is not sufficient to explain how complex systems are organized and function by harnessing their internal functional complexity and stored information. What we propose instead is that we are missing a fundamental biotic principle based on some yet unknown physical principle. “Information” points us in the right direction, but a biological theory to account for its workings and effects remains a beguiling challenge.

The second arm of Schrödinger’s dilemma, one closely related to the first, arises from the notion that all the required information to sustain the life of the organism is embedded in the structure of its genetic code. But this view seems archaic given the growing appreciation that such information is useless without the supporting cellular machinery required for DNA/RNA functioning. While the structural coding contains basic instructions on how to prepare many components of the machinery—namely, proteins—it is unlikely to contain full instructions on how to assemble them into multi-molecular structures to create a functional cell.

For eukaryotes, the difficulty is even more challenging inasmuch as mitochondria carry their own genetic code [74–76]. The problem may be conceptually related to Gödel’s theorems [7,77–84]. It is commonly argued [7,79] that by using Gödel-like mapping of the genetic code into numbers, or by mapping the synthesis of organic molecules and other metabolic functions onto a computer program, one might deduce that the stored genetic code is both self-consistent and complete in describing

the organism's lifecycle. This implies that Schrödinger was wrong in looking for missing principles of physics.

The line of argument presented here is that Schrödinger was right and that organisms must glean additional information from their surroundings, perform information processing, and then generate new information. Only in this way can they maintain the level of freedom of response and flexibility required for life.

In line with this train of thought, we cited earlier the new picture of the “cybernetic” genome [77–79] which is emerging following the complete sequencing of various organisms. The recent discoveries [85–87] about the previously dubbed “junk DNA” and the multi-functionality of genes that are too few to account for the number of proteins that appear during an organism's life cycle led to a more dynamic picture of genomic function. For example, the human genome project that revealed less than expected genes and more than expected transposable elements led the Celera team to exclaim in wonder [88]:

Taken together the new findings show the human genome to be far more than a mere sequence of biological code written on a twisted strand of DNA. It is a dynamic and vibrant ecosystem of its own, reminiscent of the thriving world of tiny Whos that Dr. Seuss' elephant, Horton, discovered on a speck of dust ... One of the bigger surprises to come out of the new analysis, some of the “junk” DNA scattered throughout the genome that scientists had written off as genetic detritus apparently plays an important role after all.

Genome cybernetics has been proposed to explain the reconstruction of the coding DNA nucleus in ciliates [87]. The specific strains studied have two nuclei, one that contains only DNA coded for proteins and one only non-coding DNA. Upon replication, the coding nucleus disintegrates and the non-coding is replicated. After replication, the non-coding nucleus builds a new coding nucleus. This is accomplished by using the transposable elements in a computational process.

Some observations hint that the collective intelligence of the intra-cellular mitochondrial colonies plays a crucial role in these processes of self-improvement [89–93]. These findings point to Schrödinger's prescient musings that the simple mechanical explanations and principles heretofore offered were inadequate for the task at hand.

7. Concluding remarks in Schrödinger's footsteps: plausible metaphoric bridging with quantum mechanics

Punctuated throughout philosophy's modern history of debate about free will and self-determination, mechanical metaphysics regarded free will as an illusion since, in principle, it contradicts a physics whose fundamental principles include a strictly linear causal determinism (in closed systems) and time causality (also in open systems). This view is most famously illustrated by Laplace's Universe and Laplace's Demon:

An intellect which at any given moment knew all the forces that animate Nature and the mutual positions of the beings that comprises it. If this intellect were vast

enough to submit its data to analysis, could condense into a single formula the movement of the greatest bodies of the universe and that of the lightest atom: for such an intellect nothing could be uncertain: and the future just like the past would be present before its eyes.

But with the development of quantum mechanics, a system's unpredictability to an external observer is commonly accepted. Yet, the older metaphysics remains well ensconced to hold that nature as a whole, and any of its parts, must in principle be predetermined, that is, subject to causal determinism [94], and time causality [95]:

Causal determinism is the thesis that all events are causally necessitated by prior events, so that the future is not open to more than one possibility. It seems to be equivalent to the thesis that the future is *in principle* completely predictable (even if in practice it might never actually be possible to predict with complete accuracy). Another way of stating this is that for everything that happens there are conditions such that, given them, nothing else could happen, meaning that a completely accurate prediction of any future event could in principle be given, as in the famous example of Laplace's demon.

Clearly, self-determination cannot have an ontological reality in a closed universe subject to "causal determinism". Therefore, within this picture, all living organisms, from bacteria to humans, could be nothing but Turing machines, created and evolved by random number generators. And, correspondingly, all faculties of cognition, beyond storage and computer-like information processing, are just illusions derived from human projections of subjective experience.

The clash of these metaphysical pictures is germane to our project. The fundamental assumption in the studies of complex adaptive systems is that the behavior of organisms is determined by accumulations of accidents. According to this view, decision-making is a macro-level illusion in response to a random process occurring at a micro-level. The following is a quote from Gell-Mann, one of the founders of this paradigm [96,97]:

Any entity in the world around us, such as an individual human being, owes its existence not only to the simple fundamental law of physics and the boundary condition on the early universe but also to the outcomes of an inconceivably long sequence of probabilistic events, each of which could have turned out differently. Now a great many of those accidents, for instance most cases of the bouncing of a particular molecule in a gas to the right rather than the left in a molecular collision, have few ramifications for the future coarse-grained histories. Sometimes, however, an accident can have widespread consequences for the future, although those are typically restricted to particular regions of space and time. Such a "frozen accident" produces a great deal of mutual algorithmic information among various parts or aspects of a future coarse-grained history of the universe, for many such histories and for various ways of dividing them up.

Here we argue that such constructivism is insufficient to explain natural intelligence. Instead, we seek a global "generativism" where the foundations of

cognition are related to nested generation of meaning on all levels [7,13]. We are referring to a sensed-based generation of meaning that occurs at all levels of an organism's hierarchy of function. Meaning requires on-going information processing, self-organization, and contextual alteration by each constituent of the biotic system at all levels—from the genome to the cell's internal structure to the regulation of systems to their final integration. With this picture in mind, the system's hierarchical organization enables the smaller scales to contain information about the larger scale they themselves form. The macro scale selects between the possible lower scale organizations that are in an entangled state of different options.

Metaphorically, the above picture is similar to the notion of quantum mechanical collapse of a superposition caused by measurements. There are two fundamental differences, however, between the selection from an entangled state of options and collapse of the superposition state: (1) in quantum measurement, the external observer directly causes the collapse of the system on a specific eigenstate he pre-selects. In the organism's decision-making (selection of an option) an external stimuli or received information initiates the selection of an internal specific option. Hence, the specific consequent response or the option that will be selected is *in principle* undetermined (not even probabilistically) to an external observer who does not have information about the intra-cellular state of the cell and its internally stored information. (2) In quantum measurement, the previous possible (expected) eigenvalues of the other eigenstates are erased and assigned new uncertainties. In the organism's decision-making the process is qualitatively different: Both the external information about the stimuli and the selection process itself are stored and can generate an effect on an array of new options and consequent selection processes. Therefore, the unselected past options are expected to affect subsequent decision-making.

We suggest that this approach to understanding the foundation of cognition as an information based projection (stimulated by external stimuli) of an entangled state of options onto an eigen-like intra-cellular informational states leads us safely away from Laplace's Demon. Whether we are offering a viable hypothesis that can be translated to concrete laboratory investigations or only an armchair conjecture with some seductive appeal but little else remains to be determined. And in the meantime, re-reading Schrödinger provokes and sustains our own venture. We conclude with the following phrase attributed to Schrödinger:

Democritus introduces the intellect having an argument with the senses about what is 'real'. The intellect says; 'Ostensibly there is color, ostensibly sweetness, ostensibly bitterness, actually only atoms and the void.' To which the senses retort; 'Poor intellect, do you hope to defeat us while from us you borrow your evidence? Your victory is your defeat.'

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Note added During the refereeing process new studies related to mutation in plants demonstrate that in principle there is intra-cellular inheritable extra sequence information. In the specific example shown the information is about pre-existing genes. This information can be used to build non-existing gene. Hence it demonstrates that in principle there are intra-cellular mechanisms to build genes from internally stored information not coded in the DNA sequence. Lolle, S.J., et al. (2005) Genome-wide non-Mendelian inheritance of extra-genomic information in *Arabidopsis* *Nature*, vol 434, 506–509.

Appendix A. The foundations of abiotic self-organization

Diverse non-living open systems, when forced to be far from equilibrium, respond by forming complex hierarchical spatio-temporal organizations [71,98,99]. In the early 1950's, Alan Turing motivated by the attempt to understand morphogenesis in living systems, proposed that complex structures emerge in open systems only when there is competition between two or more tendencies [100–102]. He thus started the field of self-organization and set its first principle—patterning via competition.

Often, competition is between global and local approaches towards equilibrium. In such cases, the global kinetics drive the system towards decorated, irregular, scale-free shapes, while the local dynamics imposes local characteristic length-scales and order as well as overall symmetries and organization. For example, in the formation of a snowflake, the local dynamics at the interface, giving rise to surface tension, surface kinetics and growth anisotropy competes with the diffusion of water molecules towards the growing flake. The outcome is that the six-fold symmetry of the ice crystal is imposed on the overall symmetry of the flake.

The surprising discovery is that, despite these vast differences in length-scales (from nanometer to millimeter), the macro-level can cause the micro-level dynamics to act as a singular perturbation: When the system is driven farther from equilibrium, the global tendencies are intensified and amplify the local effects to the extent that small changes on the micro-level can alter the macro-level organization. By the same token, modifications on the global level (possibly caused by micro-level modifications) can act as a singular feedback, i.e. can reach down and affect the micro-level organization by favoring one particular micro-level structure over the others [73].

Only recently have we come to appreciate that an emergent pattern is determined via a singular interplay between the macro- and micro-levels subject to a microscopic solvability principle. Moreover, the two-level picture is often insufficient. In such cases, a hierarchical multi-level organization is generated as the only possible solution to a hierarchical self-consistency principle of self-organization.

Ben-Jacob and Garik proposed [72] that, farther from equilibrium, the selected morphology is that which is fastest growing, since at this limit the global tendency dominates the growth over the local one. Closer to equilibrium, the selection is a simple, local, geometrical organization, as the local tendency is dominant at this limit [4,6]. Such regularly ordered patterns have relatively low complexity. The disordered patterns very far from equilibrium are of a similar relatively low complexity.

The above observations are in agreement with the commonly accepted criteria about complexity. Namely, that both ordered and disordered patterns should have similarly low values of complexity and patterns with hierarchical or scale-free organization should have the highest complexity. Structural complexity might be an appropriate quantity, instead of entropy production, to describe the response of open systems to external imposed conditions — especially when these conditions vary in time and/or space [72,73]. In this regard, a new principle of “complexity-based-flexibility” was suggested [13]. Ordinary notions of stability, as used for closed systems or open systems with regular steady states, are not valid for the hierarchical or scale-free spatio-temporal complex patterns formed during abiotic self-organization. In such cases, higher complexity elevates the flexibility of the system, thus imparting it higher tolerance and robustness.

The fundamental principles of abiotic self-organization enable one to engineer or pre-design conditions that form desired patterns by the system during its self-organization, a process dubbed, “engineered self-organization” [59]. One of the most fundamental aspects of biological systems is that they can use internally stored relevant information to self-design their own “engineered” self-organization [103]. Moreover, during the process, internal and external information is processed and used to alter the engineering of the very same self-organization process enabling the system with the special capabilities and characteristics described in this review.

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 In these publications, Gell-Mann refers to top-level emergence (i.e., the basic constituents are not altered during the emergence process itself) in adaptive complex systems as sufficient mechanism together with the principles of the Neo-Darwinian paradigm to explain Life saying that: “In my opinion, a great deal of confusion can be avoided, in many different contexts, by making use of the notion of emergence. Some people may ask, “Doesn’t life on Earth somehow involve more than physics and chemistry plus the results of chance events in the history of the planet and the course of biological evolution? Doesn’t mind, including consciousness or self-awareness, somehow involve more than neurobiology and the accidents of primate evolution? Doesn’t there have to be something more?” But they are not taking sufficiently into account the possibility of emergence. Life can perfectly well emerge from the laws of physics plus accidents, and mind, from neurobiology. It is not necessary to assume additional mechanisms or hidden causes. Once emergence is considered, a huge burden is lifted from the inquiring mind. We don’t need something more in order to get something more. Although the “reduction” of one level of organization to a previous one—plus specific circumstances arising from historical accidents—is possible in principle, it is not by itself an adequate strategy for understanding the world. At each level, new laws emerge that should be studied for themselves; new phenomena appear that should be appreciated and valued at their own level”. He further explains that: “Examples on Earth of the operation of complex adaptive systems include biological evolution, learning and thinking in animals (including people), the functioning of the immune system in mammals and other vertebrates, the operation of the human scientific enterprise, and the behavior of computers that are built or programmed to evolve strategies for example by means of neural nets or genetic algorithms. Clearly, complex adaptive systems have a tendency to give rise to other complex adaptive systems”.
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