Seeking the Foundations of Cognition:

From Thermodynamics to Contextual Information and Back

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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]

Schrödinger's Biotic Principle –
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 the 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. (ibid. 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 challenged 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" (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 are, or can these features are, 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. (ibid. 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 that to maintain life, it was not sufficient for organisms just to feed on energy, like man-made machines considered from an equilibrium thermodynamic perspective. Instead, internal metabolism required that organisms must absorb low-entropy energy and exude high-entropy waste products. More specifically, in consistency with the second low 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 re-framed the well-appreciated energy flow of the organic food chain of life on earth. The latter is performed by photosynthesizing bacteria or by former bacteria - chloroplasts in ameba or plant cells. These ‘biotic machines’ operate at room temperature of about 300^{o}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 “intake 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...(ibid. 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. (ibid. pp. 74-5)

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]. Following Schrödinger, we begin from his perspective of equilibrium statistical physics and show that even on this simplified level additional requirements must be supplied to explain organic function. 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 model 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. Here we further explore this speculative path.

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 difference between the high 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 $\epsilon \equiv \delta W/\delta Q_h$,. 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 $\delta S = 0$,[no cycle] 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 that operates on coupled sub-cycles. The first uses imbalances to extract energy to perform work. While the second 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. The coordination of the two open sub-cycles 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). Hence unlike man-made machines, the state of an organism at the end of the cycle is not pre-determined [Ben Jacob and Tauber in preparations].

A simple analysis of such a hybridized thermodynamic machine yields an inconsistency if we assume that the two processes are executed in parallel. Say that a fraction x of the work extracted by the engine is used to reduce the entropy, then

$$\delta S = x\,(\delta Q_h - \delta Q_c)/T_m$$

Where T_m, is the machine temperature. But at the same time, the entropy change should also be equal to,

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

As we describe below, to solve this inconsistency, the biotic machines must, first, maintain a non-equilibrium (evolving) state, where both their internal structure and composition are regulated by internally stored information. Contextual information then allows these machines to operate on an incompletely closed cycle, in contrast to the closed cycle of an ideal thermodynamic machine. Second, biotic machines possess a membrane which enables them to generate from the external environment local large 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 of the biotic machine and that of its surrounding.

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 genetic information and the 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 self biotic machine according to its specific needs and stored knowledge. This is perhaps the most essential difference between man-made and biotic machines: Simply, man-made systems with information-based feedback do not feed energy into a specific set of the machine's physical (microscopic) levels.

Ordinarily, entropy is produced when ordered energy (say mechanical work), is distributed homogeneously into micro-level degrees of freedom. Using ATP nano-machines, the biotic systems feed ordered energy into a specific spatio-temporal micro-level distribution. In light of the above, we suggest that the ATP machinery actually can be viewed as a molecular sensory system, which uses the ADP-ATP cycle as a mode of information processing. On this schema, ATP/ADP becomes a sensor, transferring relevant information from the surrounding via low entropy energy coins into specific sites where they are used for further information processing in the form of generating complex organic molecules or as energy substrates for proper enzymatic or structural functioning. We provide specific examples below, but note, we emphasize that the ATP machinery plays the crucial role in all cases of bacterial sensing, and accordingly, may be regarded as the mediator of information in these systems. Indeed, *contextual information* is the crucial component permitting the biotic machine to remain open.

Bacteria 'Taste' Before Feeding

Feeding and sensing faculties must have evolved hand in hand. To fulfill energy needs, bacteria first assess the energy source level at their location and then actively move towards a region with a higher supply of food. This directed motion, chemotaxis [21-26], distinguishes bacteria behavior 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 'taste' the food before eating it. The net result is a biased random walk (or drift), towards a higher concentration of food.

Bacteria rely on measuring the level of food before they consume it and thereby alter the local (intra-cellular) concentration, where second order processes operate. For example, consider how tasting before eating is the preferred consumption of specific foods when several 'dishes' are available. For that discernment, bacteria need to perform continuous measurements of the various available energy sources and perform internal computations [27,28]. For example, *E. coli* bacteria have different sets of genes for digesting (producing metabolic enzymes) 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. So when it is 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 CAP (catabolic activator protein), 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 illustrates what we mean by internal information processing and to justify the notion of 'tasting' food as a cognitive act. A similar tasting mechanism is used in other cases of bacterial taxis. For example, photosynthesizing bacteria 'taste' light and assess its level to perform photo-taxis 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]

Gleaning Information and Assigning Meaning: Characteristics of Bacteria Cognition

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 (Figure 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 organism, with increased sensory capacities and elevated complexity-based plasticity. With these more complex cognitive capabilities, the colony senses many aspects of the environment and its own internal state, processes the information, and then responds in a manner that affords improved adaptability to the environmental conditions. 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). Group selective process must account for such adaptations by individuals, since the colony elevates species durability by improved adaptability to the environment, which, in turn, is based on evolving the faculties required for creating greater complexity [13].

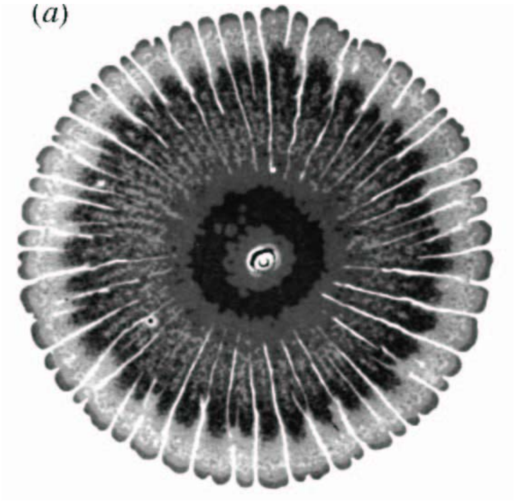
Figure1. Hierarchical colony pattern generated by *Paenibacillus vortex* bacteria. Each vortex (the condensed group of bacteria) is composed of many organisms that swarm collectively around their common center at about 10 micron/sec. The vortices vary in size from tens to millions of bacteria, according 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 x500; 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. This ongoing communication 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.

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 (virulence genes, e.g.) once the species density exceeds a threshold. A typical case arises in *Vibrio fischeri,* where production of a membrane-permeable homoserine lactone by LUXI is sensed by the LUXR protein 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 [8-14]. Collectively, bacteria can glean relevant information from the environment and from other organisms, interpret the information in an existential "meaningful" way, develop common knowledge, and learn from past experience.
Each bacterium has intricate intracellular signaling mechanisms involving signal transduction networks [27] and genetic language [28]. These are used to generate intrinsic meaning for contextual interpretations of the chemical messages and for formulating appropriate 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].

This ability to form cooperative collectives is an evolutionary novelty: New cognitive features appear at every level of colonial self-organization -- from the internal cellular gel to the growth of the colony as a whole – to facilitate this new 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 can not 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 intracellular flexibility, involving signal transduction networks and genomic plasticity, to collectively create the colony, maintain its integrity by sharing interpretations of chemical cues and the exchange of meaning-bearing chemical messages. The ensuing dialogues are nothing less than meaning-based communication [4,7,13,39-46], which permits the colony purposeful alteration of structure and decision-making. These features represent primordial social intelligence and cognition [47-56].

Individual Sensing: In the co-operative 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 (Figure 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.



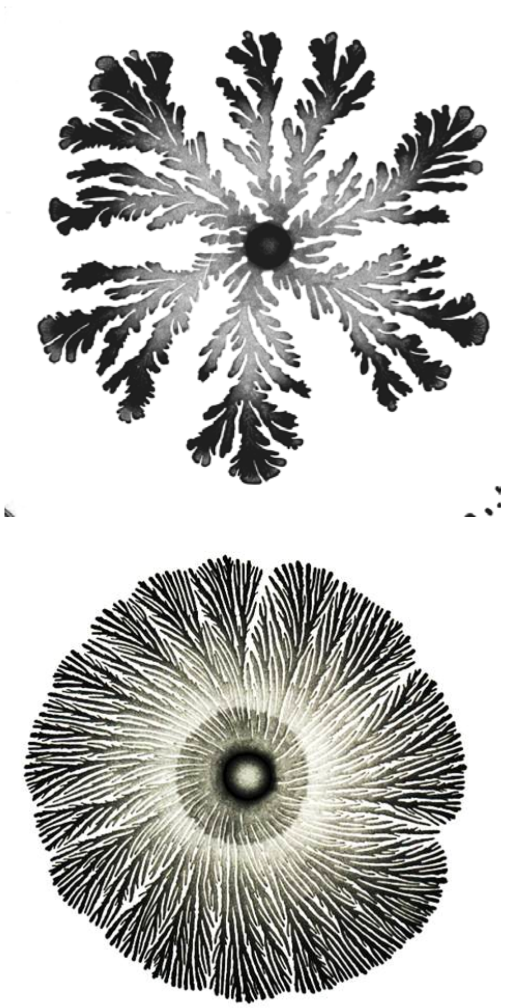


Figure2. Examples of different branching patterns formed during colony formation by *P. dedritiformis*. To self-engineer their colonial structure these bacteria regulate the balance between attractive and repulsive chemotactic signaling as well as their food chemotaxis [13]. The top panel shows the pattern 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 recently identified, autoinducer AI-2 in *V. 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.

Collective decision-making: An example of the advantage of bacterial discourse is the starvation response exhibited in many species is provided by sporulation [52]: When growth conditions become too stressful, bacteria can transform themselves into inert, enduring spores. Sporulation is a process executed collectively and beginning only after "consultation," which is an assessment of the colonial stress as a whole which is 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.

Learning from experience: In Fig 3, we show two different colonial patterning 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 in 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].

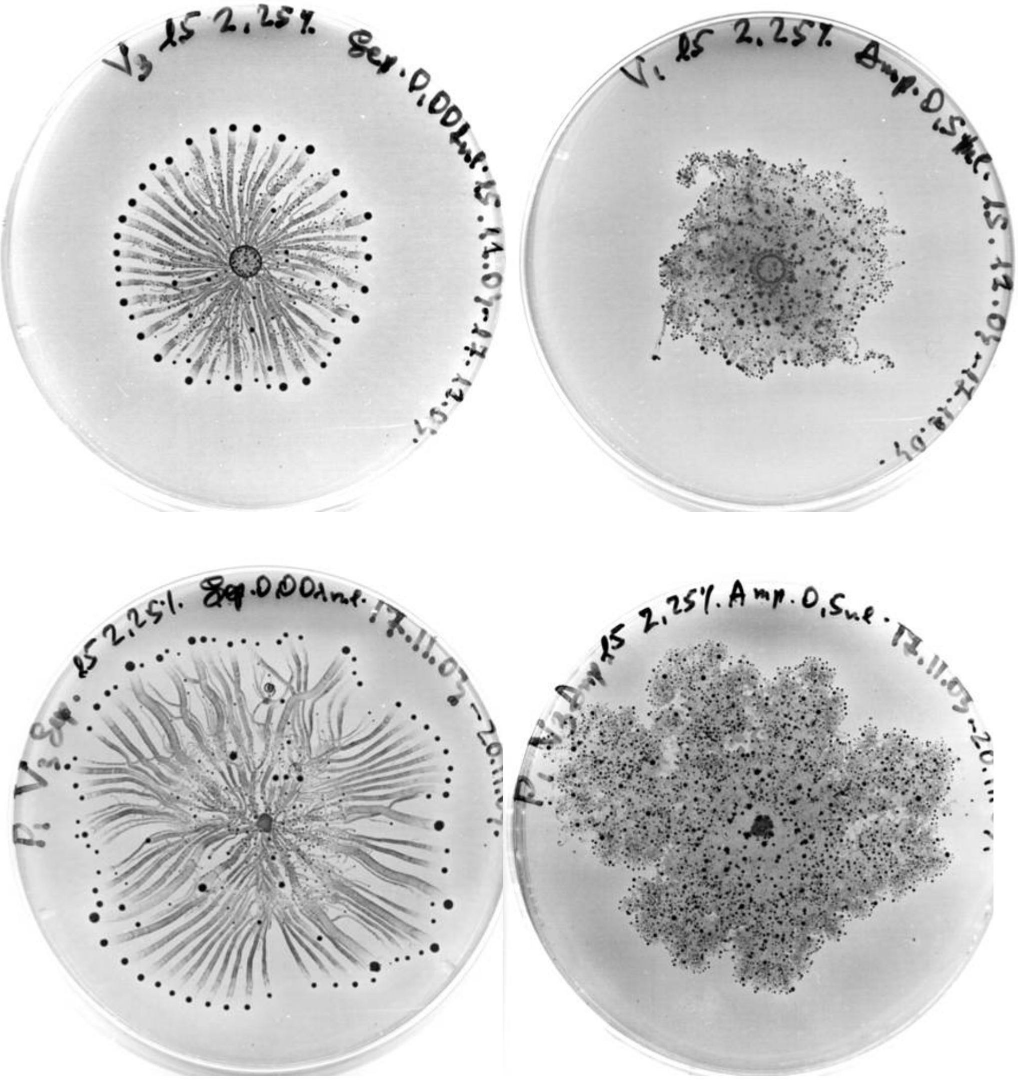


Figure3. Effect of antibiotics on colony formation of *P. dedritiformis*. The top left panel shows the effects of co-trimazole (Septrin) in altering colony by *P. dedritiformis*. This antibiotic inhibits synthesis of folic acid and thus suppresses cell reproduction [4]. In response to Septrin the bacteria 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. 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 already had ben exposed to an antibiotic – were then grown under the same conditions, i.e., again exposed to the same antibiotic. Left panel shows the effect of Septrin and 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 compensated accordingly.

Clashes of bacterial intelligence: The predator Myxobacteria uses communicative devices for cooperative feeding on other bacteria, controlled cell differentiation and generation of colonial identity to signal out ‘cheaters’. These bacteria have a variety of strategies they can use when 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 difficult 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 intelligence and social skills for future adaptive cooperative responses. Another example is the no winning rock–paper–scissors game played between strains of *Escherichia coli* - strains (C) produce colicins, that kill other, colicin-sensitive (S) strains which out compete colicin-resistant (R) strains, which close the circle by out competing C [60]. Expectedly in this game of no prevailing strategy all three strains survived. However, in a recent *in vivo* version played by feeding the strains to different mice strains (C) tend to loose with time [61].

These examples are representative of many bacterial collective patterns of behavior that reflect fundamental faculties of cognition. It is now realized that bacteria can develop collective memory, use and generate common knowledge, develop group identity, recognize the identity of other colonies, learn from experience to improve their collective state, and do so by engaging in group decision-making. These are the bacteria faculties we refer to when using the term ‘fundamental cognition.’ (We emphasize that these features should be distinguished from the analytical intelligence based symbolic cognition special to human beings.)

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 random mutation [62-65]: Non-resistant bacteria were exposed to a lethal level of bacteriophage, and they postulated that only those bacteria that happened to go through random mutation would survive and be observed. These experiments were then taken as a crucial support for the Neo-Darwinian dogma that *all* mutations are random and can occur *only* during DNA replication [66-69]. Schrödinger 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 the development might call for additional fundamental principles. Although such principles emerged in nascent form a decade later following Turing's seminal work and the elucidation of DNA's structure, the following extract describes Schrödinger's ontogenetic dilemma, which we have cause to reconsider even with our 21st century understanding:

> **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 Delbruck'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. 68-9)**

Schrödinger's dilemma about the conversion of 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, development can be explained solely (in a complete and self-consistent manner) by the information stored in genetic material (DNA or RNA). Hence, Schrödinger's dilemma is generally perceived as a mere misconception due to the historical moment he was writing. Accordingly, 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 view and propose that as Schrödinger feared, the current view is itself misconceived, or at least, incomplete, and as he himself pointed out, following him (as already quoted) "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. The first 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 with a power plant. The fact that we know 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 cognitive functioning of management and workers, especially regarding decision-making and administrative functions. 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 also emphasize 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 can not 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 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 detailed examinations of the kind that dominate the current biological literature will not provide answers as to how complex system are organized, primarily because the research is not formulated to address that level of inquiry. What we propose instead, and the opinion we assume Schrödinger would also have taken, 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]. But even for prokaryotes, membranes, for example, contain lipids, which are not internally coded but are rather absorbed from food according to the functional state of the organism. Not to mention that bacteria exchange meaningful information including genetic material (like plasmids), which integrates into the genome.

The problem is not simply biological, i.e. epigenetic influences, supporting structures and functions, etc., but may be conceptually related to Russell's self-reference paradoxes and Gödel's theorems: Is it possible, *in principle,* to construct mapping between genetic information and statements [7,77-84] about genetic information?

Others [7,79] have argued 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 second issue is similar to the line of argument presented here, namely, that organisms must glean 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 our example, a bacterial colony involves self-organization and contextual alteration of its constituents on all levels of function. The alterations are based on stored information, external information, information processing and collective decision-making following 'semantic' and 'syntactical' communication between each level – both intra- and extra-cellular.

Accordingly, in the colony, communication allows collective alterations of the intracellular state of the individual bacteria, including the genome, the intracellular gel, and the membrane.

In line with this train of thought, we cite a new picture of a 'cybernetic' genome [77-79] which is emerging following the complete sequencing of various organisms. The recent discoveries [85-87] about the previously regarded '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 has 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.

More recent work shows that transposable elements can effectively re-program the genome between replications [85,86]. In yeast, these elements can insert themselves into messenger RNA and give rise to new proteins without eliminating old ones. These findings illustrate that rather than wait for mutations to occur randomly, cells can apparently keep some genetic variation on tap and move them to 'hard disk' storage in the coding part of the DNA if they turn out to be beneficial over several life cycles. Some observations hint that the collective intelligence of the intracellular 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.

Meaning-Based Natural Intelligence

In light of a rejuvenated cybernetic orientation, might we fruitfully reflect on a *meaning-based natural intelligence*? We refer to that common trait shared by all organisms, from bacteria to humans, which confers some fundamental cognitive abilities crucial to their very survival. Our chain of reasoning begins with the simple motives of contextual causations for intrinsic and extrinsic sensing, which are required for individual, as well as cooperative, survival. We propose that the ability to assign contextual meaning to externally gathered information is a meaning-generating process, as it gives the organism the intelligence (and freedom) for life-enhancing decision-making. By contextual, we mean that any information, whether generated from external or internal sources, must be placed within a framework in which its significance, i.e., 'meaning' is derived. In this sense, as in linguistic communication, a semantic component is understood within its supporting syntactical structure. These 'linguistic' characteristics are the fundamentals of natural intelligence that any living creature must have. (By intelligence we 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 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].

Two developments of the 1950s, Noam Chomsky’s universal grammar and the structural code of the DNA, later led to linking linguistics and genetics. The first suggested universal structural motifs and combinatorial principles (syntactic rules) at the core of all natural languages, and the second provided analogous universals for the genetic code of all living organisms. Chomsky’s meaning-independent syntactic grammar approach, along with computational linguistic methods, irrespective of its problematic status among current linguists, is widely used now in biology, especially in bioinformatics and structural biology but increasingly also in systems biology and ecology. The focus has been mainly on the structural aspects used to exchange information. Employing formal linguistics [39-44], two levels must be coordinated: lexical - formation of words from their components (e.g. characters and phonemes); syntactic - organization of phrases and sentences in accordance with well- defined grammar rules.

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].

When reading a text, for example, one has semantic freedom to assign to it different meanings. Each reader has cognitive flexibility to assign his own meanings to the text, according to personal knowledge as well as specific expectations, or purpose in reading the text. The meaning of a text is often captured only after reading it several times. At of the iterations, words, sentences and paragraphs may assume different meanings in the reader’s mind. Iterative reading is necessary, since there is a hierarchical organization of contextual extraction of meaning. Namely, each word contributes in the reader’s mind to the interpretation of the entire sentence that the word is part of. Yet, at the same time the generated meaning of the whole sentence can change the meaning he assigns to each of the words of which the sentence is composed.

Beyond the individual semantic level of linguistics, some linguists identify a dialogue among converser (discourse or goal-driven conversation), using shared semantic meanings as the pragmatic level of linguistics [4]. This higher level of linguistic communication requires the conversers to have a common goal in conducting the dialogue, i.e., shared knowledge and mutual intensions and expectations (presupposition, implicature and attribution). The group usage of a dialogue can vary from activity coordination through collective decision-making to the emergence of a group self-identity.

To fulfill the fundamental cognitive functions we have described, bacteria must sustain 'semantic' communication. Drawing upon human linguistics, with regard to bacteria, semantics would imply contextual interpretation of chemical messages, i.e., each bacterium has some freedom (plasticity) to assign meaning according to its own specific, internal and external, contextual state. For that, a chemical message is required to initiate an intra-cellular response that involves internal restructuring - self-organization of the intracellular gel and/or the gene-network or even the genome itself.

Such internal processes might be regulated by some master switch in the gene regulation network capable of producing intracellular messages – transcription-factors that can modify the expression levels of the self-same genes. So, an external message can initiate the proper context-dependent transition between different operating states of the network. In this schema, cells have to memorize internal processes that can be invoked by messages; much like what our brain does to obtain the semantic meaning of sentences. It is already 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 macro-colony-level sensing-based communication.

To sustain a dialogue based on semantic messages, the bacteria should have in addition a common pre-existing knowledge (collective memory) together with the 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, yet to be discovered.

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. In yeast, these elements can insert themselves into messenger RNA and give rise to new proteins without eliminating old ones. Rather than wait for mutations to occur randomly, cells can apparently keep some genetic variation on tap.

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In summary, on our view, semantic and syntactical communication (the 'linguistic' construction) are coupled to assign and generate meaning, formation of self-identity (as well as associated identity, i.e., of the group the individual belongs to), intentional behavior, decision-making, self-designed adaptations and alterations, and finally, cognizance of another's 'consciousness'. The most intriguing challenges associated with such a natural intelligence and its linguistic formulation is to resolve 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-networks 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 comments.

Final Musings

Punctuated throughout philosophy's modern history of debate about free will and self-determination, mechanical metaphysics regarded free will is an illusion since, in principle, it contradicts a physics whose fundamental principles include a strictly linear causal determinism and time causality. 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], which must go hand in hand with 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 universe subject to 'causal determinism'. Therefore, within this picture, all living organisms, from bacteria to humans, could be nothing but watery 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 all levels of cognition are composed in a generative context to create meaning and to allow for will and choice [7,13]. By global 'generativism,' 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 – metaphorically, like the formation of meanings by organizing words into sentences [39-44]. The macro scale (the analog of the sentence and the reader's previous knowledge), selects between the possible lower scale organizations (the analogue of a word meaning).

Metaphorically, the above picture of decision-making is similar to the notion of quantum mechanical collapse of a superposition caused by measurements. For example a particle in a double well potential can be in a superposition of residing in the right and the left parts of the well. Simply phrased, an external measurement of the particle location leads to a collapse of the superposition state on the particle being left or right. There are two fundamental differences, however, between the projection of the entangled state 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. Namely, the eigenstate (say of being left or right in the above example), is predetermined while its corresponding eigenvalue is not. In the organism's decision-making, the external stimuli initiate the selection of a specific option (projection on a specific response). Hence, the specific consequent response is *in principle* undetermined (not even probabilistically) to an external observer as he does not have the organism's previously acquired internal information.. The initiated internal decomposition of the mixed states and the selection of a specific one are performed according to stored past 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: The external stimuli initiate decomposition of the mixed states by the organism itself. The information about the other available options is stored after the selection of the specific response. Therefore, the unselected past options are expected to affect consequent decision-making. Nevertheless, we suggest that this approach for understanding cognition as a projection of entangle state onto an eigen-like informational states leads us safely away from Laplace's Demon. Whether we are offering a viable hypothesis that will direct future 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.

Acknowledgments

E. B-J. thanks the organizers and participants of the EXYSTENCE Thematic Institute "From Many-Particle Physics to Multi-Agent Systems" Dresden July-September 2004 for stimulating conversations and Y. S. thanks the Chair in Physics of Complex Systems for partial support.

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 appreciated 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 [100]. In this regard a new principle of "flexibility follow complexity" 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. 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 chapter.

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[96]Gell-Mann, M. (1992) Nature Conformable To Herself *The Bulletin of the Santa Fe Institute*, **7,1**, 7-10, (1992) ; (1995/6) *Complexity*, **1,4.** 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 han 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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