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Bacterial wisdom, Gödel's theorem and creative genomic webs

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Abstract

This paper is devoted to presenting an alternative approach to the Darwinian one. The basic assumption is that the creativity observed in nature is not an illusion but part of an objective reality. In the new picture evolutionary progress is not a result of successful accumulation of mistakes, but is rather the outcome of designed creative processes in the genome.

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1. Introduction

The reductionist approach has long governed western philosophy and underpinned our view of the world and our scientific thought [1]. The Universe is Laplace's mechanical universe, in which there is no room for renewal or creativity. On the contrary, the assumption is that systems in nature, when left alone, approach maximum entropy according to the second law of thermodynamics.

Concepts like cognition, intelligence or creativity are regarded as our illusions. The amazing process of evolution – from inanimate matter, through organisms of increasing complexity, to the emergence of intelligence – is claimed to be merely a successful accumulation of errors (random mutations) enhanced by natural selection (the Darwinian picture) [2–6].

The reductionist hegemony in scientific thought is largely due to the undeniable achievements of science, which have not been hindered by the still unsolved fundamental questions. The power of the Darwinian picture lies not only in its

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achievements, but also in the dismay evoked by what seems to be the only alternative – Vitalism [7].

But is Vitalism the only alternative? Or could there be another picture, neither Darwinian nor Vitalistic? This manuscript is devoted to presenting an alternative approach. My basic assumption is that the observed creativity in nature is not an illusion but part of an objective reality, and as such should be included in our scientific description of reality [8]. However, if we understand science as the ability to predict the future state and behavior of a system based on the present knowledge about the system, then a creative process contradicts the tenets of scientific description. After all, creation means emergence of something new and unpredictable, something not directly derivable from the present.

My proposed solution to the above paradox leads to a new evolutionary picture, where progress is not a result of successful accumulation of mistakes in replication of the genetic code, but is rather the outcome of designed creative processes. Progress happens when organisms are exposed to paradoxical environmental conditions – conflicting external constraints that force the organism to respond in contradicting manners. Clearly, an organism cannot do it within its current framework. The new picture of creative cooperative evolution is based on the cybernetic capacity of the genome (as is described in Section 6) and the emergence of creativity as the solution cooperative complex systems apply to an existential paradox.

I start in Section 2 with the classical experiments of Luria and Delbrück that demonstrated for the first time the existence of random mutations prior to the application of the selective pressure [9]. These findings were viewed as a proof of the Darwinian picture and led to the current Neo-Darwinian paradigm in the life sciences. A decade later (during the 1950s and early 1960s) a number of major discoveries were made, of which only one (the double-helix structure of the DNA) is widely known. In Section 3 I briefly review these important findings which should have changed the paradigm, since they showed that the genome is a dynamic entity capable of changing itself. They are a fundamental basis to our new picture of the genome. I continue, in Section 4, with the recent developments in adaptive mutagenesis demonstrating direct mutation in response to a non-lethal selective pressure. In all of these experiments, the selective pressure acts on the individual bacteria. My belief in cooperative genetic changes led me to a new experimental endeavor, in which the selective pressure was on the colony. The new experiments led to important new observations (Section 5) of morphotype transitions in stressed colonies. These are genetic changes which are beneficial to the colony but may not be beneficial directly to the individual cells.

The new picture of the genome as an adaptive cybernetic unit with self-awareness is presented in Sections 6–8. The genome, as I see it, is not merely a storage device, but a sophisticated cybernetic entity well beyond a universal Turing machine [10]. Metaphorically speaking, it includes a user, a computational unit, and a hardware engineer and technicians. The computational unit itself supersedes the universal Turing machine, since during computations the structure is dynamic and changes adaptively according

to the needs dictated by the computations. The crucial component is the "user" which can recognize difficulties imposed by the environment and formulate problems requiring solution. This "user" possesses information about the past and present abilities of the system, which it can apply when searching for a solution to a current problem. It also has the potential for interpreting and assigning meaning to the computations. I further assume that the genome has self-awareness. In Section 7 I propose that the following requirements must be fulfilled by a system to possess self-awareness: (1) It has to be a cell composed of agents (vs. sets composed of elements). (2) It has to evolve in time. (3) It has to be an open system – constantly exchanging energy and information with the environment. (4) It has to have an advanced language (with self-reference to sentences and to its grammar).

At first it seems that the assumption that the genome is an adaptive cybernetic unit with self-awareness will suffice to explain evolution (Section 8). However, this is not so. A lemma extended from Gödel's theorem sets limitations on self-improvement. Naively phrased, it says that a system cannot design another system which is more complex than itself.

In Section 10, I use the distinction between Kuhn's normal science (problem solving within the scientific paradigm) and scientific revolutions (creation of a new scientific paradigm) as a metaphor to define horizontal genomic changes vs. vertical genomic leaps. The extension of Gödel's theorem would imply that the genome is not capable of performing genomic leaps. Yet these may be the most relevant changes in evolution.

Are we back to random mutations? Could it be that the horizontal genomic changes are self-designed changes in response to the environment, and the more dramatic vertical genomic leaps are due to Darwinian evolution? I do not think so, and suggest a new picture of cooperative evolution as an alternative.

First, I propose that the vertical genomic leaps are in response to an existing paradox. In Section 10 I present the creativity paradox, and my picture in which the paradoxes are the gears of creativity, serving as the new principles on which the new paradigm is established. Next (Section 11), based on the contemporary knowledge of genetic communication in a stressed colony, I propose that the colony forms a genomic web (I use the term web instead of network to emphasize that the building blocks are self-aware agents and not elements. For example, Hopfield's neurons are elements and not agents.). The genomic web is a "super-mind" relative to the individual genome. Thus, a paradox for the genome is a problem for the web, which in turn exercises its creativity on the genome level. Or, in other words, the web is far more complex than the individual genome, so it can design a new and more advanced genome which would represent a vertical leap beyond the previous genomic version. This is why I use the terms cooperative self-improvement or cooperative evolution. I would like to emphasize that random mutations do exist and also affect evolution. However, I propose that the designed changes have a more crucial role in evolution.

I conclude in Section 12 with some implications of the new picture, and speculate about its validity to eukaryotes.

2. Luria and Delbrück experiments: Pre-existing random mutations

The origin of mutations became one of the most fundamental question in the biological sciences, ever since Charles Darwin gave mutations a key role in his theory of natural selection. Darwin himself did not consider mutations (variations between individuals) to be necessarily random, and thought the environment can induce specific (adaptive) mutations. He did comment, however, that it is reasonable to treat them as random, as long as we do not know their origin [11].

In 1943, Luria and Delbrück [9] performed a cornerstone experiment to prove that random mutations (i.e. mutations that are not related to the environment) do exist. They exposed bacteria to a lethal selective pressure – bacteriophage T1. As this bacteriophage immediately kills non-resistant cells, only cells with a pre-existing specific mutation to resist the bacteriophage could survive the treatment (the selective pressure). Luria and Delbrück exposed populations of bacteria to such lethal environment, and analyzed the number of surviving cells in the different populations (different petri-dishes). From the distribution of surviving cells, they concluded that the relevant mutations had occurred randomly before the bacteria were exposed to the selective pressure, i.e. the mutations arose randomly and were not induced by the environment.

As Delbrück himself pointed out [12], only cells with a pre-existing specific mutation could survive the experiment, as the non-adapted cells died immediately without an opportunity to mutate in response to the pressure. The experiments did prove the existence of random mutations, but they did not rule out the possibility that there are also non-random mutations. Nevertheless, these experiments were taken as a support of the Neo-Darwinian dogma which states that *all* mutations are random, and occur only during DNA replication. This "twist" in interpretation can be understood as part of the aim of Neo-Darwinism – or "the modern synthesis" – to remove any vitalistic or teleological notions from biology by employing only mechanistic explanations to all phenomena.

3. New developments in the 1950s: From genes to genome

The findings of Luria and Delbrück of pre-existing random mutations fitted well the reductionist approach. It also seemed to be in agreement with the developments of quantum mechanics in physics, as is reflected in the influential book (at that time) of Schroedinger "what is life"? [13]. Delbrück, who has started as a Physicist influenced by Schroedinger, tried to fit evolution, including the emergence of the mind, within the reductionistic views of Physics. In his book "Mind over matter" he hints about the encountered difficulties, but it seems he has adopted the reductionist approach [14]. The latter gained tremendous support with the discovery of the helical structure of the DNA in 1953 [15]. This, together with the evidence for the "one gene–one enzyme" theory found five years earlier [16,15] and the discoveries of the messenger RNA and transfer RNA, led to the establishment of the Neo-Darwinian picture in which the gene is the

key basic element. It is defined [16,15] as a hereditary unit that occupies a specific position within the genome or chromosome, a unit that has one or more specific effects on the phenotype of the organism and can mutate to various allelic forms, a unit that recombines with other such units. Three classes of genes are recognized at present: (1) structural genes that are transcribed into mRNA, which are then translated into proteins; (2) structural genes which are transcribed into rRNA or tRNA molecules; (3) regulatory genes that are not transcribed, whose primary function is to regulate the rate of synthesis of the product of other genes; these can also activate and de-activate other genes.

The regulatory genes and the theory of the operon (a number of genes that function coordinately under the control of a regulatory gene) were proposed by Jacob and Monod in 1961 [15]. This is one of the number of great discoveries during the 1950s which should have shattered the picture of a static genome which serves as a storage unit only. Indeed, hints about the need for a new picture are presented in Jacob's book "The logic of life" [17]. The other discoveries I refer to are:

(1) The discovery of transposable elements by McClintock in 1950 [18]. These are a class of DNA sequences that can move from one chromosomal site to another. They can also be transferred (carrying, e.g. antibiotic resistance) between plasmids (sometimes referred to as mobile elements).

(2) Discoveries about bacteriophages e.g. that the DNA can enter the host while most of the proteins remain outside, genetic recombination with the host chromosome, exact structure of various phages, non-infectious replication of phages, etc. [16,15].

(3) Discoveries of the plasmids and their properties starting with the Lederbergs' discovery of the lambda (then called episome) plasmid [16,15]. In general, plasmids are extra-chromosomal genetic elements found in a variety of bacterial species, that usually confer some evolutionary advantage to the host cell (e.g. resistance to antibiotics, production of colicins, etc.).

The plasmids, which serve as a major tool in natural as well as man-made genetic engineering [19] are double-stranded, closed DNA molecules ranging in size from 1 to 200 Kb. Plasmids can be integrated into the host chromosome. Their replication is either autonomous or coupled to that of the host. The number of plasmids per host cell may be from 1 to 100. The plasmids can be used to transfer DNA sequences between cells. Some can initiate conjugation (a temporary union of two cells for exchange of genetic materials), some can be transferred during conjugation, and others can help transfer non-mobilizable plasmids. Plasmids can also replicate genes, move genes from one location to another and control genes like the regulatory genes do. It is important to emphasize that the activity of the plasmids themselves may be regulated either by the internal conditions or by the external conditions, as if they have direct communication channels to the surroundings of the cell.

(4) In 1954 Ryan demonstrated that genetic changes can occur not during replication [20]. To do so he exposed bacteria to non-lethal selective pressure. He provided the bacteria with food they could not "digest" and low level of digestible food, insufficient for the bacteria to replicate. He observed the appearance of new mutants that could digest the food, which indicated genetic changes not during replications.

The above findings, put together, should have led to a new picture of a dynamic genome, but they did not. Today the genome is still defined simply as the collection of all genes carried by a single gamete [16,15].

I propose a new picture of the genome as an adaptive cybernetic unit with self-awareness. In this picture, the genome includes the chromosome, all the extra-chromosomal elements and all the "chemical machinery" (like enzymes) involved in genomic activity and the production of proteins. The new picture is based on the findings described above and on contemporary knowledge about additional genetic elements (which I do not have room to describe here).

The term "element" is misleading, as those are actually agents [6]. I further propose to refer to them as cybernetic agents, or cybernators (see Section 6). My new picture is also based on the known abilities of the genome to change itself and the experimental findings described in Sections 4 and 5.

4. Adaptive mutagenesis

While Ryan demonstrated genomic changes not during replication, he failed to show that the changes were according to the applied specific selective pressure. In 1984 Shapiro [21] performed a similar experiment. However, he used genetically engineered bacteria with a deletion mutation which prevented them from "digesting" specific food. He observed the appearance of corrective mutations (i.e. mutations which enabled the bacteria to digest the food). The mutations did not occur immediately after the onset of selective pressure (exposure to a high level of indigestible food), but began to appear after a delay of about two days, and then continued to appear in an almost constant rate for several days. (This and later observations about the specific nature of those mutations led us to believe [22] that a two days period is taken by the bacteria to identify the problem posed to them and to find a solution, as I discuss in Section 8.)

In 1988 Cairns et al. [23] showed the specifity of those mutation events. They showed that a specific mutation will occur in high frequencies only when needed to remove the selective pressure, i.e. during a selection for that mutation and not in other stressful conditions, and that the former selection, which triggers the specific mutation, does not trigger other mutations. Cairns et al., concluded that those mutations were adaptive, i.e. that the bacteria somehow mutate in order to adapt to the selective pressure. These experiments and the conclusions triggered a furious debate in the biological community and led to various additional experiments. The latter ruled out several more conventional interpretations, and showed the active role of the bacteria in the events of adaptive mutations (for details see Ref. [24] and references therein).

One of the most interesting set of experiments related to this subject is Hall's experiments of double mutations [25,26]. In those experiments two mutations in two genes were needed to enable bacterial growth. The most important feature of the results is the doubling of the delay time preceding the appearance of the adapted mutants.

Recent experiments by Galitski et al. [27] and Radicella et al. [28] began to confirm Ben-Jacob et al. [22] hypothesis, that in order to perform adaptive mutations (and other non-random mutations) the bacteria employ cybernetic agents (plasmids, in the case of Galitski et al. [27]), that can transfer mutations from cell to cell [28]. Thus, mutations can be "synchronized, autocatalytic and cooperative genetic variations" [22]. Although far from being generally accepted, a picture of problem-solving bacteria capable of adapting their genome to problems posed by the environment might be emerging. This is a picture radically different from the contemporary picture of lifeless, passive DNA used as a memory storage for protein production.

5. Colonial stress and morphotype transitions

It is now understood that bacteria paved the way for life on earth as we know it, and are crucial for its continuation [29]. Yet, the view of bacteria as unicellular primitive microbes, or a collection of non-interacting passive "particles", has persisted for generations. Only recently have the notions of smart bacteria [30,31] and bacteria as multicellular organism [22,30,32–40] (both with respect to bacterial colonies) started to gain attention. Armed with the new developments in the study of patterning in non-living systems [41–45], I set out to promote the above notions.

The study of diffusive patterning in non-living systems teaches us that the diffusion field drives the system towards decorated irregular fractal shapes. Hence, one expects complex patterns to be developed by nutritionally stressed colonies as has been demonstrated by Matsushita and coworkers [46–50]. We have created such hostile growth conditions in a petri-dish by using low levels of nutrients and a hard thin substrate (high agar concentration). Indeed, we observed some very complex patterns.

Moreover, the colonies exhibit richer behavior than patterning of non-living systems, reflecting the additional levels of complexity involved [22,33,34,36,37,39,51–56]. The building blocks of the colonies are themselves living systems, each having its own autonomous self-interest and internal degrees of freedom. At the same time, efficient adaptation of the colony to adverse growth conditions requires self-organization on all levels – which can only be achieved via cooperative behavior of the individual cells. It may be viewed as the action of singular interplay [22,33,37,54,57–59] between the micro-level (the individual cell) and the macro-level (the colony) in the determination of the emerging pattern.

To achieve the required level of cooperation, the bacteria have developed various communication capabilities, such as: (1) direct cell–cell physical and chemical interactions [56,60], (2) indirect physical and chemical interactions, e.g. production of extracellular "wetting" fluid [61,62], (3) long-range chemical signaling, such as quorum sensing [63,64], and (4) chemotactic signaling (chemotactic response to chemical agents which are emitted by the cells [65–67]).

The colonial communication, regulation and control in the formation of complex patterns during colonial development justify the notion of smart (in the weak sense)

bacteria. Had we demonstrated colonial adaptive morphogenesis (inherited colonial morphological characters) resulting from environmental stress on the colony, it would provide strong support to the notion of bacterial colonies as a multicellular organism. Motivated by the new "fastest growing morphology" selection principle developed by Ben-Jacob and Garik [43], we setup experiments with the above special goal in mind. The working hypothesis was that transitions were expected from a morphotype [68] (a colonial geometric character which is inherited and can be carried by an individual bacterium) which expands slowly to another morphotype which is a faster expanding one. This means that the colony which can propagate faster on the agar surface has an advantage in reaching for the food. Transitions between two of the morphotypes we have identified (for more details see Refs. [22,33,34,37,51,52,54]) the tip-splitting $\mathscr{T}$ and the chiral $\mathscr{C}$ morphotypes have been observed. As expected, we observed $\mathscr{T} \rightarrow \mathscr{C}$ transformations on softer surfaces for which $\mathscr{C}$ is the faster morphotype, and the reverse $\mathscr{C} \rightarrow \mathscr{T}$ transformations on harder surfaces on which $\mathscr{T}$ is the faster one. Since the growth velocity is a colonial property, our observations indicate that some selective colonial pressure is invoked. This would be an extension to living systems of the "fastest growing morphology" selection principle.

Now, we are facing two riddles. One is the manner in which colonial pressure can reach down to the single bacterium and cause genetic changes in the individual cells such that a transformation from the $\mathscr{T}$ type to the $\mathscr{C}$ type occurs. Another, related riddle has to do with the morphotype bursts. Sparse cells of the $\mathscr{C}$ morphotype scattered among the $\mathscr{T}$ cells within a $\mathscr{T}$ colony have no individual advantage and no effect on the colonial structure even during growth on soft substrate for which the $\mathscr{C}$ morphotype is the preferred one. Only finite nucleation of the $\mathscr{C}$ cells (a regime of high concentration of the specific cells) has an advantage (on soft substrate), as it can lead to a burst of the preferred morphotype in a manner analogous to phase transitions (say from liquid to solid) via finite nucleation in non-living systems. The riddle is then how the finite nucleation in the morphotype transition is formed. One possible explanation which was suggested in Refs. [22,33,34,37,54,58], is that of autocatalytic or synchronized genetic changes. If so, a mechanism for such changes needs to be proposed.

6. Three levels of information transfer and the concept of cybernators (cybernetic agents)

The morphotype transitions have led Ben-Jacob et al., to propose a new cybernetic framework [22,33,37,54,58]. The latter is also motivated by the experimental findings about adaptive mutagenesis and is based on the contemporary knowledge about the genetic agents (e.g. plasmids, transposons, phages, as well as other dynamic agents) discussed in Section 3. I have mentioned that these autonomous genetic agents, which can perform genetic changes in the host cell, can have their own "self-interests" and their own direct communication channels to the conditions outside the cell.

In the new picture, we designate autonomous genetic agents whose function is regulated by holoparameters (i.e. colony parameters such as growth kinetics, cellular density, density of metabolic byproducts, level of starvation, etc.) as cybernators. I emphasize that an agent here is not necessarily a specific single macromolecule. It could be a combination of units or even a collective excitation of the genome performing the specific function. In other words, generally it should be viewed as a conceptual unit, although specifically it might be one macromolecule or a collection of molecules. The crucial point is that, since the cybernators' activity is regulated by holoparameters, it can produce changes in the genome's activity and structure that modify the individual cells in a manner beneficial to the colony as a whole. Thus, the bacteria possess a cybernetic capacity which serves to regulate three levels of interactions: the cybernator, the cell and the colony. The "interest" of the cybernator serves the "purpose" of the colony by readjusting the genome of the single cell. For example, when bacteria are exposed to antibiotic it can lead to an increase in the replication of plasmids which carry the resistance to the antibiotic. The cybernator provides a singular feedback mechanism as the colony uses it to induce changes in the single cell, thus leading to consistent adaptive self-organization of the colony.

7. Genomic adaptation and genomic learning

I proceed here with a detour to present two additional ideas that emerged from the observations of the $\mathscr{T} \rightleftharpoons \mathscr{C}$ morphotype transitions. Clearly, the potential to perform the transitions from one morphotype to another in response to environmental conditions is available within the bacteria, as well as the capacity for "deciding" to go through the transition (although the "decision" can be a collective action of many bacteria in the colony).

Whether the mechanism is based on activation of cybernators (as is proposed in Refs. [22,33,37,54]), is "ordinary" epigenetics [69] phase variations [16], or another mechanism yet to be revealed, the important point is that it provides the colony with the potential to select the preferred morphotype according to the environmental conditions.

To emphasize the special nature of such morphotype transition, to distinguish it from ordinary reversible phenotypic adaptation and to draw upon the possible relations with adaptive mutagenesis, I refer to it as cooperative genomic adaptation. The advantage of the latter (over phenotypic adaptation) is probably with respect to more severe but less frequent changes in the environmental conditions, e.g. soft soil vs. hard soil in different seasons of the year. Indeed, the concept of time has a major role in the process of genomic adaptation, as will be discussed in Ref. [70].

The possession at present of the potential for genomic adaptation means that it had to be acquired by the genome sometime in the past during its course of evolutionary history. I refer to the above process of acquisition as genomic learning, to emphasize my assumption that it is not a result of Darwinian evolution. For the genome to perform learning in the sense of "learning from experience", the following requirements must

be fulfilled:

(1) Exposure of the bacteria to several cycles of alternating environmental conditions (e.g. wet and dry soil).

(2) Stored information about past environmental conditions.

(3) Self-information: information about past and present abilities of the genome.

(4) Means for the genome to recognize difficulties and formulate problems and for problem solving according to the collected and processed information, both about internal state and external conditions (including state of other bacteria).

(5) Cybernetic capacity: means for the genome to change itself according to solutions to problems. Ranging from reorganization and restructuring [19] (e.g. activation and deactivation of genes, replication of genes, moving genes, etc.) to actual interlacing of new sequences as we propose [70].

The acquisition of the potential for the $\mathscr{T} \rightleftharpoons \mathscr{C}$ morphotype transitions is only one out of many examples of genomic learning (see Ref. [70] for more examples). In all cases if genome learning is assumed, the above requirements must be fulfilled.

8. The genome as an adaptive cybernetic unit with self-awareness

Back in 1992 [22] we referred to our observations of complex colonial patterning as an example of adaptive self-organization, and proposed that "the genome can be viewed as an adaptive cybernetic unit". We have concluded that "along the above assumptions, the colony organization (being the environment) can directly affect the genetic metamorphosis of the individuals. Hence, we expect to observe synchronized, autocatalytic and cooperative genetic variations of the colony, either spontaneous or in response to imposed growth conditions".

In a follow-up publication submitted a year later [33], we suggested a possible mechanism based on the concept of cybernators to provide the singular feedback between the colony and the individual bacteria as I described in Section 6. The two publications (Refs. [22,33]) were primarily devoted to report our experimental observations, and the new picture remained somewhat fuzzy. Now, it is time to clarify things. I devote this section to elaborate on the new proposed picture of the genome, and I try to clarify what are the known facts and what are our new assumptions and conclusions.

As is described in Section 3, there is a vast amount of knowledge about the structure and functions of the extra-chromosomal elements in the genome. The introduction of the new terminology of cybernators is to emphasize the new interpretation of their role as part of the cybernetic capacity of the genome.

It is well known that the genome can change itself. We have proposed that the changes are neither random nor automatic but rather self-designed by the environment. Trivially, the ability to design changes requires computational capabilities. Indeed, Shapiro [19] proposed "...thinking of genomes as complex interactive information systems, in many ways comparable to those involving computers."

We have referred to the genome as an adaptive cybernetic unit [22,33] in order to emphasize that, in our view, it is beyond a universal Turing machine [71]. As I mentioned in the introduction, metaphorically speaking, the genome includes a user with a computational unit and a hardware engineer with a team of technicians for continuous design and implementation of changes in the hardware. Such a complex is beyond a universal Turing machine. In the latter, the structure is static and is decoupled from the input/output and the computation process. The genome is a dynamic entity. If its structure changes adaptively it does so according to the performed computations. It implies that the genome is capable of self-reference, has self-information and, most crucially, has self-awareness. The user represents the ability of the genome to recognize that it faces a difficulty (imposed by the environmental conditions), formulate the problem associated with the difficulty and initiate a search for its solution. As discussed in Section 7, the genome employs its past experience in the process. The user also represents the ability of the genome to interpret and assign meaning to the outcome of its computations and compare it with its interpretation of the environmental conditions.

It might seem that I have been carried away from facts to fantasy. So before going on I would like to emphasize that it is not necessarily so. We know that the genome can change itself, and in some cases we know that it is done purposely, in order to adapt to the environment. If we combine this information with the assumption that the acquisition of the potential for $\mathscr{T} \rightleftharpoons \mathscr{C}$ transformations is via genomic learning, it directly implies that the genome is an adaptive cybernetic unit with self-awareness (i.e. it has all the features described above).

To refer to the genome as being self-aware is a very strong statement with far-reaching implications. The issue will be presented in a forthcoming publication [70]. I briefly describe here the main points needed for this presentation. Our logic and mathematics are based on the notion of a set composed of elements. Implicitly, the set is closed and static, the elements have a fixed identity (it does not change due to the fact that they are part of the set) and they either do not have internal structure or, if they do, it is not relevant to the definition of the set. The set is defined by an external observer, i.e. it is not a result of self-assembly of the elements under a common goal. The elements, being passive and of no structure, do not have any information about the set. The definition of sets leads to logical paradoxes (Russel-type, like the famous barber paradox: a barber is a person who cuts the hair of every man who does not cut his own hair.) when we try to include a notion of self-reference. Russel and others have devoted much effort to construct formal axiomatic systems free of inherent logical paradoxes. Gödel's theorem [72,73] proved that they all have to be "incomplete", including the Principa Mathematica of Russell and Whitehead. It is important to emphasize that Gödel's theorem applies to closed systems which are also fixed in time. I propose that one has to take an entirely different approach and not start with the notion of sets of elements. I believe that here is exactly where the reductionist approach fails. We cannot reach self-awareness starting from passive elements, no matter how intricate is their assembly. I propose to replace elements by agents, that possess internal structure,

purpose and some level of self-interest, and whose identity is not fixed. The notion of a set is replaced by a cell, which refers to a collection of agents with a common goal and mutual dependence. It also implies that the system of agents is open, i.e. it exchanges energy and information with the environment. I argue that, in order for a cell of agents to be self-aware, it must have an advanced language, i.e. a language which permits self-reference to sentences and to its grammar. The language also enables the individual agents to have information about the entire system. In addition the cell has strong coupling with the environment. The "self" emerges through this coupling. There is no meaning of "self" in a closed system.

9. Gödel's theorem and the limitations of self-improvement

Gödel's theorem (paraphrased by Hofstadter into a more "digestible" form) states [73]:

> All consistent axiomatic formulations of the number theory include undecidable propositions.

The great achievement of Gödel was the connection of the idea of self-referential statements in language with number theory. Clearly, mathematical statements in number theory are about the properties of whole numbers, which by themselves are not statements, nor are their properties. However, Gödel had the insight that a statement of number theory could be about a statement of number theory (even about itself, i.e. self-reference).

For this, numbers should be mapped (one-to-one mapping) to statements, by a certain code, and Gödel has indeed constructed one. This coding trick enables statements of number theory to be understood on two different levels: (1) as statements of number theory; and (2) as statements about statements of number theory [73].

Using his code, Gödel teleported the Epimenides paradox ("This statement is false": true-false-true-...) into number theory in a version "This statement of number theory does not have any proof in the system of Principia Mathematica (or any fixed axiomatic system)". One implication of Gödel's theorem is that no fixed axiomatic system, no matter how complex, could even represent the complexity of the whole numbers. Gödel's theorem cannot be directly applied to the genome. One can do the same trick and map the DNA sequence either to the whole numbers or to statements in language. However, Gödel's theorem deals with infinite systems while the genome is finite [74,75].

To apply Gödel's theorem, another mapping should be considered – that performed in Nature. This is the mapping from DNA sequence to proteins. The proteins define a finite set of "words" in an infinite "language" [76]. Functional combinations of proteins are then sentences, and the interactions between them are the grammar. This picture might be supported by studies of correlations in DNA sequences and applications of Zipf's

tests [77,78]. Once we have an infinite language, Gödel's theorem can be applicable. To escape the limitations posed by the theorem, the sequence must change in time.

Let me elaborate on this point. The set of all possible environmental conditions poses an infinite number of problems which cannot be solved within any given language. Luckily, at a given instance of time the organism faces only a finite number of relevant problems. So there should be a version of the language which allows solutions to the current problems.

We have proposed that the genome is capable of performing self-designed genomic changes. Thus, at first it seems that assuming the genome to be an adaptive cybernetic unit with self-awareness is sufficient to explain evolution. This is not the case. A lemma extended from Gödel's theorem sets limitations on self-improvements (Ref. [70]). Simply put, it would state that "a system cannot self-design another system which is more advanced than itself" (this is in contradiction to the claim in Ref. [79]). Note that a system can be improved by successful accumulation of random changes but not in a self-designed manner.

In Section 10 I define two types of genomic changes – horizontal changes vs. vertical leaps. The individual genome is capable of performing the first kind, but not the second. Only a genomic network is capable of vertical leap, which are creative events.

10. Problems vs. paradoxes and horizontal genomic changes vs. vertical genomic leaps

It is customary to borrow ideas from the picture of evolution of organisms to describe the evolution of scientific theories. Here I engage in a reverse intellectual exercise. For reasons to be clarified below, I draw on the metaphor of the advancement of scientific ideas and propose to distinguish between two types of genetic changes. The identification is done according to the level of difficulties faced by the bacteria, the nature of the means required to cope with the difficulties and the type of genetic changes performed to cope with the difficulties.

Kuhn identifies two types of scientific progress – "normal science" and "scientific revolutions". Most scientific activities belong to the category of normal science. This proceeds by solving problems within a well-defined conceptual plane or within a given theoretical framework with specified "rules of the game". The problems are also formulated within the conceptual plane of the present paradigm. To the other category belong the rare events of scientific revolutions that transcend science from a given theoretical framework to a new one. Scientific revolutions are initiated when scientists encounter a paradox, that is a problem which cannot be solved within the conceptual boundaries of the current paradigm. To solve a paradox, a new paradigm must be created, with an enlarged conceptual space and new "rules". The paradox is both the motive to the event of the creation of a new paradigm and the conceptual gear connecting the old paradigm to the new one. The paradox itself becomes the core principle upon which the new theoretical framework is constructed.

What relevance does the above bear to genetic changes of real living organisms? Organisms face at times difficulties best characterized as problems, and at times ones that could only be regarded as paradoxes. By problem I mean here, a difficulty or existential hazard the solution to which can be obtained by using the tools at the disposal of the organism. A trivial example would be exposure to antibiotic for which the bacterium has a silent (inactive) gene that the bacterium must activate. Adaptive mutagenesis is another example of problem solving. The nature of the genetic changes performed to cope with these difficulties is such that an organism undergoing them may still be considered the same organism, though an improved one. So I propose to refer to changes resulted from "problem solving" as "horizontal genomic changes". I have in mind a picture of these changes as a trajectory on a plane defined by the organism, in analogy with "normal science" which is a trajectory on a plane defined by the paradigm.

At present I do not have a good definition for the plane of the organism, and must rely on intuition. In the future we intend to use Gödel's approach (Section 9) to reach a definition.

Genetic changes which move the organism a step higher on the evolutionary axis represent "vertical genomic leaps" which are transitions from one plane to another. In analogy to scientific revolutions, I expect the "vertical genomic leap" to be a solution to a paradox, not a problem. A paradox here would be a difficulty to which the genome cannot find a solution using its own tools, since the solution is a new genome which is more advanced in comparison to the original one. For example, I believe that the emergence of sporulating bacteria is a "vertical genomic leap". What paradox could have led to such a solution? Sporulation enables bacteria to survive otherwise lethal conditions. The "decision" to sporulate (which is reached collectively) is based on the prediction that conditions will become lethal. The need to learn from lethal conditions could have been the paradox that forced the bacteria to come up with a vertical leap in order to survive.

11. The colonial wisdom: genomic webs and emergence of creativity

According to the extension of Gödel's theorem, the genome can design and perform horizontal genomic changes but not vertical leaps involving paradox solving. Are we back to random mutations? Could it be that the simpler horizontal changes resulted from designed changes and the more relevant (for evolution) vertical leaps are the outcome of random mistakes? The dilemma is solved when we assume cooperative behavior.

Say, you would like to design a new, more advanced computer for a certain task. The best strategy would be to construct a network of computers to do the designing. Even though each individual computer is less advanced than the new computer, their network can, in principle, be superior to it. There exists a computer searcher for the ground states of spin glass where eight processors, due to their communication and their learning

from each other, solve the same problem in less than $\frac{1}{8}$ of the time a single processor needs (D. Stauffer, a private communication). Back to the bacteria. It is known that in a stressed colony, some of the bacteria become competent by rendering their membrane more permeable to genetic material, while other bacteria go through lysis: break open and deposit their genetic material in the media [16,15]. In addition, direct genetic connections between the bacteria are formed by means of conjugation or transduction [16,15]. We propose that these features indicate that the stressed colony turns into a genetic network, which is the highest level of colony cooperation. To emphasize that the network is composed of agents (each genome is by itself a cybernetic agent), I refer to it as a "genomic web". I further assume, that in order to establish the genomic web, the bacteria produce (or activate) special cybernators enhancing the efficient and sophisticated genomic communication. Once formed, the genomic web is a "super-mind" relative to the individual genome. Thus, a paradox for the genome is a solvable problem for the web. The web, being more complex than the individual genome, can design and construct a new and more advanced genome relative to the original ones, i.e. perform a vertical genomic leap. Such a leap is best described as a cooperative self-improvement or cooperative evolution.

The formation of a creative web is far from being trivial and requires very special environmental conditions. Not every assembly of agents leads to a more sophisticated entity. As we well know from daily experience, a committee composed of very intelligent individuals can be a fairly dumb entity. It depends on the balance between the agents' self-interest and their level of awareness of the new entity. In other words, the environmental conditions should be such that the individual bacteria will give up most of their awareness as individual entities [70].

In principle, the genome is capable of solving problems on its own, but it is more efficient to solve problems cooperatively. Hence, I expect that genomic webs are also employed for the task of problem solving. The harder the problem, the more advanced the genomic web formed. Indeed, as I mention in the introduction, we now have evidence that adaptive mutagenesis requires cooperation of the bacteria.

The picture of a creative genomic web is very appealing. Yet a nagging conceptual difficulty is left. We would expect the colonies of new bacteria which are the outcome of a vertical genomic leap to be more advanced than the colonies of the original bacteria. But, if we truly regard the colony as a multicellular organism, it will be in contradiction with the extension of Gödel's theorem; if we regard the colony as our system, it would imply that a system is capable of designing a system more advanced than itself. I believe that the colony of the new bacteria can only be improved relative to the original colonies, and not more complex. In order to keep the picture consistent, we have to assume that genetic communication between many colonies of the same bacteria, or a number of colonies of different bacteria, are required for the design of a vertical leap on the colonial level (we discuss this point in Ref. [70]).

12. Possible implication of the new picture and Darwinian evolution vs. Cooperative evolution

The new picture I have presented here has many potential implications, both practical and philosophical. For example, at present, the bacteria seem to be winning the war we fight against them with antibiotics, developing drug resistance as fast as we develop new drugs, or faster. In order to outsmart them, we must first realize how smart they are, and accordingly develop new strategies for treatment. If, as I claim, the strength of the bacteria lies in colonial communication and cooperation, then a way to go would be to blackout and jam their communication rather than (or along with) disable the individual bacteria [55].

All along, I was referring to bacterial colonies and drawing conclusions from observations of bacteria. However, I believe that the idea of the emergence of creative web under stress is universal. I believe that eukaryotes (single-cell organisms that their cells have a nucleus or multi-cell organisms) have not lost the option of genetic communication in the course of evolution from prokaryotes, and that under stress, colonies of single-cells eukaryotes establish genetic networks in very much the same way as bacteria do. Some initial hints, that this might be the case, are provided by observations of adaptive mutagenesis in yeast.

In multicellular eukaryotes I expect continuous exchange of genetic information between cells. There are fragments of knowledge which, put together, could support a picture of genetic communication in multicellular organisms. However, in the absence of a proper theory, some were discarded as meaningless and others were studied separately. They were never put together and considered as parts of one picture.

There are reports from the 1970s about circulating nucleic acids in higher organisms [80] and from the sixties and the seventies about released DNA segments from cells of eukaryotes [81–84]. These observations met with strong skepticism and, as they were not considered to be of any importance, have not been tested again.

It is known that cancer cells can emit genetic material which induces other cells to become cancerous. This is clearly a case of transfer of genetic information between cells. Another recently studied phenomenon that involves such transfers is the death of cells. It is known that the dying processes of cells are very complicated (programed cell death) and involve restructuring of the DNA into packed units which are deposited into the blood stream when the cell dies [85].

I assume genetic communication in multicellular organisms with the hope that in the future the fragments of knowledge can be collected to provide a solid proof.

If there is indeed genetic communication in eukaryotes, then the state of the eukaryote can directly affect genetic changes in its individual cells, in the same manner that the state of the colony affects genetic changes in the individual bacterium. I would like to emphasize that indeed macro to micro singular feedback should exist for efficient control. In this regard, I believe that there are cells specialized in producing cybernators. The latter affect germ cells, thus, providing a plausible mechanism for designed changes

in eukaryotes, changes brought about by the creative acts of genomic webs established within the organism.

A collection of eukaryotes can establish a web whose basic element is an individual eukaryote. Any means of communication between the organisms, if it is capable of affecting the state of the organism, indirectly affects the genetic level of each one. Hence, a genetic web of eukaryotes can be formed.

I expect strong coupling between the genetic webs of different species which are functionally coupled. This coupling will cause induction of genetic changes from one web to another which can provide a plausible mechanism for the observed avalanche effects in evolution [86].

To conclude, I hope I was successful in convincing the reader that Vitalism is not the only alternative to Darwinism. I propose a new option, that of cooperative evolution based on the formation of creative webs. The emergence of the new picture involves a shift from the pure reductionistic point of view to a rational holistic one, in which creativity is well within the realm of Natural sciences.

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References

[1] S. Rose, The Conscious Brain, Vintage Books, New York, 1976.
[2] R. Dawkins, The Extended Phenotype, Freeman, Oxford, 1972.
[3] R. Dawkins, The Selfish Gene, Oxford University Press, Oxford, 1976.
[4] S.J. Gould, Ever Since Darwin, Norton, New York, 1977.
[5] R. Dawkins, The Blind Watchmaker, Norton, New York, 1986.
[6] S. Kauffman, At Home in the Universe, Oxford University Press, New York, 1995.
[7] R. Wesson, Beyond Natural Selection, The MIT Press, London, 1993.
[8] H. Bergson, Creative Evolution, Macmillan, London, 1911.
[9] S.E. Luria, M. Delbrück, Mutations of bacteria from virus sensitivity to virus resistance, Genetics 28 (1943) 491–511.

[10] R. Penrose, Shadows of The Mind, Oxford University Press, Oxford, 1994.
[11] C. Darwin, The Origin Of Species, 1859, "I have hitherto sometimes spoken as if the variations ... were due to chance. This, of course, is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the cause of each particular variation. ... [The facts] lead to the conclusion that variability is generally related to the conditions of life to which each species has been exposed during several successive generations", ch. V.
[12] M. Delbrück, Heredity and variations in microorganisms, Cold Spring Harbor Symp. Quant. Biol. 11 (1946) 154.
[13] E. Schroedinger, What is Life, Cambridge University Press, Cambridge, 1944.
[14] M. Delbrück, Mind from Matter?, Blackwell Scientific Publishing, Oxford, 1986.
[15] F. Joset, J. Guespin-Michel, Prokaryotic Genetics, Blackwell Scientific Publishing, London, 1993.
[16] R.C. King, W.D. Stanfield, A Dictionary of Genetics, Oxford University Press, Oxford, 4th ed., 1990.
[17] F. Jacob, The Logic of Life, A History of Heredity, Princeton University Press, Princeton, 1993.
[18] E.F. Keller, A Feeling for The Organism: The Life and Work of Barbara McClintock, Freeman, San-Francisco, 1983.
[19] J.A. Shapiro, Natural genetic engineering in evolution, Genetica 86 (1992) 99–111.
[20] F.J. Ryan, L.K. Wainwright, Nuclear segregation and the growth of clones of spontaneous mutants of bacteria, J. Gen. Microbiol. 11 (1954) 364–379.
[21] J.A. Shapiro, Observations on the formation of clones containing *arab − lacz* cistron fusions, Mol. Gen. Genet. 194 (1984) 79–90.
[22] E. Ben-Jacob, H. Shmueli, O. Shochet, A. Tenenbaum, Adaptive self-organization during growth of bacterial colonies, Physica A 187 (1992) 378–424.
[23] J. Cairns, J. Overbaugh, S. Miller, The origin of mutants, Nature 335 (1988) 142–145.
[24] P.L. Foster, Adaptive mutation: The uses of adversity, Annu. Rev. Microbiol. 47 (1993) 467–504.
[25] B.G. Hall, Adaptive evolution that requires multiple spontaneous mutations. i. mutations involving an insertion sequence, Genetics 120 (1988) 887–897.
[26] B.G. Hall, Adaptive evolution that requires multiple spontaneous mutations: mutations involving base substitutions, Proc. Natl. Acad. Sci. USA 88 (1991) 5882–5886.
[27] T. Galitski, J.R. Roth, Evidence that *f* plasmid transfer replication underlies apparent adaptive mutation, Science 268 (1995) 421–423.
[28] J.P. Rasicella, P.U. Park, M.S. Fox, Adaptive mutation in *Esherichia coli*: a role for conjugation, Science 268 (1995) 418–420.
[29] B. Dixson, Power Unseen, Freeman, New York, 1994.
[30] E. Ben-Jacob, I. Cohen, A. Czirók, Smart bacterial colonies, in: Physics of biological systems: from molecules to species, Lecture Notes in Physics, Springer, Berlin, 1997, pp. 307–324.
[31] E. Ben-Jacob, I. Cohen, A. Czirók, Smart bacterial colonies: from complex patterns to cooperative evolution, Fractals 1997, in press.
[32] J.A. Shapiro, Bacteria as multicellular organisms, Sci. Am. 258(6) (1988) 62–69.
[33] E. Ben-Jacob, A. Tenenbaum, O. Shochet, O. Avidan, Holotransformations of bacterial colonies and genome cybernetics, Physica A 202 (1994) 1–47.
[34] E. Ben-Jacob, O. Shochet, A. Tenenbaum, I. Cohen, A. Czirók, T. Vicsek, Communication, regulation and control during complex patterning of bacterial colonies, Fractals 2(1) (1994) 15–44.
[35] J.A. Shapiro, The significances of bacterial colony patterns, BioEssays 17(7) (1995) 597–607.
[36] E. Ben-Jacob, I. Cohen, O. Shochet, I. Aranson, H. Levine, L. Tsimring, Complex bacterial patterns, Nature 373 (1995) 566–567.
[37] E. Ben-Jacob, O. Shochet, I. Cohen, A. Tenenbaum, A. Czirók, T. Vicsek, Cooperative strategies in formation of complex bacterial patterns, Fractals 3 (1995) 849–868.
[38] J.A. Shapiro, M. Dworkin, editors, Bacteria as Multicellular Organisms, Oxford University Press, New York, 1997.
[39] E. Ben-Jacob, I. Cohen, A. Czirók, T. Vicsek, D.L. Gutnick, Chemomodulation of cellular movement, collective formation of vortices by swarming bacteria, and colonial development, Physica A 1997, in press.
[40] R. Losick, D. Kaiser, Why and how bacteria communicate, Sci. Am. February 1997.
[41] D.A. Kessler, J. Koplik, H. Levine, Pattern selection in fingered growth phenomena, Adv. Phys. 37 (1988) 255.

[42] J.S. Langer, Dendrites, viscous fingering, and the theory of pattern formation, Science 243 (1989) 1150–1154.
[43] E. Ben-Jacob, P. Garik, The formation of patterns in non-equilibrium growth, Nature 343 (1990) 523–530.
[44] E. Ben-Jacob, From snowflake formation to the growth of bacterial colonies, part I: Diffusive patterning in non-living systems, Contemp. Phys. 34 (1993) 247–273.
[45] E. Ben-Jacob, From snowflake formation to the growth of bacterial colonies, part II: Cooperative formation of complex colonial patterns, Contemp. Phys. 38 (1997) 205.
[46] H. Fujikawa, M. Matsushita, Fractal growth of *Bacillus subtilis* on agar plates, J. Phys. Soc. Japan 58 (1989) 3875–3878.
[47] M. Matsushita, H. Fujikawa, Diffusion-limited growth in bacterial colony formation, Physica A 168 (1990) 498–506.
[48] H. Fujikawa, M. Matsushita, Bacterial fractal growth in the concentration field of nutrient, J. Phys. Soc. Japan 60 (1991) 88–94.
[49] T. Matsuyama, M. Matsushita, Fractal morphogenesis by a bacterial cell population, Crit. Rev. Microbiol. 19 (1993) 117–135.
[50] T. Matsuyama, R.M. Harshey, M. Matsushita, Self-similar colony morphogenesis by bacteria as the experimental model of fractal growth by a cell population, Fractals 1 (3) (1993) 302–311.
[51] E. Ben-Jacob, O. Shochet, A. Tenenbaum, I. Cohen, A. Czirók, T.Vicsek, Generic modeling of cooperative growth patterns in bacterial colonies, Nature 368 (1994) 46–49.
[52] E. Ben-Jacob, I. Cohen, O. Shochet, A. Czirók, T. Vicsek, Cooperative formation of chiral patterns during growth of bacterial colonies, Phys. Rev. Lett. 75 (15) (1995) 2899–2902.
[53] A. Czirók, E. Ben-Jacob, I. Cohen, T. Vicsek, Formation of complex bacterial colonies via self-generated vortices, Phys. Rev. E 54 (1996) 1791–1801.
[54] E. Ben-Jacob, I. Cohen, Cooperative formation of bacterial patterns, in: J.A. Shapiro, M. Dworkin (Eds.), Bacteria as Multicellular Organisms, Oxford University Press, New York, 1997, pp. 394–416.
[55] E. Ben-Jacob, I. Cohen, D.L. Gutnick, Cooperative organization of bacterial colonies: from genotype to morphotype, Ann. Rev. Microbiol. 1997, in press.
[56] E. Ben-Jacob, I. Cohen, D.L. Gutnick, Adaptive self-organization and colonial pattern formation, Comments Mol. Cell. Biophys. 1997, in press.
[57] E. Ben-Jacob, O. Shochet, A. Tenenbaum, Bakterien schließen sich zu bizarren formationen zusammen. in: A. Deutsch (Ed.), Muster des Ledendigen: Faszination inher Entstehung und Simulation, Vieweg, Braukschweig, 1994.
[58] E. Ben-Jacob, I. Cohen, Adaptive self-organization of bacterial colonies, in: F. Schweitzer (Ed.), Self-Organization of Complex Structures: From Individual to Collective Dynamics, Gordon and Breach, London, 1997, pp. 243–256.
[59] N.H. Mendelson, Helical Bacillus subtilis macrofibers: morphogenesis of a bacterial multicellular macroorganism, Proc. Natl. Acad. Sci. USA, 75 (5) (1978) 2478–2482.
[60] P. Devreotes, *Dictyostelium discoideum*: a model system for cell–cell interactions in development, Science 245 (1989) 1054–1058.
[61] T. Matsuyama, K. Kaneda, Y. Nakagawa, K. Isa, H. Hara-Hotta, I. Yano, A novel extracellular cyclic lipopeptide which promotes flagellum-dependent and -independent spreading growth of *serratia marcescens*, J. Bacteriol. 174 (1992) 1769–1776.
[62] R.M. Harshey, Bees aren't the only ones: swarming in gram-negative bacteria, Mol. Microbiol. 13 (1994) 389–394.
[63] W.C. Fuqua, S.C. Winans, E.P. Greenberg, Quorum sensing in bacteria: the luxr-luxi family of cell density-responsive transcriptional regulators, J. Bacteriol. 176 (1994) 269–275.
[64] A. Latifi, M.K. Winson, M. Foglino, B.W. Bycroft, G.S. Stewart, A. Lazdunski, P. Williams, Multiple homologues of luxr and luxi control expression of virulence determinants secondary metabolites through quorum sensing in *pseudomonas aeruginosa pao1*, Mol. Microbiol. 17 (1995) 333–343.
[65] E.O. Budrene, H.C. Berg, Complex patterns formed by motile cells of *escherichia coli*, Nature 349 (1991) 630–633.
[66] Y. Blat, M. Eisenbach, Tar-dependent and -independent pattern formation by *Salmonella typhimurium*, J. Bac. 177(7) (1995) 1683–1691.
[67] E.O. Budrene, H.C. Berg, Dynamics of formation of symmetrical patterns by chemotactic bacteria, Nature 376 (1995) 49–53.

[68] This terminology was suggested by D. Gutnick, personal communication.
[69] E. Jablonka, M.J. Lamb, Epigenetic Inheritance and Evolution, Oxford University Press, Oxford, 1995.
[70] E. Ben-Jacob, I. Cohen, A. Tenenbaum, Paradoxes as the origin of cooperative self-improvement in creative evolution, unpublished.
[71] H.T. Siegelmann, Computation beyond the turing machine, Science 268 (1995) 545–548.
[72] K. Gödel, On Formally Undecidable Propositions, Basic Books, New York, 1962.
[73] D.R. Hofstadter, Gödel, Escher, Bach: an eternal golden braid, Basic Books, New York, 1979.
[74] G. Stent, Explicit and implicit semantic content of the genetic information, in: Proc. 4th Int. Conf. on The Unity of Sciences, New York, 1975.
[75] G. Steiner, After Babel: Aspects of Language and Translation, Oxford University Press, New York, 1975.
[76] S. Jones, The Language of The Genes, Flaming, Glasgow, 1993.
[77] C.K. Peng, S. Buldyrev, A. Goldberger, S. Havlin, F. Sciortino, M. Simons, H.E. Stanley, Long-range correlations in nucleotide sequences, Nature 356 (1992) 168–171.
[78] A. Czirók, R.N. Mantegna, S. Havlin, H.E. Stanley, Correlations in binary sequences and generalized zipf analysis, Phys. Rev. E 52 (1995) 446–452.
[79] R. Laing, Artifial organisms: history, problems, directions, in: C. Langton (Ed.), Artificial Life, Addison-Wesley, New York, 1989, pp. 49–61.
[80] M. Stroun, P. Anker, P. Maurice, P.B. Gahan, Circulating nucleic acids in higher organisms, Int. Rev. Cyto. 51 (1977) 1–48.
[81] L. Ledoux (Ed.), Informative Molecules in Biological Systems, North-Holland, Amsterdam, 1971.
[82] A. Bendich, T. Wilczok, E. Borenffreund, Science 148 (1965) 374.
[83] R.A. Roosa, E. Bailey, J. Cell Physiol. 75 (1970) 137.
[84] B.L. Reid, P.M. Blackwell, Aust. J. Med. Technol. 2 (1970) 44.
[85] R.C. Duke, D.M. Ojcius, J.D. Young, Cell suicide in health and disease, Sci. Am. Dec. (1996) 48.
[86] E. Szathmary, J. Maynard Smith, The major evolutionary transitions, Nature 374 (1995) 227–232.