Libertas Academica
FREEDOM TO RESEARCH

PERSPECTIVE

Global Consensus Theorem and Self-Organized Criticality: Unifying Principles for Understanding Self-Organization, Swarm Intelligence and Mechanisms of Carcinogenesis

Simon Rosenfeld

NIH, National Cancer Institute, Rockville, Maryland, USA. Corresponding author email: sr212a@nih.gov

Abstract: Complex biological systems manifest a large variety of emergent phenomena among which prominent roles belong to self-organization and swarm intelligence. Generally, each level in a biological hierarchy possesses its own systemic properties and requires its own way of observation, conceptualization, and modeling. In this work, an attempt is made to outline general guiding principles in exploration of a wide range of seemingly dissimilar phenomena observed in large communities of individuals devoid of any personal intelligence and interacting with each other through simple stimulus-response rules. Mathematically, these guiding principles are well captured by the Global Consensus Theorem (GCT) equally applicable to neural networks and to Lotka-Volterra population dynamics. Universality of the mechanistic principles outlined by GCT allows for a unified approach to such diverse systems as biological networks, communities of social insects, robotic communities, microbial communities, communities of somatic cells, social networks and many other systems. Another cluster of universal laws governing the self-organization in large communities of locally interacting individuals is built around the principle of self-organized criticality (SOC). The GCT and SOC, separately or in combination, provide a conceptual basis for understanding the phenomena of self-organization occurring in large communities without involvement of a supervisory authority, without system-wide informational infrastructure, and without mapping of general plan of action onto cognitive/behavioral faculties of its individual members. Cancer onset and proliferation serves as an important example of application of these conceptual approaches. In this paper, the point of view is put forward that apparently irreconcilable contradictions between two opposing theories of carcinogenesis, that is, the Somatic Mutation Theory and the Tissue Organization Field Theory, may be resolved using the systemic approaches provided by GST and SOC.

Keywords: nonlinear dynamics, global consensus theorem, swarm intelligence, self-organized criticality, Lotka-Volterra population dynamics, neural networks, biomolecular networks, carcinogenesis, darwinian evolution

Introduction

In the Darwinian view of evolution, the phenomenon of life is painted in dramatic colors of struggle for survival encompassing all the levels of organic existence. It is taken as a self-evident postulate that any participant of this struggle values its life as the most precious commodity, and from this fundamental premise the motivation for survival originates. In this epic battlefield, the fittest is expected to have better chances for transferring the beneficial traits to progeny. A loser dies soon and has less chance to perpetuate its lineage. Evolution is considered as a drift towards perfection resulting from myriads of elemental steps in this incessant warfare. Complex combinations of individualistic and mutualistic tendencies within and among the populations lead to the emergence of various forms of self-organization such as collective self-defense, decision-making, and quorum sensing. Swarm intelligence of social insects and microbial colonies vividly demonstrate how far the evolution may progress having at its disposal only simple rules of interaction between unsophisticated individuals.[1,2] On the other hand, in large communities of interacting units, a variety of dynamic patterns may occur which may hardly be regarded as a progress towards more orderly behavior, let alone any sort of perfection. Among examples of the kind, one may find various forms of oscillations, chaotic dynamics and self-destruction.[3] Complexity of the phenomena frequently occurring in even comparatively simple systems, intricate dependencies on system's and environmental parameters require formulation of the problem in well-defined, self-consistent mathematical terms. The Lotka-Volterra model,[4,5] being among the first models of the kind, shows how complex may be the behaviors of even a simple food web consisting of only one predator and one prey. The repertoire of behaviors of multispecies populations is virtually unlimited. Century-long development of population dynamics revealed many forms of self-organization naturally occurring in these systems. In particular, it has been demonstrated that swarm intelligence may originate from rather mundane reasons rooted in simple rules of interactions between these entities, living or not.

Because of tight links to the Lotka-Volterra family of models, the systems of ordinary differential equations with quadratic nonlinearities are traditionally referred to as equations of population dynamics. The equations themselves though have been studied long before the Lotka's and Volterra's discoveries, and have a wide range of applications in other disciplines far beyond the originally biological context.[6–8] Similarities in mathematical description of these dissimilar processes suggest the idea that the phenomena of self-organization observed in one of these systems is likely to have counterparts in other systems, with the reasons for their occurrence being purely mechanistic and devoid of any Darwinian connotations of struggle for survival. The primary goal of this paper is to provide a review of properties of the multidimensional nonlinear systems having the potential of producing the phenomenon of self-organized behavior and manifesting themselves as *swarm intelligence*.

The Lotka-Volterra Systems (LVS) and neural networks (NN), along with the S-Systems,[9–11] belong to a wider class of nonlinear dynamical systems which are called *competitive networks*. All the aforementioned mathematical models are analytically transformable to each other[12] and well suited for describing the organizationally complex systems.[13,14] Global Consensus Theorem (GCT) discussed in subsequent sections is an all-encompassing conjecture pertaining to asymptotic stability of these systems. Generality and universality of the GCT provide a mathematically rigorous foundation for describing the behaviors of wide class of multidimensional systems, whether in animate or inanimate realms.

The simplicity of building blocks and universality of elementary rules governing evolution towards self-organization and swarm intelligence allow a for a unified vision of such diverse systems as biological networks, communities of insects, stock markets, robotic communities, social networks, microbial communities, communities of somatic cells, and many other systems. In particular, the community of cancer cells satisfies all the general principles outlined above. Empirically established and well documented phenomena of biological robustness, acquired chemoresistance, adaptivity and quorum sensing suggest the idea that the communities of cancer cells may be seen as a superorganism possessing all the essential features of swarm intelligence.[15]

Another realm of very simple mechanistic rules leading to very complex behaviors is known under the name of Self-Organized Criticality (SOC).

As an example of the application of SOC, in this paper a novel point of view is put forward that apparently irreconcilable contradictions between two opposing theories of carcinogenesis, that is, the Somatic Mutation Theory (SMT) and the Tissue Organization Field Theory (TOFT), may be resolved using the systemic approaches provided by SOC.

Swarm Intelligence: Definitions, and Manifestations

By definition, swarm intelligence is "the organized behavior of large communities without global organizer and without mapping the global behavior onto the cognitive/behavioral abilities of the individual members of the community".[2] It should be emphasized that what is called here communities are not necessarily the communities of living entities like bee hives, or ant hills, or microbial colonies. Moreover, the complexity of collective behavior of the community as a whole does not require its individual members to have any extensive analytical tools or even memory on their own. As will be discussed at length later in this paper, the key prerequisite for the possibility of community-wide self-organization is that individual members may interact following the stimulus-response rules. According to commonly accepted language, these members are called unsophisticated (or dumb) individuals.[16] The channels of communication (stimuli), as well as the physical reactions to them (responses), may be simple or complex, but the individual memories and analytical capabilities of members may not reflect anything beyond individual experiences. Large-scale community-wide behaviors and self-organized modalities are completely determined by these low-level rules of local interactions.

There are a number of closely related but distinctly different aspects of swarm intelligence. These are collective memory, adaptivity, division of labor, cooperation, sensing of environment (also known as stigmergy), and quorum sensing. All these aspects are the emergent properties resulting from local member-to-member interactions without a general plan of action, without a supervisory authority, and without a system-wide information infrastructure. From the mathematical standpoint, a large system of locally interacting units is a dynamic network governed by the laws of nonlinear dynamics. The following

question, therefore, is in order: what exactly are the laws of local interactions leading to the emergence of complex behaviors which are referred to as swarm intelligence?

Swarm Intelligence of Natural and Artificial Neural Networks

We begin our survey of relevant facts with a comparatively simple, and abundantly well studied, case of the systems known as neural networks (NN); for a background of biological origins, terminology, and a historical perspective, see.[17,18] NN functionality originates from and closely mimics the neuronal networks constituting the nervous systems of higher organisms populating the Earth. In mathematical terms, NN is a multidimensional nonlinear function, $\mathbf{F(x)}$, constructed as follows. Let $\mathbf{x}$ be an N-dimensional input vector serving as an argument, and $\boldsymbol{\alpha} + \mathbf{Wx}$ be a linear transformation of $\mathbf{x}$ with $\boldsymbol{\alpha}^{(M)}$ being a vector of biases, and $\mathbf{W}^{(N*M)}$ being a matrix of input weights. Let $\sigma(z)$ be a univariate function with $d\sigma/dz > 0$, which in NN terminology is usually referred to as an activation function. We introduce a set of nonlinear transformations $\mathbf{z} = \sigma\,(\boldsymbol{\alpha} + \mathbf{Wx})$, which are traditionally seen as belonging to the hidden layer of NN; M and $\mathbf{z}^{(M)}$ are said to be the number of neurons and the vector of outputs of the hidden layer, respectively. Finally, we perform a linear transformation $\mathbf{y} = \mathbf{Uz}$ with $\mathbf{U}^{(L*M)}$ being the matrix of output weights and vector $\mathbf{y}^{(L)}$ being the output of NN. Thus, in the component-wise notation, $\mathbf{y} = \mathbf{F(x)}$ means

$$y_k = \sum_{j=1}^{M} U_{k,j}\,\sigma\!\left(\alpha_j + \sum_{i=1}^{N} W_{j,i} x_i\right),\ k = 1, \ldots, L \quad (1)$$

As is well known, a fundamental property of NNs is that they are the *universal approximators*; that is, given a sufficiently large dimension of the hidden layer, an NN may approximate, per appropriate adjustment of parameters, any smooth multidimensional nonlinear function with any prescribed accuracy.[19] The core NN structure (1) may be extended in many directions. In particular, the function $\mathbf{F}$ may be applied iteratively, thus producing the NNs with two or more hidden layers. It is also possible to connect the input and output layers

directly thus bypassing the nonlinear transformation produced by the hidden layer

$$y_k = \sum_{j=1}^{N} V_{k,j} x_j + \sum_{j=1}^{M} U_{k,j} \sigma\left(\alpha_j + \sum_{i=1}^{N} W_{j,i} x_i\right), \, k = 1, \ldots, L \tag{2}$$

where $V^{(L*N)}$ is the shortcut matrix.

Among the analytical tools collectively known as artificial intelligence, NNs retain the leading positions in a variety of computational tasks; among them are pattern recognition and classification, short- and long-term storage of information, prediction and decision-making, optimization, and other. It is beyond the scope of this paper to elucidate all the numerous aspects of the artificial intelligence of NN; comprehensive reviews may be found in.[18,20] Our goal here is different: we would like to highlight a tight analogy between the properties of NN and those of a large community of identical simple-minded (dumb) individuals devoid of any personal intelligence. All of the aforementioned intelligent tasks being solved by the NN as a whole are performed through the learning/training process, which consists in specializing the parameters α, U, V. These parameters quantify the signal transduction within the NN. Notably, the units in the hidden layer (neurons) remain unchanged by learning or training; they are capable of only one operation governed by a simple rule of transformation: given an input signal, (stimulus), z, they produce an output signal (response), $\sigma(z)$. The internal mechanism of the neurons does not allow them to have any impression of the environment or general structure of the NN. In this sense, they are *dumb* individuals. Each element in the input layer, x_i, represents a certain aspect of the environment, and neurons process some integral visions of them, that is, $(\alpha + \mathbf{W}\mathbf{x})$. Output signals, y_k, represent the *solution* of the problem, that is, the integral reaction of the NN to the totality of environmental stimuli.

Obviously, the above outlined organization is not something that may be implemented only as a computational procedure. In principle, any ensemble of individual units acting in accordance with stimulus-response rules, (eg, electronic circuits, robots, insects, cells) may be organized into a structure similar to NN. By the very logic of the NN paradigm, these communities of individual units may possess similar intelligent capabilities *as a whole* without being intelligent by themselves. The best examples of the kind are the biological neural (ie, neuronal) networks.

Cognitive/analytical capabilities of NN may be grossly amplified if instead of univariate activation, $z = \sigma(x)$, a more sophisticated algorithm is employed. In such an enhanced NN, internal mechanics of ith neuron may be described by the system of nonlinear differential equations

$$dz_{i,j}/dt = \sigma_i\left(\alpha_{ij} + \sum_{n=1}^{N} W_{n,j,i} x_{n,i}\right), \tag{3}$$

where $\{\sigma_i\}$ is the set of neuron-specific activation functions, $\{x_n\}_i$ is a batch of signals transmitted by the ith element of the input layer, and $\{z_i\}_j$ is a batch of output signals. In engineering, this type of NN is known as cellular neural network (CNN). In the CNNs, the neuron's output is no longer a static signal; depending on the parameters in (3), a neuron may generate delays, periodic oscillations and chaotic dynamics. It is worth noting, however, that the more complex neuron's functioning in the CNN still belongs to the realm of stimulus-response rules; the difference with ordinary NNs is that neurons in CNNs are capable of receiving multichannel stimuli and producing multichannel delayed responses. Therefore, similar to those in NN, these more sophisticated neurons should still be regarded as *dumb individuals*, although with a much more elaborate internal organization. Since their discovery in 1988,[21] it has been expressly demonstrated that CNNs are highly efficient in solving a variety of complex problems in artificial intelligence such as pattern recognition, image analysis, multiple parallel computation, and others. In particular, it has been proven that CNN consisting of n cells may store up to 2^n stable memory patterns,[22] which is an enormously large number even for a CNN of modest size. In biological world, a close analogy to CNN are the networks of somatic cells (as the very name of CNN would suggest). In fact, the biological cells are even more powerful signal-processing machines; each somatic cell is embedded in the extracellular matrix and communicates with its neighbors through numerous signal transduction pathways. A cell does not process each signal individually; instead, it reacts to the totality of signals as a whole by modification of its internal states (eg, metabolic and gene expression profiles). Therefore, it would not be a big leap of imagination to hypothesize that a community of somatic cells as a whole can

possess the problem-solving skills, collective memory, and other faculties of swarm intelligence, at least at the level of sophistication comparable to CNNs in engineering. Neuronal cells of nervous systems are not unique in these capabilities.

Due to the fundamental property of being universal approximators, the NNs are capable, in principle, of representing any nonlinear dynamical system. Let **G** be a dynamical system governed by the equation $d\mathbf{x}/dt = \mathbf{F}(\mathbf{x}|\theta)$, where $\mathbf{x}^{(N)}(t)$ is the time-dependent vector of states, $\mathbf{F}^{(N)}(\bullet)$ is a multidimensional nonlinear vector-function, and $\theta^{(L)}$ is the set of system's parameters. In particular, function **F** may be structured in accordance with (2)

$$\frac{d\mathbf{x}}{dt} = \mathbf{V}\mathbf{x} + \mathbf{U}\sigma(\alpha + \mathbf{W}\mathbf{x}) \qquad (4)$$

These systems are usually referred to as dynamic NNs. An important subclass of these systems is the one in which matrix **V** is diagonal with all the diagonal elements being negative, $V_{i,j} = -\lambda_i \delta_{ij}$. In this case, the dynamic NNs are called *competitive*. Competition between natural extinction presented by the first term in (4) is dynamically balanced with reproduction presented by the second term. Dynamic equilibrium between these two tendencies, if it does exist, may produce very complex behaviors. In particular, the system may possess a number of asymptotically stable attractors. This means that starting with a large variety of initial conditions belonging to a certain basin of attraction, the system may evolve towards one of the several well-defined stable manifolds. This process is in fact nothing other than *classification* of initial states, which occurs in the system without any organizational force or supervisory authority. To this end, the next key question to ponder is whether or not a system of class (4) has asymptotically stable attractors and what the structures of these attractors can be. This question has been extensively studied within a wide class of dynamical systems which are discussed in the following sections.

Competition, Decision, and Consensus in Multispecies Lotka-Volterra Systems

The Lotka-Volterra System (LVS) is a large class of dynamical systems described by the ordinary differential equation with quadratic nonlinearities.[23]

$$\frac{dx_i}{dt} = \lambda_i x_i + \sum_{k=1}^{N} \alpha_{ik} x_i x_k, \, i = 1, \ldots, N \qquad (5)$$

Comparing (5) and (4), one may notice that LVS is similar to NN in which the activation function is selected to be linear. Originally inspired by ecology and population dynamics, the LVS theory largely retains their flavors and terminology. In particular, $\{x_i\}$ are assumed to be the population levels of corresponding species, $\{X_i\}$; the coefficients $\{\lambda_i\}$ describe the rates of reproduction or extinction, and matrix α_{ik} describes interaction between the species. An LVS system is considered competitive if $\alpha_{ik} < 0$ and cooperative if $\alpha_{ik} > 0$ (see[24] for a more elaborate classification). In order to avoid direct ecological connotations, the entities $\{X_i\}$ are often called quasi-species thus emphasizing that the nature of these species is of secondary importance; all the systems described by equation (5), whether belonging to biological, physical, technological, social, or financial realms, will have similar dynamic behaviors and analogous emergent properties.

A fundamental question pertaining to competitive LVS is the question of stability. In the context of population dynamics, stability means that, despite the fact that all the species are struggling with each other, they may nevertheless come to some sort of peaceful coexistence or consensus regarding the distribution of limited resources. Since nothing except the pairwise interactions is included in LVS dynamics, this consensus cannot be a result of collective decision-making or planning. The challenge and fundamental importance of the question of stability have been articulated by Grossberg:
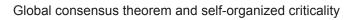
> "The following problem, in one form or another, has intrigued philosophers and scientists for hundred of years: How do arbitrarily many individuals, populations, or states, each obeying unique and personal laws, ever succeed in harmoniously interacting with each other to form some sort of stable society, or collective mode of behavior? Otherwise expressed, if each individual obeys complex laws, and is ignorant of other individuals except via locally received signals, how is social chaos averted? How can local ignorance and global order, or consensus, be reconciled? … What design constrains must be imposed on a system of competing populations in order that it be able to generate a global limiting pattern, or decision, in response to arbitrary initial data? … How complicated can a system be and still generate order?"[25]

The questions outlined above have been successfully resolved within a wide class of nonlinear dynamical systems introduced by the equation:

$$\frac{dx_i}{dt} = a_i(\boldsymbol{x})\left[b_i(x_i) - c(\boldsymbol{x})\right], \ i = 1, \ldots, N, \quad (6)$$

where $\{a_i\}$ and $\{b_i\}$ are smooth non-negative functions; $c(\boldsymbol{x})$ is a scalar function satisfying the *condition of competition* $\partial c / \partial x_i \geq 0$. This condition basically says that resistance to growth increases when individual population levels increase (see[25] for mathematically rigorous definitions). Equation (6) is very general and includes as particular cases both the Lotka-Volterra and Neural Networks dynamics. The fundamental *Global Consensus Theorem* (GCT), proved by Grossberg in a series of publications,[25–28] claims that for any initial conditions $\{x_i(0) > 0\}$ the system (6) generates an asymptotic pattern, or *decision*, $\{0 \leq x_i(\infty) < \infty\}$. It has also been shown that the system (6) may have multiple distinct asymptotic limits with well-defined dependence of stable patterns, $\{x_i(\infty)\}$, on the initial conditions, $\{x_i(0)\}$; this property is known as *multistability*. The importance of the GST cannot be exaggerated; it indicates that an autonomous (ie, devoid of any external influence or supervision) dynamic NN, being presented with some sort of fuzzy initial pattern, $\{x_i(0)\}$, will move towards a well-defined asymptotic state, $\{x_i(\infty)\}$, thus *recognizing* this pattern. Implications of the GCT are far reaching. In essence, it claims that the tendency to self-organization is rooted in a fairly simple nature of things: any complex system whose unstoppable growth is inhibited by progressively dwindling resources will end up with some sort of self-structuring and consensus regarding the distribution of resources. Generality and simplicity of the dynamics (6) guarantee its applicability to a very wide class of natural and societal phenomena. According to (6), the sequence of events constituting a transition from arbitrary initial conditions towards stable well-defined asymptotic patterns may be envisioned as follows. Let us imagine that population level x_i of a certain quasi-species X_i began to grow uncontrollably. Due to the condition of competition mentioned above, such growth will speed up extinction of X_i giving the way to other species, $X_{j \neq i}$. Transition from the dominance of one quasi-species

to another may appear as a struggle for survival, and it is indeed an existential struggle in the predator-prey food chains. Although the metaphor of struggle for survival is widely used beyond the world of living entities, it is obvious from the GCT perspective that the reasons for competitive dynamics leading to consensus may be much simpler and may have nothing to do with personal motivation of a living entity to survive. In this context, it is not out of place to recall that the co-founder of LVS, Alfred Lotka, pointed out that natural selection should be approached more like a physical principle subject to treatment by the methods of statistical mechanics, rather than as struggle of living creatures motivated by the desire to survive.[29] This premise is extremely important for understanding self-organization on cellular and subcellular levels. The cell is often seen as the smallest unit that is classified as a living thing.[30] This is because the cell is lavishly equipped with the mechanisms for maintaining its homeostasis in the face of a wide range of threats and adverse factors. Astounding complexity of the cell's internal organization and observable behaviors have led some authors even beyond the notion that the cell is simply a living entity; they claim that the cell possesses it own intelligence[31] and psychology.[32] Even without going to such extremes, it is legitimate to ask: does the cell has a *motivation* for maintaining its homeostasis or, stated differently, does it *struggle* for its own survival? Let us accept for a moment that this conjecture is true. How then should one deal with the intracellular mechanics? Tremendous complexity of even a singular act of gene expression[33,34] may lead, by induction, to the hypothesis that a gene is also a living entity and it *struggles* for successful protein production. Obviously, even such an audacious leap of imagination would not be sufficient. Looking now at how an RNA polymerase molecule, a core device in the gene transcription machinery, is assembled, it is hard to escape an impression that a large team of self-motivated protein molecules precisely *knows* how to assemble this complex molecular machine. (Parenthetically, RNAPs have molecular weights up to 2,000 kD and are recognized to be structurally more complex than an automobile; in the majority of cases they are gene-specific and are assembled anew for each transcription event.) We stop here and refrain from further descending into the abyss

of self-organized structures within the cell; however, even the next in line candidate to ponder, the protein molecule, is well suited to be ascribed self-motivation and some sort of intelligence.[35,36]

The GCT provides a deep insight into the seemingly miraculous property of complex hierarchical systems to be self-organized at each level without a supervisory authority, without informational infrastructure, without necessity for its units to have understanding of the process as a whole, and without invoking the metaphor of struggle for survival.

Collapse into the Self-Organized Mode: Role of Self-Organized Criticality

The nonlinear dynamics approach encapsulated in GCT and in equation (6) envisions self-organization as an asymptotic process of approaching stability through a series of intermediate states (also known as evolution). There exists, however, a fundamentally different process known as self-organized criticality (SOC) in which an avalanche-like transformation rapidly moves the system into a self-organized mode.[37–39] A popular metaphor for SOC is the *sandpile paradigm*. If additional sand grains are randomly added on top of a sand pile then inevitably an instance will occur when local steepness of the slope surpasses a certain critical threshold thus causing local failure of structural stability. The excess of material will cascade into adjacent areas of the pile causing their failures as well. Thus an avalanche will occur, shifting the entire sandpile into a new stable state. What is fundamentally important in this process is that a random local event quickly propagates through the entire system, thus establishing long-range correlations within the system. A simple cellular automaton describes the sandpile paradigm in more refined mathematical terms. Suppose that there exists a two-dimensional lattice of cells in which the state of each cell is characterized by a time-dependent load, $v_{ij}(t)$. Suppose also that there exists a limiting capacity of each cell, $\bar{v}_{ij}$, and every time when $v_{ij}(t) > \bar{v}_{ij}$, the excess of load, that is, $v_{ij}(t) - \bar{v}_{ij}$, is randomly redistributed between the neighboring sites. After one step of random redistribution, one or more adjacent sites may become overloaded, thus causing an *avalanche*. The word avalanche used here is a metaphor for establishing a long-range correlation within

the system and its coherent restructuring. The actual meaning of the quantity symbolized by the word *load* may vary. In particular, it may represent a certain amount of information; in this case, occurrence of the system-wide coherence may be interpreted as rapid information transfer (recall rapid rumor propagation in a community anticipating some breaking news). Obviously, the rules of the game would remain essentially the same if, instead of a lattice of cells, one considers a *network* of interacting units with an arbitrary topology. It is of crucial importance to realize that the network-wide information transfer and coherent restructuring is not a result of long-range exchange of signals, neither is it a result of collective thinking or following the orders of some sort of command center. It is solely the result of local stimulus-response interactions between the neighbors. The role of SOC in rapid system-wide restructuring has been studied in many works (see[40–42] and references therein). (As a side note, a novel model of SOC has been proposed by this author. It has been shown that a simple modification of the cellular automation rules leads to fundamentally different behavior of the system; that is, to the excitation of the self-organized self-sustained oscillations.)[38] SOC exemplifies an emergent phenomenon of system-wide organized behavior resulting from purely mechanistic reasons, ie, from member-to-member local interactions without any intelligent organizing force.

Manifestations of SOC in nature and society are numerous.[37] In physics, the avalanches are known under the name *phase transition* with the subcritical states preceding the transition being called *metastable*. The transition itself may be triggered by a minor event with little significance of its own; due to this insignificance the phase transition may appear to be spontaneous. However, spontaneity does not mean that there is no reason for the phase transition; the fundamental reason is that the system resides in a subcritical state and is ripe for collapse. A brief list of examples of SOC from other disciplines would include spontaneous crystallization and magnetization, earthquakes, wild fires, landslides, revolutions, epidemics, wars, crowd stampedes, stock market crashes, and so on. Catastrophic events sometimes happen even in science itself; they occur when irreconcilable controversies lead to the collapse

of dominating theories and fundamentally different approaches emerge; this phenomenon is known as a paradigm shift.[43] A common feature among all these diverse examples is that prior to a catastrophic event the system resides in subcritical state and is ripe for restructuring. After the catastrophe, the system moves itself into a new stable state, but this stable state is again subcritical. As to the rapid transition between sequential stable states, it is essentially a random process; in this sense stability is often said to exist on the *edge of chaos*. In summary, the natural history of such systems represents patterns of intermittancy in which periods of prolonged stability are interrupted by rapid catastrophic restructuring. Closer to a biological agenda, SOC is a key to understanding the well documented phenomenon of punctuated equilibrium in the evolution of species.[44,45] The relevance of SOC to carcinogenesis will be touched upon later in this paper.

SOC is intimately connected to the general principles of nonlinear dynamics, including the GCT, LVS, and NN. In open systems in which the influx of resources is compensated by their dissipation and outflow, the SOC systems are capable of permanently residing in subcritical state on the verge of chaos thus forming a special case of dynamic attractor. Existence on the verge of chaos is often seen as a hallmark of living entities (for example, see[46,47]).

Swarm Intelligence of Biochemical Systems

A large system of concurrent chemical reactions is usually called a *chemical network*, and a number of mathematical disciplines study their dynamical properties (see review[48] by this author). However, it is not immediately evident from these theories whether or not the chemical constituents interacting through stimulus-response rules (chemical reactions) may form a network capable of solving intelligent tasks such as pattern recognition or computation. In this context, the first question to be resolved involves constructing, on a purely chemical basis, a single excitable unit acting as a neuron. The simplest model of a chemical neuron has been proposed by Okamoto et al.[49] It has been shown in this work that a set of chemical reactions involving the cycling enzymes and governed by kinetic equations mathematically equivalent to the McCulloch-Pitts' neuronal equations may serve

as a chemical ON-OFF switch. Simulations showed that such a switch may be as reliable as the solid-state electronic switching circuits. The possibility of *connecting* the Okamoto-type chemical neurons into a network has been analyzed in-depth in the series of publications by Hjelmfelt and Ross.[50–53] In particular, in the study,[52] the feasibility of a *chemical finite-state computing machine* has been demonstrated; such a machine would include the most fundamental elements of traditional electronic computers, namely binary decoder, binary adder, stack of memory, and internal clock. The possibility of a *programmable* chemical NN capable of storing patterns and solving pattern recognition problems has been proven in.[53] At last, an ultimate computer science conjecture— whether or not a Turing Machine can be constructed from oscillating chemical reactions—has been also resolved affirmatively.[50] A summary of these results, as well as a long list of well-characterized chemical species suitable for constructing the computational devices, have been presented in.[54]

A systematic study of biochemical information-processing systems has been undertaken in.[55] The authors consider in much detail three basic NN-type biochemical systems which differ in the ways of exchanging molecular signals between the chemical neurons. These different modalities of information exchange correspond to different NN topologies. A detailed comparison of computational capabilities of NNs and those of biochemical networks (Table 2)[55] suggests the idea that these capabilities have very much in common. The authors even make a notable observation that "the processing based on a few enzymatic reactions is less complex than the processing of electrical signals as achieved by neural nerve cells." In a more general context, it should be noted that any system representable through NN may be considered as a version of a Turing Machine. And an even more powerful statement is valid: any function computable by a Turing Machine can be also computed by an appropriately parameterized processor net defined by equation (2).[56] In practical terms, all this means that each biochemical network may be thought as an entity performing certain computation and may be formally represented through an appropriately constructed Turing Machine. Conversely, any function computable by a Turing Machine may also be computed by a specially designed biochemical network.

A striking similarity between the information-encoding biopolymers (DNA, RNA) and the data tape in Turing Machines suggests the idea that these macromolecules may be used for physical implementation of a molecular computing machine. One of the first working examples of such machine has been reported in.[57] In this work, an autonomous programmable molecular computer utilizing DNA and DNA-manipulating enzymes has been developed. The hardware of this computer included restriction nuclease and ligase, the software and input data were encoded in the double-stranded artificially synthesized DNA, and programming consisted in selection of the set of appropriate molecules. Upon mixing all these components in the test tube, the system went through cascades of restrictions, hybridizations and ligations ending up with detectable quantities of molecules representing the results of computation. In these experiments, up to 10^{12} biomolecular automata sharing the same input ran independently and collectively provided, as reported in,[57] "the fidelity of computations greater than 99.8%." A landmark result in this line of research has been achieved in[58] where the molecular machine based on the above outlined principles demonstrated the ability of computing the square root of an arbitrary real number.

The famous question posed by Alan Turing in his groundbreaking paper "Can a machine think?"[59] continues to be a highly disputed topic in computer science, cognitive science, and philosophy.[60] Perhaps it is one of the eternal questions that will never be conclusively resolved (a detailed discussion may be found in).[61] However, given the convincingly demonstrated equivalence between NNs and Turing Machines, between chemical networks and NNs, and between NNs and population dynamics, it seems reasonable to pose similar questions: "Can a chemical network think?"; "Can a population of dumb individuals, as a whole, think?"; "Can a microbial community think?"; "Can a community of cells think?" From the discussion above, it is reasonable to infer that a swarm of locally interacting individuals lacking any personal intelligence *can think at least in the same sense and at the same level of intelligence as Turing Machines and computers*.

Swarm Intelligence of Robotic Communities

In the literature on swarm intelligence, the word 'dumb' is not supposed to have a derogatory connotation. It is just a brief, mostly technical, characterization indicating that a member of the community does not possess a physical ability of mapping the world, the actions of other members, and the global plan of action onto its own internal behavioral/cognitive/analytical capabilities. In particular, a community of inanimate robots mutually interacting only through stimulus-response rules but lacking any analytical tools for premeditated collective strategy is well qualified to be such a community of dumb individuals. Proof of the principle that these communities may possess the elements of self-organization and swarm intelligence has been expressly demonstrated in.[62,63] In these works, a group of memoryless micro-robots have been programmed to mimic individual behaviors of cockroaches. The micro-robots, however, were not hard-wired to have any analytical tools to gather information regarding the behaviors of other robots or regarding the general plan of action. It has been shown experimentally that this community is capable of reproducing some patterns of collective behavior similar to those of real cockroaches. Division of labor in the communities of robots has been studied in.[64] The authors point out:

> "The robots we used for our experiments are quite simple. They have very limited computational power, they do not communicate with each other and they are equipped with simple sensors. The sensors are too simple to allow them to build a map or any other model of the environment. Nevertheless, we show that they are able to cooperate in order to increase the efficiency of the group."

A comprehensive review of various aspects of swarm intelligence in communities of robots and biological entities is given in.[1] Cooperative behaviors in communities of autonomous mobile robots has been reviewed in.[65] Recent developments in technological and behavioral aspects of swarm robotics have also been summarized in.[66]

Powerful impetus to the idea of robotic communities has been given by nanotechnology. The strategies of utilizing quorum sensing in various tasks for communities of nano-robots have been explored in a series of simulation experiments.[67] Although only the first steps have been undertaken in practical implementation of this intriguing idea, the results already achieved are impressive. For example, Maltzahn et al[68] constructed a system in which the synthetic

biological and nanotechnological components communicate *in vivo* to enhance disease diagnostics and delivery of therapeutic agents. In these experiments, the swarms typically consisted of about one trillion nanoparticles. It has been shown "that communicating nanoparticle systems can be composed of multiple types of signaling and receiving modules, can transmit information through multiple molecular pathways, *can operate autonomously* and can target over 40 times higher doses of chemotherapeutics to tumors than non-communicating controls" (italics by SR).

Swarm Intelligence of Microbial Communities

Highly sophisticated forms of swarm intelligence have been observed in microbial communities. These communities represent a perfect example of species in competition governed by the Lotka-Volterra dynamics.[69–71] Bacteria have at least two advanced features which make the behaviors of microbial communities astoundingly rich and elaborate. First, bacteria possess the property of genomic plasticity, which may be thought of as a rudimentary form of internal memory. Second, bacterial cells are capable of transferring individual genomic traits to their progeny. Social organization of bacterial communities have been extensively analyzed in.[72] A number of important conclusions have been reached in this work. Firstly, bacterial communities are found to possess a form of inheritable collective memory and an ability of maintaining self-identity. Secondly, bacterial communities are capable of collective decision-making, purposeful alterations of the colony structure, and recognition and identification of other colonies. In the essence, bacterial communities as a whole may be seen as multicellular organisms with loosely organized cells and sophisticated form of intelligence. It is also important to realize that the genomic profiles and epigenetic modifications of bacterial subgroups are shaped by their roles and positions in the community. This means that bacterial clonal diversity within a colony reflects not simply the multitude of genomic structures but also the division of labor between the subgroups. It should also be noted that fancy external architectural forms created by the bacterial communities are the direct continuation of their internal metabolic architecture and genomic profiles

coherently structured for quorum sensing and other forms of cooperation.[73]

The capability of the same bacterial community to shape itself, depending on the environmental conditions, into different architectural forms, topological structures, and metabolic profiles, is deeply rooted in the mechanistic property of multistability. Complex internal structures of microbes and existence of internal memory (defined as "recording of experience that can modify behavior")[74] make bacterial communities quite similar to the CNNs described above. In particular, intra-microbial dynamics generate a set of distributed delays, which in turn make a system multistable.[75] Qualitatively, it may be said that the totality of all individual delays is a representation of the collective community-wide experience, whereas individual delays by themselves reflect nothing more than individual experiences.

Self-Organization in Communities of Somatic Cells

There is an essential difference between somatic and microbial cells: somatic cells are immobilized in the extracellular matrix and tissue thus forming an actual physical network with relatively stable links.[16] Hence, in contrast to microbial communities, which have a freedom of spatial restructuring, self-organization in a community of somatic cells is mostly manifested through the collective shaping of their internal phenotypic traits (eg, gene expression profiles or/and metabolic pathways). In particular, a gene network may utilize the property of multistability for mounting an adaptive response through the fitness-induced attractor selection.[76] All this means that a community of somatic cells acts as a self-sufficient intelligent super-organism capable of taking care of its own survival through cooperative manipulation with intracellular states. As mentioned in,[73] "Bacteria invented the rules for cellular organization." In this regard, the biofilms, ie, the microbial communities immobilized in thin layers of extracellular polymeric substances (EPS) may serve as a reasonably close analogy to the communities of somatic cells. It has been demonstrated in a number of publications that

"Microbial communities do not exist as solitary cells, but are colonial organisms that exploit elaborate systems of intercellular communication to facilitate their adaptation to changing environmental conditions. The languages by which bacteria communicate

take the form of chemical signals, excreted from the cells, which can elicit profound physiological changes. The term quorum-sensing has been coined to describe this ability of bacteria to monitor cell density before expressing a phenotype."[77,78]

From the perspective of Lotka-Volterra dynamics, somatic cells are just another example of locally inter-acting units possessing, as a community, the emergent property of swarm intelligence. Self-organization in such communities is governed by the general laws outlined by GCT and LVS. In this context, one of the key questions to ponder is what is the nature of the interactions between the cells? Are they competi-tive or mutualistic? Or, stated differently in a less for-mal manner: what is it that the cells are struggling for? What is their natural (default) state? These questions are of utmost importance in cancer research; hence, a deeper insight into this issue seems to be in order.

Two drastically different approaches to understand-ing the driving forces behind cancer onset and prolifer-ation have been crystallized through years of research. These are the Somatic Mutation Theory (SMT) and the Tissue Organization Field Theory (TOFT). The essence of SMT is that cancer is derived from a single somatic cell that has successively accumulated multiple DNA mutations, and that those mutations occur on genes that control cell proliferation and cell cycle. Thus, in the SMT the neoplastic lesions that destroy normal tissue archi-tecture are the results of DNA-level events. Conversely, according to the TOFT, carcinogenesis is primarily a problem of tissue organization: carcinogenic agents (eg, environmental chemicals, inflammation, viruses) destroy the normal tissue architecture thus disrupting the cell-to-cell signaling and compromising genomic integrity. Hence, in the TOFT the DNA mutations are the effect, and not the cause, of the tissue-level events.[79] It is beyond the goals of this paper to delve deeper into the detailed discussion of the pros and cons of SMT and TOFT. A large number of in-depth explorations pertain-ing to this complex issue have been published to date. The stakes in successful resolution or reconciliation of these conflicting viewpoints are high. In particular, as indicated in the recent review,[80] more than 50 years of the SMT dominance failed to produce a self-consistent picture of carcinogenesis. On the other hand, a growing body of evidence has emerged, which is very hard to explain, if possible at all, within the SMT but may be naturally explained within the TOFT.[79,81]

According to Sonnenschein and Soto,[82] the SMT versus TOFT dichotomy may be boiled down to the following core question: what is the *default* state of the cell, proliferation or quiescence? The authors write:

> "Based on an evolutionary perspective and on our experience using a variety of cell culture models and their animal coun-terparts, we favor the concept that the 'default' state of cells in metazoa, like those of unicellular organisms and metaphyta, is proliferation."

In these considerations, it is tacitly postulated that there exists an intrinsic property of the cell, which is called the 'default' state, that belongs to the cell itself and is largely independent of the specific circumstances in which the cell is functioning. This premise is not easy to justify. As demonstrated in many works including those cited above,[69,70,72,73,77,78] the phenotypic traits of individual cells are shaped by interactions within their respective communities. Therefore, the default state of the cells "freed from the restraints of tissue structure" may not be identical with, or even similar to, those that are densely packed and immobilized in tissue.

Furthermore, the concept of default state is not quite satisfactory from a purely logical perspective. It is not self-evident as to why the cells would deserve the honor to have some characteristic default states, but the community of cells, as a whole, would not. The observed astounding coherence between all of the elementary processes on various levels of biological organizations allows one to see the community of cells as a superorganism or even as a separate organ,[83,84] and to talk about its defensive tactics.[85] Systemic views of tumors as organs and as superorganisms has been discussed in-depth in many works.[84,86] The most fun-damental property of a superorganism is the "shared purpose of its existence".[87] Therefore, it is legitimate to ask: what is the default state (or default behavior) of this superorganism? This kind of troubling question may be continued inside the cell. Patterns of highly organized behavior are observed in intra-cellular processes.[88] After ascribing some natural default state to the cell as a whole, should we now continue the quest inward by declaring that the default state of a gene is synthesizing mRNA, the default state of RNA polymerase is getting self-assembled and reading the genetic code, the default state of a polypeptide chain is folding into the protein molecule, and so on and so

forth? If one starts making such hypotheses at a certain hierarchical level and then continues the proceed by extending to adjacent hierarchical levels, then ultimately all the systems of knowledge will be morphed into a set of *a priori* descriptors of the default states. No further scientific inquiry would be required if all the default states and behaviors are already appropriately defined and described. All this is to say that the claims regarding defaultness of cellular states may be a shaky basis for erecting a massive edifice of theory of carcinogenesis.

Disruption of Quorum Sensing as a Prerequisite for Triggering Carcinogenesis

Carcinogenesis is a complex systemic phenomenon encompassing the entire hierarchy of biological organization. Hornberg et al[89] write:

> "The action of regulatory circuits, cross-talk between pathways and the non-linear reaction kinetics of biochemical processes complicate the understanding and prediction of the outcome of intracellular signaling. In addition, interactions between tumor and other cell types give rise to a complex supra-cellular communication network."

As seen from this excerpt, as well as from many other publications (for instance, see the discussion and extensive bibliography in[83]), a great emphasis in carcinogenesis is placed on the role of disruption of the cell-to-cell signaling. In the TOFT briefly outlined above, this disruption is seen as a central component of a bigger process of tissue disorganization. Originators of the TOFT, Sonnenschein and Soto, refer to this totality of all structural elements as tissue architecture.[79,82,90] Such terminology (as well the very name TOFT featuring the tissue field) leaves out of scope another important constitutive element of biological organization, namely its societal aspect. The viewpoint being advanced in this paper is that a community of the cells is not simply a collection of units dwelling within certain architectural structures. This is indeed a community—a network—possessing the faculty of swarm intelligence as one of its emergent properties. With the destruction of signaling pathways, not only are the normal regulation of individual cellular processes damaged, but a blow is also dealt to the, so to speak, *mental* capabilities of the community as a whole. Its collective memory is wiped out or distorted, the customary division of labor between the

subpopulations is shifted towards aberrant modalities, community-wide self-defensive mechanisms are weakened or broken. In summary, the community as a whole falls into the state of *disarray and amnesia* in which it is feverishly searching for new ways towards survival. These processes in turn cause shift in expression profiles and metabolic dynamics eventually penetrating to the level of DNA and causing multiple mutations.

Quorum sensing (QS) is an important aspect of swarm intelligence. The word *sensing* here is a metaphor for a process of establishing community-wide correlations between individual behaviors and phenotypes. As highlighted before, such a system-wide coherence is an epiphenomenon of local member-to-member interactions and does not assume existence of supervisory authority, system-wide information infrastructure, or any other global forcing. There is a growing consensus in the cancer research community regarding the fundamental importance of disruption of quorum sensing in cancer onset and proliferation. Agur et al[91] provide a brief review of relevant biological facts and propose a mathematical model of QS boiled down to its simplest mechanistic elements. They conclude "that no model simpler than the QS model can retrieve tissue homeostasis" and hypothesize "that cancer initiation is driven by disruption of the QS mechanism, either by genetic mutations, complying with the current notion of cancer evolution, or purely by the environment, *genetic mutations being only a side-effect of* excessive proliferation" (italics by SR). A detailed analysis of societal interactions and quorum sensing mechanisms in ovarian cancer metastases is given in.[92] These authors present compelling arguments supporting the view that QS "provides a unified and testable model for many long-observed behaviors of metastatic cells." QS is found to be a promising target in oncology, and a number of peptide drugs are currently under investigation for their preventive, diagnostic, and therapeutic properties. As discussed in much detail in the work by this author,[15] QS and other aspects of swarm intelligence contribute to the phenomena of biological robustness and acquired chemoresistance.

Are the SMT and TOFT Irreconcilable?

According to Sonnenschein and Soto,[82] TOFT and SMT "belong to distinct levels of biological complexity and therefore, are incompatible, as are their philosophical stances (reductionism versus organicism)."

Indeed, the cornerstone of SMT is the notion that carcinogenesis is triggered by a single aberrant cell which happened to acquire multiple DNA mutations, and these mutations predominantly damage the genes responsible for cell cycle and apoptosis.[30] The classical argument in favor of this viewpoint is that:

> "Cytogenetic studies have demonstrated that in many primary tumors all cells show the same abnormal karyotype; the immunoglobulin produced by plasma cell tumors has in almost every case the homogeneity characteristic of a single clone."[93]
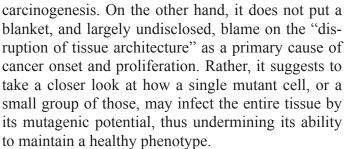
As an ultimate manifestation of this paradigm, direct evidence of a single catastrophic event triggering carcinogenesis has been presented by Stephens et al.[94] The authors report:

> "The model to explain the distinctive genomic structures described here is that the overwhelming majority of rearrangements occur in a single catastrophic event. In this scenario, the chromosome or chromosomal region shatters into tens to hundreds of pieces, some (but not all) of which are then stitched together by the DNA repair machinery in a mosaic patchwork of genomic fragments ... A cell suffering tens to hundreds of DNA breaks in a single cataclysmic event would be expected to undergo apoptosis. That a cell can survive such an insult and progress to become cancerous suggests that the extensive remodeling of the genome may confer significant selective advantage to that clone."

In direct opposition to these views, the TOFT depicts carcinogenesis as the general deterioration of tissue microenvironment due to extracellular causes. This deterioration hinders normal cell-to-cell signaling thus making normal functioning of the intracellular machinery impossible and eventually leading it to its breaking point. In such a scenario, the deleterious mutations should be scattered all over the genome randomly and incoherently, with little chance for clonal homogeneity.

In this paper, we propose a plausible scenario in which a single, and insignificant on its own, catastrophic event may cause a system-wide catastrophic restructuring. Such a scenario may be envisioned and conceptualized in the framework of SOC. Using analogy, in a society overburdened by internal strife and misery, a charismatic self-motivated leader may grab attention of the disoriented crowd, become a seed for the rapid transition to new modalities of existence, and ultimately lead the society to catastrophe;

historical examples are too well known to delve into them here.[95,96] From a systemic point of view, such catastrophic developments follow the pattern of avalanche. Prior to an avalanche, the system resides in a subcritical state (on the edge of chaos), metastable but ripe for collapse. A single grain of sand may trigger the sandpile slide. A large-scale devastating forest fire may be sparked by a single cigarette butt, but availability of flammable dry wood is the prerequisite. In the biomolecular context, it should be taken into consideration that genetic regulatory networks represent an example of inherently unstable dynamical systems. This view is in line with the vision formulated by R. May in his seminal paper, "Will a large and complex system be stable?"[97] Burstiness and sporadicity in genetic regulation are vivid manifestations of dynamic instabilities.[98] (This topic has been explored in the series of publications by this author[48,99–103] and elsewhere.)[104–107] The central message of this line of reasoning is that a large and complex network cannot behave in a smooth assembly-line manner, with spontaneous failures (eg, traffic jams, backlogs, loss of synchronization) being unavoidable circumstances surrounding their functioning. Each of these events may initiate a domino-effect of secondary failures, thus moving the genetic regulatory systems in individual cells unidirectionally towards destabilization.[101] In this sense, such systems always reside on the verge of collapse. If on top of that an organ or tissue is weakened due to adverse extraneous factors (inflammation, injury, carcinogens, multiple scattered mutations), then, figuratively speaking, a community of cells becomes similar to flammable material in a dry forest. Under these circumstances, a single catastrophic event, like the birth of a mutant cell with advantageous survival capabilities, may spark rapid genomic restructuring of the entire tissue or organ, thus leading to tumorigenesis. Here the fundamental driving forces stipulated by the TOFT and SMT may come into confluence and complement each other in sparking carcinogenesis.

A novel point of view proposed in this paper, if proven to be correct, may have far-reaching consequences in cancer research and clinical practices. It may represent a step towards a long awaited paradigm shift and resolution of the paradigm instability in the theory of carcinogenesis.[108] This point of view would not diminish the importance of molecular pathways and gene level events in search for explanations of

carcinogenesis. On the other hand, it does not put a blanket, and largely undisclosed, blame on the "disruption of tissue architecture" as a primary cause of cancer onset and proliferation. Rather, it suggests to take a closer look at how a single mutant cell, or a small group of those, may infect the entire tissue by its mutagenic potential, thus undermining its ability to maintain a healthy phenotype.

In the literature, there is no lack of metaphoric characterizations of tumors as superorganisms, as having defensive tactics, as being robust, resilient, smart, adaptive, and so on. In this paper, we attempt to convey the notion that that there is much more than simply metaphoric meanings in these characterizations. Rather, they represent the various aspects of an active force capable of setting goals and developing defensive tactics; this force is called swarm intelligence. It should be clearly understood that swarm intelligence is not a metaphor; it is an actual and ubiquitous emergent property of complex systems governed by simple mechanistic rules. It is, therefore, admissible to conjecture that when developing therapeutic strategies against cancer one needs to take into consideration not only the tumor's clonal diversity,[109] and not only the existence of automatic negative feedback loops mitigating external disturbances,[110] but to also recognize that *the enemy is intelligent, capable of discerning the weapon applied against it, and creative enough to devise a counteroffensive.*

A Clash of Paradigms: Alive and Self-Motivated Versus Dead and Self-Organized

Everyone would agree that an individual ant is a living creature. In this capacity, based on the immediate information and accumulated personal experience, it *knows* what to do in any particular situation. In this sense, an ant is a self-motivated creature. But would it be also legitimate to consider an entire ant colony as a self-sustained living creature, a superorganism? This question may be directed towards any community of living creatures: bees, birds, fish, termites, humans, microbes, as well as towards inanimate communities of micro- and nano-robots. The profound nature of this question inspired a massive body of literature; for an in-depth discussion and extensive bibliography, see.[87] In this paper we limit ourselves by a simplified common-sense consideration of the problem. Imagine a large

community of individuals (dumb or not, alive or not) tightly interconnected into an interaction network and possessing the property of self-replication. Suppose that through generations of its existence, the network developed various aspects of swarm intelligence such as collective memory, adaptivity, division of labor, quorum sensing, and ability to heal itself. It has been demonstrated throughout this paper that due to some comparatively basic laws of nonlinear dynamics it is indeed possible. Hence, the question to be resolved is this: would it be sufficient to regard such a network as a self-motivated intelligent superorganism? This question seems to be mostly philosophical in nature; however, as discussed above, conflicting visions regarding the default state of the cell may lead to drastically different conceptualizations of carcinogenesis with many reverberations in scientific policies, clinical practices, and funding strategies. In a sense, the presumed existence of a default state would mean that the cell is *alive and self-motivated*, and that its natural propensity is to struggle for its life. An alternative view advocated in this paper is that the cell is not alive in any greater sense than the highly organized components it consists of, or the highly organized superstructures it belongs to, but obeys the blind mechanistic laws dictated by the cell's internal physico-chemical structure as well as by the dynamics of the superorganism it is embedded in. *GCT and SOC are universal mechanistic principles governing these systems*. It is not out of place to mention that phenomena quite analogous to cancer have been observed in societies other than the societies of cells,[111] and that once again points to commonality and universality of the laws governing all these processes.

Conclusion

Complex hierarchy of perfectly organized entities is a hallmark of biological systems. Attempts to understand the why's and how's of this organization lead inquiring minds to various levels of abstraction and depths of interpretation. Within the natural sciences, one wants to see the mechanisms and explanations of how this organizational complexity came to existence. The claim that the observed biological complexity is a result of billions of years of evolution is not sufficient by itself for explaining complexity. It is imperative to determine what are the driving forces of these evolutionary processes, and how these forces,

acting on drastically different levels of biological hierarchy, come to synchronization and coherence. In this paper, we have attempted to convey the notion that there exists a set of comparatively simple and universal laws of nonlinear dynamics which shape the entire biological edifice, as well as all of its compartments. These laws are equally applicable to individual cells, to biochemical networks within the cells, to the societies of cells, to the societies other than the societies of cells, as well as to the populations of individual organisms. These laws are blind, automatic, and universal; they do not require the existence of a supervisory authority, of a system-wide informational infrastructure, or of some sort of premeditated intelligent design. In large populations of individuals interacting only by stimulus-response rules, these laws generate a large variety of emergent phenomena, with self-organization and swarm intelligence being their natural manifestations.

Acknowledgments

Author Contributions

Wrote the first draft of the manuscript: SR. Contributed to the writing of the manuscript: SR. Made critical revisions and approved final version: SR. The author reviewed and approved the final manuscript.

Funding

Competing Interests

Author discloses no potential conflicts of interest.

Disclosures and Ethics

The author has read and confirmed his agreement with the ICMJE authorship and conflict of interest criteria. The author has also confirmed that this article is unique and not under consideration or published in any other publication.

References

1. Bonabeau E, Dorigo M, Theraulaz G. *Swarm Intelligence: From Natural to Artificial Systems*. New York: Oxford University Press; 1999.

2. Garnier S, Gautrais J, Theraulaz G. The biological principles of swarm intelligence. *Swarm Intelligence*. 2007;1:3–31.

3. May RM. *Stability and Complexity in Model Ecosystems (Princeton Landmarks in Biology)*. Princeton: Princeton University Press; 2001.

4. Volterra V. Variations and fluctuations of the number of individuals in animal species living together. In Chapman RN, editor. *Animal Ecology*. New York: McGraw-Hill; 1931:409–48.

5. Lotka AJ. Contribution to the theory of periodic reaction. *J Phys Chem*. 1910;14:271.

6. Zhang D, Gyorgyi L, Peltier WR. Deterministic chaos in the Belousov-Zhabotinsky reaction: Experiments and simulations. *Chaos*. 1993;3(4): 723–45.

7. Lorenz E. Deterministic nonperiodic flow. *Journal of the Atmospheric Sciences*. 1963;20(2):130–41.

8. Zaslavskii GM, Sagdeev RZ. *Introduction to Nonlinear Physics*. Moscow: Nauka; 1988. Russian.

9. Savageau MA. Biochemical systems analysis. I. Some mathematical properties of the rate law for the component enzymatic reactions. *J Theor Biol*. 1969;25(3):365–9.

10. Savageau MA. Biochemical systems analysis. II. The steady-state solutions for an n-pool system using a power-law approximation. *J Theor Biol*. 1969; 25(3):370–9.

11. Voit EO. *Computational Analysis of Biochemical Systems: A Practical Guide for Biochemists and Molecular Biologists*. Cambridge: Cambridge University Press; 2000.

12. Hernández-Bermejo B, Fairén V. Lotka-Volterra representation of general nonlinear systems. *Math Biosci*. 1997;140(1):1–32.

13. Savageau MA. A theory of alternative designs for biochemical control systems. *Biomed Biochim Acta*. 1985;44(6):875–80.

14. Savageau MA. Mathematics of organizationally complex systems. *Biomed Biochim Acta*. 1985;44(6):839–44.

15. Rosenfeld S. Biomolecular self-defense and futility of high-specificity therapeutic targeting. *Gene Regul Syst Bio*. 2011;5:89–104.

16. Seeley TD. When is self-organization used in biological systems? *Biol Bull*. 2002;202(3):314–8.

17. Bose NK, Liang P. *Neural Network Fundamentals with Graphs, Algorithms, and Applications (McGraw-Hill Series in Electrical and Computer Engineering)*. New York: McGraw Hill, Inc.; 2012.

18. Haykin S. *Neural Networks: A Comprehensive Foundation*, 2nd ed. Upper Saddle River: Prentice Hall; 1999.

19. Cybenko G. Approximation by superpositions of a sigmoidal function. *Mathematics of Control, Signals, and Systems*. 1989;2:303–14.

20. DARPA Neural Network Study (US) *Darpa Neural Network Study: October 1987–February 1988*. Fair Lakes: AFCEA International Press; 1988.

21. Chua L, Yuang L. Cellular neural networks. Applications. *IEEE Transactions on Circuits and Systems*. 1988;35:1273.

22. Zeng Z, Huang DS, Wang Z. Memory pattern analysis of cellular neural networks. *Phys Lett A*. 2005;342(2005):114–28.

23. Ikeda M, Šiljak DD. Lotka-Volterra equations: decomposition, stability, and structure. *J Math Biol*. 1980;9(1):65–83.

24. Duarte P, Fernandes R, Oliva W. Dynamics of the attractor in the Lotka-Volterra equations. *J Differ Equ*. 1998;149(1):143–89.

25. Grossberg S. Competition, decision, and consensus. *J Math Anal Appl*. 1978;66:470–93.

26. Grossberg S. Decisions, patterns, and oscillations in nonlinear competitive systems with applications to Volterra-Lotka systems. *J Theor Biol*. 1978; 73(1):101–30.

27. Grossberg S. Biological competition: Decision rules, pattern formation, and oscillations. *Proc Natl Acad Sci U S A*. 1980;77(4):2338–42.

28. Grossberg S. Pattern formation by the global limits of a nonlinear competitive interaction in n dimensions. *J Math Biol*. 1977;4(3):237–56.

29. Lotka AJ. Natural Selection as a Physical Principle. *Proc Natl Acad Sci U S A*. 1922;8(6):151–4.

30. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. *Molecular Biology of the Cell*, 5th ed. New York: Garland Science; 2004.

31. Albrecht-Buehler G. Is cytoplasm intelligent too? In: Shay J, editor. *Muscle and Cell Motility VI*. 1985:1–21.

32. Gates E. Methods of research and importance of cellular psychology. *The American Therapist*. Dec 14, 1895;IV(6):157–83.

33. Yu J, Xiao J, Ren X, Lao K, Xie XS. Probing gene expression in live cells, one protein molecule at a time. *Science*. 2006;311(5767):1600–3.

34. Lemon B, Tijan R. Orchestrated response: a symphony of transcription factors for gene control. *Genes Dev*. 2000;14(20):2551–69.

35. Grosberg A. Statistical mechanics of protein folding: some outstanding problems. In: Attig N, Binder K, Grubmuller H, Kremer K, editors. *Computational Soft Matter: From Synthetic Polymers to Proteins*. Jülich: John von Neumann Institute for Computing. 2004;23:375–400.

36. Whitty A. Cooperativity and biological complexity. *Nat Chem Biol*. 2008; 4(8):435–9.

37. Bak P. *How Nature Works: The Science of Self-Organised Criticality*. New York: Copernicus Press; 1996.

38. Rosenfeld S. Critical self-organized self-sustained oscillations in large regulatory networks: towards understanding the gene expression initiation. *Gene Regul Syst Bio*. 2011;5:27–40.

39. Turcotte DL, Rundle JB. Self-organized complexity in the physical, biological, and social sciences. *Proc Natl Acad Sci U S A*. 2002;99 Suppl 1: 2463–5.

40. Turalska M, Lukovic M, West BJ, Grigolini P. Complexity and synchronization. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2009;80(2 Pt 1):021110.

41. Turlaska M, Geneston E, West BJ, Allegrini P, Grigolini P. Cooperation-induced topological complexity: a promising road to fault tolerance and hebbian learning. *Front Physiol*. 2012;3:52.

42. Vanni F, Luković M, Grigolini P. Criticality and transmission of information in a swarm of cooperative units. *Phys Rev Lett*. 2011;107(7):078103.

43. Khun TS. *The Structure of Scientific Revolutions*. Chicago: University of Chicago Press; 1962.

44. Bak P, Sneppen K. Punctuated equilibrium and criticality in a simple model of evolution. *Phys Rev Lett*. 1993;71(24)4083–6.

45. Gould SJ, Eldredge N. Punctuated equilibrium comes of age. *Nature*. 1993;366(6452):223–7.

46. Kauffman SA. *The Origins of Order: Self Organization and Selection in Evolution*. Oxford: Oxford University Press; 1993.

47. Shmulevich I, Kauffman SA, Aldana M. Eukaryotic cells are dynamically ordered or critical but not chaotic. *Proc Natl Acad Sci U S A*. 2005;102(38): 13439–44.

48. Rosenfeld S. Mathematical descriptions of biochemical networks: stability, stochasticity, evolution. *Prog Biophys Mol Biol*. 2011;106(2):400–9.

49. Okamoto M, Sakai T, Hayashi K. Biochemical switching device realizing McCulloch-Pitts type equation. *Biol Cybern*. 1988;58(5):295–9.

50. Hjelmfelt A, Weinberger ED, Ross J. Chemical implementation of neural networks and Turing machines. *Proc Natl Acad Sci U S A*. 1991;88(24): 10983–7.

51. Hjelmfelt A, Ross J. Chemical implementation and thermodynamics of collective neural networks. *Proc Natl Acad Sci U S A*. 1992;89(1):388–91.

52. Hjelmfelt A, Weinberger ED, Ross J. Chemical implementation of the finite-state machines. *Proc Natl Acad Sci U S A*. 1992;89(1):383–7.

53. Hjelmfelt A, Schneider FW, Ross J. Pattern recognition in coupled chemical kinetic systems. *Science*. 1993;260(5106):335–7.

54. Arkin A, Ross J. Computational functions in biochemical reaction networks. *Biophys J*. 1994;67(2):560–78.

55. Filo O, Lotan N. *Information Processing by Biochemical Systems: Neural Network-Type Configurations*. Hoboken: John Wiley & Sons, Inc.; 2010.

56. Siegelmann T, Sontag ED. Turing computability with neural nets. *Appl Math Lett*. 1900:77–80.

57. Benenson Y, Paz-Elizur T, Adar R, Keinan E, Livneh Z, Shapiro E. Programmable and autonomous computing machine made of biomolecules. *Nature*. 2001;414(6862):430–4.

58. Qian L, Winfree E. Scaling up digital circuit computation with DNA strand displacement cascades. *Science*. 2011;332(6034):1196–201.

59. Turing AM. Computing machinery and intelligence. *Mind*. 1950;49: 433–60.

60. Penrose R. *Shadows of the Mind: A Search for the Missing Science of Consciousness*. Oxford; Oxford University Press; 1994.

61. Saygin A, Cicecli I, Akman V. Turing test: 50 years later. *Minds and Machines*. 2000;10:463–518.

62. Garnier S, Jost C, Gautrais J, et al. The embodiment of cockroach aggregation behavior in a group of micro-robots. *Artif Life*. 2008;14(4):387–408.

63. Garnier S, Jost C, Jeanson R, et al. Aggregation behavior as a source of collective decision in a group of cockroach-like-robots. In: *Lecture Notes in Artificial Intelligence. Vol 3630. Advances in Artificial Life*. Berlin: Springer; 2005:169–78.

64. Labella TH, Dorigo M, Deneubourg JL. Division of labor in a group of robots inspired by ants' foraging behavior. *ACM Transactions on Autonomous and Adaptive Systems*. 2006;1(1):4–25.

65. Cao YU, Fukunaga AS, Kahng A. Cooperative mobile robotics: antecedents and directions. *Auton Robots*. 1997;4(1):7–27.

66. Şahin E, Spears W, editors. *Proceedings of the Swarm Robotics Workshop: State-of-the-art Survey*. Berlin, Germany. 2005;3342:98–111.

67. Chandrasekaran S, Hougen D. Swarm intelligence for cooperation of bio-nano robots using quorum sensing. Proceedings of BMN '06. San Francisco, CA, USA; 2006:15–8.

68. Von Maltzahn G, Park JH, Lin KY, et al. Nanoparticles that communicate in vivo to amplify tumour targeting. *Nat Mater*. 2011;10(7):545–52.

69. Gaki A, Theodorou A, Vayenas DV, Pavlou S. Complex dynamics of microbial competition in the gradostat. *J Biotechnol*. 2009;139(1):38–46.

70. Kooi BW, Bower MP, Kooijman SALM. Complex dynamic behaviour of autonomous microbial food chains. *J Math Biol*. 1997;36(1):24–40.

71. Pepper JW, Rosenfeld S. The emerging medical ecology of the human gut microbiome. *Trends Ecol Evol*. 2012;27(7):381–4.

72. Ben Jacob E, Becker I, Shapira Y, Levine H. Bacterial linguistic communication and social intelligence. *Trends Microbiol*. 2004;12(8):366–72.

73. Bassler BL. How bacteria talk to each other: regulation of gene expression by quorum sensing. *Curr Opin Microbiol*. 1999;2(6):582–7.

74. Morimoto BH, Koshland DE Jr. Short-term and long-term memory in single cells. *FASEB J*. 1991;5(7):2061–7.

75. Nie X, Cao J. Multistability of competitive neural networks with time-varying and distributed delays. *Nonlinear Anal Real World Appl*. 2009; 10(2):928–42.

76. Kashiwagi A, Urabe I, Kaneko K, Yomo T. Adaptive response of a gene network to environmental changes by fitness-induced attractor selection. *PLoS One*. 2006;1:e49.

77. Frederick MR, Kuttler C, Hense BA, Eberl HJ. A mathematical model of quorum sensing regulated EPS production in biofilm communities. *Theor Biol Med Model*. 2011;8:8.

78. Whitehead NA, Barnard AM, Slater H, Simpson NJ, Salmond GP. Quorum-sensing in Gram-negative bacteria. *FEMS Microbiol Rev*. 2001; 25(4):365–404.

79. Sonnenschein C, Soto AM. Somatic mutation theory of carcinogenesis: why it should be dropped and replaced. *Mol Carcinog*. 2000;29(4):205–11.

80. Baker S. Paradoxes in carcinogenesis should spur new avenues of research: an historical perspective, disruptive science and technology. *Disruptive Science and Technology*. 2012;1(2):100–7.

81. Soto AM, Sonnenschein C. The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory. *Bioessays*. 2011; 33(5):332–40.

82. Sonnenschein C, Soto AM. Theories of carcinogenesis: an emerging perspective. *Semin Cancer Biol*. 2008;18(5):372–7.

83. Radisky D, Hagios C, Bissell MJ. Tumors are unique organs defined by abnormal signaling and context. *Semin Cancer Biol*. 2001;11(2):87–95.

84. Egeblad M, Nakasone ES, Werb Z. Tumors as organs: complex tissues that interface with the entire organism. *Dev Cell*. 2010;18(6):884–901.

85. Kitano H. Cancer robustness: tumour tactics. *Nature*. 2003;426(6963): 125.

86. Grunewald TG, Herbst SM, Heinze J, Burdach S. Understanding tumor heterogeneity as functional compartments—superorganisms revisited. *J Transl Med*. 2011;9:79.

87. Queller DC, Strassmann JE. Beyond society: the evolution of organismality. *Philos Trans R Soc Lond B Biol Sci*. 2009;364(1533):3143–55.

88. Misteli T. The concept of self-organization in cellular architecture. *J Cell Biol*. 2001;155(2):181–5.

89. Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J. Cancer: a Systems Biology disease. *Biosystems*. 2006;83(2–3):81–90.

90. Sonnenschein C, Soto AM. *The Society of Cells: Cancer and Control of Cell Proliferation*. New York: Springer-Verlag; 1999.

91. Agur Z, Kogan Y, Levi L, et al. Disruption of a Quorum Sensing mechanism triggers tumorigenesis: a simple discrete model corroborated by experiments in mammary cancer stem cells. *Biol Direct*. 2010; 5:20.

92. Hickson J, Diane Yamada S, Berger J, et al. Societal interactions in ovarian cancer metastasis: a quorum-sensing hypothesis. *Clin Exp Metastasis*. 2009;26(1):67–76.

93. Nowell PC. The clonal evolution of tumor cell populations. *Science*. 1976;194(4260):23–8.

94. Stephens PJ, Greenman CD, Fu B, et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. *Cell*. 2011;144(1):27–40.

95. Brunk GG. Why do societies collapse? A theory based on self-organized criticality. *J Theor Polit*. 2002;14(2):195–230.

96. Kron T, Grund T. Society as a self-organized critical system. *Cybernetics and Human Knowing*. 2009;16(1–2):65–82.

97. May RM. Will a large complex system be stable? *Nature*. 1972;238(5364):413–4.

98. Golding I, Paulsson J, Zawilski SM, Cox EC. Real-time kinetics of gene activity in individual bacteria. *Cell*. 123(6):1025–36.

99. Rosenfeld S. Stochastic oscillations in genetic regulatory networks: application to microarray experiments. *EURASIP J Bioinform Syst Biol*. 2006:59526.

100. Rosenfeld S. Stochastic cooperativity in non-linear dynamics of genetic regulatory networks. *Math Biosci*. 2007;210(1):121–42.

101. Rosenfeld S. Why do high-dimensional networks seem to be stable—A reflection on stochasticity of dynamically unstable nonlinear systems. In: Gauges R, Kummer U, Pahle J, Willy P, editors. *Fifth Workshop on Computation of Biochemical Pathways and Genetic Networks*. Heidelberg: University of Heidelberg; 2008:101–12.

102. Rosenfeld S. Origins of stochasticity and burstiness in high-dimensional biochemical networks. *EURASIP J Bioinform Syst Biol*. 2009:362309.

103. Rosenfeld S. Patterns of stochastic behavior in dynamically unstable high-dimensional biochemical networks. *Gene Regul Syst Bio*. 2009;3:1–10.

104. Blake WJ, Kaern M, Cantor CR, Collins JJ. Noise in eukaryotic gene expression. *Nature*. 2003;422(6932):633–7.

105. Kepler TB, Elston TC. Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations. *Biophys J*. 2001;81(6):3116–36.

106. McAdams HH, Arkin A. It's a noisy business! Genetic regulation at the nanomolar scale. *Trends Genet*. 1999;15(2):65–9.

107. Raser JM, O'Shea EK. Noise in gene expression: origins, consequences, and control. *Science*. 2005;309(5743):2010–3.

108. Baker SG, Cappuccio A, Potter JD. Research on early-stage carcinogenesis: are we approaching paradigm instability? *J Clin Oncol*. 2010;28(20):3215–8.

109. Merlo LM, Shah NA, Li X, et al. A comprehensive survey of clonal diversity measures in Barrett's esophagus as biomarkers of progression to esophageal adenocarcinoma. *Cancer Prev Res (Phila)*. 2010;3(11):1388–97.

110. Thomas R, D'Ari R. *Biological Feedback*. Boca Raton: CRC Press; 1990.

111. Amdam GV, Seehuus SC. Order, disorder, death: lessons from a superorganism. *Adv Cancer Res*. 2006;95:31–60.