Libertas Academica
FREEDOM TO RESEARCH

PERSPECTIVE

Biomolecular Self-Defense and Futility of High-Specificity Therapeutic Targeting

Simon Rosenfeld

National Cancer Institute, EPN 3108, 6130 Executive Blvd., Rockville, Maryland 20892, USA.
Corresponding author email: sr212a@nih.gov

Abstract: Robustness has been long recognized to be a distinctive property of living entities. While a reasonably wide consensus has been achieved regarding the conceptual meaning of robustness, the biomolecular mechanisms underlying this systemic property are still open to many unresolved questions. The goal of this paper is to provide an overview of existing approaches to characterization of robustness in mathematically sound terms. The concept of robustness is discussed in various contexts including network vulnerability, nonlinear dynamic stability, and self-organization. The second goal is to discuss the implications of biological robustness for individual-target therapeutics and possible strategies for outsmarting drug resistance arising from it. Special attention is paid to the concept of swarm intelligence, a well studied mechanism of self-organization in natural, societal and artificial systems. It is hypothesized that swarm intelligence is the key to understanding the emergent property of chemoresistance.

Keywords: biological robustness, swarm intelligence, biological networks, chemoresistance, cancer therapeutics, dynamic stability, adaptivity

This article is available from http://www.la-press.com.

Introduction

Robustness has been long recognized to be a distinctive property of living entities. According to,[1] robustness is the ability of biological systems "to maintain phenotypic stability in the face of diverse perturbations arising from environmental changes, stochastic events and genetic variations." A detailed account of the concept of biological robustness has been given in.[2] In this paper, robustness is defined as "a property that enables the system to maintain its functionalities against external and internal perturbations." Being a universal mechanism of maintaining integrity of life, robustness also contributes to drug resistance and imposes stringent requirements in drug design.[3] In particular, single molecular targeting has been shown to have low efficacy in many complex diseases like cancer or diabetes.[4] On the other hand, notable success of non-steroidal anti-inflammatory drugs (NSAID) in treating or alleviating wide range of medical conditions suggests that low-specificity multiple targeting may be more efficient in therapeutic modification of complex biomolecular networks.[5]

While there exists a reasonably wide consensus regarding the conceptual meaning of robustness and its all-pervading importance in cellular functioning and medical applications, the biomolecular mechanisms underlying this systemic property are still open to many unresolved questions. In the literature, the attempts of theoretical explanations rarely go beyond the analogies of automatic control theory with strong emphasis on the concept of feedback loops.[2,6] Import of engineering analogies into biology often comes with a heavy price of tacitly adopted, but poorly substantiated, assumptions such as linearization, stationarity, stability, and others.[7] Due to mathematical difficulties, one of the most salient features of biological systems, that is, multiple interactions between the system's components, often remains beyond the scope of existing theories. Theoretically sound handling of these interactions inevitably leads to strongly nonlinear dynamical systems of very high dimensions. The mathematical construct of *network* with links to nonlinear dynamics and graph theory provides a natural description of such systems.[8–10] The property of robustness is inherent in many natural and societal systems. Notable examples include Internet, social networks, insect colonies, and ecological systems, to name just a few. However, it should be noted that robustness is not an inalienable self-evident property of all networks. In order to formulate more precisely which networks are indeed robust and which are not, several prerequisites are required. First, a mathematically definitive and self-consistent description of the networks should exist. Second, the concept of robustness should be formulated in an unambiguous quantitative manner. Third, the methods should exist for estimating the quantitative measures of robustness from observational data. Based on the literature currently available, it may be rightfully stated that the mathematical science of robustness is still in its infant stage, and relatively few examples of reasonably well founded methodologies have been proposed so far. As indicated in Ref:[2] "Given the importance of robustness for the understanding of the principles of life and its medical implications, it is an intriguing challenge to formulate a mathematically solid, and possibly unified theory of biological robustness that might serve as a basic organizational principle of biological systems. Such a unified theory could be a bridge between the fundamental principles of life, medical practice, engineering, physics and chemistry. This is a difficult challenge in which a number of issues have to be solved, particularly to establish mathematically well-founded theories. However, the impact would be enormous."

This paper is intended to fulfill, at least in part, the overall goal formulated above. In particular, it provides an overview of existing approaches to characterization of robustness in mathematically sound terms. Among many aspects of robustness and many ways of conceptualizing this systemic property, special attention has been paid in this paper to the concept of *swarm intelligence*, a well studied mechanism of self-organization in many natural, societal and artificial systems. The second goal is to discuss the implications of biological robustness for individual-target therapeutics and possible strategies for outsmarting drug resistance arising from it.

Quantitative Measures of Robustness

Intuitively, it seems natural to consider robustness as some sort of stability. This qualitative analogy, however, is a shaky basis for introducing the quantitative measures of robustness. The concept of robustness is wider than the concept of stability.

As discussed in,[2,11,12] robustness is a property of maintaining the *functional stability* but not necessarily the *structural invariance* and *phenotypic stability*. In contrast, stability per se is the characteristic of dynamic behavior of a system with a pre-specified and invariant configuration; hence, dynamic stability may be seen as a simple form of robustness. We now consider several approaches to quantifying the property of robustness.

Robustness as tolerance to attack and resistance to damage

In this approach, robustness is seen as a characteristic of the network in its ability to perform certain functions under adverse conditions. It is *postulated* that efficiency in performing these functions strongly depends on the existence and density of alternative pathways between the network's nodes. If some links between the nodes are broken then average lengths of the pathways between any two nodes selected at random may increase and the network may even become fragmented. This increase in the average length of the path is interpreted as degradation in performance.[13,14] Such a notion of robustness is introduced on a purely intuitive level; telecommunication networks, traffic infrastructures, social networks, power grids, citation networks and many others provide fertile ground for supporting such intuition. Adopting this notion as a starting point for further logical and mathematical constructs, one may move on towards quantification of robustness. To this end, the concept of *efficiency* should be defined. Among many possibilities of the kind, perhaps the simplest and intuitively most appealing one can be introduced as follows.[14] Suppose that d_{ij} is the shortest number of steps which are necessary to travel, or transmit information, from the node i to the node j within the network, $\mathbf{G}$; this number is often called the *network distance*. Efficiency, ε_{ij}, of the $\{i, j\}$ link is defined as $\varepsilon_{ij} = d_{ij}^{-1}$, and the *global efficiency* as the average of the pair-wise efficiencies over the network

$$E(\mathrm{G}) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d_{ij}} \qquad (1.1)$$

Vulnerability to damage caused by the deactivation of the set of nodes $\{i\}$, $V_{\{i\}}$, may now be defined as decrease in global efficiency: $V_{\{i\}} = E(\mathrm{G}) - E_{\{i\}}(\mathrm{G})$, and the *global vulnerability to damage* as the average of individual vulnerabilities over all the subsets $\{i\}$ of the same size

$$V(G) = \frac{1}{N} \sum_{\{i\}} V_{\{i\}}(G), \qquad (1.2)$$

where N is the total number of possible combinations $\{i\}$. Given these definitions, robustness may be quantified as the inverse or the opposite of the $V(\mathbf{G})$: the less vulnerable is a network the more robust it is.

Two notes are in order regarding this approach to robustness. Firstly, not all the networks of interest, especially those of biological nature, are readily amenable to such a definition. As an *ad hoc* example, in population dynamics, the predator-prey relationships within the food webs can hardly be characterized in terms of transmission of information of some sort or travel between the nodes. In molecular biology, genetic regulatory networks can not be always reduced to the pair-wise interactions. The list of examples for which the above formulated quantification of robustness is not well suited may be continued. Secondly, the concept of robustness introduced above does not have any direct links to the notion of dynamic stability. In part, this is because in the above outlined graph-theoretical approach to robustness, neither the links nor the nodes are assumed to possess any dynamic time-dependent properties; essentially such networks are static.

Robustness as manifestation of dynamic stability

In this approach, the system of interest is considered as a nonlinear dynamical system whose behavior may be described, at least in principle, through the laws of interaction between the system's components. Let $\mathbf{S}$ be a dynamical system whose governing equation is written in the form

$$d\mathbf{x}/dt = \mathbf{F}(\mathbf{x}|\boldsymbol{\theta}), \qquad (1.3)$$

where $\mathbf{x}(t)$ is the time-dependent vector characterizing the state of the system, and $\boldsymbol{\theta}$ is the vector of structural parameters of the system. Let also $\{\mathbf{x}_p\}$ be a set of *fixed points*, that is, the points in which $\mathbf{F}(\mathbf{x}_p|\boldsymbol{\theta}) = 0$.

In applications, such points are often referred to as the *points of equilibrium or steady states*. It should be noted, however, that in general existence of a point of equilibrium does not mean that this equilibrium is necessarily stable, and therefore does not automatically imply that $\mathbf{x}_p$ are the *steady* states. In order to infer stability of a system at a fixed point, $\mathbf{x}_0 \in \{\mathbf{x}_p\}$, one needs to linearize (1.3) thus transforming it to the form

$$\mathbf{F}(\mathbf{x}) = \mathbf{J}(\mathbf{x}_0)(\mathbf{x} - \mathbf{x}_0), \qquad (1.4)$$

where $\mathbf{J}(\mathbf{x}_0) = \|\partial F_i/\partial x_j\|$ is the *Jacobian matrix*. According to general theory, the system is stable if all the eigenvalues of the $\mathbf{J}(\mathbf{x}_0)$ have negative real parts. This condition guarantees that any initial perturbation will exponentially decrease with time.[15] If at least one of eigenvalues has a positive real part then the system is unstable (a more detailed discussion may be found in the works[12,16] by this author). It should be noted that in multidimensional systems, the conditions of Jacobian stability impose a set very stringent constraints of high algebraic order (such as Routh-Hurwitz and Lyapunov criteria)[17] and have very little chance to materialize naturally.[18] For example, it has been shown numerically in[19] that multidimensional equations of chemical kinetics almost certainly *are unstable* in the Jacobian sense. This conclusion has far reaching implications.[11] It suggests that observed robustness must have much deeper roots than those associated with the Jacobian stability. Furthermore, the Jacobian analysis of stability provides little guidance regarding the patterns of long term behavior of the system. A key concept in studying such behavior is the quantity called *phase space compressibility*, $\chi(t)$. It is defined as the *trace* of the time-dependent Jacobian matrix

$$\chi(t) = \mathrm{Tr}\mathbf{J}(t) = \sum_{i=1}^{N} J_{ii}(t) \qquad (1.5)$$

This quantity is the measure of the rate of relative decrease or increase of the phase space volume moving with the flow along the system's trajectories in its phase space. If $\chi(t) > 0$ then the trajectories initially lying within some small domain, $\Omega(t|t_0)$, will diverge with time, and the distance between them will grow to infinity when $t \to \infty$. Such behavior signifies

high sensitivity to initial conditions, and is equivalent to *asymptotic dynamic instability*. In the opposite case, when $\chi(t) < 0$, the phase volume, $\Omega(t|t_0)$, is contracting with time. This means that initially distant trajectories become closer to each other and ultimately will enter a certain compact set in the phase space to stay there forever. This situation is usually referred to as *asymptotic dynamic stability*. If the volume $\Omega(t|t_0)$, is deforming with time uniformly in all directions then initially distant trajectories asymptotically approach the same limiting trajectory thus forming a *limit cycle*. The concept of asymptotic dynamic stability provides an avenue for quantification of robustness. If the system is asymptotically stable then knocking the system out of its repertoire (trajectory) will have no lasting effect because the system is supposed to return back to the same asymptotic domain. Note that the concept of asymptotic dynamic stability is a concise expression of existence of multiple negative feedback loops. On top of that, since the limit cycles in asymptotically stable systems may be multidimensional and inseparable, the concept of asymptotic dynamic stability is also a concise, mathematically self-consistent, expression of *interaction* between the feedback loops belonging to different dimensions of the system.

Robustness as manifestation of multistability

Existence of multiple attracting domains in complex dynamical systems (for brevity, often called *multistability*) provides a mechanistic basis for a switch-like behavior in which a system can make a sudden jump from one attractor to a drastically different attractor under seemingly gradual change in stimulus, environmental factors or small random perturbations.[20] In molecular biology, multistability is considered to be an important mechanism of cell differentiation.[21] As mentioned above, in multidimensional systems, local fixed points almost certainly are unstable in the Jacobian sense. However, existence of *multiple* fixed points may drastically change the scenario of the system's behavior: it can travel from one fixed point to another thus creating very complex but dynamically stable patterns. Such patterns of behavior have been experimentally observed in a number of biological phenomena; the circadian clock is a prominent example.[22] Multiplicity of attractors creates complexity of the behavior and may serve

as an indirect measure of the number of alternative repertoires available for the system. The key question arising in this context is how many attractors may exist in the system of interest? Evaluation of the number of attractors in multidimensional systems is a difficult mathematical task. A notable example amenable to direct analytical exploration has been considered in.[23] In this example, dynamics of the system is governed by the Lotka-Volterra equation, the mathematical model widely used in population dynamics of interacting species[24,25]

$$\frac{dx_i}{dt} = \varepsilon_i x_i + \sum_{k=1}^{N} \alpha_{ik} x_i x_k; \quad i = 1, .., N, \quad (1.6)$$

where $\{x_i\}$ are the population abundances and $\{\varepsilon_i\}$ are the corresponding rates of production. It has been demonstrated in this work that existence of multiple attractors is associated with the existence of the *autocatalytic cycles* and can be found through the eigenvalues of the *interaction matrix, α_{ik}.* Another promising approach has been developed in[26] for the dynamical systems presented as random Boolean (Kauffman) networks. It has been shown that in such systems the number of attractors *grows with the system's size*. Generally, the question of number of attractors in a large dynamical system is wide open for further inquiry.

Robustness as tolerance to variations of structural parameters

Tolerance to perturbation of structural parameters is yet another property of dynamical systems that may be interpreted as a form of robustness. As an *ad hoc* example of such perturbations, let us recall that in complex biochemical systems the kinetic rates are temperature-dependent through the Arrhenius factor $\exp(Q/RT)$, where Q is the caloric effect of reaction, R is the universal gas constant, and T is the absolute temperature.[27] Hence, even moderate variations in ambient temperature may cause drastic changes in kinetic rates and overall dynamics of the system. To formalize this concept, let us suppose that in the equation (1.3) governing the system, the structural parameters, $\boldsymbol{\theta}$, are subject to some perturbation, $\delta\boldsymbol{\theta}$. Obviously, trajectories of the perturbed system will also change, and the question arises how sensitive

are the solutions to this modification. The core quantitative characteristic to reflect this sensitivity is the matrix $\| \partial F_i / \partial \theta_k \|$ (often called *sensitivity matrix*). Given identical initial conditions, the evolution of differences between the perturbed and unperturbed solutions is described by the equation

$$x_i(t|\boldsymbol{\theta} + \delta\boldsymbol{\theta}) - x_i(t|\boldsymbol{\theta}) = \int_0^t \{F_i[x(t|\boldsymbol{\theta} + \delta\boldsymbol{\theta})|\boldsymbol{\theta} + \delta\boldsymbol{\theta}] - F_i[x(t|\boldsymbol{\theta})|\boldsymbol{\theta}]\}dt, \quad (1.7)$$

which for sufficiently small perturbations reduces to

$$\delta x_i(t|\boldsymbol{\theta}) = \int_0^t \sum_k (\partial F_i / \partial \theta_k) \delta\theta_k dt, \quad (1.8)$$

Sensitivity analysis proved to be a highly efficient instrument in the design of robust engineering systems. With the advent of high throughput data gathering techniques and computational systems biology, the concepts of sensitivity analysis began to gain popularity in the analysis of complex biomolecular phenomena.[28] It should be noted, however, that in highly nonlinear systems, even a small change of parameters may throw the system into an entirely different dynamic regime (the phenomenon known as *bifurcation*).[15] High degree of nonlinearity is quite typical in the biomolecular world; hence, despite obvious usefulness, applicability of the essentially linear *sensitivity analysis* to complex biological phenomena may be limited.

Robustness as tolerance to random perturbations

Any biological system is functioning in the presence of uncontrolled, and mostly unknown, disturbances covered by the blanket term *noise*. There are numerous ways of including noise in the system's dynamics[29] among which the *additive model* is the simplest and intuitively most appealing

$$d\mathbf{x}/dt = \mathbf{F}(\mathbf{x}|\boldsymbol{\theta}) + \boldsymbol{\xi}_t, \quad (1.9)$$

where $\boldsymbol{\xi}_t$ is a stochastic process. Mathematically tractable results may be obtained by transforming the stochastic differential equation (1.9) into the

Fokker-Plank equation describing the temporal evolution of probabilities of finding the system in a certain domain of phase space.[30] Quantitatively, the vector or time-dependent variances, $\{\sigma^2[x_i(t)]\}$ may serve as a measure of tolerance against random noise: the smaller are these variances, the more robust is the system. This would mean that the system is functioning *approximately right* even despite the presence of uncontrollable disturbances.

Robustness as manifestation of functional redundancy

In engineering, functional redundancy is the design principle requiring duplication or triplication of the modules critically important for reliability of the system. Transplanted into biological context, redundancy is often thought to be a major contributor to biological robustness by enacting the backup mechanisms in the essential life-sustaining functions. For example, Kitano[2] indicates: "Robustness can be enhanced if there are multiple means to achieve a specific function, because failure of one of them can be rescued by others. Here, I call this mechanism 'alternative', or 'fail-safe'. This concept encompasses redundancy, overlapping function and diversity, as the differing degrees of similarity between the various alternative means that are available." Unquestionably, redundancy is a pervasive phenomenon on every level of biological organization. However, the notion that redundancy is always beneficial in terms of robustness is not so indubitable. An obvious counterargument is that multiplication of operational capabilities would require multiplication of all the supporting resources. Mother Nature (a.k.a. "evolutionary pressure") would probably want to produce not only reliable but also parsimonious designs. Turning again to engineering analogy, an aircraft built up to withstand all possible storms and all conceivable equipment failures would probably be too heavy, require too much fuel and, as a result, be too expensive for beating the competitors and staying on the market. Biological pros and cons of redundancy have been the subject of many important works.[31–35] To keep this paper within a reasonable size, we limit ourselves by mentioning here only several key ideas. A fundamental, and not completely resolved, theoretical issue is whether or not biological redundancy may be evolutionary stable.[36,37] If, for example, there 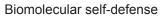are two genes with duplicate functions, then one of them with higher expression rate would experience a higher mutation rate, thus having a higher tendency to extinction. In large populations of rapidly dividing cells, there will be even a tendency towards *anti-redundancy*, that is, an elevated sensitivity to deleterious mutations. On the other hand, in small populations of slower growing organisms, the evolution towards redundancy may prevail.[31] It should be noted, that the general term redundancy covers a number of distinctly different mechanisms and phenomena. Thus, it is possible that a gene is engaged in two or more different pathways leading to the same terminal metabolite. In this case, a failure in one pathway may be compensated by the success in the other. It is also possible that there are several functionally similar genes acting independently. A most surprising situation may occur when identical results are achieved even without functional similarity between the genes, the phenomenon dubbed as *backup without redundancy*.[32] In genomic context, the key evidence of redundancy is that the gene regulatory system often continues to function normally even after deletion of the critically important genes. Indeed, these *gene deletion experiments* do suggest that perhaps there are the *backup genes* in existence somewhere in the genome.[34] However, an alternative view is also possible: the genes that seem to be non-essential are activated under the extreme environmental circumstances or under the conditions not yet studied in the laboratory.[38] Essentially, this would mean that there is no redundancy. As seen from this brief overview, interrelations between biological robustness and redundancy involve many subtle, often poorly understood, issues. Mathematical models for these relations are notoriously difficult to formulate.[31] In our opinion, it would be safe to claim that at this time there is no compelling evidence that redundancy plays a universally significant role in the phenomenon of biological robustness.

Robustness of genetic regulatory networks

As an example of application of the above formulated concepts, we briefly summarize the results reported by this author in.[16] Using the nonlinear formalism of S-Systems,[39] several important facts have been established. First, any genetic regulatory network (GRN) has at least one point of equilibrium (fixed point).
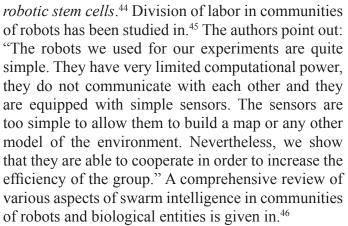
Second, at this point the GRN is *unstable* in the Jacobian sense. This result is significant. It says that the GRN can never reside it a steady state in which all the numerous concurrent processes tangled into the genome-wide gene expression are perfectly balanced, thus resulting in constancy of all the biochemical entities involved. Large spontaneous deviations from the point of equilibrium such as backlogs, bottle-necks, and loss of synchronization are inevitable properties of GRNs. Third, under the fairly general conditions, a GRN may be *dynamically asymptotically stable*. Essentially, the necessary conditions stipulate absence of the *massively autocatalytic* gene expressions, that is, the situation when a large number of genes require the proteins to serve as transcription factors to express the very same genes they originate from. Qualitatively, dynamic asymptotic stability means that there exists a regime of stable oscillations in which all the constituents are perpetually changing their concentration. If to rule out a fairly exotic possibility of chaotic dynamics, this type of behavior signifies robustness of genetic regulatory system in the sense described above in the Section devoted to dynamic stability. Due to very high dimensionality of these oscillatory patterns, it is admissible to characterize this type of motion in stochastic terms, as was discussed in the works[11,19] by this author. It is interesting to mention that, as established in,[16] the sign of phase space compressibility (1.5), is *largely independent of the kinetic rates* of biochemical reactions involved in gene expression; only the topological structure of GRN turned out to be crucial. This result may be interpreted as a manifestation of robustness in the sense of independence on variations of structural parameters.

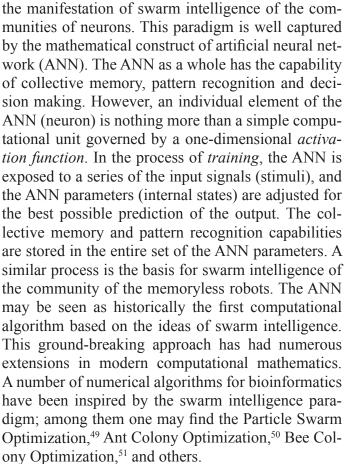## Robustness as Manifestation of Swarm Intelligence

From the logical standpoint, the considerations of this Section are applicable to any network, regardless of its physical or biological content; the nodes of the network could represent any system, simple or complex, and the links could correspond to interactions of any nature. In particular, the cells may be considered as nodes and the cell-to-cell signaling pathways as links. The considerations of robustness are fully applicable to this level of systemic representation as well. If for example, the genetic regulatory system in

any of the participant cells becomes unstable, or the gene expression process runs into the chaotic mode, the system as a whole, that is the *network of cells*, still retains vast resources to maintain its functional stability.

However, a fundamentally new emergent property appears in large systems where the interactions between subunits are complex multifunctional processes by themselves. This ability has been termed *swarm intelligence*, which by definition 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 community*.[40] Social insects provide a vast universe of astounding examples of elaborate collective strategies in solving routine problems and struggling for survival. Importantly, 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. Somewhat paradoxically, intelligent individuals would have a tendency to develop a community-wide information infrastructure and a central supervisory authority;[41] success of the organization as a whole will then strongly depend on the ability of individual members to be *timely informed* and their willingness to *obey the orders* without re-analyzing or re-interpreting them. The best example of successes and perils of this type of organization is human society. It is quite possible that communities of individuals acting completely within the stimulus-response rules (in terminology of,[41] the *dumb individuals*) may be more successful in their struggle for survival rather than the communities of more intelligent beings. Proof of the principle that a large community of *dumb individuals* may possess the elements of self-organization and swarm intelligence has been vividly demonstrated in.[42,43] In these works, a group of memoryless micro-robots have been programmed to mimic *individual* behaviors of cock-roaches. The micro-robots, however, were not hard-wired to have any informational and analytical tools regarding behavior of other robots or 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 cock-roaches. An important aspect of swarm intelligence is the ability of self-healing and self-repair, as been demonstrated by computational experiments with the

robotic stem cells.[44] Division of labor in communities of robots has been studied in.[45] 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.[46]

Powerful impetus to the idea of robotic communities has been recently given by nanotechnology. If the swarms of micro-robots can behave in self-organized intelligent manner then why wouldn't *nano-robots*? Various strategies of utilizing the quorum sensing in various goal-seeking tasks for communities of nano-robots have been explored in the series of simulation experiments.[47] Although only the first steps have been made in practical implementation of this intriguing idea, the results already achieved are impressive. For example, Maltzahn et al[48] constructed the 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 of 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" (italicized by SR).

The capability of the community of individuals devoid of any traces of personal memory or personal intellect to produce some forms of collective memory and collective intellect seems to be a sort of miracle at first sight. Two well known examples remind us that it is not so. Communities of neurons (nervous cells) form the basis for highly sophisticated human intellect, as well as for the intellect of animals. Meanwhile, the neurons themselves are nothing more than comparatively simple stimulus-response devices with the only capability to transmit electrical impulses to other neurons. It may be rightfully said that our own intellect, at least in part, is the manifestation of swarm intelligence of the communities of neurons. This paradigm is well captured by the mathematical construct of artificial neural network (ANN). The ANN as a whole has the capability of collective memory, pattern recognition and decision making. However, an individual element of the ANN (neuron) is nothing more than a simple computational unit governed by a one-dimensional *activation function*. In the process of *training*, the ANN is exposed to a series of the input signals (stimuli), and the ANN parameters (internal states) are adjusted for the best possible prediction of the output. The collective memory and pattern recognition capabilities are stored in the entire set of the ANN parameters. A similar process is the basis for swarm intelligence of the community of the memoryless robots. The ANN may be seen as historically the first computational algorithm based on the ideas of swarm intelligence. This ground-breaking approach has had numerous extensions in modern computational mathematics. A number of numerical algorithms for bioinformatics have been inspired by the swarm intelligence paradigm; among them one may find the Particle Swarm Optimization,[49] Ant Colony Optimization,[50] Bee Colony Optimization,[51] and others.

Highly sophisticated forms of swarm intelligence have been observed in bacterial communities. Compared to the *dumb individuals* mentioned above, bacteria have at least two advanced features which make the behaviors of bacterial 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 microbial communities has been extensively analyzed in.[52] A number of important conclusions have been reached in this landmark work. Firstly, the bacterial communities possess the form of *inheritable collective memory* and the ability of maintaining *self-identity* through the mechanisms of signal transduction and genomic plasticity. Secondly, using a wide range of bacterium-to-bacterium chemical communications and stigmergic sensing of environment, the bacterial *communities* are capable of collective decision-making, purposeful alterations of the colony structures, recognition and identification of other colonies. In essence, a bacterial community

as a whole may be seen as a *multicellular organism* with loosely organized cells and a 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 be also 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.[53]

The high level of self-organization observed in colonies of social insects and microbial communities gives rise to the concept of *superorganism*. Superorganism is not simply a complex system or a compartmentalized community of individuals with functionally distinct modules. The most fundamental property of a superorganism, built upon all other systemic properties, is the *shared purpose* of its existence.[54] This shared purpose may coexist with rivalry for shared resources between individuals or group of individuals within the superorganism. Assuming again that there is neither central authority which governs the superorganism nor mapping of the collective behavior onto the cognitive capabilities of individual members, it is admissible to ask: how is that possible that a superorganism may achieve its purpose despite the internal conflicts, injuries, losses and constantly changing environmental conditions? The concept of swarm intelligence helps to resolve this fundamental issue.

All that is said above is fully applicable to the somatic cells. As stated in:[53] "Bacteria invented the rules for cellular organization." There is, however, an essential difference between the somatic and microbial cells pointed out in.[41] The somatic cells are immobilized in the extracellular matrix and tissue thus forming an actual *physical network* with relatively stable links. In contrast to microbial communities, which are free to move their members in space, the swarm intelligence of the community of somatic cells is mostly busy with shaping their *internal* structural elements such as gene expression profiles and metabolic pathways. Similar to microbial cells, the somatic cells possess a number of properties which

may be interpreted as short-term memory (defined as the *recording of experience that can modify behavior*).[55] In particular, a gene network may utilize the property of multistability for adaptive response through fitness-induced attractor selection.[56] All this means that a community of somatic cells acts as a self-sufficient intelligent being taking care of its own survival through *cooperative manipulation with their internal states*.

Attacking the Network

Suppose that the task at hand is to inflict fatal damage to a robust network possessing some or all of the aforementioned functional capabilities. Depending on the network's structure and self-healing mechanisms, the strategies for attack may be quite different.

Static network perspective

In a *scale-free network*, the probability that a randomly selected node has exactly k links follows the law, $P(k) \sim k^{-\gamma}$. For the majority of real network topologies, γ is a positive number between 1.5 and 3.5. This type of probabilistic structure indicates that a non-vanishing probability exists that there are nodes in the network which have very large number of links.[57] If, for example, $\gamma = 2.5$, then, in the network with 10,000 nodes, the average number of links per node is as small as $\bar{k} = 1.94$, whereas about 14 nodes will have more than 50 links. These highly connected nodes are usually called *hubs*. An essential part of the network functionality depends on the well-being of the hubs. Scale-free networks are comparatively resistant to *multiple random* attacks. However, knocking out even one of its hubs may be lethal.[14] Scale-free networks are widespread in nature and society; commonality of their structure lies in the similarity of mechanisms of their evolutionary growth through *preferential attachment*.[57] It has been repeatedly demonstrated that many intracellular networks follow the scale-free law; notable examples include protein-protein interaction and metabolic networks.[58] The strategy of attacking the scale-free network is quite obvious: the hubs should be targeted first. However, it is never known in advance which set of nodes do actually serve as the hubs. Therefore, as a part of the overall strategy for attack, targeting the hubs may be costly and time consuming because of the necessity of preliminary

reconnaissance for uncovering the network's topological structure. In contrast, random attacks do not require such foreknowledge and may eventually be more efficient in terms of cost-benefit balance, as will be discussed later.

In the exponential networks, $P(k) \sim \exp(-\gamma k)$ for large k; therefore, the probability of occurrence of *hubs* is negligible. A characteristic feature of such networks is existence of the *small worlds*, that is, comparatively small groups of tightly interconnected nodes.[59] Due to absence of the high-value targets, random attacks is the only reasonable strategy against such networks.

The aforementioned strategies are based on a purely static vision of the system. Static networks do not possess a mechanism of *knowing* that they are under attack, and, figuratively speaking, do not *feel pain* caused by damage to its nodes. In more refined terms, this means that neither the considerations of dynamical stability, nor the possibility of emergence of swarm intelligence, nor the ability of the network to respond through reorganizing itself are included in the static vision. For example, the success of removing the leader of a terrorist network may turn out to have only a fleeting effect because, after a certain period of turmoil, the network may elect a new leader and become even stronger through adaptation and learning from negative experience.

Nonlinear dynamics perspective

If a complex dynamical system is *globally asymptotically stable* then any limited-time perturbation applied to the system will dissipate, and the system, sooner or later, will end up within its unique asymptotic attractor. In order to modify the functional behavior of such a system, the system should be first *disorganized* to the point of becoming chaotic. As paradoxical as it may sound, chaotic states are comparatively easy to control. It follows from the very essence of chaoticity whose hallmark property is high sensitivity of the phase space trajectories to the initial conditions and governing parameters. This means, in particular, that only slight modifications of those may completely change the scenario of motion. Moreover, it has been established by a number of authors [60](and references therein) that a chaotic attractor is usually embedded within a dense manifold of *stable periodic orbits*. In order to stabilize chaotic motion, one would need to tailor a small *time-dependent* perturbation to push the system towards one of already existing periodic orbits. The first example of this kind has been presented in the seminal paper by Ott, Grebogi, and Yorke.[61] The authors point out: "It is interesting to note that if the situation is such that the suggested method is practical, then the presence of chaos can be a *great advantage*. The point is that any one of a number of different orbits can be stabilized, and the choice can be made to achieve the best system performance among those orbits. If, on the other hand, the attractor is not chaotic but is, say, periodic, then small parameter perturbations can only change the orbit slightly. Basically we are then stuck with whatever system performance the stable periodic orbit gives, and we have no option for substantial improvement, short of making large alterations in the system". This fundamental result has been first established through fairly involved theoretical considerations and supported only by numerical simulations. Upon publication, there has been a concern in the nonlinear dynamics community that this result could be primarily of academic interest with no easy way to experimentally demonstrate its validity, let alone any practical applications. This concern has been quickly dispelled experimentally.[62] The authors summarize their remarkable findings as follows: "In conclusion, we have demonstrated the first control of chaos in a physical system, using the method of Ott, Grebogi, and Yorke. Some advantages of this method are the following: (1) no model for the dynamics is required; (2) the computations required at each iterate are minimal; (3) the required changes in the parameter can be quite small; (4) different periodic orbits can be stabilized for the same system in the same parameter range; (5) control can be achieved even with imprecise measurements of the eigenvalues and eigenvectors; and (6) this method is not restricted to periodically driven mechanical systems, but extends to any system whose dynamics can be characterized by a nonlinear map." Further developments expressly demonstrated that the vision outlined in[61] was truly prophetic. Comprehensive review[63,64] cites more than 300 applications of the idea of controllable chaos covering a wide range of disciplines, including medical and biological fields. Perhaps, the most impressive among them were treatment of

cardiac arrhythmia, reduction of the level of chaotic oscillations in seasonal epidemics, and controlling blood sugar in diabetes (see[63,64] for more detail and extensive bibliography).

As discussed above, it is quite typical for a complex dynamical network to have multiple attractors, the phenomenon often referred to as *multistability*.[65] If the system resides in a stable state associated with some sort of *malicious* activity then a possible strategy of forcing the system into a more *benign* regime would be moving it to a different steady state. Such possibility of controlling complex systems by moving them between different attractors has been demonstrated in many works; for recent examples and review, see.[66]
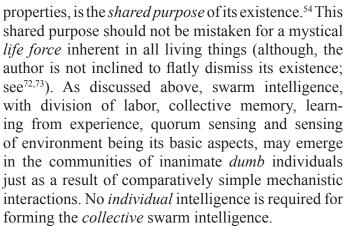
Swarm intelligence perspective

As discussed above, a complex system possessing the elements of swarm intelligence has the capability of restructuring itself in response to external adverse influences. Figuratively speaking, it is capable of *healing and defending* itself. Even though the behaviors of individual members of the system may lie completely within the realm of simple stimulus-response rules, the reaction of a system as a whole may be far more complex and much less predictable. If a necessity arises to modify or terminate the system's malicious behavior, two fundamentally different approaches may be undertaken: the system may be *obliterated* or, alternatively, the system may be *outsmarted*. In the latter approach, the cognitive/behavioral properties of the network should be explored much in the same manner as the communities of bees, or ants, or fish schools have been studied for decades.[40,46] Among many systemic characterizations of the collective behavior, several are of uttermost importance. These are the *division of labor*, *collective memory*, and *quorum sensing*. Obviously, these characteristics cannot be merely reduced to the quantification of biological or clonal diversity (which are rightfully regarded to be the driving forces of evolution, eg,[67]) It should be also noted that in populations counting in millions, it would not make much sense to launch a fight against individual members of the community. Likewise, it may be futile to attach any special significance to individual members or individual traits in their ability to be representative of the behavior of the entire community (eg, serve as *biomarkers*). A successful strategy against a network possessing a collective faculty of swarm intelligence would require understanding the vital resources of the network's existence and driving forces of its self-defense.

Tumor as a Robust Intelligent Superorganism

Among the many theories of cancer onset and progression, two approaches may be regarded as somewhat diametrically opposite, with innumerable variations and flavors between them. These are the Somatic Mutation Theory (SMT) and the Tissue Organization Field Theory (TOFT). The essence of the 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 the cell cycle.[68] In SMT, the neoplastic lesions that destroy normal tissue architecture are the results of the DNA-level events. Conversely, according to the TOFT, carcinogenesis is primarily a problem of the tissue organization: carcinogenic agents (environmental chemicals, inflammation, viruses, etc.) destroy the normal tissue architecture thus disrupting the cell-to-cell signaling pathways, inflicting damage to intracellular homeostasis and compromising the genomic integrity. In TOFT, the DNA mutations are the result, and not the cause, of the tissue-level events.[68] Numerous hybrid approaches (eg,[69] and references therein) maintain, generally, that alterations in the tissue microenvironment contribute to selective clonal expansion of mutated cells thus forming a positive feedback mechanism for tumor growth and proliferation. It is becoming increasingly clear that carcinogenesis is a systemic phenomenon transversing the entire hierarchy of biological organization from the level of gene expression to the levels of tissues and organs.[70] It is highly unlikely that it will ever be possible to single out any element or organizational level in this system that bears a primary responsibility for cancer onset and progression. This fundamental complexity and inseparability naturally leads to the notion that tumors are in fact the self-sustaining and self-motivating superorganisms.[71]

As mentioned above, the most fundamental property of a superorganism, built upon all other systemic

properties, is the *shared purpose* of its existence.[54] This shared purpose should not be mistaken for a mystical *life force* inherent in all living things (although, the author is not inclined to flatly dismiss its existence; see[72,73]). As discussed above, swarm intelligence, with division of labor, collective memory, learning from experience, quorum sensing and sensing of environment being its basic aspects, may emerge in the communities of inanimate *dumb* individuals just as a result of comparatively simple mechanistic interactions. No *individual* intelligence is required for forming the *collective* swarm intelligence.

Numerous observations confirm the notion that a cancer tumor may be regarded as a society of cells possessing the faculty of swarm intelligence. One of the important aspects of swarm intelligence is *adaptivity* which is a form of learning from experience. In literature, in attempts to conceptualize this complex phenomenon, there is a reductionist tendency to associate adaptivity with multiple layers of negative feedback loops.[74] For example, on the cellular level, tumor overexpression of MDM2 may cause degradation of P53 thus blocking apoptosis. Hence, it may be said that the MDM2-P53 interaction functions as a negative feedback loop for maintaining optimal P53 level.[75] Examples of the kind are too numerous to be discussed here.[76] On the level of a tumor as a whole, multiple feedback loops are activated between the tumor cells and extracellular matrix, vasculature, other tumor cells and tumor microenvironment. Each individual feedback control seems to act as a blind and automatic stimulus-response mechanism. It is obvious, however, that the entire system cannot succeed in fulfilling its task unless these individual controls are working *coherently*, sharing a common goal. Observed astounding coherence between all the innumerable elementary processes comprising tumor adaptivity allows one to see tumor as a *separate organ*,[77,78] and to talk about its *defensive tactics*.[3] Obviously, these words are more than simple metaphors. Each neoplasm has to build up its specific self-defensive tactics in the process of evolutionary growth and learning from experience *during its lifetime*. Fundamentally, such capabilities are nothing else than manifestations of swarm intelligence in the community of tumor cells. It is, therefore, admissible to hypothesize that, when developing therapeutic strategies against cancer, one needs to take

into consideration not only the tumor clonal diversity,[79] and not only the existence of blind automatic feedback loops, but also to recognize that the *enemy is intelligent*, capable of discerning the weapon applied against it and mounting a counteroffensive.

Acquired Chemoresistance as a Manifestation of Swarm Intelligence

It has been long recognized that cancer cells, after the fleeting inhibitory effect of a chemotherapeutic agent, may develop the capabilities of resistance to treatment. Numerous examples of the kind pertaining to breast cancer are given in.[80] In particular, these authors indicate: "Interestingly, some patients have an early recurrence even though they have a tumor with good prognostic features and at a favorable stage. These recurrences have been explained by the existence of certain cellular characteristics at the molecular level that make the tumor cells resistant to therapy." And further: "No tumor response is observed in some cases despite the use of appropriate therapy. The tumor continues growing during treatment in such cases, a phenomenon called primary resistance to therapy." These capabilities of evading attack are interchangeably termed *adaptivity*, or *chemoresistance*, or *acquired resistance*, and, regardless of the name, all of them are the manifestations of robustness of cancer cells, both individually and collectively. High probability of relapsing after a certain period of apparent success has led to the necessity of distinguishing between the *response rate* and the *success rate* in chemotherapy. In recent comprehensive review,[76] numerous mechanisms and various aspects of chemoresistance have been elucidated. The authors point out that: "to overcome the toxic effects of curative compounds, cancer cells have to continuously develop the capability to implement and strengthen normal physiological functions or to mature de novo mechanisms of resistance against single selected compounds or multiple agents, often apparently unrelated. Nearly any type of chemoresistance is a multifactorial process involving induction of drug-detoxifying mechanism, quantitative and qualitative modification of drug targets, arrest of cell cycle, regulation of DNA replication or reparation mechanisms, and modulation of apoptosis. These modifications are acquired in response to a selection pressure." It should be noted, however, that even a detailed *description* of a mechanism is far from

being an *explanation* of how and why this mechanism comes to existence. Furthermore, it is not sufficient to just describe these *individual* mechanisms; it is equally important to comprehend how all the biochemically disparate processes belonging to different time scales, to different cellular compartments and to different cell subpopulations may come to synergy and coherent collaboration. The concept of *selection pressure* used in the above excerpt can hardly be recognized as an *explanation* of the chemoresistance without falling into the *nominal fallacy* of confusing naming with explaining. The concept of selection (or evolutionary) pressure is applicable only to the populations of cells (including their current generations and progeny), rather than to individual cells. In order to acquire evolutionary advantages, the cancer cell population should not only accumulate a rich arsenal of inheritable mechanisms of resistance, but also develop the ways of their coherent interaction. This means that the *internal mechanisms* of individual cells should co-evolve in consistency with the *shared goals* of the entire cell population. This class of evolutionary changes is in fact very fast: its characteristic times are of the order of the lifespan of a tumor. The concept of swarm intelligence, well substantiated theoretically, richly supported by observations and demonstrated experimentally, is *the key to understanding the emergent property of chemoresistance*.

Futility of High-Specificity Therapeutic Targeting

As mentioned above, a troubling aspect of chemoresistance is that it represents an integrated cellular response in which numerous individual pathways of resistance are acting synergistically. In,[81] this integrated response is summarized as follows: "Resistance pathways are interdependent or interconnected and affect the delivery, stability and function of anticancer drugs. It is however worth noting that the precise contribution of specific resistance pathways to anticancer drug efficacy in specific cancers *remains to be fully elucidated*. It is likely that in many cases, resistance may arise through multiple mechanisms that develop in parallel. We have generated a solid understanding of many of the main pathways and the respective relevance of these in the resistant phenotype in vivo continues to engender lively debate. These issues urgently need to be addressed to shape or prioritize future strategies

designed to overcome this considerable impediment to a major form of cancer treatment" (italicized by SR). Even those mechanisms of chemoresistance that are relatively well established are still open to many unresolved questions. For example, a crucial role of the P53 protein in establishing balance between the cell cycle arrest and apoptosis has been very well understood. However, an exact way of how the correct balance between the cell cycle arrest and programmed death is established is still unknown. Being a highly connected node in the gene regulatory network, the TP53 gene is involved in many activities simultaneously. Due to this high sensitivity, chemotherapeutic targeting the TP53 may cause many effects, wanted and unwanted.[82] Another crucial issue is the delivery of a chemopreventive agent into the cell. At this time, the mechanism by which the drug is taken into the cell remains largely unknown.[83] Examples of the kind are virtually endless.

Taking into consideration the rich history of failures in targeting individual pathways,[84] and given the fact that perhaps only a small part of them has been yet discovered, it does not require much imagination to hypothesize that targeting individual pathways *may never be entirely successful*. As in a battle of an army against other army, an integrated and highly organized defense requires an equally organized integrated assault. Contrary to this most obvious proposition, the philosophy of *magic bullet* and *one gene, one drug* paradigm remains the prevalent *modus operandi* in biomarker discovery and drug design. The emerging field of network biology and network medicine provides some clues in which direction to proceed to overthrow chemoresistance.[12,85–87] As discussed above in Section "Attaking the network", and as convincingly demonstrated in,[88] "multiple weak hits confuse complex system". In this work, various attack strategies have been tested using the *E.coli and S.cerevisiae* regulatory networks as examples. A notable result is that even *partial* attenuation of a small number of nodes may produce a larger effect on the network structural integrity than complete elimination of a single high value target. Translated into the language of pharmacology, this means that a high-affinity drug which completely knocks out a target may have a lesser effect than multiple drugs designed to attenuate certain nodes but not knock them out. Relative success of multitarget drugs such

as aspirin, Gleevec and other NSAIDs in treating a wide range of diseases may serve as an indirect corroboration of these conclusions.[89]

The concept of swarm intelligence opens new avenues in therapeutic targeting and drug design. In particular, disruption of quorum sensing has recently come into focus as a key reason for the tissue break down under the assault of cancer cells.[90] These authors hypothesize that "cancer initiation is driven by disruption of the quorum sensing mechanism, either by genetic mutation, complying with current notion of cancer evolution, or purely by the environment, genetic mutations being only a side-effect of excessive proliferation." In the detailed review,[91] disruption of quorum sensing is regarded to be a key culprit in ovarian cancer metastatic colonization. These authors indicate that "quorum sensing provide a unifying and testable model for many long-observed behaviors of metastatic cells."

Conclusion

In his recent presidential address to the American Society of Clinical Oncology, Dr. G. Sledge said: "Genomic chaos forms the basis for the 'smart' tumors. These tumors aren't hard targets, because we haven't found a single 'magic bullet.' There will be no 'magic bullets' for these tumors, because they don't have a single driving mutation: we need to think in terms of a 'magic shotgun,' loaded with pellets aimed at multiple targets in multiple pathways".[92] It is the author's view that the words 'smart tumor' used above are not simply a metaphor or an eloquent figure of speech. The tumors are 'smart' in a more direct and literal sense: they possess the property of swarm intelligence and are capable of self-organizing, self-healing and self-defending. And this is why a 'magic shotgun' may not be much more successful than a 'magic bullet.' An intelligent enemy requires a more intelligent approach.

Acknowledgments

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.
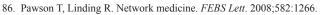
References

1. Stelling J, Sauer U, Szallasi Z, Doyle FJ III, Doyle J. Robustness of cellular functions. *Cell*. 2004;118:675.
2. Kitano H. Biological robustness. *Nat Rev Genet*. 2004;5:826.
3. Kitano H. Cancer robustness: tumour tactics. *Nature*. 2003;426:125.
4. Kitano H. A robustness-based approach to systems-oriented drug design. *Nat Rev Drug Discov*. 2007;6:202.
5. Csermely P, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci*. 2005;26:178.
6. Thomas R, D'Ari R. *Biological Feedback*. CRC Press; 1990.
7. Huang Y, Tienda-Luna IM, Wang Y. A survey of statistical models for reverse engineering gene regulatory networks, IEEE signal. *Process Mag*. 2009;26:76.
8. Ideker TE. Network genomics, systems biology, Springer, Berlin. *Heidelberg*. 2007:89–115.
9. Newman MEJ. The structure and function of complex networks. *SIAM Review*. 2003;45:167.
10. Strogatz S. Nonlinear dynamics and chaos: with applications to physics, biology, chemistry and engineering. *Springer-Verlag*. 1994.
11. 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, eds. Fifth workshop on computation of biochemical pathways and genetic networks, university of Heidelberg. *Heidelberg*. 2008:101–12.
12. Rosenfeld S. Mathematical descriptions of biochemical networks: Stability, stochasticity, evolution. *Prog Biophys Mol Biol*. 2011.
13. Albert R, Jeong H, Barabasi AL. Error and attack tolerance of complex networks. *Nature*. 2000;406:378.
14. Latora V, Marchiori M. How the science of complex networks can help developing strategies against terrorism. 2004:69–75.
15. Guckenheimer J, Holmes P. Nonlinear oscillations, dynamical systems, and bifurcations of vector fields. *Springer*. 2002.
16. Rosenfeld S. Characteristics of transcriptional activity in nonlinear dynamics of genetic regulatory networks. *Gene Regul Syst Bio*. 2009;3:159.
17. Gantmacher FR. Applications of the theory of matrices, interscience, NY. 1959.
18. May RM. Will a large complex system be stable? *Nature*. 1972;238:413.
19. Rosenfeld S. Origins of stochasticity and burstiness in high-dimensional biochemical networks, EURASIP. *J Bioinform Syst Biol*. 2009:362309.
20. Beisner BE, Haydon DT, Cuddington K. Alternative stable states in ecology. *Frontiers in Ecology and Environment*. 2003;1:376.
21. Laurent M, Kellershohn N. Multistability: a major means of differentiation and evolution in biological systems. *Trends Biochem Sci*. 1999;24:418.
22. Goldbeter A. Computational approaches to cellular rhythms. *Nature*. 2002;420:238.
23. Jain S, Krishna S. Graph theory and the evolution of autocatalitic networks. In: Bornholdt S, Shuster HG, eds. Handbook of graphs and networks: from the genome to the internet. *Wiley-VCH*. 2003;356–95.

24. Ikeda M, Siljak DD. Lotka-volterra equations: decomposition, stability and structure. *J Math Biology*. 1980;9:65.
25. Hernanades-Bermejo B, Fairen V. Lotka-volterra representation of general nonlinear systems. *Math Biosci*. 1997;140:1.
26. Samuelsson B, Troein C. Superpolynomial growth in the number of attractors in Kauffman networks. *Phys Rev Lett*. 2003;90:098701.
27. Levin RD. Molecular Reaction Dynamics, Cambridge University Press; 2005.
28. Stelling J, Gilles ED, Doyle FJ III. Robustness properties of circadian clock architectures. *Proc Natl Acad Sci U S A*. 2004;101:13210.
29. Arnold L. Qualitative Theory of stochastic non-linear systems. In: Arnold L, Lefever R, eds, stochastic nonlinear systems, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo. 1981:86–99.
30. Gardiner CW. Handbook of stochastic methods: for physics, chemistry and the natural sciences. *Springer-Verlag*. 1983.
31. Krakauer DC, Plotkin JB. Redundancy, antiredundancy, and the robustness of genomes. *Proc Natl Acad Sci U S A*. 2002;99:1405.
32. Li J, Yuan Z, Zhang Z. The cellular robustness by genetic redundancy in budding yeast. *PLoS Genet*. 2010;6:e1001187.
33. Pasek S, Risler JL, Brezellec P. The role of domain redundancy in genetic robustness against null mutations. *J Mol Biol*. 2006;362:184.
34. Wagner A. Distributed robustness versus redundancy as causes of mutational robustness. *Bioessays*. 2005;27:176.
35. Wagner A, Wright J. Alternative routes and mutational robustness in complex regulatory networks. *Biosystems*. 2007;88:163.
36. Brookfield J. Can genes be truly redundant? *Curr Biol*. 1992;2:553.
37. Brookfield JF. Genetic redundancy. *Adv Genet*. 1997;36:137.
38. Papp B, Pal C, Hurst LD. Evolution of cis-regulatory elements in duplicated genes of yeast. *Trends Genet*. 2003;19:417.
39. Voit EO. Canonical nonlinear modeling. S-system approach to understanding complexity. *Van Norstand Reinhold N Y*. 1991.
40. Garnier S, Gautrais J, Theraulas G. The biological principles of swarm intelligence. *Swarm Intelligence*. 2007;1:3.
41. Seeley TD. When is self-organization used in biological systems? *Biol Bull*. 2002;202:314.
42. Garnier S, et al. The embodiment of cockroach aggregation behavior in a group of micro-robots. *Artif Life*. 2008;14:387.
43. Garnier S, et al. Aggregation behavior as a source of collective decision in a group of cockroach-like-robots, advances in artificial life. *Lecture Notes in Computer Science*. 2005:169–78.
44. Rubenstein M, Sai Y, Chuong C, Shen W. Regenerative patterning in Swarm robots: mutual benefits of research in robotics and stem sell biology. *The International Journal of Developmental Biology*. 2009;53:869.
45. Labella T, 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;1:4.
46. Bonabeau E, Dorigo M, Theraulaz G. Swarm intelligence: from natural to artificial systems, Oxford University Press, New York Oxford; 1999.
47. Chandrasekaran S, Hougen D. Swarm intelligence for cooperation of bio-nano robots using quorum sensing, BMN '06, San Francisco, CA, USA. 2006:15–8.
48. Maltzahn G, et al. Nanoparticles that communicate in vivo to amplify tumor targeting. *Nature Naterials*. 2011;10:545.
49. Kiranyaz S, Ince T, Yildirim A, Gabbouj M. Evolutionary artificial neural networks by multi-dimensional particle swarm optimization. *Neural Netw*. 2009;22:1448.
50. Shmygelska A, Hoos HH. An ant colony optimisation algorithm for the 2D and 3D hydrophobic polar protein folding problem, BMC. *Bioinformatics*. 2005;6:30.
51. Karaboga D, Basturk B. A powerful and efficient algorithm for numerical function optimization: artificial bee olony (ABC) algorithm. *J Glob Optim*. 2007;39:459.
52. Ben-Jacob E, Becker I, Shapira Y, Levine H. Bacterial linguistic communication and social intelligence. *Trends Microbiol*. 2004;12:366.
53. Bassler BL. How bacteria talk to each other: regulation of gene expression by quorum sensing. *Curr Opin Microbiol*. 1999;2:582.
54. Queller DC, Strassmann JE. Beyond society: the evolution of organismality. *Philos Trans R Soc Lond B Biol Sci*. 2009;364:3143.
55. Morimoto BH, Koshland DE Jr. Short-term and long-term memory in single cells. *FASEB J*. 1991;5:2061.
56. 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.
57. Barabasi AL, Albert R. Emergence of scaling in random networks. *Science*. 1999;286:509.
58. Albert R. Scale-free networks in cell biology. *J Cell Sci*. 2005;118:4947.
59. Strogatz SH. Exploring complex networks. *Nature*. 2001;410:268.
60. Grebogi C, Ott E, Yorke JA. Unstable periodic orbits and the dimensions of multifractal chaotic attractors. *Phys Rev A*. 1988;37:1711.
61. Ott E, Grebogi C, Yorke JA. Controlling chaos. *Phys Rev Lett*. 1990;64:1196.
62. Ditto WL, Rauseo SN, Spano ML. Experimental control of chaos. *Phys Rev Lett*. 1990;65:3211.
63. Andrievskii B, Fradkov A. Control of chaos: methods and applications. part 1. methods. *Automation and Remote Control*. 2003;64:673.
64. Andrievskii B, Fradkov A. Control of chaos: methods and applications. part 2. applications. *Automation and Remote Control*. 2004;65:505.
65. Feudel U, Grebogi C. Multistability and the control of complexity. *Chaos*. 1997;7:597.
66. Goswami BK, et al. Control of stochastic multistable systems: experimental demonstration. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2009;80:016211.
67. Shibata D. Clonal diversity in tumor progression. *Nat Genet*. 2006;38:402.
68. Sonnenschein C, Soto AM. Theories of carcinogenesis: an emerging perspective. *Semin Cancer Biol*. 2008.
69. Laconi E. The evolving concept of tumor microenvironments. *Bioessays*. 2007;29:738.
70. Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. *Nat Med*. 2011;17:320.
71. Grunewald TG, Herbst SM, Heinze J, Burdach S. Understanding tumor heterogeneity as functional compartments—superorganisms revisited. *J Transl Med*. 2011;9:79.
72. Dunne BJ, Jahn RG. Consciousness, information, and living systems. *Cell Mol Biol*. (Noisy. -le-grand) 2005;51:703.
73. Gates E. Methods of Research and Importance of Cellular Psychology. *The American Therapist*. 1895;4:157.
74. Kitano H. Cancer as a robust system: implications for anticancer therapy. *Nat Rev Cancer*. 2004;4:227.
75. Lev Bar-Or R, et al. Generation of oscillations by the p53-Mdm2 feedback loop: a theoretical and experimental study. *Proc Natl Acad Sci U S A*. 2000;97:11250.
76. Fodale V, Pierobon M, Liotta L, Petricoin E. Mechanism of cell adaptation: when and how do cancer cells develop chemoresistance? *Cancer J*. 2011;17:89.
77. Radisky D, Hagios C, Bissell MJ. Tumors are unique organs defined by abnormal signaling and context. *Semin Cancer Biol*. 2001;11:87.
78. Egeblad M, Nakasone ES, Werb Z. Tumors as organs: complex tissues that interface with the entire organism. *Dev Cell*. 2010;18:884.
79. Merlo LM, 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;3:1388.
80. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Adv Exp Med Biol*. 2007;608:1.
81. Mellor HR, Callaghan R. Resistance to chemotherapy in cancer: a complex and integrated cellular response. *Pharmacology*. 2008;81:275.
82. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. *Nature*. 2000;408:307.
83. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. *J Pathol*. 2005;205:275.
84. Mukherjee S. The Emperor of all maladies: a biography of cancer. *Scribner*. 2011.
85. Chuang HY, Lee E, Liu YT, Lee D, Ideker T. Network-based classification of breast cancer metastasis. *Mol Syst Biol*. 2007;3:140.

86. Pawson T, Linding R. Network medicine. *FEBS Lett*. 2008;582:1266.
87. Barabasi AL. Network medicine—from obesity to the "diseasome". *N Engl J Med*. 2007;357:404.
88. Agoston V, Csermely P, Pongor S. Multiple weak hits confuse complex systems: a transcriptional regulatory network as an example. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2005;71:051909.
89. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4:682.
90. Agur Z, 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.
91. Hickson J, et al. Societal interactions in ovarian cancer metastasis: a quorum-sensing hypothesis. *Clin Exp Metastasis*. 2009;26:67.
92. Goldberg P. Prepare for tsunami of genomic information, sledge urges in ASCO presidential address. *The Cancer Letter*. 2011;37:1.