The Laws of Complexity and Self-organization: A Framework for Understanding Neoplasia

Nat Pernick(✉)

30100 Telegraph Rd, Suite 408, Bingham Farms, MI 48025, USA
NatPernick@gmail.com

Abstract. Background: Current biologic research is based on reductionism, through which organisms and cells are merely combinations of simpler systems. However this approach has failed to substantially reduce cancer-related deaths. Complexity theory suggests that emergent properties, based on unpredictable, nonlinear interactions between the parts, are important in understanding fundamental features of systems with large numbers of independent agents, such as living systems.

Methods and Findings: The laws of complexity and self-organization are summarized and applied to neoplasia:

1. In life, as in other complex systems, the whole is greater than the sum of the parts.
2. There is an inherent inability to predict the future of complex systems.
3. Life emerges from non-life when the diversity of a closed system of biomolecules exceeds a threshold of complexity.
4. Much of the order in organisms is due to generic network properties.
5. Numerous biologic pressures push cellular pathways towards disorder.
6. Organisms resist common pressures towards disorder through multiple layers of redundant controls, many related to cell division.
7. Neoplasia arises due to failure in these controls, with histologic and molecular characteristics related to the cell of origin, the nature of the biologic pressures and the individual's germline configuration.

Conclusions: Cells maintain order by redundant control features that resist inherent biologic pressures towards disorder. Neoplasia is due to the accumulation of changes that undermine these controls. Studying neoplasia within this context may generate new therapeutic approaches by focusing on the underlying pressures on cellular networks.

An expanded version of this paper is available at http://natpernick.com/TheLawsJune2017.pdf.

1 Introduction

1.1 The War on Cancer

On 23 December 1971, President Richard M. Nixon signed the National Cancer Act of 1971, generally viewed as beginning the "war on cancer" in the United States [1]. Fifteen years later, Bailar and Smith concluded that "we are losing the war against

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cancer, notwithstanding progress against several uncommon forms of the disease, improvements in palliation, and extension of the productive years of life" [2]. Recent data indicate that the 5-year relative survival rate has increased from 49% in 1975–1977 to 69% in 2005–2011 [3]. However, although the U.S. National Cancer Institute has spent over $100 billion on this effort [4], progress has been limited in reducing mortality from common, advanced carcinomas of the lung, colon, breast, and pancreas, and overall U.S. cancer deaths are projected to rise to 609,640 in 2018.

1.2 Reductionism: The Current Approach to Biology

Current research efforts in biology are based on the reductionist approach, summarized as "the whole is equal to the sum of its parts". This "gold standard" for learning about the world is based on the works of Descartes, Galileo, Newton and LaPlace, postulating that the workings of our mind and body and all matter in the universe unfold under the same set of fundamental laws [5]. With this approach, cells can theoretically be completely understood by analyzing all components and the connections between them, which are assumed to be additive and linear [6, 7]. Under this view, diseases are studied by finding and understanding defective genes, proteins, or other biomolecules in a cell, tissue, or organ. For example, follicular lymphoma is due to the t(14;18) (q32; q21) translocation, present in 80–90% of tumors, which brings the *bcl2* proto-oncogene under the transcriptional influence of the immunoglobulin heavy chain gene, leading to overexpression of the Bcl2 protein, which inhibits apoptosis. This inhibition allows additional genetic mutations to accumulate, which leads to neoplasia [8]. But this reductionist model does not explain the myriad network changes facilitating the translocation or the web of network changes it induces.

The goals of this paper are to discuss how complexity theory may relate to neoplasia, to explain to the pathology community why the reductionist model is inadequate and to suggest that effective cancer research should incorporate the laws of complexity and self-organization.

1.3 Complexity: Variability that Is not Predictable

Complexity refers to systems with large numbers of independent agents with a high and variable degree of connectivity [9]. Complex systems exhibit many nontraditional properties [10]. First, they have variable behavior that obeys the laws of physics, but cannot be reliably predicted by reproducible experiments [11]. Behavior also varies due to self-organized criticality, a dynamic process that drives large extended systems to a network state that is poised at criticality, analogized to a sand pile created by dropping individual sand grains [11]. Small avalanches may be predictable, but the overall behavior of the sand pile is best described by catastrophic, not gradual, changes.

Second, complex systems possess a robustness that makes them resistant to significant changes. The maintenance of cellular phenotypes and stability in physiologic processes has been attributed to "attractors" associated with a complex gene regulatory network, which maintains and reestablishes specific gene expression patterns, even after large perturbations [12].

Third, complex systems possess emergence, an organizational, bottom-up property, due to agents that spontaneously self-organize without any oversight or planning [9] (p. 11). Larger entities arise through interactions among simpler entities and possess properties or exhibit features not found or even thought possible from the simpler entities and that require fundamental research to understand. In biological systems, self-organization has been described as a process in which global patterns emerge solely from numerous lower level interactions, even though the rules specifying interactions are executed using only local information [13]. Neoplasia cannot be well understood without knowledge of emergence.

Fourth, similar appearing behavior and features may be due to markedly different inputs. In colon carcinoma, alterations to dissimilar molecular pathways may produce morphologically similar tumors [14].

2 The Laws of Complexity and Self-organization

The Laws of Complexity and Self-Organization relevant to neoplasia are:

1. In life, as in other complex systems, the whole is greater than the sum of the parts.
2. There is an inherent inability to predict the future of complex systems.
3. Life emerges from non-life when the diversity of a closed system of biomolecules exceeds a threshold of complexity.
4. Much of the order in organisms is due to generic network properties.
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7. Neoplasia arises due to failure in these controls, with histologic and molecular characteristics related to the cell of origin, the nature of the biologic pressures and the individual's germline configuration.

2.1 In Life, as in Other Complex Systems, the Whole Is Greater Than the Sum of the Parts

The reductionist approach is inadequate for understanding living systems and diseases such as cancer; biology cannot be reduced to physics alone [5]. In living systems, the interactions between molecules create life. Individually, the molecules can be considered as "dead." Collectively, they develop emergent properties, the missing features that make the whole greater than the sum of its parts [15]. Mitosis is an emergent property with obvious importance in neoplasia. Various molecules engage in linked processes whose end result cannot be predicted even by examining a large subset of the processes. As Kauffman notes, "it is a closure of work tasks that propagates its own organization of processes" [5] (p. 94).

2.2 There Is an Inherent Inability to Predict the Future of Complex Systems

In 1814, Laplace claimed that one could determine the entire future and past of all particles in the universe and their motions if supplied with their instantaneous positions and velocities [16]. However, the ability to predict planetary motion or the tides does not extend to complex systems, for several reasons.

First, the chaotic nature of complex systems precludes predictability. Chaotic properties are characterized by nonlinear equations, which are exquisitely sensitive to initial conditions. Lorenz found that his computer model of the weather experienced exponential divergence when he reran it substituting the Fig. 0.506 for 0.506127 [17]. This inability to predict the future of systems that are well understood is an inherent property of the nonlinear world in which we live. Second, emergent properties are not predictable. In neoplasia, we can document the presence or absence of specific mutations but cannot precisely predict their impact. Third, the function of molecules may be dependent on evolutionary pressures, which themselves cannot be predicted [18]. Selection may favor individuals heterozygous for the human sickle cell mutation at codon 6 of the *beta* gene, but only in geographic areas where falciparum malaria is endemic, where this mutation protects erythrocytes from infection [19]. However, we cannot predict the impact of this particular mutation on survival in the local environment without knowing the evolutionary pressures of all other human molecules and how they reinforce or counteract each other.

2.3 Life Emerges from Non-life When the Diversity of a Closed System of Biomolecules Exceeds a Threshold of Complexity

According to Kauffman, life is the emergent collective property of a modestly complex mix of biomolecules (DNA, RNA, proteins, and others) which catalyze each other's formation [20] (Chapter 7). Individually, each molecule is relatively inert. However, with a large enough collection of molecules of sufficient complexity, confined to a small space to promote interaction, a self-sustaining web of reactions may form that can reproduce and evolve [21, 22].

This model of the origin of life may explain why free living cells have an apparent minimal complexity. *Mycoplasma mycoides JCVI-syn1.0* [23] and *M. genitalium* [24] are the smallest known genomes that constitute a cell, with 473 to 482 protein-encoding genes, a large number for the simplest organism. A collection of fewer genes would apparently lack the complexity to create a self-staining network.

2.4 Much of the Order in Organisms Is Due to Generic Network Properties

Each cell coordinates the activities of 20,000 genes and their products [25]. Activities as complex as mitosis occur through spontaneous interaction of biomolecules without external oversight. To obtain a deeper understanding of cancer, we need to better understand how order arises in cells. The traditional view is that the sole source of order in organisms is natural selection as described by Darwin. An alternative view is

that order is an expected emergent property of molecular networks, based on structural properties of networks not dependent on details of the particular molecules [20].

Genes, RNA, and proteins form a complex parallel processing network in which molecules are connected to other molecules and control their activation. Theoretically a cell with 20,000 types of gene products, one copy of each and two possible properties for each gene product would have a state cycle of length $2^{20,000}$, or approximately $10^{6,000}$. However, a state cycle this large does not happen due to the surprising finding that if each gene product is regulated by at most two inputs, the median length of the state cycle is only the square root of the number of gene products, or 141 if N is 20,000 [20, 26]. This network property creates inherent stability even in networks with large numbers of gene products, as the cell network is localized to a very small percentage of its possible state space. In addition, stability is promoted when genes are regulated by "canalyzing" Boolean functions [27, 28], which means that one input can completely determine the property of the gene.

The ability of cells to maintain stable phenotypic states is due to the settling down of a gene regulatory network into attractors [29], what Kauffman terms "order for free". Mutations can change functional connections but usually do not greatly change the stability of the network due to these order inducing properties.

2.5 Numerous Biologic Pressures Push Cellular Pathways Towards Disorder

Tension exists in living systems between order and disorder, a result of the tradeoffs inherent to achieve compromise between conflicting interests [30]. Order is required for proper functioning of cells, tissues, and organs. Yet network flexibility is required for development, inflammation, and adapting to numerous environments. Neoplasia subverts the physiologic mechanisms that provide this network flexibility and prevents reversion to an ordered state [31]. To understand neoplasia better, it is important to understand how physiologic disorder arises, how cells manage it, and how neoplasia disrupts it.

First, creating an autocatalytic network promotes disorder, as it produces an increasing number of new molecules, which catalyze further reactions. Second, natural selection disfavors rigid order in living systems, which would doom species amidst environmental shifts [32]. Third, the ability of living systems to maintain viability after mutational changes demonstrates an inherit flexibility not present in a completely ordered regime. Kauffman believes that organisms maintain a position between order and disorder that he terms the "edge of chaos," an evolution-derived compromise between order and surprise that may be optimal to coordinate complex activities and to evolve further [33] (p. 86) [34]. Finally, physiologic biologic pressures promote disorder. Infections, infestations, autoantigens, inflammation, and hormone expression, alone and particularly in combinations, push some cells into an active cell cycle, a less stable state, and eventually into neoplasia.

2.6 Organisms Resist Common Pressures Towards Disorder Through Multiple Layers of Redundant Controls, Many Related to Cell Division

Organisms have multiple layers of redundant controls that resist these pressures towards disorder. First, based on interactions between the components, a large "frozen" component forms, whose state does not easily change over time, even as the states of other molecules change [20, 35]. Second, cellular membranes act as "border controls" to limit the entry of novel molecules that might create new reactions or alter existing ones and to compartmentalize existing molecules to limit unexpected reactions. Third, cells have robust processes to limit errors during cell division, such as DNA repair [36], which dramatically reduce transcription error rates [37]. Fourth, cells have several mechanisms to respond to injury or DNA damage, which might eventually alter proteins and pathways, including apoptosis, cycle arrest, autophagy, or protein synthesis shutoff [38]. Fifth, key cellular processes have numerous controls that tightly regulate their activity, such as delay of cell cycle progression during mitosis in the presence of DNA or spindle damage [39, 40]. Finally, the immune system is a final supervisory system of error correction by destroying cells with disordered properties [41]. Their importance is suggested by the association of immunosuppression with a markedly elevated risk of malignancy [42].

2.7 Neoplasia Arises Due to Failure in These Controls, with Histologic and Molecular Characteristics Related to the Cell of Origin, the Nature of the Biologic Pressures, and the Individual's Germline Configuration

The laws of complexity and self-organization provide a framework to better understand neoplasia, which is required for optimal cancer treatment. Cells are end product of networks with emergent features whose ultimate impact often cannot be predicted (laws 1–3). Although these networks possess a great deal of stability (law 4), they are under constant pressure to breach the control mechanisms that maintain order (law 5). Only the presence of multiple redundant controls at various levels leads to adequate order and function (law 6), consistent with the multiple-hit theory of neoplasia [43, 44].

Cell of Origin. A neoplasm's characteristics are related to the network state of the cell of origin, the nature of the biologic pressure, and the germline configuration. The cell's network state determines response to cellular pressures. For example, the t(14;18) translocation is apparently only found in B lymphocytes [45] and is due to an illegitimate V(D)J recombination, an activity restricted to B cells [46].

Nature of Biologic Pressures. We have proposed that an alternative classification to morphology or molecular changes characterizes neoplasia by the nature of the biologic pressures [47]. For example, gastric MALT lymphomas are caused not by mutations, but by antigen-driven lymphoproliferation.

Germline Configuration. The nature of the neoplasia is affected by the germline configuration, including familiar cancer syndromes [48] as well as more subtle variations in networks affecting any of the numerous control factors described above.

3 Summary

The original contributions of this paper are (a) proposing that the failures of the War on Cancer are due to medicine's rigid adherence to reductionism; (b) summarizing complexity and self-organization as they relate to neoplasia; (c) proposing that scientists study chronic pressures that disturb physiologic networks leading to neoplasia; and (d) suggesting that treatments which reverse these pressures or alter networks towards less lethal pathways may be useful.

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