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

Nat Pernick, M.D.

30100 Telegraph Rd, Suite 408
Bingham Farms, MI 48025
Telephone: 248-646-0325
Email: NatPernick@gmail.com

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Last revised 4 June 2017

Abstract

Background: Current biologic research is based on a reductionist approach. Complex systems, including organisms and cells, are presumed to merely be combinations of simpler systems, which can then be studied more readily. The whole is equal to the sum of the parts, interacting in a predictable, linear way. This approach, although adequate for understanding some diseases, has failed to bring about the knowledge necessary 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. Applying complexity theory to neoplasia may yield a greater understanding of physiologic systems that have gone awry.

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 germ line configuration.

Conclusions: In the framework of the laws of complexity and self-organization, cells maintain order by redundant control features that resist inherent biologic pressures towards disorder. Neoplasia can be understood as the accumulation of changes that undermine these controls, leading to network states associated with dysregulated growth and differentiation. Studying neoplasia within this context may generate new therapeutic approaches by focusing on the underlying pressures on cellular networks and changes to associated cofactors, instead of tumor-specific molecular changes.

Key Words: Reductionism; Emergent properties; Biologic networks; Disordered networks; Origin of life

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 (**note 1**). Fifteen years later, Bailar and Smith, assessing the age-adjusted mortality rate for all cancers in the U.S., concluded that "we are losing the war against cancer, notwithstanding progress against several uncommon forms of the disease, improvements in palliation, and extension of the productive years of life" (Bailar & Smith, 1986). In a 1997 update, Bailar and Gornik proclaimed, "The war against cancer is far from over. Observed changes in mortality due to cancer primarily reflect changing incidence or early detection. The effect of new treatments for cancer on mortality has been largely disappointing (Bailar & Gornik, 1997), but see also (Jemal, Ward, & Thun, 2010; Kort, Paneth, & Vande Woude, 2009; Soneji, Beltran-Sanchez, & Sox, 2014).

Recent data indicates that death rates due to cancer have decreased for both sexes (Ryerson et al., 2016), and the five-year relative survival rate has increased from 49% in 1975-1977 to 69% in 2005-2011 (American Cancer Society, 2016). However, although the U.S. National Cancer Institute has spent over $100 billion on this effort (Kolata, 2009), 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 595,690 in 2016.

1.2. Reductionism: the current approach to biology

Current research efforts in biology are based on the reductionist approach, which is 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 Descarte, 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 (S. A. Kauffman, 2008)(page 2). To understand human physiology, we reduce it to combinations of organ systems, which can be further subdivided into activity in tissues and cells. As Weinberg stated, "the explanatory arrows always point downward" to particle physics (Weinberg,

1994). Francis Crick explained, “the ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry” (Crick, 2004).

With this approach, complex systems, including cells, can theoretically be completely understood by analyzing all components and the connections between them, which are assumed to be additive and linear (Mazzocchi, 2008; Van Regenmortel, 2004). A corollary states that if everything obeys the same fundamental laws, then only scientists working on these laws are studying anything really significant (Anderson, 1972)(page 393).

Under this reductionist view, diseases are studied by finding and understanding defective genes, proteins or other biomolecules in a cell, tissue, or organ. For example, in follicular lymphoma, the key change is t(14;18)(q32;q21), present in 80-90% of tumors, which brings the BCL2 proto-oncogene under the transcriptional influence of the immunoglobulin heavy chain gene. This translocation leads to the overexpression of a functionally normal bcl2 protein, which inhibits these cells from their usual propensity to undergo apoptosis. This inhibition allows additional genetic mutations to accumulate, which leads to neoplasia of follicular center cells (Ott & Rosenwald, 2008).

Reductionist thinking is logical and predictable and has led to high survival rates for childhood Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic leukemia/lymphoma, CNS tumors, Ewing sarcoma, neuroblastoma, osteosarcoma, retinoblastoma, rhabdomyosarcoma, and Wilms tumor (American Cancer Society, 2016)(page 12), as well as gestational choriocarcinoma (H. O. Smith et al., 2003), papillary thyroid carcinoma and testicular cancer (American Cancer Society, 2016)(pages 17-18). However, survival remains poor for advanced malignancies of the lung, colon, breast, and pancreas, which account for the major causes of cancer-related deaths. This situation may be because reductionist-based research ignores fundamental properties of complex systems, which are based on interactions between the parts. These properties are not logical and predictable, but may be crucial in obtaining a better understanding of physiologic systems that have gone awry during neoplasia. Towards this end, we analyze and summarize the laws of complexity and self-organization and apply them to neoplasia. This paper is based primarily on these works of Dr. Stuart A. Kauffman (S. A. Kauffman, 1993, 1995, 2000, 2008). The Origins of Order (S. A. Kauffman, 1993) contains detailed discussions supporting the underlying theories.

1.3. Complexity: variability that is not predictable

Complexity generally refers to systems with large numbers of independent agents with a high and variable degree of connectivity (Waldrop, 1992)(page 11). Because the systems are characterized by the relationships between agents, they are modeled as networks, which can capture and quantify these relationships.

Complex systems exhibit many nontraditional properties (Rickles, Hawe, & Shiell, 2007). First, they have variable behavior that obeys the laws of physics, but cannot be reliably predicted by reproducible experiments (Bak,

1996)(page 8). This behavior includes the chaotic property that trivial differences in initial conditions may cause dramatically different behaviors instead of the expected subtle change. For example, in sickle cell disease, a mutation in a single nucleotide for hemoglobin may produce a marked changed in function with profound clinical impact. Behavior also varies due to self-organized criticality, a dynamical 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 (Bak, 1996). Small avalanches may be predictable, but the overall behavior of the sand pile is best described by catastrophic, not gradual, changes. Although the grains of sand are dropped locally, the avalanches occur because of the structure of the entire system, which develops independent of any known laws.

Second, and conversely, complex systems also possess a robustness that often 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 (Huang, Ernberg, & Kauffman, 2009). Consistent with this theory, age-related physiologic declines have been attributed to loss of complexity-related stability, causing diminished adaptive responses to the stressors of everyday life (Manor & Lipsitz, 2013; Yaniv, Lyashkov, & Lakatta, 2013).

Third, complex systems possess emergence, an organizational, bottom-up property due to agents that spontaneously self-organize, without any oversight or planning (Waldrop, 1992)(page 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 (Camazine, 2001). Examples include flocking, the collective motion of birds, fish, bacteria and insects, which emerges as organisms follow simple rules, but without any central coordination (Wikipedia, 2016b), and the chirality of amino acids and simple sugars. Thus, in contrast to the reductionist beliefs of Weinberg and LaPlace, we cannot always reason upwards from physical laws to larger scale events in a useful way (S. A. Kauffman, 2008)(page 17).

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 (Colussi, Brandi, Bazzoli, & Ricciardiello, 2013). In convergent evolution, organisms not closely related, such as the dolphin and the shark, may independently evolve similar traits as they respond to the same engineering problems (Parker et al., 2013). In addition, proteins with disparate amino acid composition, such as sugar kinases, may have similar enzymatic functions (Bork, Sander, & Valencia, 1993).

Finally, complex systems have adaptive properties, to increase their survival in a changing environment (Theise & d'Inverno, 2004). Tumors have similarly been described as complex ecosystems containing heterogeneous cell populations, which interact with a variety of nontumor cells, microenvironments and treatments in a constantly evolving manner (Du & Elemento, 2015).

2. The Laws of Complexity and Self-Organization

The Laws of Complexity and Self-Organization relevant to neoplasia are summarized in Table 1 and discussed below:

Table 1 - The Laws of Complexity and Self-Organization Relevant 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 germ line 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; biology cannot be reduced to physics alone (S. A. Kauffman, 2008)(page 11). In living systems, it is the interactions between molecules that create life. Individually, the molecules can be considered as "dead." Collectively, these molecules develop emergent properties, the missing features that make the whole greater than the sum of its parts (Corning, 2002). For example, the properties of a protein are not equivalent to the sum of the properties of each amino acid in its structure. Proteins bind to other biomolecules and catalyze chemical reactions due to their tertiary and quaternary structures, which cannot be reliably predicted *a priori* from knowledge of their amino acid sequence (Mazzocchi, 2008). Their properties also vary based on the network state of a large number of neighboring biomolecules.

Mitosis is another 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” (S. A. Kauffman, 2008)(page 94). Although no laws of physics are broken, it is not reducible to physics or its simple equations. How this process works is something science “hardly knows how to talk about” (S. A. Kauffman, 2008)(page 47). Thus, this first law of complexity and self-organization is essentially a recognition that emergent properties exist, are important for living systems, and are not explained by the traditional reductionist approach.

2.2. There is an inherent inability to predict the future of complex systems.

In 1814, based on the deterministic nature of Newton’s three laws of motion (Newton, Motte, & Machin, 1729)(volume 1, page 19), see also (Steinbach, 2010), 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 (Hawking, 1999). However, this claim is incorrect. The ability to predict planetary motion, the tides and other noncomplex systems 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 (for examples of chaos in biologic systems, see (Laudanski, Sumner, & Coombes, 2010; Schelin, Karolyi, de Moura, Booth, & Grebogi, 2009; Trzeciakowski & Chilian, 2008). Although we can model the weather by a series of equations, we cannot predict it with long-term accuracy (Lorenz, 1963). Lorenz, in his pioneering work on chaos theory, found that his computer model of the weather experienced exponential divergence when he reran it substituting the figure 0.506 for 0.506127 (Dizikes, 2011). This finding is often called “the butterfly effect” because the apparently trivial effect of a butterfly flapping its wings in one city can trigger changes that severely alter weather across the world (Lorenz, 1972). This inability to predict the future of systems that are well understood is not due to our lack of intelligence and will not be improved by more powerful computers. It is an inherent property of the nonlinear world in which we live.

Second, emergent properties are not predictable. An exhaustive study of the properties of hydrogen and oxygen cannot predict the emergence of water or even suggest its major properties. A complete genome map of an organism is inadequate to predict what it will look like or its basic features. In neoplasia, we can document the presence or absence of specific mutations but cannot precisely predict their impact.

In “More is Different”, Anderson explains why emergence renders reductionism inadequate:

The ability to reduce everything to simple fundamental laws does not imply the ability to start from those laws and reconstruct the universe. The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. At each level of complexity entirely new properties appear. Psychology is not applied biology, nor is biology applied chemistry. We can now see that the whole becomes not merely more, but very different from the sum of its parts. (Anderson, 1972).

Complex systems have been compared to an incompressible algorithm, which has no shorter means to predict what it will do than to observe what happens (S. A. Kauffman, 1995)(page 23). We would like a model that provides a short description, such as an equation. However, if each part of the living system contributes to the whole, then a model of only part of the system will inherently be inaccurate. All we can do is attempt to explain features after the fact.

Third, the function of molecules may be dependent on evolutionary pressures, which themselves cannot be predicted (Allison, 1964). 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 (Sabeti, 2008). 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. In addition, we must be able to predict how the physical environment will change over time, how the genomes of competing organisms will change over time, and how all these factors will interact. Yet none of these factors are predictable, and we have no natural laws to predict specific evolutionary changes. In addition, hemoglobin and other biomolecules, as well as the cells, tissues, and organs that they comprise, have multiple actual and potential functions, which may assume different degrees of relevance in different contexts that are affected by the same evolutionary pressures.

Fourth, organisms have causal powers, in that they themselves change the physical evolution of the universe, not just because they are a combination of particles (S. A. Kauffman, 2008)(page 43). The pioneering use of aminopterin by Dr. Sidney Farber to induce remissions in childhood leukemia (Farber & Diamond, 1948) cannot be understood in any meaningful way by breaking down his work into interactions of subatomic parties. Its impact and understanding were profound (Mukherjee, 2011), but beyond prediction.

Finally, to predict the future, we would need to predict the adjacent possible, the set of all reactions possible in the next moment of time, and have a rational basis for choosing between them (Beckage, Gross, & Kauffman, 2011; S. A. Kauffman, 2008)(pages 5 and 64). However, the chaotic and emergent properties of complex systems, coupled with evolution and causal powers of organisms and their components, appear to render this impossible.

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 (S. A. Kauffman, 1993)(Chapter 7). Individually, each of the molecules 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 (Smith, Steel, & Hordijk, 2014; Sousa, Hordijk, Steel, & Martin, 2015). Unlike some models of the origin of life, the molecules do not reproduce themselves. Rather, the last step in formation of each molecule requires catalysis by another molecule.

Under the right circumstances, there is a high probability that a subset of a large set of complex molecules will form a network of molecules that catalyze the formation of each other (Hordijk, Kauffman, & Steel, 2011). A complex protein has numerous clefts or grooves on its surfaces, which may bind the transition states of reactions, a requirement for a catalyst (Matthews, Craik, & Neurath, 1994). Although the likelihood that a specific molecule will catalyze a specific reaction is very low, with a large number of molecules and possible reactions, the probability that *some* molecule will catalyze *some* reaction is high (S. A. Kauffman, 1995)(Chapter 3). [This counterintuitive finding is illustrated by "the birthday problem." In a group of 50 people, the probability that any will have the same birthday as the first is only 49/365 (13%), but the probability that any two people in the group will have a common birthday is 97% (WIkipedia, 2016a)].

As reactions are catalyzed, additional molecules are created, which can act as substrates or catalysts for future reactions. The number of possible catalyzed reactions increases faster than the number of molecules. Eventually, a threshold is crossed in which a network of molecules exists that constitutes a collectively autocatalytic set, in which each molecule's formation is catalyzed by other molecules, to produce a living system. Many alternative pathways are possible to produce this autocatalytic network, but only one of them is required (S. A. Kauffman, 2008)(page 59).

This self-organization is illustrated by "random graphs". Suppose we have 10,000 buttons and randomly tie a string between two of them. Then, we randomly pick up a button and determine the size of the button cluster (i.e., how many other buttons are picked up with it). Then, we repeat the process and graph the number of buttons in each "cluster" over time. Initially the clusters are a size of one or are very small. However, at some point, there is a sharp increase in cluster size, at a type of phase transition, as most buttons are connected in some way to each other, analogous to the connections in an autocatalytic network (S. A. Kauffman, 2008)(page 61).

This model of the origin of life suggests an answer to the question of why free living cells have an apparent minimal complexity. *Mycoplasma mycoides JCVI-syn1.0* (Hutchison et al., 2016) and *Mycoplasma genitalium*

(Fraser et al., 1995) 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.

Cells are nonequilibrium systems with a complex metabolism linking the synthesis and transformation of thousands of small organic molecules in complicated, interconnected networks (S. A. Kauffman, 2008)(page 47). Life consists of numerous collections of these autocatalytic networks, triggered by each other, as well as by outside stimuli. Particular networks appear to ebb and flow, based on inputs created and removed based on physiologic needs. Although, ultimately, neoplasia is due to excess mitotic activity, understanding how it arises requires us to understand the networks that drive this mitotic activity.

2.4. Much of the order in organisms is due to generic network properties.

Each cell coordinates the activities of some 20,000 genes and their products (International Human Genome Sequencing, 2004). Activities as complex as mitosis occur through spontaneous interaction of biomolecules without external oversight. To obtain a deeper understanding of diseases whose secrets have defied decades of determined study, we need to better understand general principles underlying these processes, including how order arises in cells.

The traditional view is that the sole source of order in organisms is natural selection as described by Darwin (Darwin, 1859): the patterns of a pine cone or the artistry of mitosis are due to “chance caught on the wing,” a description of natural selection by Jacques Monod (Monod, 1972). An alternative view, advanced by Kauffman and others, 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 (S. A. Kauffman, 1993).

Genes, RNA and proteins form a complex parallel processing network in which molecules are connected to other molecules and turn them on and off. Consider gene product A, designated active or not based on its state of phosphorylation. Due to inputs from kinases or other gene products, protein A may change its properties in the next instant of time. Any change to gene product A may affect other gene products it connects to in the network, for which it acts as an input. If we consider all the gene products in a cell, we can designate their properties at a particular moment in time as the “state” of the cell. In the next instant, each gene product may change its properties based on relevant inputs, leading to a new state. The path that a network traverses over time, based on changes in the state of each gene product at each moment in time, is called its state space or state cycle.

Theoretically, a cell with 20,000 types of gene products, and numerous copies of each, could have an almost infinite length to its state cycle. A network of N=20,000 gene products, with only one copy and two possible

properties for each gene product, would have a state cycle of length 2^N, or approximately 10^{6000}. However, a state cycle this large does not happen, due to two generic network properties that induce order. First, order is induced by 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 (S. Kauffman, 1969b; S. A. Kauffman, 1993)(page 479). 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. These networks appear to represent the edge of the chaotic phase transition (S. A. Kauffman, 2000)(page 174) (Derrida & Pomeau, 1986); for example, networks with 5 or more inputs per gene product are inherently unstable and never return to a prior state (S. A. Kauffman, 1993)(page 194).

The second network property that maintains order occurs when genes are regulated by “canalyzing” Boolean functions (Murrugarra & Dimitrova, 2015; Murrugarra & Laubenbacher, 2011), which means that one input can completely determine the property of the gene. This property has been described for various cell types (Nikolajewa, Friedel, & Wilhelm, 2007; Zhou, Samal, d'Herouel, Price, & Huang, 2016). In the Boolean OR function, if one input is active, then the result is active, regardless of the value of the other input. A series of canalyzing functions, such as a network of genes each regulated by the OR function, is considered a “forcing structure,” because changing one input to active propagates the “active” status throughout the network. If there is a loop, then the network is frozen in this active state. In fact, stability is promoted even if some genes are not regulated by canalyzing functions (Dimitrova, Yordanov, & Matache, 2015; S. Kauffman, Peterson, Samuelsson, & Troein, 2004).

The ability of cells to maintain stable phenotypic states is due to the settling down of a gene regulatory network into an equilibrium state called an attractor, based on the mutual regulation of network elements (S. Kauffman, 1969a). Attractors are graphically represented as a low energy stable state at the bottom of a well, representing the “basin of attraction” of neighboring, less stable states, that tend to move towards the attractor from different directions (Huang, Eichler, Bar-Yam, & Ingber, 2005; Huang et al., 2009). Kauffman terms the results of these network properties “order for free”, as they lead to a substantially smaller state cycle than otherwise predicted. Mutations and other perturbations can change the functional connections between some of the molecules in the network, but this usually does not greatly change the stability of the network due to these order-inducing properties.

These generic network properties have profound implications. Cellular networks, once they arise, have an inherent order independent of the particular molecules or reactions involved. This order is part of the interactions between the parts described above that makes the reductionist approach inadequate for understanding biologic systems.

2.5. Numerous biologic pressures push cellular pathways towards disorder.

How do the laws of complexity and self-organization relate to neoplasia? Tension exists in living systems between order and disorder, a result of the tradeoffs inherent to achieve compromise between conflicting interests (Torres-Sosa, Huang, & Aldana, 2012). Order is required for proper functioning of cells, tissues, and organs. Yet a certain amount of disorder, or 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 (Mukherjee, 2011). To understand neoplasia better, it is important to understand how physiologic disorder arises, how cells manage it, and how neoplasia disrupts it.

First, the process of creating an autocatalytic network itself promotes disorder. As a closed network of molecules begins reacting with itself, it produces an increasing number of new molecules, which catalyze further reactions. This exponential expansion of the network, coupled with the second law of thermodynamics, tends to create continuing disorder, with no natural stopping point until limiting factors are reached (Sharov, 2009). As a result, cells must use their limited resources to counter these reactions. For example, cells create and maintain extensive membrane-bound compartments to contain biomolecules and prevent them from disrupting existing networks (Cooper, 2000).

Kauffman suggests that the earth's environment is supracritical, a multi-dimensional variation of an uncontrolled nuclear reaction, which also puts pressure on living systems to breach their orderly constraints (S. A. Kauffman, 1995)(Chapter 6). Life may have begun with a small collection of amino acids (Hill & Nuth, 2003; Miller, 1953), but today, over 120 million unique organic and inorganic molecular substances have been cataloged (American Chemical Society, 2016). The presence of these molecules throughout our biosphere exerts constant pressure on living systems to interact with them in novel ways.

Second, natural selection disfavors rigid order in living systems. From the Cambrian explosion onwards, the fossil record shows a number of large extinction events that wiped out a significant fraction of Earth's species, possibly due in part to loss of habitat and environmental changes (Sole and Newman, 2002). Although organisms have the ability to maintain genetic information unchanged over long time periods, as exhibited by the 16S ribosomal RNA gene (Isenbarger et al., 2008), rigid order amidst environmental shifts would doom species.

Third, the ability of living systems to maintain viability after mutational changes demonstrates an inherit flexibility not present in a completely ordered regime. Many systems are incapable of sustaining small changes without substantial loss of function. For example, some scientists speculate that life began with an "RNA world" dominated by RNA polymerase (Gilbert, 1986). However, a simple network with this type of polymerase is subject to "error catastrophe" (Summers & Litwin, 2006) because a small change in the polymerase may cause an exponential increase in erroneous replication if no error correction mechanism exists. Computer programs are

also exquisitely sensitive to changes. Almost any change to valid computer code leads to a nonfunctioning program. Thus, the ability of complex systems to survive small changes and actually improve in function should not be taken for granted.

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 (S. A. Kauffman, 1995)(page 86) (Shmulevich, Kauffman, & Aldana, 2005). This “edge of chaos” has also been described as a dynamical phase transition in terms of instabilities and attractor states (Davies, Demetrius, & Tuszynski, 2011). Others have described complex systems as maintaining self-organized criticality (Bak, 1996) in that they often show regular and predictable behavior, but minor changes can cause the massive changes described above as the “butterfly effect”.

Finally, physiologic biologic pressures promote disorder, even if temporarily. Infections, infestations, autoantigens, inflammation, and hormone expression, among others, push some cells into an active cell cycle, a less stable state, and eventually into neoplasia. Combinations of these pressures are more likely to move cellular pathways towards a disordered state.

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 the above pressures towards disorder. The first layer is the inherent structure of biologic networks, described above, which limit the behavior of a network to a small portion of its state space. 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 (S. A. Kauffman, 1993)(page 206) (S. A. Kauffman, 1990). In addition, transient changes to the state of a gene product tend not to propagate to the remainder of the network. This tendency not only maintains network stability against minor changes but also provides the basis for cellular homeostasis. Although cells can theoretically exhibit an almost infinite number of states, there are only approximately 300 cell types, which maintain a consistent phenotype due to the relatively stable expression of a large percentage of their gene products (S. A. Kauffman, 1993)(page 467). Thus, a cardiac myocyte does not transform to a glial cell, and only rarely do mature cells change their state of differentiation at all.

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 (Weyand et al., 2008). For example, hematopoietic stem cells produce c-Abl tyrosine kinase, which is sequestered in the cytoplasm by binding to 14-3-3 proteins (Yoshida, Yamaguchi, Natsume, Kufe, & Miki, 2005).

In response to DNA damage, c-Abl is targeted to the nucleus, but only under tightly controlled conditions (Hazlehurst, Bewry, Nair, & Pinilla-Ibarz, 2009). In chronic myeloid leukemia, the t(9;22) translocation leads to a bcr-abl fusion protein in hematopoietic stem cells, which leads to constitutive tyrosine kinase activation and the translocation of the fusion protein from the nucleus to the cytoplasm. In this neoplastic state, the fusion protein now has numerous additional targets for catalysis based on its new location, which may disrupt existing networks.

Third, cells have robust processes to limit errors during cell division. In humans, at least 169 enzymes participate in DNA repair or influence DNA repair processes (Wood, 2014); even *E. coli has* 100 genes involved in DNA repair (Fraser et al., 1995); half of the human genes are directly involved in 5 common repair mechanisms: base excision repair; nucleotide excision repair; recombinational repair; mismatch repair; and direct reversal. These constitutive repair process reduce the transcription error rate from one per hundred thousand (Pray, 2008) to one per hundred million base pairs, which limits changes to protein structure and function that might disturb existing network interactions or create new ones. Cells also limit common causes of DNA damage, such as reactive oxygen species (McCord & Fridovich, 1969; Sturtz, Diekert, Jensen, Lill, & Culotta, 2001).

Fourth, cells have several mechanisms to respond to injury or DNA damage, which might eventually alter proteins and pathways. Through an undetermined intracellular audit, some injured cells undergo apoptosis through the activation of caspases and bcl2 family members (Wyllie, 2010). In addition, transcription factors and signaling molecules can recognize potentially lethal stimuli and initiate cycle arrest, autophagy, or protein synthesis shutoff (Rosenfeldt & Ryan, 2011). The importance of the apoptotic pathway is suggested by the high frequency of a defective p53 response in most cancers, often due to p53 gene mutations or deletions (Hollstein, Sidransky, Vogelstein, & Harris, 1991).

Fifth, key cellular processes have numerous controls that tightly regulate their activity. For example, mitotic checkpoints ensure genomic integrity by delaying cell cycle progression in the presence of DNA or spindle damage (Chin & Yeong, 2010; Stracker, Usui, & Petrini, 2009). These multiple levels of control prevent the inappropriate initiation of mitosis or other key processes, which reduces the reproduction of cells with genetic damage.

The immune system is a final supervisory system of error correction. An army of B and T cells, NK cells and macrophages have both innate and adaptive properties and maintain order by destroying cells with disordered properties (Grivennikov, Greten, & Karin, 2010). Their importance is suggested by the association of immunosuppression with a markedly elevated risk of malignancy (Rama & Grinyo, 2010).

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 germ line configuration.

The laws of complexity and self-organization provide a framework to better understand neoplasia. Cells are not just the linear sum of 20,000 gene products interacting in a predictable way, but the 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 (Knudson, 1971; Nordling, 1953).

2.7.1. Cell of origin

A neoplasm's characteristics are related to the network state of the cell of origin, the nature of the biologic pressures and the germ line configuration. The cell's network state determines its state of differentiation; cells with identical genotypes have different phenotypes due to differing active gene regulatory networks, leading the cells into different attractors, as discussed above. The variable network state between cells may affect the response to the cellular pressures discussed above. For example, the t(14;18) translocation is apparently only found in B lymphocytes (Limpens et al., 1995) and is due to an illegitimate V(D)J recombination, an activity restricted to B cells (Marculescu, Le, Simon, Jaeger, & Nadel, 2002).

The network state may also be affected by unknown maturational factors. For example, mutations may have a different impact in neonates, children and adults. Perhaps part of the reason Wilms tumor or neuroblastoma occur primarily in children/young adults is that the cells in older adults have developed additional control mechanisms or different network pathways that make these cells more resistant to the alterations which initiate these neoplastic conditions.

2.7.2. Nature of biologic pressures

In addition to morphologic or molecular classifications, it may be useful to classify neoplasia by the nature of the biologic pressures. For example, certain MALT lymphomas are caused not by mutations, but by antigen-driven lymphoproliferation, due to chronic infections or autoimmune disorders, which can be considered the ultimate neoplastic cause. Low-grade gastric MALT lymphoma is strongly associated with chronic *Helicobacter pylori* infection (Nakamura et al., 2012). The infection induces chronic lymphoid proliferation, which makes the inherently unstable lymphocytes more prone to additional network alterations (Bende, van Maldegem, & van Noesel, 2009) and increases the risk of transformation of clones that are dependent on antigenic stimulation (Suarez, Lortholary, Hermine, & Lecuit, 2006). In effect, the chronic inflammation induces changes to parts of the

lymphocyte's cellular network that were previously "frozen". Remarkably, this neoplastic process is usually reversed by *H. pylori* eradication therapy (antibiotics), apparently by removing the lymphoproliferative stimulus. A similar process occurs with *Campylobacter jejuni* infection in the small intestine (Lecuit et al., 2004), chronic *Chlamydia psittaci* infection in ocular adnexa (Ferreri et al., 2004), and chronic *Borrelia burgdorfer*i infection in the skin in endemic areas (Goodlad et al., 2000).

2.7.3. Germ line configuration

The nature of the neoplasia is also affected by the germ line configuration. Genetic variation is rare; nucleotide differences between a randomly chosen pair of humans are estimated to average only 1 per 1000 to 1500 (Jorde & Wooding, 2004; Wade, 2007). A large percentage of genes have more than one allele, and many individuals are heterozygous for a large fraction of these alleles (Lewontin, 1974). To date, at least 54 familiar cancer syndromes have been identified, with mutations in p53 or other known oncogenes (Lindor et al., 2008). However, more subtle variations in networks affecting any of the numerous control factors described above, directly or indirectly, may also influence neoplasia in a less traceable way. Alterations of control mechanisms may only have impact in select circumstances, based on cellular pressures on the network. For example, the wild type CCR5 gene, present in 80% of Caucasians, encodes the principal receptor for macrophage tropic viruses. After HIV1 exposure, its presence leads to infection, impairment of immune surveillance and development of HIV1-associated malignancies. In contrast, the CCR5 delta 32 mutation does not produce an effective receptor, leading to HIV resistance, but this effect was not noticeable in the pre-HIV era (Liu et al., 1996; Parczewski et al., 2011).

The laws of complexity and self-organization suggest a different approach to cancer treatment, based on patterns of network change, instead of changes to a specific molecule or pathway. In many cases, the ultimate neoplastic cause is upstream of the specific molecular changes identified in the tumor, as discussed with *Helicobacter pylori*, or conditions that damage the immune system. There are several advantages to focusing on the upstream changes. First, targeting them may prevent the neoplastic process from arising. Second, treatment may be simpler or more effective because the upstream changes are more uniform than the diverse molecular changes they often cause. Third, other types of neoplasia, currently without effective treatments, may have common upstream changes that present possibilities for improved treatment.

3. Summary

In the framework of the laws of complexity and self-organization, cells maintain order via redundant control features that resist the inherent biologic pressure in the cell towards disorder. Neoplasia can be understood as the accumulation of changes that allow cells to override these control features, leading to altered networks, which may lead to the dysregulation of growth and differentiation. The nature of the neoplasia is affected by the type of

biologic pressures, the network state of the cell of origin and the individual's germ line configuration. A better understanding of how these factors interact with each other may generate new approaches to treatment.

4. Note

(1) The National Cancer Act followed President Nixon's pledge in his State of the Union address on 22 January 1971:

I will also ask for an appropriation of an extra $100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal.

See also

* Video of State of the Union address at **https://www.youtube.com/watch?v=peb47Z-jPqc** at 15:03, retrieved 30 October 2016
* Summary of The National Cancer Act of 1971 at **https://www.cancer.gov/about-nci/legislative/history/national-cancer-act-1971**, retrieved 30 October 2016
* Video of President Nixon signing the National Cancer Act of 1971 into law at **https://www.youtube.com/watch?v=E2dzEDnGqHY**, retrieved 30 October 2016

5. Acknowledgments

The author thanks Christine Billecke, PhD, for her excellent editorial assistance in preparing this manuscript.

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