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The Application of Chaos Theory and Fractal Mathematics to the Study of Cancer Evolution: Placing Metabolism and Immunity Centre Stage

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Abstract

Despite the undoubted triumphs that have occurred in the treatment of some cancers, overall, the outcomes for disseminated disease remain poor. A change in perspective is therefore required to develop more effective treatment strategies. This review provides an overview of the potential contribution of chaos theory and fractal mathematics to the study of cancer evolution. The atavistic model of cancer proposes that cancer represents a reversion to an evolutionarily ancient proliferative phenotype, and suggests that cellular metabolism and the immune system are targets to which cancer may be susceptible. The approaches of chaos theory and fractal mathematics point to the same targets, and the synergy of these two perspectives will be explored. The emerging unifying concept which emerges is that the cellular machinery of the differentiated cell resists entropy in favour of stable structure. Each evolutionary development from multicellular organisms upwards, diverts more energy away from entropy. When malignant transformation occurs, the cell succumbs to the draw of the thermodynamic laws, maximizing fractal entropy, reverting to its ancient proliferative phenotype and moving, in its increased dynamic state, into greater chaos. Changes in the chaotic dynamics of cellular function evolve in parallel with changes in the fractal geometry of cellular structure. If the dynamics of the cancer cell can be worked out mathematically, it may be possible to use these dynamics to plan treatment strategies in the way that chaos theory is currently used to, for example, guide satellites. Although the responses of the tumour to the suggested targets may be weaker, they may also be more sustainable, and produce fewer side effects, than the current modalities and the emerging molecularly targeted therapies.

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Introduction

The lifetime risk of cancer is now approximately 50% in Western societies, and despite the undoubted triumphs that have occurred in the treatment of some cancers, overall, the outcomes for disseminated disease remain poor. Current therapy is based on radiation, chemotherapy and surgery. The modus operandi of the former two modalities is to target cancer cell proliferation by damaging DNA. The molecular biology revolution has led to an explosion of new information and has fueled the development of specific molecularly-targeted therapies. However, these have, overall, proved to be less selectively toxic than was hoped, partly because the pathways being targeted also have normal functions in normal cells, and partly because no drug is ever truly specific to just one target. In addition, the benefit of these drugs is often short lived, characterized by an often dramatic reduction in tumour mass initially, followed by recurrence as resistance sets in. This effect occurs because tumours are heterogeneous and their growth and development is subject to the forces of Darwinian evolution. Targeted therapies produce a short-term reduction in the tumour bulk, but they also create a selection pressure which favours resistant tumour cells, thereby driving the further evolution of the tumour. There are some drugs available which target the mechanisms of resistance, but, in the end, the same dynamics inevitably lead to a recurrence of the tumour. Although molecularly-targeted therapies do have a role to play, they have not produced the dramatic improvement in survival which is being sought. There is therefore a clear need to adapt our strategy.

The US National Cancer institute recognized this need and, to this end, they invited the cosmologist Paul Davies to look at cancer from the perspective of a physicist. He worked together with Charley Lineweaver, an astrobiologist, and Marc Vincent, an oncologist, to develop the 'atavistic' model of cancer progression (Lineweaver, Davies, & Vincent, 2014). The thesis of this model is that cancer represents the re-expression of an ancient preprogrammed trait which evolved hundreds of millions of years ago, before the advent of multicellularity. The ancestral cells were not terminally differentiated cells but were proliferators. Immortality of the cell would have been beneficial to these early single cells, but was later confined to eggs and sperm as multicellular organisms emerged. However, when the cell faces an environmental threat, it jettisons its higher functions and, in a misguided effort to survive at all costs, reactivates its dormant ability to proliferate unchecked. Once triggered, this program is pursued by the cell with ruthless abandon. This model immediately suggested to its proposers how our therapeutic strategy needs to change. Rather than targeting proliferation, which is the cell's most protected, entrenched and redundant capability, the weaknesses of cancer, capabilities known to have evolved more recently in evolution, should be targeted. The authors identified cancer's metabolic phenotype, its vulnerability to the immune system, transmembrane pumps and DNA repair mechanisms as key targets (Lineweaver et al., 2014). While these targets may not result in complete eradication of the tumour, they could improve morbidity and survival by achieving sustainable control of a reduced tumour mass.

The aim of this review is to discuss the application of chaos theory, and fractal mathematics, with which it is irrevocably intertwined, to our understanding of cancer evolution. The work that has been done on these perspectives has proceeded independently of the development of the atavistic model but, fascinatingly, also points to the immune system and metabolism as therapeutic targets. There is therefore a clear synergy between the two perspectives which this review will explore. Much of this discussion is speculative in nature, and my aim is to provoke some radical thoughts and suggest directions for future work.

The Dynamics of Biological Systems

Biological systems, at all levels of organization, are capable of exhibiting a wide range of dynamics. The simplest is homeostatic equilibrium, which describes a system at rest. Periodic and quasi-periodic dynamics occur when the system has a repeating rhythm, as seen in many of the body's circadian rhythms or the electrophysiological behavior of the heart or nervous system. These three states are often described as representing 'order', a reference to the fact that their dynamics are linear or, in other words, equal to the sum of their parts. Deterministic chaos represents the next level of complexity, that of non-linear dynamics, where the behavior of the system is greater than the sum of its parts. Deterministic chaos describes a system which is no longer confined to repeating a particular rhythm but is free to respond and adapt. A system in deterministic chaos is constrained only by 'boundary conditions' imposed to prevent it from collapsing. Such systems exhibit such complex behavior that it gives the illusion of randomness. However, if the raw measurements obtained from such systems are examined in the correct way, the pattern, and therefore the deterministic nature of the system, is revealed. Randomness represents a true breakdown in order of the system in which the system becomes uncoordinated.

Deterministic chaos was officially (and accidentally) discovered by Edward Lorenz in 1963 (Lorenz, 1963). Lorenz was a meteorologist who was about to rerun a weather simulation he had already done. To save time, he used data from a previous computer readout and started the simulation from its halfway point. To his surprise, he found that the results of the new simulation were markedly different. The computer readout he had used to start the simulation had approximated the 6 figure readout of the computer to 3 figures. This small difference in initial conditions (using a 3 rather than a 6 digit input) was enough to substantially alter the outcome. This is the 'butterfly effect', famously illustrated by the example of a butterfly triggering a tornado thousands of miles away by beating its wings, also referred to as the 'sensitivity to initial conditions'. Because of this phenomenon, the behavior of a chaotic system such as the weather can never be accurately predicted in the long term. Be that as it may, knowledge of the behavior of a chaotic system can still be of immense practical value. An example is given by the successful interception of the comet Gicobini/Ziner in 1985. The 3rd Interplanetary Communication Explorer, which was launched for this mission, was equipped with small rockets from which hydralazine fuel could be ejected to place the satellite in the required orbit. The mission encountered an immediate disaster after launch when the satellite used up nearly all its fuel escaping the Earth's atmosphere, leaving it without the fuel needed to achieve the required stable orbit. Rather than abandoning the mission, mathematicians used their knowledge of chaos theory and non-linear dynamics to figure out a way to nudge the satellite into a series of unstable orbits using the remaining fuel. The result was a successful interception of the comet (Dalgleish, 1999). Similar approaches have been successfully used in space exploration ever since. If our knowledge of chaos theory can be used to such good effect in space exploration, can it not also be used with equally good effect in the treatment of human disease?

A Brief Overview of Chaos Theory

In 1901, Willard Gibbs pioneered the use of phase space to represent the state of a system, and the Belgian physicist Ruelle then used this approach to study the behavior of chaotic systems (Ruelle & Takens, 1978). Phase space is an abstract, usually, two or three-dimensional space in which the x, y and z- axes represent key parameters which describe the state of the system. In reality, there is no limit to the number of dimensions which can be used, as is discussed later. The state of the system at any given moment can then be represented as a point in phase space by applying mathematical transformations to the raw data in a process called *embedding*. The state of a dynamic system is continuously changing, and by plotting the state of a system over time on a phase space diagram, one

obtains a graphical representation of all possible states of the system. There is a tendency for dynamical systems to evolve towards a particular state or behavior, and, on a phase space plot, this state or behavior is represented as a set of points known as the attractor (Ruelle & Takens, 1978). The attractor can be a fixed point (equilibrium), a limit cycle (periodic behavior), a limit torus (quasi-periodic behavior) or a fractal (deterministic chaotic behavior). In the latter example, the attractors of chaotic systems are referred to as strange attractors. The existence of an attractor is a property of a deterministic system; random systems do not have a true attractor.

Physiological systems can change their dynamics. This phenomenon is called bifurcation and can be detected on a phase space plot by a change in the attractor. Bifurcations which cascade a system move it towards deterministic chaos whereas bifurcations which provide negative feedback loops stabilize a system away from deterministic chaos towards the simpler dynamics. This phenomenon gives the system a remarkable flexibility (see (Bassingthwaighte, Liebovitch, & West, 1994; Goldberger et al., 2002; Goldberger, Rigney, & West, 1990; Oestreicher, 2007; Trzeciakowski & Chilian, 2008) for a more complete discussion), and a system which exists at the boundary between chaos and the simpler dynamics has the ability to exhibit either behavior according to its needs.

Fractal Mathematics

Fractal mathematics is a fundamentally new kind of geometry which is now receiving increasing attention by the medical, scientific and general communities. It has three applications in biology: the study of physical structure, the study of the structure of processes in time and the study of the dynamics underlying behavior. The latter two applications are distinguished by whether the data are embedded as part of the analysis. In the study of the structure of processes in time, the data are not embedded. In the study of dynamics, fractal mathematics plays a role if, after the data are embedded, the system is found to be chaotic and therefore to have a strange attractor.

In the 1970's, Benoit Mandelbrot described a fractal as "a rough or fragmented geometric shape which can be split into parts, each of which is (at least approximately) a reduced-sized copy of the whole" (Mandelbrot, 1982). The self-similarity of a fractal can be either perfect (geometrical) or statistical. Perfect self-similarity is a mathematical ideal, a geometrically perfect fractal. Nature never conforms to such ideals. Most fractals in nature exhibit statistical self-similarity, meaning that the fractal is approximately self-similar at different scales; put another way, the statistical properties of the part are proportional to the statistical properties of the whole. Examples of such self similarity in the human body include self-similar invaginations of alveolae in the lungs and the intestinal tract which increase the surface area for absorption, or the self-similar branching pattern of the dendritic, bronchial and vascular trees (Caserta et al., 1990; Goldberger et al., 1990; Kassab, Rider, Tang, & Fung, 1993; Smith, Marks, Lange, Sheriff, & Neale, 1989; West, Bhargava, & Goldberger, 1986). Biological processes in time can also exhibit fractal properties in that fluctuations at a given timescale resemble the fluctuations of the same process observed at a smaller timescale. Finally, as mentioned above, the strange attractor of a chaotic system is always a fractal, and fractal geometry therefore has a role to play in describing dynamics.

Cellular Dynamics

The central dogma of molecular biology has long asserted that a hierarchy exists within the cell in which each organizational level has its task. DNA is the information store, RNA is the information processor, proteins are the executors of genetic instructions and metabolites provide the fuel and some fine tuning. However, the true distribution of cellular functions is less rigid. The proteome can store information, at least in the short term, the metabolome can control gene expression and miRNAs can influence gene expression and regulate the subcellular

targeting of the proteome (Bhalla & Iyengar, 1999; Bray, 1995; Hartwell, Hopfield, Leibler, & Murray, 1999; Jeong, Tombor, Albert, Oltvai, & Barabasi, 2000; Oltvai & Barabasi, 2002). The genome, transcriptome, proteome and metabolome exist in complex interconnected networks which are all organized according to the same principles and form a type of network which is referred to as 'scale-free' (Barabasi & Albert, 1999). In a scale free network, the number of interconnections formed by a node, referred to as its degree, obeys a power-law distribution i.e. there are groups of nodes which form large numbers of interactions, and others which form only a few (Oltvai & Barabasi, 2002).

The dynamics of cellular networks are exemplified by the metabolic pathways. The metabolic network (which incorporates substrate supply, energy production in the mitochondria, energy utilization, and gene regulatory functions) is scale-free. Chaotic behavior has been frequently related to the interaction that occurs between oscillators, and metabolic pathways are replete with them. There are ultradian rhythms in oxygen consumption. Within the metabolic machinery, there are more irregular oscillators. Glycolytic flux can be constant or periodic when glucose supply is constant. When glucose supply becomes periodic, glycolytic flux can be either periodic or chaotic depending on the amplitude and frequency of the glucose input (Markus & Hess, 1985; Markus, Kuschmitz, & Hess, 1984). Most biochemical pathways probably exist in a number of oscillatory states and can bifurcate from periodic to chaotic behavior. Our technology limits our ability to study such phenomena; it is not easy to track and record metabolites in real time.

The evolutionary origins of these cellular dynamics can be understood using the concept of self organization. This is a phenomenon, described by Alan Turing, which can be understood as follows (Turing, 1990). Initally, the system is random; its components exhibit no meaningful interactions. However, because of their own properties, the components of the system will start to interact with some of their neighbours and repel others. As the interactions become stronger, a series of cascading bifurcations can drive the system towards deterministic chaos and then towards order. From an initial state of randomness, a new more complex and meaningful behavior emerges. This process is exemplified by the spontaneity with which fish come together to form shoals or birds come together to form flocks. In order for the new network to stabilize, the interactions of its components need to be strong enough that it is reinforced, not broken down, by repeated cycles of feedback. However, the interactions must not be too strong, or the network will become rigid and lose its ability to adapt. From an evolutionary perspective, self-organization creates complex systems which are then moulded until they exist at the boundary between order and chaos, held there by an intricate system of feedback. The system can use deterministic chaos when needed and then return to order, maintaining its flexibility without losing its structure (Kauffman, 1993; Langton, Taylor, Fanner, & Rassmussen, 1992).

Little is known about how the first cellular networks evolved, but it is tempting to speculate about the possibilities raised by the principle of self-organization. Network dynamics within the cell can be understood, at least in part, in terms of wave propagation through an excitable medium, because chemical reactions can spread in an oscillating manner akin to wave propagation. According to a theory first developed by Alan Turing, oscillations and chemical waves self organize into a network (Turing, 1990). A chemical, such as a second messenger, is synthesized rapidly at a particular location but diffuses slowly. At the moment of synthesis, there is a localized peak concentration. The chemical then diffuses into the surrounding medium and the concentration at the site of synthesis slowly falls. The next burst of synthesis gives rise to a second peak, and the process repeats itself. This results in the creation of a chemical oscillator sending out chemical diffusion waves. These can exhibit any dynamic (Winfree, 1972).

The chemical diffuses out to interact with neighbouring processes and targets, and can elicit responses not only by its unique

chemical identity, but by its temperospatial signature. As many such oscillators interact and self-organise, spatial organization of signaling and architecture emerge and the collective behavior of the system can suddenly bifurcate to produce a more complex behavior, forming a functional module. Additional structures, such as cytoskeletal elements, can refine the module's function.

Self-organization creates complexity independently, and provides an explanation of how function can gradually emerge from a sea of random behavior. From evolutionary perspective, this poses an intriguing dilemma as, in order for the new behavior to be passed on, there would need to be traits to the behavior which are heritable. One would expect that the first time a new complex behavior appears, it will probably be lost. However, if a particular genetic background favors the generation of complex behaviors which improve survival, the favorable traits will be passed on and allow for the continued appearance of beneficial complex behaviors which will eventually survive in the species. The genome may gradually evolve to encode more of the behavior, essentially 'recording' as much of it as is needed to ensure that the behavior is passed on. However, in a non-linear system, it is not necessary for the genome to record every detailed instruction; in fact, the genome lacks the necessary power to encode everything. The genome just needs to have enough instructions to recreate the required microenvironment so that the behavior can be sufficiently replicated within the required space to serve the required function. The final result is therefore a division of labour between programs encoded by the genome, and processes which rely on self organization guided by the microenvironment. Examples of this division of labour are well documented. The number of neural interactions, for example, greatly exceeds (by 2 logarithms) the number of genes encoding the nervous system. Likewise, structures such as the bronchial tree, small blood vessel networks or even fingerprints are not genetically encoded (identical twins do not have identical fingerprints). The structure which emerges from these self-organising processes is a fractal structure. It can therefore be seen that fractal structure, which begets chaotic non-linear behavior, is necessary for life (Dalgleish, 1999).

Unifying the Atavistic Model with Chaos Theory

In cancer, the cell is driven into a state of genetic instability and assumes the phenotype of anaplasia. It is unclear where this places the cell in the spectrum between ordered and random behavior. Functionally, the most feasible speculation is that chaos is increasing in the cell as the genetic instability accumulates and control is lost (Janecka, 2007). There is some evidence for this, particularly in breast cancer (Schneider & Kulesz-Martin, 2004). The atavistic model suggests that the bifurcation that occurs when the old proliferative program reactivates leads to a jettisoning of many of the younger pathways which evolved to keep the cell at the boundary between order and chaos. This moves the cell closer to the boundary between randomness and deterministic chaos from which the first pathways emerged. In an example of the sensitivity of this process to initial conditions, one study demonstrated that a single base substitution in one allele of the phosphatidylinositol-3 kinase (PI3K) was sufficient to induce a phenotype similar to that of basal-type human breast cancer in a human breast epithelial line (Hart et al., 2015). The phenotype included changes in the expression profiles of genes not known to be related to PI3K. While this may reflect an incomplete understanding of the role of PI3K, it is equally likely to reflect the extensive and non-linear nature of the interconnectivity of the cellular pathways as a whole. In the atavistic model, it is an example of how a single base substitution can reactivate the proliferative phenotype. Similarly, at the level of the tumour as a whole, deterministic chaos can be seen to operate. For example, in breast cancer, small numbers of so-called 'cancer stem cells' can be selected and propagated, reproducing a tumour mass whose genetic diversity is similar to the tumour mass from which they were derived (Al-Hajj, Wicha, Benito-Hernandez, Morrison, & Clarke, 2003). The breadth of the

heterogeneity suggests that there is underlying genomic instability, and is another example of the sensitivity to initial conditions. The reproducibility of the phenotype suggests that this instability is not random, but due to deterministic chaos. The heterogeneity thus generated can be acted upon by external selection pressures, thereby driving the evolution of the tumour.

The proliferative, increasingly chaotic, phenotype of cancer cells, conventionally referred to as anaplasia, is intriguing and difficult to explain using the conventional model of tumour development. Despite the wide range of cancer types, and mutations which have been associated with them, cancer cells exhibit remarkably similar behavior (increased proliferation, invasion, migration, inactivation of apoptosis etc.), although they clearly differ in the aggressiveness with which they exhibit their behavior. Both the atavistic and chaos theory models provide the same explanation for this – the cell is reverting to an evolutionarily older phenotype (Lineweaver et al., 2014). One possible interpretation of the atavistic model, if the cell exhibited only linear dynamics, would be that there is a single ancient program which is reactivated in all cancers. However, such an assertion misrepresents the actual structure and function of the cell. If the cell is in deterministic chaos, then the atavistic model does not represent the reactivation of a linear program but a bifurcation of the system to an evolutionarily ancient strange attractor. It would then be this strange attractor which embodies the ancient proliferation program.

The development of the anaplasia phenotype is usually (but not always) associated with a loss of architectural integrity which worsens as cancer development progresses and which produces the morphological changes with which histopathologists are very familiar: abnormalities in the size and shape of the cells, loss of nuclear polarity, an increase in the nuclear to cytoplasmic ratio, irregular nuclear outlines, irregular chromatin, prominent nucleoli, atypical mitoses and so on. Although beyond the scope of this review, these morphological features are also amenable to analysis using fractal geometry. For example, there is evidence that fractal measurements can be used to distinguish squamous cell carcinoma from adenocarcinoma of the lung (Lee et al., 2014), or for primary site assignment of a poorly differentiated tumour (Vasiljevic et al., 2012). In other words, changes in the chaotic dynamics of cellular function evolve in parallel with changes in the fractal geometry of cellular structure. Although the fractal shape of the cell changes with anaplasia, what does not change is the fact that the cell has fractal structures. This is in keeping with the proposed ancient evolutionary origins of fractal structure. Indeed, the speculation implied by Alan Turing's model of self organization is that fractal structure is as old as the very first pathways, older than the first cells.

Fractal Entropy

Fractal entropy is a model recently proposed by Garland which again places metabolism centre stage in cancer development (Garland, 2013). Garland also pointed out the paradox, discussed above, regarding the common profile of cancer cells, and noted that many of the genetic and epigenetic pathways involved in cancer development either directly or indirectly also influence energy management. These alterations divert energy away from the construction and maintenance of stable cellular structure towards the dynamic activities of anaplasticity, namely proliferation, motility, migration and architectural fluidity. The Warburg effect (the reliance of tumour cells on glycolysis in the presence of oxygen) is only part of what is a widespread remodeling of the metabolic machinery. This diversion of energy, in Garland's model, represents entropy, a dissipation of energy which occurs in accordance with the laws of thermodynamics. Garland proposes that this entropic dissipation follows a fractal structure, not unlike that which might have emerged from the early processes of self-organisation, and that the malignant transformation is one in which the network switches to state which favours maximum entropy (Garland, 2013). Unifying this concept with the atavistic model

and chaos theory, one arrives at the concept that the cellular machinery of the differentiated cell resists entropy in favour of stable structure. Each evolutionary development from multicellular organisms upwards, diverts more energy away from entropy. When malignant transformation occurs, the cell succumbs to the draw of the thermodynamic laws, maximizing fractal entropy, reverting to its ancient proliferative phenotype and moving, in its increased dynamic state, into greater chaos.

The metabolic pathways could be targeted by any strategy which prevents the fractal network from favouring entropy or which exploits the weaknesses this increased entropy creates. Switching on mitochondria, limiting glucose supply, increasing the oxygen tension and increasing the pH of the microenvironment are examples of some of the strategies which could be employed (Lineweaver et al., 2014).

The Immune System in Cancer

The immune system is one of the key systems of the body which interacts with environment. It functions at many levels, from mucosal and innate immunity to highly specific and targeted humoral and cell-mediated responses, and is exquisitely tuned to distinguish self from non-self. This is a remarkable feat, as the antigens found on microorganisms can be very similar to self antigens. Dalgleish suggested that the immune system exhibits deterministic chaos and focuses around strange attractors (Dalgleish, 1999). It makes intuitive sense that the immune system would benefit immensely from this dynamic. The immune system has to continuously adapt, learning and imprinting its environment. If it were a linear system, one would expect clonality to be the norm in all responses, which is the exact opposite of the true situation. In an embellishment of the well-studied role of HLA and immunoglobulin in distinguishing self from non-self, Cohen suggested that the reason the immune system focuses on regions of HLA and immunoglobulin is that these are the regions that have been most hijacked by pathogenic microorganisms (Cohen & Young, 1991; Dalgleish, 1999). In this case, the strange attractor has evolved appropriately by focusing the attention of the immune system on a vulnerable and frequently attacked target.

Inappropriate focusing of the immune system is a well-established phenomenon in chronic disease. In cancer, melanoma, prostate cancer, colorectal cancer, lymphomas and myelomas are all associated with a depression of Th1 response (cell mediated responses associated with interleukin-2, interferon γ and interleukin 12) and enhancement of Th2 responses (humoural responses associated with interleukins 4,5,6 and 10) (Dalgleish, 1999). A similar phenomenon occurs in HIV infection and AIDS (Dalgleish, 1999). From the perspective of chaos theory, this represents a partial collapse of the immune network reflected by a change in the strange attractor of the system. This bifurcation of the system alters the focus of the immune system and thereby shifts its relationship with the disease. Non-specific stimulants of the immune system are known to have anti-tumour activity in a range of tumours; examples include BCG, interferon, interleukin II and tumour vaccines(Dalgleish, 1999). These therapies may act, in part, to refocus the strange attractors. The promise of the application of chaos theory is that, by resetting the attractors to their normal state, the response rate of the tumour to immune stimulation could be increased. It is now well-accepted that escape from the control of the immune system is a key step in carcinogenesis, and there is intense interest in developing strategies to prevent this escape. This approach dovetails with the atavistic model, which states that the functioning of the immune system in the microenvironment of the cancer cell reverts to an early evolutionary state, before adaptive immunity emerged (Lineweaver et al., 2014). However, if the tumour is attacked by an insult which requires adaptive immunity as a defence, this would be an attack to which it is vulnerable. This idea provides a justification for the approach of using tumour vaccines.

Can We Use Chaos Theory to Treat Cancer?

It makes intuitive sense that strange attractors of the cellular systems must exist, and that they change in cancer. However, this has not been validated using objective data and we currently have no idea what the 'healthy' and 'unhealthy' strange attractors look like. It is not even clear what a definition of the 'system' should be to obtain the phase space plot of the system, what data needs to be collected, how often and how the data should be embedded. Dhruba Deb recently developed an art-science model in which the ten hallmarks of cancer were represented in 10 dimensional phase space (Deb, 2016). The use of multiple dimensions is commonplace in physics and cosmology but is still somewhat alien to mainstream biological sciences. Although I explained phase space above in the terms of two or three dimensional plots, as these are intuitively easier to grasp, there is, in fact, no limit to the number of dimensions that can be employed in the embedding process. To obtain an artistic two-dimensional visual representation of the 10-dimensional phase space, the author used techniques from cubism to produce a contour map (a projection of a high dimensional object on lower dimensions, frequently used in quantum mechanics) (Deb, 2016). The author did not derive the plots using experimentally-derived data and presented this as a work of abstract expressionism. However, it presents an intriguing approach to the embedding process and the subsequent representation of the attractor.

The first step in being able to properly derive the actual strange attractors is to determine the correct embedding procedure to use. The nature of non-linear systems is that the equations derived from the study of one such system are not usually applicable to another. It is not, therefore, valid to use embedding equations derived from the study of, for example, weather systems and apply them to cancer. The correct embedding equations to use in biological systems need to be worked out in those systems. This will require collaboration with mathematicians and scientists who are experienced with non-linear mathematics and its applications.

Most of our current diagnostic and research modalities in human cancer provide a single snapshot of the cancer in time. The construction of the phase space plot requires repeated sampling. Experimental derivation of strange attractors could proceed initially using animal models to measure all the parameters that are deemed necessary to derive the phase space plot. It is unclear how this should be translated into the clinic using samples from real patients. The degree of repeated tissue sampling required to generate a phase space plot is unlikely to be ethically justifiable. Studies on circulating tumour cells in the blood or using radiological approaches may be more feasible or, if the tumour mass is easily accessible to fine needle aspiration, cytology could also be used. Other approaches on biopsy and resected material may also be possible, but the issues raised are difficult. Would it be valid to pool the data of large numbers of patients and construct an average phase space plot for each cancer type? How should cancers be grouped for this purpose? Should integrated genomics approaches be used to group the cancers? Should morphological criteria be used? In addition, tumours are heterogenous, and therefore the strange attractors may vary even within the same tumour mass. In addition, it will be important to select the appropriate period over which to sample. If the sampling period is too long, it is possible that bifurcations may occur, and be missed, during the sampling process, giving rise to a plot which actually represents the 'average' of several bifurcations. If the sampling period is too short, there will be insufficient data to derive any attractor.

Aside from the challenges of data acquisition, there are also profound analytical challenges to be faced. The first is that the imposition of measurement error on a phase space plot can create the artefactual appearance of a strange attractor when the data are actually derived from a periodic or quasiperiodic system. Secondly, a strange attractor can also be artefactually produced if a systematic bias is present in the sampling of a random system. Both these influences could

also produce an erroneous shape of a strange attractor even if the system is truly in deterministic chaos. Clearly, a form of statistical testing is required to account for these artefacts, but therein lies another problem.

Strange attractors, as discussed above, are always fractals. In a fractal system, the measurement of any parameter depends on the resolution at which the measurement is taken. If one is measuring length, for example, the value of the measured length would increase as the finer details are revealed. The measurement does not therefore have a 'true' value. Rather, there is a relationship, referred to as a scaling relationship, between the measurement and the resolution. This has a profound consequence. We are used to using means and variances to describe data, and the sample mean we obtain by experiment is meant to reflect the population mean of the parameter. As the sample size is increased, the sample mean should approach the 'true' value of the population mean. For fractals, however, something very different happens when this tried and tested method is applied. As the sample size increases, the value of the sample mean continues to change and diverge to either zero or infinity, never approaching a 'true mean'. This situation arises because the value of the parameter depends on the scale at which it is measured, and can therefore never have a single true value. Repeated measurement simply results in the parameter being measured at finer and finer scales, and the conflicting measurements thus obtained either cancel each other out, tending towards zero, or compound each other, tending towards infinity. Self-similarity at multiple scales can also affect variance, because smaller fluctuations in the data are amplified as the resolution is increased by repeated sampling. The measured variance therefore increases as the sample size or sample time increases, and tends towards infinity. This renders our traditional approach to statistical hypothesis testing useless (see (Bassingthwaighte et al., 1994) for review). If there is no mean and infinite variance, there is currently no way to determine what the parameters of the system are, so we have no way of detecting a change in those parameters. Furthermore, because the system has no true mean, the value of the calculated mean will be seen to change *even if the underlying process remains unchanged*.

Despite the enormity of the challenge, it is vital that the work to properly measure and characterize the deterministic chaos of cancer is done. Only then will it be possible to use deterministic chaos to inform the details of the treatment regimens directed against the weak points of cancer. As exemplified by the applications in space exploration, a successful outcome requires exact calculation meticulously and precisely applied. This is only possible if we have an accurate mathematical representation of the system we are targeting.

Conclusion

If the 'war on cancer' is to be won, it is clear that we need to change our strategies. There is no doubt that the emerging molecularly targeted therapies will continue to play a role in reducing tumour bulk, but new approaches are needed to exploit the weaknesses of cancer and, essentially, use its evolutionary biology against it. The atavistic model provides a fascinating approach to selecting which weaknesses to strike. The promise of chaos theory and fractal mathematics is to provide the details of the tactics. The hope is that this approach will produce sustainable control of the tumour. In the words of Sun Tzu, "just as flowing water avoids the heights and hastens to the lowlands, so an army avoids strength and strikes weakness".

References

1. Al-Hajj, M., Wicha, M. S., Benito-Hernandez, A., Morrison, S. J., & Clarke, M. F. (2003). Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A, 100*(7), 3983-3988, 10.1073/pnas.0530291100 0530291100 [pii]
2. Barabasi, A. L., & Albert, R. (1999). Emergence of scaling in random networks. *Science, 286*(5439), 509-512,
3. Bassingthwaighte, J. B., Liebovitch, L. S., & West, B. J. (1994). *Fractal Physiology*. New York: Oxford University Press.
4. Bhalla, U. S., & Iyengar, R. (1999). Emergent properties of networks of biological signaling pathways. *Science, 283*(5400), 381-387,
5. Bray, D. (1995). Protein molecules as computational elements in living cells. *Nature, 376*(6538), 307-312,
6. Caserta, F., Stanley, H. E., Eldred, W. D., Daccord, G., Hausman, R. E., & Nittmann, J. (1990). Physical mechanisms underlying neurite outgrowth: A quantitative analysis of neuronal shape. *Phys Rev Lett, 64*(1), 95-98,
7. Cohen, I. R., & Young, D. B. (1991). Autoimmunity, microbial immunity and the immunological homunculus. *Immunol Today, 12*(4), 105-110, 0167-5699(91)90093-9 [pii] 10.1016/0167-5699(91)90093-9
8. Dalgleish, A. (1999). The relevance of non-linear mathematics (chaos theory) to the treatment of cancer, the role of the immune response and the potential for vaccines. *QJM, 92*(6), 347-359,
9. Deb, D. (2016). Understanding the unpredictability of cancer using chaos theory and modern art techniques. *Leonardo, 48*(2), 66-67, 10.1162/LEON_a_01099
10. Garland, J. (2013). Energy management - a critical role in cancer induction? *Crit Rev Oncol Hematol, 88*(1), 198-217, S1040-8428(13)00081-4 [pii] 10.1016/j.critrevonc.2013.04.001
11. Goldberger, A. L., Amaral, L. A., Hausdorff, J. M., Ivanov, P., Peng, C. K., & Stanley, H. E. (2002). Fractal dynamics in physiology: alterations with disease and aging. *Proc Natl Acad Sci U S A, 99 Suppl 1*, 2466-2472,
12. Goldberger, A. L., Rigney, D. R., & West, B. J. (1990). Chaos and fractals in human physiology. *Sci Am, 262*(2), 42-49,
13. Hart, J. R., Zhang, Y., Liao, L., Ueno, L., Du, L., Jonkers, M., et al. (2015). The butterfly effect in cancer: a single base mutation can remodel the cell. *Proc Natl Acad Sci U S A, 112*(4), 1131-1136, 1424012112 [pii] 10.1073/pnas.1424012112
14. Hartwell, L. H., Hopfield, J. J., Leibler, S., & Murray, A. W. (1999). From molecular to modular cell biology. *Nature, 402*(6761 Suppl), C47-52,
15. Janecka, I. P. (2007). Cancer control through principles of systems science, complexity, and chaos theory: a model. *Int J Med Sci, 4*(3), 164-173,
16. Jeong, H., Tombor, B., Albert, R., Oltvai, Z. N., & Barabasi, A. L. (2000). The large-scale organization of metabolic networks. *Nature, 407*(6804), 651-654,
17. Kassab, G. S., Rider, C. A., Tang, N. J., & Fung, Y. C. (1993). Morphometry of pig coronary arterial trees. *Am J Physiol, 265*(1 Pt 2), H350-365,
18. Kauffman, S. A. (1993). *The Origin of Order: Self Organization and Selection in Evolution*. Oxford: Oxford University Press.
19. Langton, G. C., Taylor, C., Fanner, D., & Rassmussen, S. (1992). *Artificial Life II* (Vol. 10). Redwood City, California: Addison-Wesley.
20. Lee, L. H., Tambasco, M., Otsuka, S., Wright, A., Klimowicz, A., Petrillo, S., et al. (2014). Digital differentiation of non-small cell carcinomas of the lung by the fractal dimension of their epithelial architecture. *Micron, 67*, 125-131, S0968-4328(14)00149-8 [pii] 10.1016/j.micron.2014.07.005
21. Lineweaver, C. H., Davies, P. C., & Vincent, M. D. (2014). Targeting cancer's weaknesses (not its strengths): Therapeutic strategies suggested by the atavistic model. *Bioessays, 6*(9), 827-835, 10.1002/bies.201400070
22. Lorenz, E. N. (1963). Deterministic nonperiodic flow. *American Meteorological Society Journal, 20*, 130-141,

23. Mandelbrot, B. (1982). *The Fractal Geometry of Nature*. New York: W.H. Freeman and Company.
24. Markus, M., & Hess, B. (1985). Input-response relationships in the dynamics of glycolysis. *Arch Biol Med Exp (Santiago), 18*(3-4), 261-271,
25. Markus, M., Kuschmitz, D., & Hess, B. (1984). Chaotic dynamics in yeast glycolysis under periodic substrate input flux. *FEBS Lett, 172*(2), 235-238,
26. Oestreicher, C. (2007). A history of chaos theory. *Dialogues Clin Neurosci, 9*(3), 279-289,
27. Oltvai, Z. N., & Barabasi, A. L. (2002). Systems biology. Life's complexity pyramid. *Science, 298*(5594), 763-764,
28. Ruelle, D., & Takens, F. (1978). Thermodynamic formalism: The mathematical structures of classical equilibrium statistical mechanics. In G. C. Rota (Ed.), *Encyclopedia of Mathematics and its Applications* (Vol. 5). Menlo Park, California: Addison-Wesley.
29. Schneider, B. L., & Kulesz-Martin, M. (2004). Destructive cycles: the role of genomic instability and adaptation in carcinogenesis. *Carcinogenesis, 25*(11), 2033-2044, 10.1093/carcin/bgh204 bgh204 [pii]
30. Smith, T. G., Jr., Marks, W. B., Lange, G. D., Sheriff, W. H., Jr., & Neale, E. A. (1989). A fractal analysis of cell images. *J Neurosci Methods, 27*(2), 173-180,
31. Trzeciakowski, J., & Chilian, W. M. (2008). Chaotic behavior of the coronary circulation. *Med Biol Eng Comput, 46*(5), 433-442,
32. Turing, A. M. (1990). The chemical basis of morphogenesis. 1953. *Bull Math Biol, 52*(1-2), 153-197; discussion 119-152,
33. Vasiljevic, J., Reljin, B., Sopta, J., Mijucic, V., Tulic, G., & Reljin, I. (2012). Application of multifractal analysis on microscopic images in the classification of metastatic bone disease. *Biomed Microdevices, 14*(3), 541-548, 10.1007/s10544-012-9631-1
34. West, B. J., Bhargava, V., & Goldberger, A. L. (1986). Beyond the principle of similitude: renormalization in the bronchial tree. *J Appl Physiol, 60*(3), 1089-1097,
35. Winfree, A. T. (1972). Spiral Waves of Chemical Activity. *Science, 175*(4022), 634-636,

