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EDUCATIONAL SECTION

Tumour biology, chaos and non-linear dynamics

David A. Rew

University of Leicester, UK

Introduction

Mathematical concepts can be helpful in representing the biological world in various ways. Descriptions of linear and non-linear systems, chaos theory, fractal geometry and neural networks all find relevance to the study of oncological problems. We are accustomed to looking for cause and effect patterns in the search for the aetiology and treatment responses of human tumours, as for example in the dosage of chemo- or radiotherapy. Such simple, proportional relationships are described by linear mathematics. However, the complexity of biological processes, and the inter-relationships of many different factors, serve to obscure simple, mechanical models in biological behaviour patterns, whether on the genetic, cell, tissue, organ, whole body or tumour scale. We may consider whether the concepts of non-linear mathematics are applicable and helpful to the study of tumour biology and in the interpretation of cancer research findings.

In a linear system, a linear input will produce a predictable, proportional, 'linear' or log-linear response. Many concepts in biology may be better explained in the mathematics of non-linear systems, whereby causes and effects do not appear to be proportionate. Dynamic mathematics describes systems that move or change in space and time. This is the nature of biological processes. One form of such mathematics is the study of simple functions and equations which are iterated over and over again, thus producing some unexpected results. These include complex and self-replicating forms and images, described by the French mathematicians Gaston Julia in the 1920s and Benoit Mandelbrot in the 1970s. Some dynamic systems are predictable, while other are not.[1] Exponential growth is one example of a dynamic process which can be readily described mathematically. The cellular growth of a malignant tumour cannot be so easily described. While neoplastic growth represents serial linear events on a massive scale, for example through cell replication and apoptosis, the evolving complexity rapidly escapes description or deconvolution by simple linear mathematics.

We may consider events and processes which occur in nature as being determined by previous events, or conversely as being unpredictable (probablistic). In deterministic theory, the future can be predicted from the past, a concept of which the French scientist Pierre Laplace (1749–1821) was a key exponent. In his book on Celestial Mechanics, he propounded the view that the future of the universe is entirely predictable from its present state. In contrast, in probablistic theory, the future is only related randomly to the past, and cannot be determined from it. Heisenberg's Uncertainty Principle and the laws of quantum mechanics describe a physical world predicated upon probabilities and uncertainty.

Prediction is nevertheless important, whether in relation to the motion of planets and comets, weather patterns, structural failure of engineering or architectural artefacts, or to the metastatic behaviour of tumours. In recent decades, new mathematical approaches have been adopted in an effort to unravel the complexity inherent in natural physical systems, and to develop new predictive tools. Deterministic chaos theory, commonly known as chaos, is one such tool.[1–3]

Chaos is the mathematics of the seemingly complex behaviour which may arise from subtle changes in simple, non-linear systems. The mathematics of chaos can be applied to every physical system in the Universe. Mathematical chaos is *not* random behaviour. There are three characteristics which define chaos.[2] Firstly, it is an irregular oscillatory process. Secondly, chaotic events are deterministic phenomena which resemble but are not random (stochastic) processes. They obey the fundamental laws of physics and nature, but are subject to disorder, complexity and unpredictability. Thirdly, chaotic systems are highly responsive to the initial conditions. A measurable input may produce a quite unexpected output, or chaotic behaviour, depending upon the initial conditions of the system. Chaotic instability arises when more than one force or process affects the system.

Catastrophe theory

Catastrophe theory is derived from chaos theory. It addresses the dramatic changes which can follow from small changes in inputs, variables or parameters. It has a specific terminology. A bifurcation is a transforming event, and an attractor is a mathematical description of the behaviour of

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a particle moving in a confined region of space according to deterministic laws. This may be a point, an ellipse, or a permanently erratic motion within the space. Catastrophe theory has not been formally applied to cell and tissue systems. Nevertheless, in biological terms, we might consider a bifurcation as a genomic change which moves a cell from normal to malignant behaviour, and an attractor as a pattern of behaviour which describes the normal or abnormal growth parameters of the cell, tissue or tumour.

Fractal geometry

Fractal geometry is a descriptive geometry of complex and self-replicating images and structures.[4] It is the geometry of deterministic chaos. It describes the boundary between regular and chaotic motion. These forms are often underpinned by relatively simple mathematical formulae and quadratic functions. Snowflakes may provide one example of this in practice. Every snowflake displays a unique pattern, and yet the underlying components (water molecules), physical constraints (the freezing point of water, and the inter-molecular forces, for example) and the hexagonal geometry are constant.

Fractal mathematics suggests that the complexity in natural systems may arise from relatively simple rules and mathematical descriptions. Fractals are irregular, but it is important to recognize that not all irregularities are fractal. The 'self-similarity' of fractal images allows precise reproduction of form at any level of magnification. Thus, the irregularity of a continental coastline may reappear in scanning microscopy of fragments of its constituent pebbles. It is also possible to reproduce natural forms such as images of trees, mountain ranges, land forms, clouds and planets in computer games and artificial reality systems such as flight stimulators using fractal data sets.

Fractals and 'scale invariance'

A fractal pattern cannot be described by simple linear measurements, because it is the same at various scales. One way to circumvent this problem is by the use of the concept of the 'fractal dimension', which is an index of the space filled by the fractal structure. A more finely branching structure may thus have a higher fractal dimension than a 'bare branch' pattern. Scale invariance may be an organizing principle in biology of necessity, in order to obtain maximum form from minimum genetic code. Fractal patterns have been studied in electrophysiological signals by Goldberger *et al.*[5,6] They may also apply in embryogenesis and developmental biology, in genetic function and expression, and in consequences of mutational disorder. We may thus also conceive of this fractal-like process at work in the growth of human tissues and tumours.

Fractal-like patterns seem to appear in human tissues, as, for example, nerve networks, the folding of gastrointestinal mucosa, and the branching of blood vessels and the biliary tree, or the morphology of the brain. Subunits may resemble the larger scale structure, as in the vascular system, and may share function on various scales, including the scale of time. Such patterns may also influence tumour growth. Histopathological experience teaches how some tumours are sparsely infiltrative, while others are dense or efflorescent structures, like the villi of mucosa and adenomas.

Signal complexity and its resolution in non-linear biological systems

The signal is the pattern which a chaotic system displays. Simple signals, such as a pure tone note in music, have minimal complexity, where as complex signals tend to have a broad spectrum of components, such as, to pursue the music analogy, an orchestra at play. Random and chaotic systems tend to occupy a broad spectrum of signal frequencies. This observation has led Goldberger *et al.*[5,6] to suggest that physiological ageing and senescence of the body reflect a loss of chaotic complexity in system function, as, for example, the high tone loss of presbyacusis, changes in the dynamic range of electro-encephalograms, or the loss of sensitivity of cardiac pace-setting.[7] In these circumstances, the mathematics of Fourier analysis can be applied to determine the constituent frequencies of the signal.

Artificial neural networks (ANNs) are computerized modelling tools which may help analyse chaos and fractal geometry in biological processes. They act as a data processor which can store experimental data and can 'learn', so as to draw generalizations. They draw upon fuzzy logic, using soft linguistic system variables (such as large, small), continuous values in the range (0, 1), a rule computable function and are particularly useful for addressing problems which are imprecise, which have sufficient modelling data, for which expert system rules are difficult to apply, and for which results are often probablistic. Uses of ANNs and fuzzy logic in oncology include image analysis, experimental prognostication, cytopathology, and diagnosis.[8]

The biological implications and consequences of chaos

The concepts of deterministic chaos find practical applications in the physical world, such as in weather forecasting, but there is no conclusive evidence that the mathematics of chaos, catastrophe theory and fractals are relevant to the biological world. The limitations of chaos theory in biology follow from the sheer complexity of the mathematics. Chaotic motions diverge at exponential rates, and any input error escalates as a function of time. The calculation is rapidly overwhelmed, as is its predictive power. Even simple, chaotic physical systems, must be modelled on powerful computers.

Chaos mathematics is thus something of a one-way street. It is possible to produce demonstrably chaotic systems using mathematics but very difficult to resolve the underlying equations in biological systems to assess whether or not they are indeed chaotic. The problem for biologists lies in the reverse analysis. After a very small number of iterations, or steps through a non-linear system, the number of possible permutations becomes enormous. The original conditions of the system cannot then be deduced, thus nullifying the

use of fractal mathematics as an analytical (as opposed to a descriptive) tool.

Stable and unstable biological systems

Dynamic systems may be stable or unstable. Evolution has imposed profound stability on biological systems. This is well illustrated at many levels. Cells display reproductive and morphological stability over thousands of generations. Embryogenesis displays remarkable consistency and accuracy of developmental processes such that billions of cells, tissues and organisms are reliably reproduced. The mature tissue is precisely stable in the steady state. Highly proliferative tissues, such as bone marrow or the mucosal crypt, have stable morphology because cell accretion is perfectly balanced with cell loss.

Nature nevertheless imposes considerable instability on all biological systems by virtue of periodic environmental fluctuations, be they predictable, such as day and night, seasons of the year, or longer-term patterns in weather (e.g. Ice Ages) predicated upon the precessional orbit of the earth; or unpredictable, such as extinction level events on evolutionary timescales, or man-made environmental changes. These interlocking periodic environmental frequencies may resemble a true chaotic structure. These frequencies are reflected within individual bodies by physiological frequencies such as circadian rhythms of endocrine function, and by all other aspects of normal behaviour. All cells and tissues are similarly exposed to instabilities, be they as simple as the variable rate of pulsatile flow of blood.

There is some evidence for deterministic chaos at work in normal tissue and organ physiology in the human body.[7] We do not yet have good predictive models of diseases based on chaos, but we may expect that within the patterns of disease which we recognize, such models may emerge. If disease states do represent a *loss of complexity*, then normal homeostasis may be a function of many interlocking fractal systems.

Chaos and cancer: non-linear dynamics and tumour biology

The fundamental deterministic processes in biology reside in the cell nucleus, where linear information in the genetic code is converted into all of the functions and forms of life and behaviour. All change, linear and non-linear, must originate in the genome. It is here that we must look for clues to deterministic chaos. We now know that the stability of normal biology can be corrupted by relatively minor disruption to the genetic code, such as through a single-base mutation in key regulatory proteins. This might have disproportionate consequences upon cell function several orders of magnitude removed from the initial damage as a result of cascade effects. Tumours can display gross functional disturbance when compared with their host tissues, and yet display minimal genetic difference from their tissues of origin. This problem has been clearly expounded by Schipper *et al.*[9]

Resolving and identifying chaos in tumours

The difficulty in applying fractal and chaotic mathematical processes to tumour biology is clear from the paucity of useful models in clinical practice. Tumours are nevertheless unstable systems, as illustrated by their heterogeneity in tumour genetics, aneuploidy, morphology and growth patterns, for example. The change from cumulative minor genetic dysfunctions to catastrophic malignancy may thus have mathematical parallels. If chaotic signals do emanate from tumours, we may find them in the structural morphology of the whole tumour or its component parts, in the dynamic growth characteristics, in their patterns of behaviour or even in their response to therapy. It is the instability associated with a tumour (volume increase, invasion or metastasis) rather than the existence of the tumour which kills. The restoration of stability or steady state symbiosis of a tumour with its neighbouring tissues may be an important objective in therapeutics.

Chaos at the genetic level

Mutation and dysfunction of normal, regulatory genes which have a role in key processes such as proliferation, apoptosis, growth regulation and differentiation, produces dysfunctional proteins, whose consequences may appear throughout the cell, on the cell membrane or in cell signalling systems. *Oncogenes* gain malignant function through mutation or chromosomal defect or through viral acquisition into the genome. *Tumour suppressor* genes promote neoplasia in consequence of the loss of their normal regulation. Chaos may thus manifest in tumours as a gain of complexity (tumour promoter genes) or as a loss of complexity (allelic loss, tumour suppressor genes). *DNA repair*, *gatekeeper* and *caretaker* genes maintain DNA by operations such as the repair of strand breaks, and the facilitation of chromosome cleavage and segregation, disruption of which may produce translocation or aneuploidy.[10] Small changes in the functional expression of these genes through mutation may thus also have profound consequences for the cell. Because such changes can be specifically traced back to single mutations, they may be clear examples of deterministic chaos.[11,12]

Chaos in tumour morphology and heterogeneity

The genetic changes of cancer may also manifest in variable morphology, which is in turn dependent upon factors such as the geometry in vascularization and differentiation. Informative patterns may emerge in the morphology of the abnormal epithelial crypts of colorectal tumours or ductal systems of invasive breast cancer. Tumours vary very considerably in form and behaviour. For example, some gastrointestinal tumours are small, cicatrizing and metastatic, while others are the opposite. The variability in these patterns of growth raises the intriguing possibility of linking tumour form with genotype, and thus of predicting the specific gene defects from the macroscopic and microscopic morphology of the tumour.

Heterogeneity is found at many levels within human tumours.[13] Shankey and Shackney[14] have shown how

genomic disorder changes with time in solid tumours. The accumulation of specific defects increases the likelihood of further defects, thus suggesting the possibility of mathematical patterns within tumour micro-evolution.[15–17]

Chaos in tumour behaviour

Tumour behaviour challenges deterministic mathematics. Specific classes of tumour often display specific patterns in metastasis. Thus, for example, colorectal adenocarcinomas consistently spread first to lymph nodes, then to liver, and often only terminally to distant sites. The prediction of future behaviour from analysis of the primary tumour would be of considerable utility in cancer therapeutics, if deterministic phenomena could be identified within morphological, functional or molecular measurements of the lesion. We do not yet known whether the metastatic behaviour of individual tumours is random, non-random, probablistic or deterministic. The latter, for example, might be driven by the expression of metastasis-promoting genes. Conversely, if metastasis is a random event, then there will be no underlying metastasis-promoting mechanisms and no targets for specific therapy.

Chaos and cancer therapy

If tumour progression is partly or largely deterministic, then subtle modulation of component signals and the appropriate control mechanisms, such as of cell cycle control or apoptosis, might achieve disproportionate *benefits*. Conversely, if tumour growth is a complex chaotic system, then applying one displacing force, in the forms of radiotherapy or chemotherapy, may have very unpredictable effects, because intrinsic tumour-suppressing mechanisms may be as badly disrupted as tumour-promoting mechanisms. Manifestations of therapeutic interference in this unstable and unpredictable state might then include lack of response, and aggressive or resistant recurrence or progression, which is in fact often the case with conventional therapy.

Conclusions

The hypothesis that deterministic chaos theory and its offshoots may find practical applications in surgical oncology has yet to be tested extensively against the complexity of tumour biology. Mathematics offers descriptive tools to study the real world, which may yet be inadequate to the task. However, even where we are unable to reduce phenomena to mathematic equations, the scope of thinking engendered by non-linearity may help us to understand the behaviour of tumours and our approaches to therapy. It is conceivable that changes in regulatory processes in some tumour systems, while seemingly random, may in fact be non-random and highly ordered structures and events.

Chaos theory may indeed find no application in the study of the behaviour of solid tumours and in the prediction of their response to treatment. Such patterns as may emerge may indeed be entirely fortuitous. Even where certain components of tumour behaviour are deterministic in consequence of their genetic origins, the vagaries of tissue biology, of coexisting disease, of the workings of the immune system, of variable vascularity, nutrition and ambient physiology, and of human intervention, may be such as to swamp the potential patterns with randomness.

So far as we know, nature is fundamentally indeterministic, governed at the atomic level by quantum theory, which is probablistic and uncertain. Thus chaos is a useful descriptive and conceptural exercise, but nature will never be truly predictable, whether at the microscopic, the macroscopic, the behavioural or the astronomical scale. The idea that small events can have major consequences is not new to human thinking, but the efforts to systematize the apparently unpredictable events of nature in the mathematics of deterministic chaos are a product of the latter part of the 20th century.

Biological processes may ultimately escape such prediction, but there is clearly great utility in understanding how seemingly complex forms and function can arise from singular and limited genetic information and events. The search for complex non-linear patterns expressed in tumour form and function may lead to new tools with which to influence tumour behaviour.

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