

Issues in a SYSTEM approach to radiobiology

INTRODUCTION

After several decades of a profoundly reductionist approach to biology the research community is now being encouraged to be more "integrative" and this includes the recommendation to adopt "a systems biology" approach. I very much endorse this advice depending on what is meant by the term "systems biology". So instead I use the term "systems approach" for this presentation. I will try and demonstrate here that taking such an approach, is illuminating, requires the subject to be addressed from first principles and I warn that it will require a dedicated research effort which will be novel by traditional standards.

In explaining this system approach I am aided by the fact that systems show a high degree of self similarity, that is, they have a fractal character, which will help us to better understand their basic character.

Let us first be clear what our objective is, namely, to understand the *processes* by which radiation produces health detriment at the most fundamental level by building models at the cellular and tissue levels that will represent these processes and allow the hypotheses they generate to be tested. So this presentation is not about pragmatic approaches to limiting risk for radiation exposure but about understanding the biological bases for the effects of ionising radiation in terms of a systems approach rather than, as over the last 50 years, a reductionist approach.

In the abstract of this presentation I promised that we could find our way to a meaningful understanding of how we might achieve this objective on the basis only of logic and an intuitive

understanding of the nature of natural systems. I stand by that claim.

I have drawn a distinction above between systems biology (SB) and a systems approach. The term systems biology is heavily abused, probably because it can be used, apparently successfully, to attract research funding. So it is no longer useful as a term. In 2003 O'Malley and Dupre(1), philosophers from Exeter University, surveyed the field of systems biology and concluded that work in that area fell into two distinct categories, Type One and Type Two, with approximately 80% of the work then being undertaken in the former category.

In Type One, or "pragmatic" SB, the "integrative" and "multilevel" character of biology is recognised. "*For [Type One systems biologists], 'system' is a convenient but vague term that covers a range of detailed interactions with specifiable functions.*" Mostly the work under this category remains reductive in character.

In contrast, Type Two SB can be described as "theoretic". Such systems biologists argue that "*It is crucial to analyze systems as systems and not as mere collections of parts in order to understand the emergent properties of component interactions.*" As we will see O'Malley and Dupre signal here a very important issue: emergence is a property of only a sub-set of all systems and thus this remark, given the dismissive way in which the authors treat Type One approaches, implies a much narrower real definition of SB than would be generally accepted.

The approach I will take in this presentation is much closer to the Type Two category, namely a systems theoretic approach.

Before that let me just enlarge on one reason why I think O'Malley and Dupre were correct to be dismissive of the Type One approach. Much of Type One activity is concerned with generating or mining (from the internet) data and "reverse engineering" it to reveal the original network that gave rise to what ever was the -omic result that had been mined. Krishnan et al(2) computationally generated products from a 4 gene model network. They then tried to reverse engineer that network from the products they obtained. It proved not to be possible and they concluded that the problem is indeterminate. – a damning conclusion for what is an area of intense research activity. Their results are confirmed by Hendrickx et al(3) in the context of metabolic networks, which should be inherently simpler than genetic networks. They conclude that for real systems, due to their size, this is not possible without substantial supplementary data, such as rate constants.

THE CELL AS A SYSTEM

The instruction to be "integrative" is often taken to mean "move beyond the cellular level to the tissue". This is of course going to be obligatory in radiobiology as the health effects of radiation are to a large extent manifested at the tissue level. However, all the physics and chemistry initiated by the deposition of ionising energy is resolved within the boundaries of a single cell. There is thus a boundary conceptually between cells and tissues if we regard each as a system, the cell being a system within a system. This is a natural modularity that we can take advantage of – we don't need to consider the tissue as the only relevant system. So I will start by considering the cell as a system and asking what, on the basis of the empirical evidence we have before us, are the properties of that system?

First and foremost it is thermodynamically open – it consumes energy and matter, it metabolises. To date

mainstream biology has considered the cell to be almost everything but an open thermodynamic system. The scientific vision put before MELODI in Paris in October 2010¹ seemed to be of an organism as a homeostatic system presumably with feedback providing the complexity of the system. There are to be sure homeostatic systems and homeostasis occurs in organisms but homeostatic systems (thermostats, for example) are thermo-dynamically closed and therefore cannot be responsible for metabolism, which requires openness to material exchange with the environment. The physics of open systems, as von Bertalanffy(4) has explained, is quite different from closed systems so if our model is to have physical reality it needs to be thermodynamically open.

Secondly, it needs to be dynamically irreversible because none of us gets younger by the day or year. Once again the physics of irreversible systems is quite different from the Newtonian dynamics that is presently taken to underpin the dynamics of living systems.

Thirdly, it needs to depend on the kinetic interactions of macromolecules. Arguably this is recognised in the prevailing paradigm but it is considered mainly relevant in the interaction between proteins and DNA and much less so to the interaction between proteins. Although we have the concept of the protein interaction map these are far from complete and are largely confined to snapshots.

As radiation is an environmental or external, in systems terms, hazard, the system needs to interface with the environment. This also is acknowledged in the prevailing paradigm but predominantly in terms of environmentally caused mutations of gene coding sequences.

¹ <http://www.melodi-online.eu/WS2WeAverbeck7.pdf>

Finally, the system has to incorporate adaptiveness because this is highly characteristic of living organisms and it has to be anticipatory and that I will return to later.

When we take the first principles approach we are faced with four questions as follows:

What constitutes a system?

Under what conditions does a system become an organism?

How (through what processes) does the system interact with its environment, for example ionising radiation?

How does the cell as a system interact with that part of its environment that is the tissue in which it lives?

The answer to the first question is very simple: it is "a collection of material or immaterial things that comprises one's object of study".- in mathematical terms a set.

The theory based on this simple definition is given in Ludwig von Bertalanffy's General System Theory(4). These ideas were developed in the period from the late 1930s through to the late 1960s. For the most part, therefore, they predate the discovery of the structure of DNA. Von Bertalanffy discusses systems in their widest context, including, for example, engineered systems such as electricity power distribution and generation. Von Bertalanffy was however interested in biology as well and much of the book is devoted to discussing biological systems, mainly organisms.

From the point of view of our interest in radiobiology a crucial question is whether the cell as a system is *complex* or just complicated or, rather, *simple*.

In everyday language we may discriminate between simple and complex by saying that simple systems entail *dependencies* and complex systems entail *interactions* between components.

An electricity generation and distribution system is a *simple* system because its component parts although they are dependent upon one another do not interact one with another. If a storm brings down the distribution lines of such a system then consumers do not get electricity, so the system fails but the remainder of the component parts are unaffected and reinstatement of the missing distribution lines restores the original system.

The weather on the other hand is a *complex* system. The mathematician Edward Lorenz modelled the evolution in time of the weather based on three differential equations entailing variables x , y and z as follows:

$$\begin{aligned} dx/dt &= \sigma(y - x) \\ dy/dt &= \rho x - y - xz \\ dz/dt &= -\beta z + xy \end{aligned}$$

Note that the second equation, the differential of y , entails all three spatial variables hence the evolution of the system described emerges from the interactions between them(5).

Incidentally, Lorenz is often described as the "father of chaos" because these three equations exhibit a critical dependence on the initial conditions and so their evolution over time becomes increasingly uncertain. The weather system is chaotic, essentially increasingly unpredictable as time passes. If biology is complex then chaos may well play a role.

There is, however, another aspect of complex systems we need to consider before we look at complexity in more detail. Complex systems are contingent on their history and so if a component is lost and then replaced the system is not necessarily restored to its original state, as would be the case for simple systems.

The biophysicist Robert Rosen has examined the question of what distinguishes a simple system from a

complex one in the context of organisms(6). To understand his arguments we have to go back to the philosopher Aristotle who set out to systematise *causality*. He identified 4 basic and largely independent causes of things and those things could be just about anything we would describe as existing. He was asking of that existence "WHY?" What was it that *caused* it to come into existence?

The four causes are termed (most commonly) the *material*, the *formal*, the *efficient* and the *final*. If we take as an example of an existing object a bronze statue, the material cause is bronze, the formal cause is the person it represents; it is a likeness of that person, the efficient cause is the sculptor who sculpted the statue and the final cause is who ever it was that commissioned the sculpture.

We will be primarily interested in the *material* and *efficient* causes. The *final* cause has been an anathema in science and particularly biology, because it can imply teleology – a design or an imposed direction from some external non-scientific (e.g., divine or vitalistic) source. As I will show later, as far as biology is concerned, this does not have to be the case. For more details of Aristotle's causes can be found in Alwyn Scott's book(7)

Molecular biology is governed primarily by the material cause – phenotype is contingent on the gene products coded into the DNA sequence, which when mutated (a material change) redefine phenotype. This is the basis for the Central Dogma which inspired the genome sequencing enterprise and of the somatic mutational theory (SMT) for cancer(8).

However, when we look at the cell as a system we need to consider the efficient cause, that is, we need to examine the processes, not just the material, which gives rise to phenotype.

In Rosen's etymology(9) simple systems have an external efficient cause – they are manufactured from without, from the environment, like the statute, whereas complex systems have at least one internal efficient causal loop. That is there is closed causal loop that starts and ends within the system with no implication of fabrication from the environment.

In Rosen's view organisms are a special case of complex systems. They have only internal causation; they are completely *closed* to the efficient cause. However and rather controversially, Rosen regards organisms as the generic form of matter and the physics that they imply as the most general form of physics. The physics we are familiar with, which underpins inanimate matter and mainstream biology, is a special case of a more general physics that as yet we are unaware of. In this regard he is in agreement with Schrödinger who maintains in his book "What is Life?"(10) that we are missing a "new physics" that is the basis of life.

Inherent in this concept of the organism is the issue of self-referencing, which creates considerable conceptual complexity. In this context two other names should be mentioned, namely Alan Turing and Kurt Gödel. Turing proposed the basis for morphogenesis based on self-organisation in 1952 and Gödel demonstrated that, for example, in number theory (and in other contexts including language) there would be theorems that could not be proved or falsified from within the theory, that is, certain self-referential systems would be indeterminate without some input from outside the theory. This issue could be the subject of another lecture so it cannot be explored in detail here. In the present context it impacts on whether or not a single source of information, the genetic code, could be responsible alone for the development, fabrication and functioning of a cell. I believe that the

answer is that it cannot and a second source of information is required but this time, unlike number theory, it must come from within the system; the cell has to inherit two independent sources of information.

As we shall see the self-organisation identified by Turing also must play a significant role. Contrary to common belief self-organisation is commonplace in cell biology(11)

However, to return to the question of complexity and its role in biology: here the work of AH Louie, a one time student of Rosen, is relevant. He has been instrumental in extending and explaining Rosen's work on two important concepts, namely, the concept of an (M,R)-system(12) where M = metabolism and R = replacement/repair. This system is able to metabolise its environment (and so grow) but is also able to replace the metabolic units as and when they wear out. A central thesis of Rosen is that for a system to be a cell/organism it must be an (M,R)-system. A prerequisite of such a system is that it is closed to the efficient cause. Secondly, Louie has been instrumental in delineating the relationship between types of system(9). Figure 1 below is based on Louie's view.

There is a very important point implied here if Rosen and Louie are correct. Origin of life theories fall into two broad categories, "metabolism" first and "replication first". Metabolism first theories mostly start with a complex but non-living system (a proto-cell) that evolves to a living cell/organism. They cannot make the transition to simple systems such as biology is generally envisaged to be today. On the other hand replication first theories can entail simple systems but they cannot evolve into complex systems or organisms. Life has had to originate from a complex system.

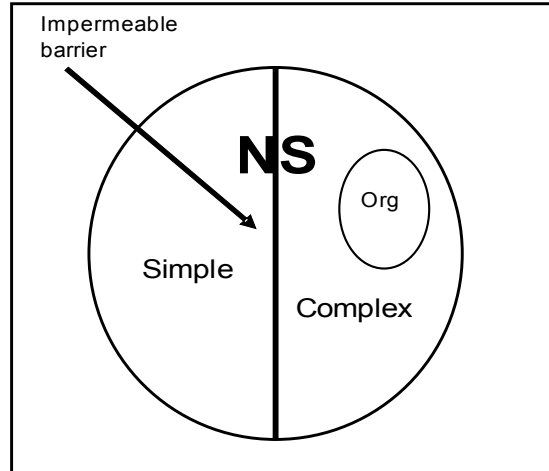


Figure 1 based on Louie(9)

These considerations may appear of little relevance to the way we do biology but the gulf between complex and simple systems has implications for, for example, understanding complex systems from a background of thinking in terms of simple systems.

The work of Rosen and Louie also poses serious constraints on the modelling process. There is no first cause of an organism so the "linear" thinking biology has been accustomed to over the past 5 decades is inappropriate. The vision of Kitano(13) of fully computational systems biology would seem to be a long a way off - something Feinendegen(14) would agree with and seems to be confirmed by the work of Yus et al.(15) for example.

So we need to take another approach and in place of pathways I suggest we look at protein profiles. This approach has been articulated by Sui Huang of the Institute for Biocomplexity in Canada(16). Huang shows how a standard genetic regulatory network (GRN) can be represented by a high dimensional attractor. There are, however a number of problems with this, a) because transcription cannot be the primary regulator of the cell, at least in multi-cellular eukaryotes and b) again only one source of information is entailed, namely the genetic code.

Point "a" can be seen in the labelling of H2AX sites at double strand breaks, which takes place within minutes of their formation, whereas, if this process were contingent on transcription, the time scale would be of the order of an hour. In addition mature sperm undergo morphological changes after ejaculation and they have no cytoplasm in which to translate the RNA to peptide. Regulation has to be much more directly associated with the interactions between gene product proteins. As far as point "b" is concerned Huang's model hinges on the idea that there are two categories of protein, functional and regulatory. Regulatory proteins, by binding at specific sites on DNA, release into the cell the functional proteins that give rise to phenotype. Huang describes this mechanism as "hardwiring" the phenotype into the genome. However, he does not address the question of how the regulatory proteins are regulated or, indeed, how the regulators of the regulators are regulated ... and so on to infinity. Having to invoke infinity is bad news for the idea. It runs into what is known as impredicativity, a form of self-reference that is the death knell for the idea in my view.

I agree with Huang that the protein profile gives rise to phenotype and that the attractor concept is appropriate (I proposed it in 2000(17)) so my proposal is to turn Huang's concept on its head and rather than saying that networks can be represented by attractors say that attractors can be represented by networks, most relevantly protein networks but recognising that these must be underpinned by transcriptional networks. In other words I am proposing that virtual as attractors might be considered to be, they do have a real existence. This can be illustrated by a system we are all familiar with, namely the person-on-bicycle system. Bicycles are never found in the upright and unsupported position unless they have rider. Every bicycle rider knows how to fall off the bicycle by trapping the

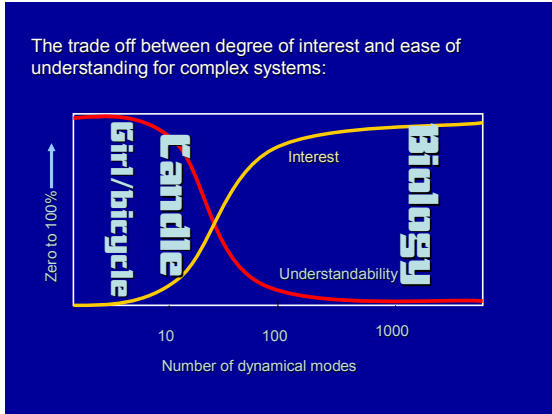
front wheel against the kerb or in a tram track. In this event we are witnessing an attractor transition from a non-equilibrium stable (albeit within limits) state to that of equilibrium, the lowest available state. The upright riding state is a dynamic attractor with four dynamical modes, namely shifting the centre of gravity of the system to either the left or right and steering the front wheel either to the left or right. Providing all four dynamical modes are in the control of the rider this relatively far from equilibrium state can be maintained. If one is lost there will be a transition to the equilibrium attractor.



The conventional model for biology, by assuming, against all the evidence, that the cell is a thermodynamically closed entity, implies the equilibrium state: there is no higher or non-equilibrium state to access. As a Japanese colleague once remarked, "the only living thing at equilibrium is a dead one".

Conceptually the problem we face is that really interesting systems are so complex that they are nearly impossible to understand but those we can easily understand, the girl/bicycle system for example, are not very interesting. We can use the number of dynamical modes as a proxy for how complex a complex system is and we see biology is way down the scale with 100,000 dynamical modes for a human cell. It is of 100% interest to us but unfortunately of almost 0% understandability. This is where the

fractal nature of systems can assist us. We can look at systems in between the girl/bicycle and biology and get some clues as to how the very complex systems might behave.



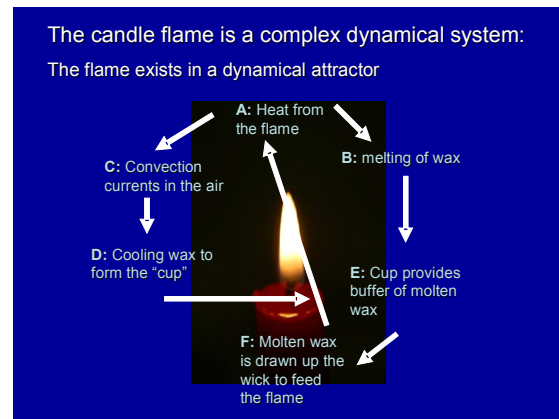
The first of these lesser complex systems is the candle.

Michael Faraday was among the UK's greatest physicists but was notably not honoured for his achievements except for relatively recently when his image was included on the £20 note. He rose from the position of a lens grinding technician to be an early Director of the Royal Institution (after Sir Humphry Davy), a renowned scientific establishment recently engulfed in scandal². A tradition of the RI started by Faraday was the Christmas lectures for children and among the lectures that Faraday presented was the "Chemical History of a Candle". Faraday would start the lecture with the following statement "There is no better, there is no more open door by which you can enter into the study of natural philosophy than by considering the physical phenomena of the candle." We shall follow his advice.

The purpose of the candle is to generate a steady light output by burning wax. Of course the candle is not self starting: the wick needs to be lit. But once alight the candle is a self-sustaining complex

²http://www.economist.com/node/15268887?story_id=15268887

dynamic system where the flame exists in a dynamic attractor. The principal dynamic modes are the heat from the flame, the melting of the wax, the generation of convection currents in the air around the candle, the formation of a constantly re-formed "cup" to contain the wax and the migration of molten wax up the wick, where it burns to produce light and heat. At the outset, just after the flame is lit, the causal process looks linear, that is, until it gets to the point where the molten wax migrates up the wick and is burned and the causal process is closed by the generation of heat in the flame.



Particularly interesting is the "cup" and I think this is what fascinated Faraday. In material terms it is constantly being replaced. This is precisely what Rosen is proposing in his (M-R) system; the constant renewal of the catalysts responsible for metabolism.

Faraday's lectures are available in book form compiled by Sir William Crookes and the text is available on the Gutenberg Project³. What we see in the candle and the girl/bicycle system is a suit of finely tuned dynamic steady states, in the case of the girl, her "control" of the dynamics of the system and in the case of the candle the physical properties of the components.

³<http://www.gutenberg.org/ebooks/14474>.

I think the first person to recognise, in print at least, the significance of these dynamic steady states might have been the physicist Max Delbrück. At a genetics symposium in Paris in 1949 he intervened in the discussion after a paper by Sonneborn who had proposed that the effect he was describing resulted from the reproduction of genes that were either favoured or inhibited by environmental factors noting that "*many systems in flux equilibrium are capable of several equilibria under identical conditions. They pass from one stable [i.e. ordered] state to another under the influence of transient perturbations*"(18).

Today we would replace the term "flux equilibrium" with "dynamic steady state" and if we have multiple dynamic steady states then we have an attractor so essentially Delbrück was the first to put forward the idea that phenotype could be represented by an attractor. In other words transitions in phenotype are attractor transitions and of course occur without any "material" change (mutation) to the DNA. This insight happened four years before the discovery of the structure of DNA by Crick and Watson and seems now to have been forgotten.

However the general idea had been around for much longer in other contexts and it even appears in Darwin's Chapter 3 of the Origin, entitled "The Struggle for existence"(19).

The stability of an ecological niche is determined, to a large extent, by the "predator - prey" relationships within the niche because the "nature" of the niche is dependent on the activities of its inhabitants. Predator- prey relationships are dynamic steady states and the stability of the niche is contingent on an attractor based on these dynamic steady states. The niche (system) can be destroyed or radically changed by the introduction from the environment, of a

new predator, or a species with no predator.

In Chapter 3 Darwin says: "*What a struggle between the several kinds of trees must here [the ancient Indian mounds, in the Southern United States] have gone on during long centuries, each annually scattering its seeds by the thousand; what war between insect and insect—between insects, snails, and other animals with birds and beasts of prey—all striving to increase, and all feeding on each other or on the trees or their seeds and seedlings, or on the other plants which first clothed the ground and thus checked the growth of the trees! Throw up a handful of feathers, and all must fall to the ground according to definite laws; but how simple is this problem compared to the action and reaction of the innumerable plants and animals which have determined, in the course of centuries, the proportional numbers and kinds of trees now growing on the old Indian ruins!*".

There is an important point for us here: The ecological niche has more dynamical modes than the candle and offers the prospect not just of transitions from a non-equilibrium state of the system to equilibrium (as with the girl-bicycle and candle) but with multiple non-equilibrium attractor states. Darwin again gives a good example of grassland grazed by cattle adjacent to forest. If the grassland is fenced off to prevent cattle grazing over time this leads to a transition of the fenced off land to forest as the seedling trees are free to grow normally. Cattle grazing and tree growth is a predator prey dynamic steady state which maintains the grassland state of the system. The fence, an environmental constraint, removes that steady state and a new attractor evolves and grass land makes the transition to forest, all other things being equal, which, of course, they rarely are. So these transitions are stochastic - or what we call *emergent*.

The cell is a system with multiple attractors at its disposal. For any given phenotype there are a few thousand dynamical modes and a state space of that magnitude is riddled with attractors most of which have never been occupied by a cell.

Most of the computational work on attractors has been carried out on Boolean networks (where nodes can take values of either 1 or 0). This is unrealistic in terms of biology where a continuum of "activities" of gene products is much more realistic. Stuart Kaufmann has pioneered the study of Boolean attractors(20) but his early work has been extended(21) to show that the number of attractors grows much faster than Kaufmann predicted. It is likely that the Boolean system significantly underestimates the rate at which attractors grow in relation to the number of dynamical modes.

Now it is important to consider the physics of the kind of system we are now starting to envisage, namely a complex high dimensional dynamic system which is thermodynamically open, that is, far from equilibrium. The key point is that the attractor transitions are not "gradual" but discrete jumps from one state (phenotype) to another. This is because each attractor is surrounded by a so-called basin of attraction so to make the transition to another attractor the system has to "get out" of the basin.

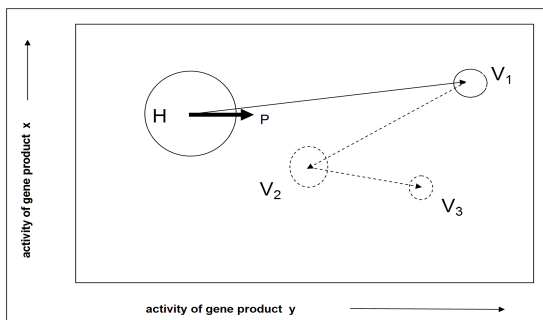


Figure 2. Illustrating a 2D slice through a multidimensional state space(22)

We can deploy the concept of a state space with one dimension for each

dynamical mode in order to envisage such a system. Figure 2 shows a slice through just two dimensions, x and y.

State space (SS) is a familiar concept to physicists. It is a virtual extension of ordinary 3D space to as many dimensions as the system has dynamical modes. Such high dimensional systems cannot be represented graphically but as each dimension is orthogonal to each of the others 2D slices can be used to illustrate how the system functions.

What we have in this diagram is the visualisation of an idealised transition from the attractor labelled H to the one labelled V₁. H is called the home attractor and is the normal attractor of a stable species which has been subject through selection to evolutionary conditioning both in respect of its position in the SS (in this case x and y coordinates) and its robustness represented by the size of the circle. The position of the attractor in the SS determines the integrity of replication. But what triggers these transitions?

To understand this we must look more closely at the attractor – what is it that gives rise to these ordered states at some places in the SS but not others? The "system components" in the cell are proteins (mainly) and they interact one with another to give rise to protein interaction maps or networks. These are the expression of the attractor or the protein profiles we referred to earlier. Underpinning these maps are "rules of engagement" (RoE) between the proteins and these are in formal terms *relations* and can be expressed as:

"IF at time t₁ the activity m of gene product "gpa", is within a specific range r_{gpa} THEN gene product "b" will be in the range r_{gpb} at time t₂" where t₂ > t₁"

Or in formal language:

$$m_{gpa}(t1) \in r_{gpa} \Rightarrow m_{gpb}(t2) \in r_{gpb}$$

where the symbol \in means "within" in this case the range $r(22)$.

There are two important points to note, 1) this relation is time irreversible and 2) that environmental factors can affect the values of m for specific gene products, potentially pushing them outside of their ranges r . This is self-organisation in action.

At the "heart" of cellular function is the "DNA degradation and repair" dynamic steady state(17). This is ongoing, even in the absence of radiation, due to hydrolysis and oxidation. Radiation therefore adds to that ongoing process in producing damage that must be repaired before the cell divides.

Radiation damage to DNA therefore has the potential to perturb this very fundamental steady state and if it does so to the extent that it depletes one of the gene products involved in the response to the damage to the extent that its permissible range of activity is exceeded (above or below), then an attractor transition will occur. It will be a stochastically determined jump to a variant attractor state or phenotype. In that jump the protein profile can change in terms of several of its components and so the functionality of the cell could be very different with some functions lost and new functions gained.

I have proposed that where these variant attractors can reproduce, i.e., the cells divide; they constitute what we observe as genomic instability(23). As the GI state is less optimally placed in the state space it is less able to perform error free replication and it therefore generates mutations and DNA damage, the hallmarks of instability.

When perturbations occur the adopted variant attractor "V" is less robust and less able to replicate the genotype faithfully. Due to the reduced robustness

further perturbations have a higher likelihood of producing further transitions (24). Loss of replicative integrity produces DNA damage and mutations characteristic of the genomically unstable state.

Before we look at tissues as systems let us see how far we have met our initial objectives:

The properties of the cell as a system we were looking for at the outset are:

Thermodynamically OPEN – exchange of energy and matter between the system and its environment, therefore NOT at equilibrium. ✓

Dynamically IRREVERSIBLE ✓

Functionally based on kinetics of MACROMOLECULES –mainly enzymes ✓

Interfaces with and is influenced by its ENVIRONMENT ✓

ADAPTIVE in so far as there are many attractors accessible to the system ✓

ANTICIPATORY in so far as the system is able to protect the final cause which entails maintaining the integrity of the DNA, through, for example, cell cycle check-points. ✓

TISSUES AS SYSTEMS

I want now to explore the implications of this for the wider systems, tissue and organism, in which the cell operates, by looking at a "living" system constituted of living systems, namely the termite mound or termitary. Termitaries "grow" from a breeding pair of once winged termites and although their structure is inanimate termitaries have many of the properties of a living organism. Mammalian bone is after all largely inorganic so the inanimate nature the termitary need not worry us unduly.

There are many species of termite and their "life-styles" can differ according to

the environment they have adopted. These differences need not concern us. An enlightening and highly entertaining account of termite life was written by the South African naturalist Eugene Marais in the 1920s and can be found on the web⁴ under the title "*The soul of the white ant*".

Essentially, we can define the "system" as the activities within the termitary and the environment as everything that is outside of that. The dynamical modes of the system are the *activities* (physical) of one "caste" of termite, the worker.

Below is very simplified diagram of the activities that build and sustain the termitary. The system relies on the manual activities of worker termites in carrying food, water and soil from the environment into the system and carrying the eggs produced by the queen to the nursery to replenish the termite population. The red double tipped arrows are dynamic steady states because the termites are making "round trips".

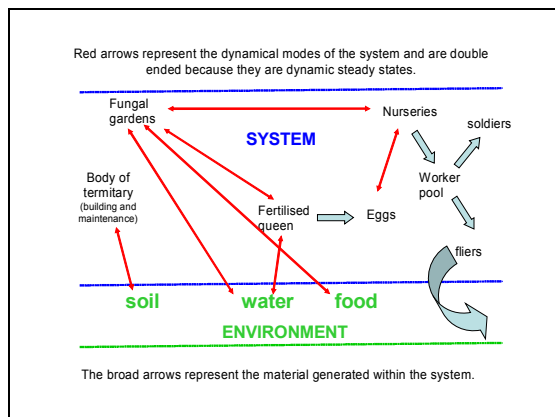


Figure 3. Schematic of activities in a termitary.

Termite mounds contain up to 12,000 tons of earth and below them have tunnels down more than 20m to reach water. The dynamical modes of the system (the activities undertaken mainly by the workers) continuously build and repair the structure, collect food and water and nurture the young which are

continuously repopulated by the queen acting as a giant egg factory. The moment the queen ceases to produce eggs the system collapses.

A principle dynamic steady state is foraging for food from the environment offset by a strong "homing instinct". Thus, although having workers leave the mound is a necessity for the system so is returning to it. However, when environmentally caused perturbations (weather damage to the mound) occur the activities of the workers are reorganised to deal with the problem.

It is safe to assume that the workers make no individual decisions – have no free will – simply they are automatons as far as the system is concerned. But clearly, since their activities do get redirected, there must be "signalling" or "communication" of some kind, probably using pheromones and to some degree sound. There must be the equivalent of rules of engagement between the activities essential to the maintenance of the system – that is, there are causal (efficient) factors acting between the dynamical modes of the system which gives the astonishing robustness of the termitary.

Mauris was puzzled as to why the system collapsed when the queen was killed, the traditional human solution to an unwanted termitary. However, from a system perspective the answer is rather simple. The structure of the termitary in terms of the access passages around the queen is such that they would easily become blocked. Thus if the egg transporters suddenly have no eggs to carry away from the queen, and the rate of egg production is a few per minute, it will not take long for the passages to become blocked with disoriented termites and the contagion would quickly spread to other activities bringing the whole thing to halt and essentially equilibrium. This system may anticipate many things but a cessation of egg production is not one of them.

⁴http://journeytoforever.org/farm_library/Marais1/whiteantToC.html#contents

What can we learn from the termitary?

The termitary is according to Rosen a complex system i.e. closed to the *efficient* cause (represented by the red arrows in the diagram above).

The *material* aspects of the system give little insight as to how the system functions are sustained.

Some form of communication within the system is vital for its proper functioning.

The dynamics of the system provide part of that communication.

Environmental perturbations (weather) which affect either the integrity of the "body" of the termitary or its functioning result in diversions of activity. This is the typical behaviour of an attractor (ability within limits to compensate, called robustness)

So let us now consider a tissue in a multi-cellular organism as a system composed of cells – the next higher system level to the cell. This is the level at which the health effects of exposure to radiation appear.

It is well accepted that one of the functions of somatic cells is to signal to, or communicate with, its neighbours. This is exemplified by the niche concept of the bone marrow cell, which dates back to 1978(25). Since a tissue is an ordered structure we can expect the communication to be highly specific, and to large extent devoted to regulating cell proliferation.

The natural tendency of single celled organisms is to proliferate. That is also the case for a cell removed from tissue and grown *in vitro*. If cellular proliferation was not controlled in multi-cellular organisms the whole concept of would be doomed.

The presence of communication is illustrated by the bystander effect (BE) where the effects of radiation exposure are seen in un-irradiated cells neighbouring an irradiated cell. One of the bystander effects is premature differentiation.

We can postulate that the BE is simply the result of abnormal signals emitted by the irradiated cell(26) which has undergone a phenotypic transition affecting its signalling functions, probably in the sense of *loss* of function rather than *gain*.

Somatic cells have multiple functions which define their phenotype and the loss or gain of just one constitutes a change of phenotype and thus *potentially* a threat to the tissue in which it resides.

If we had looked at the termitary more closely we could have discovered numerous ways in which that system was *adapted* to deal with internal as well as external threats. The fungal "gardens" generate CO₂ and the whole structure is designed such that fresh air flows through the tunnels without the ingress of light. This phenomenon could be "inverted" to say that the system *anticipates* this danger just as cell cycle check point control anticipates the danger for species integrity from the replication of un-repaired DNA damage.

If we accept the nature of the cell as we have described above an internal threat to tissue integrity is environmentally induced phenotypic transition and, therefore, disruption of function. We know of cellular processes such as apoptosis in which damaged cells are removed and apoptosis is also a product of the BE.

It is, therefore, reasonable to assume that multi-cellular systems have *adapted* to deal with this internal threat through, of course, natural selection. So we can consider that tissue is a "system" based

on cells as the dynamical modes and that the signalling functions are of paramount importance.

THE CHALLENGE

The next step is to envisage the kind of attractor that would stabilise this kind of activity. That I believe is the challenge that radiobiology and also biology in general faces. Genomic instability, which in system terms can be seen as the "root" of effects that emerge at the tissue level, can be induced by many other agents, for example, heavy metals and air pollution, so the effect is not purely radiobiological, it appears to be a generalised stress response and indeed that is how I have described it today, as the stressing of the evolved processes that ensure that a species replicates true to form.

Andrei Karotki and I have proposed that the late stochastic effects of radiation can be unified under processes involving the initial step of transition to GI in a single cell and the subsequent roles of cell proliferation control and the BE leading to cancer and non-cancer diseases at the tissue level(27). For example, we propose that the initial step in atherosclerosis is the induction of GI in an endothelial cell lining a blood vessel. If the implied phenotypic change involves impairment of signalling to neighbouring cells then a focus of cells with modified phenotypes could develop through the BE. If the collective impairment involved morphological changes that allowed the passage of unwanted blood products through the endothelial layer then the basis for an atherosclerotic lesion would exist(28).

CONCLUSION

In essence, by treating the cell as a system and following simple logic, the importance of process, the efficient cause, in biology has been brought more sharply into focus. It is the element that is neglected in mainstream molecular

biology. However, as the efficient and material causes are largely independent of one another no amount of additional knowledge of the material cause will compensate for a lack of knowledge of the efficient cause.

Gaining that *process* knowledge is not without difficulties given present research strategies and technologies. Labs are well equipped to identify and measure molecules but less so for the processes these molecules are undergoing. For this reason it is necessary to explore, within a multidisciplinary context, potential research strategies.

Interaction between proteins has been identified as an important feature not only of phenotype in a qualitative sense but of how the cell organizes itself. According to Nobel laureate Robert Laughlin the physics of this molecular "size range", the so called mesosphere, is a neglected area(29).

Transitions in SS are equated to phenotypic transitions. Some are "built into" the system in, for example, differentiation but the ones leading to genomic instability are "novel" and perhaps even totally "untried": they may even be the future in evolutionary terms(22). The SS has a structure or architecture into which the attractors are embedded. Methodologies to explore this architecture and to understand better why a given attractor occurs where it does are needed.

Traditional methods of hypothesis testing cannot, by definition, apply to systems that are adaptive. This raises the need for finding ways for assessing hypotheses on their explanatory value. Some have always held that this was superior predictive power, which should only be applied to distinguish between hypotheses that are equally plausible on the basis of explanatory power.

Thus, taking the systems approach to biology reveals much that will be of

value in furthering understanding of the effects of radiation but it will require re-thinking in depth some aspects of biological research that have remained unchallenged for half a century.

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