The Independent Attractor Model for Cell Regulation

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Introduction

In the early 1990s colleagues at the MRC Radiobiology Unit at Harwell uncovered the phenomenon of radiation induced genomic instability. As a cellular antagonist radiation has the advantage that its damaging action can be confined to a single cell generation. When the progeny of irradiated cells exhibited exposure related *de novo* DNA damage several generations later it must have been the case that that *damage* was a *purely biological response* to the earlier damage inflicted by the radiation. It is reasonable, therefore, to assume that the *de novo* damage was an expression of a modification of the cellular regulatory system. Yet the dose response was inconsistent with radiation having targeted a regulatory gene coding sequence; the target was comparable in size to the whole cell nucleus suggesting that the damage was a *generic* response of the cell and therefore an *epigenetic* effect[1]. The so called independent attractor model, which proposes the cell is regulated by an epigenetic process, was in the first place an attempt to find a biologically plausible explanation for genomic instability. However, genomic instability is now a well established phenomenon in its own right and must be regarded as a legitimate biological phenomenon as it can be induced by a diverse range of antagonists in addition to radiation. It therefore follows that cell regulation *per se* is epigenetic.

[1] I want to emphasise at the outset that when I use the word "epigenetic" I am using it in its most generic sense, namely over, or above, or beside, or beyond, genetics 1.Nanney DL: **Epigenetic Control Systems**. *Proc Natl Acad Sci U S A* 1958, **44**(7):712-717.) and not in any specific sense, for example, chromatin marking.

More recently the need for a model for epigenetic regulation has become urgent because the genetic model is challenged by evidence that has accrued over the past decade or so. I will be outlining some of that evidence below and then I will discuss a number of reasons why I think the epigenetic model I am going to propose can be seen as more plausible than the current genetic model in terms of interpreting various aspects of biology: I will address three of those aspects.

But first I want to talk about the issue of radiation induced genomic instability. This is what first led me to thinking about a need for a new model. The experiment performed at the Radiobiology Unit, at Harwell involved irradiating explanted mouse bone marrow cells with alpha particles with on average 1 alpha passage per cell [2]. Following irradiation cells were plated out individually and grown as clones. Examination of the karyotypes of the cells in a *single clone* revealed some cells with no visible damage at all while others carried a variety of complex chromosomal damage. Rationalised in terms of the inheritance of one cell to another we get a treelike structure with all the un-damaged cells in the early divisions and damaged ones at later divisions. If we take one branch of that tree (fig 1) we can see that in generations 1 to (k -1) there is no damage and then from generation k onwards damage appears and we assume that the underlying process is not reversible so no un-damaged cells can be derived from damage ones. Logically, this implies that the damage observed in later generations is not a direct result of the radiation but derives from purely biological processes *initiated* by the radiation.

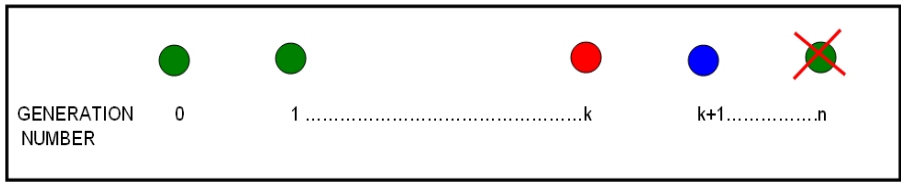

Figure 1: generation 0 is the irradiated cell and carries no damage. Generations 1 to k-1 are also damage free but generations k to n exhibit chromosomal damage which is deemed to be irreversible.

In addition, we can use target theory to make an estimate of the size of the target that initiates the effect based on the dose response relationship [3]. This indicates that the target approximates to the size of the nucleus and is in any case much larger than a gene coding sequence. The inference we can draw from this is that genomic instability is a *generic* effect of radiation and that it arises as a result of modification of cell regulation. As other agents can induce genomic instability we can regard this also as a *generic* feature of the cell and thus it has to be assumed that epigenetic regulation is a cellular feature.

Other empirical evidence that challenges the genetic regulatory paradigm

The first piece of this evidence is the experiment by Barrick et al [4] in which *E Coli* were introduced to a medium with limiting glucose and grown for 20,000 generations with periodic assessments of the adaptive fitness. In addition genome sequencing was used to detect mutations arising during growth. The result was rather surprising in that relative fitness increased by nearly 50% of the maximum value it would ultimately attain in less than 1000 generations

while mutations were acquired linearly with generation number at approximately the rate of two mutations per one thousand generations. The authors concluded that the dogma that genomic changes underlie evolutionary adaptation was clearly violated by this experiment.

The second experiment was performed by Yus and colleagues [5] and involved the bacterium *Mycoplasma pneumoniae*. The rationale for this work was that as *M. pneumoniae* has a very much simplified metabolic network (reduced genome), due to its evolved reliance on nutrients available in the lung, it would be relatively easy to model, computationally, its metabolic network. This indeed proved to be the case and the resultant model was able to predict successfully the effects of varying specific nutrient concentrations on rate of growth. However, the authors found that *M. pneumoniae* was able to exhibit functions for which it required transcription factors it had lost as a result of its genome reduction. The authors concluded that despite its apparent simplicity the organism exhibited metabolic and adaptive responses similar to more complex bacteria, indicating the possible existence of unknown regulatory mechanisms. Clearly these unknown mechanisms must be post-transcriptional and thus not genetic.

The third experiment was carried out in Japan and reported in 2006 by Kashiwagi et al. [6]. These authors wanted to investigate whether a bacterium faced with an entirely novel stress could adapt; as they argued, the space of all possible stresses must be far larger than the space of evolved bacterial responses. They constructed two mutually suppressing operons and inserted them into a plasmid which was then inserted into an *E. coli*. Each of the operons carried a gene able to produce a product which would compensate for the lack of one of two specific nutrients, and a reporter to indicate when the inserted gene was expressed. When grown in complete medium the reporters were silent and the *E. coli* was assumed to be in what was called the W attractor (see fig 2). However, when the bacteria were introduced into a medium deficient in one of the two nutrients the appropriate reporter indicated, after a marked reduction in metabolic rate, that the compensatory gene was expressed. The authors rationalised this result in the following way: when deprived of nutrient the cell expresses all the genes it has and if a combination of those genes will allow growth they are selected as an adaptive attractor. This is in effect self-organisation of the gene products at the genome level. This result also could have a bearing on the first item of evidence cited above, namely the experiment by Barrick et al which may have shown exactly the same behaviour had the adaptive fitness been assessed earlier than 1000 generations into the experiment.

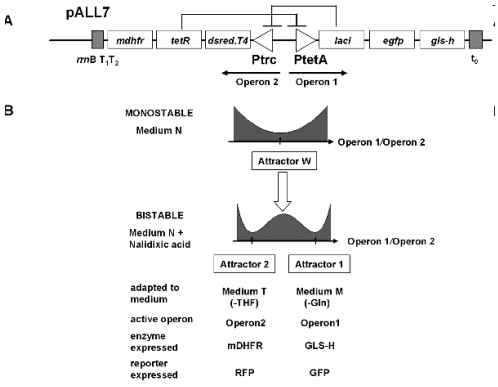

Figure 2 **A** shows the structure of the two operons. **B** shows the effect of removing one or the other nutrient leading to the deployment of the operons and an attractor transition.

The final item of evidence involves an experiment also carried out in Japan, this time on cyanobacteria [7]. The experiment involved extracting the three enzymes responsible for circadian rhythm and incubating them

together with ATP (as an energy source) *in vitro*. The result was that phosphorylation of one of the three enzymes, KaiC, adopted a 24 hour cycle which was largely tolerant of changes in temperature, as is circadian rhythm. The authors claimed to have reconstructed the circadian oscillation without the involvement of any form of transcription or genes for the involved proteins. Much more recently O'Neill et al [8, 9] reported that when transcription of the genes responsible for circadian rhythm was blocked in a eukaryote the cell was still able to express the circadian rhythm, confirming that this very basic and fundamental cellular property can operate entirely independently of transcription.

The case that I want to make today is that taken together, the situation regarding genomic instability and the evidence that I just relayed, point to the fact that regulation of the cell derives from a post transcriptional stage of the synthesis of gene products and that although necessary, transcription, which is the basis of the genetic paradigm, is not sufficient to regulate the cell. The most likely candidates for this regulatory process are the active gene products, mainly proteins, produced by the transcription process.

The hypothesis

Essentially, it is proposed that the active gene products in the cell *interact* one with another according to specific rules, termed *rules of engagement* [10]. These rules give rise to what Huang [11] calls a *protein profile* that typifies phenotype. This profile has the property that it is a stable state of the system, namely an attractor. These rules ensure that the gene products required to sustain the attractor and to progress the cell through the cell cycle are drawn from the transcribed, but so far inactive gene products. It is, thus, self-organised gene product, mainly protein, interactions that determine the phenotype. Transcription from the genotype provides the raw material for the attractor, which is consumed leading to a flux of material through the cell. In any particular cell type transcription is, of course, restricted to a subsection of the available gene coding sequences and, therefore, the available gene products undergoing these interactions is limited: I will come to that in a moment.

First it is necessary to emphasise that this model is based on the imperative that the cell is treated as an open thermodynamic system, that is, is able to import and export energy and material. The *underlying* process by which protein interaction leads to the stable state of the system is self-organisation. Self-organisation, counterintuitive in terms of closed thermodynamic systems, is a commonplace in open systems. Thermodynamic openness has many implications: for example, peptides may fold into many non-equilibrium tertiary structures potentially yielding, from a single peptide sequence, several non-identical (functionally) proteins. Additionally, as molecules approach one another their structures may become modified in such a way as to facilitate binding. It is well known that in the cell many proteins have disordered domains [12] and only adopt their tertiary structure as they approach a binding site [13]. The main implication of these empirically established features is that the "lock and key" concept inherent in the genetic regulatory model, otherwise termed "hardwiring of the genome" [11], is invalidated.

Information, as well as free energy, is a source of organisation as was clearly demonstrated by Stuart Kaufmann in his work on random Boolean networks [14]. Under certain conditions (of

relations between network nodes) these networks will settle into specific cycles of states, attractors, which constitute a very small fraction of the total number of states available to the network. This *order*, apparently for free (there can be no role for energy in these networks), is contingent on the rules between the nodes of the network, the so-called edges. Another example of this phenomenon can be found in the work of Stefan Bornholdt [15] who applied a simplified Boolean network model to a reduced (in number of nodes) network for fission yeast but using the experimentally determined rules (edges) relating the nodes and showed that a computer simulation reproduced to a very high degree the behaviour of the actual organism. As it is presently framed the independent attractor model is not elaborated in terms of networks but rather in terms of states in a state space. This can be translated into a network framework but part of the usefulness of the state space concept is that it more easily enables visualisation of transitions between states, which is of course what is of most interest.

The *rules of engagement* between active gene products are of the form "IF … THEN", i.e., *relations*, between the activities, **m**, (arbitrarily defined[2]) of the gene products and can be formalised as follows:

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

where $\mathbf{m}_{gpa}$ is the activity of gene product a and $\mathbf{r}_{gpa}$ is its range of activity consistent with the contribution of gpa to the attractor and t1 and t2 are times where t1 < t2 [10].

[2] Activity is on an arbitrary scale and cannot be interpreted as concentration. Enzyme activity is contingent on protein tertiary structure and in the thermodynamically open environment of the cell there will be no fixed relationship between activity and concentration.

Typically the human genotype provides coding information to produce in excess of 100,000 active gene products from some 20-25,000 gene coding sequences. In contrast, a specific cell based upon the human genotype expresses some 3000 active gene products and some 10,000 might be active in the cells of a single human tissue [16]. This selection at the cell level of 3,000/100,000 products is primarily the result of a regulated transcription process and is achieved by a number of mechanisms including the order of coding sequences on the chromosomes, the conformation of the chromatin and the location of the coding sequences within the nucleus. In addition, marking of the chromatin and DNA with acetyl and methyl groups respectively adds another layer of control over coding sequence transcription [17]. However, transcriptional control cannot regulate post-transcriptional events unless the process of converting mRNA to active protein simply proceeds automatically; this is not supported by the evidence (see below). As we saw earlier these post-transcriptional steps are highly relevant to the overall regulation of the cell. An important feature of this aspect of the cell is that these constraints on transcription are an example of *weak downward causation* dictated by the properties of the phenotype [16]. In evolutionary terms Shapiro [18] calls both these examples of transcriptional control *genome remodelling*. I interpret them as, in the first example, acting over the evolutionary history of the organism and in the second example, as short-term, single species-lifetime remodelling (see below).

I want now to introduce two analogies to help to explain the ideas behind this model: the first I call the *nautical analogy*. Sailors navigate safe passage through rock infested waters by the use of paper charts which display as symbols the physical marks anchored

to the seabed and visible above the ocean. Safe passage is insured by respecting the information expressed by the mark, for example, "pass on the north side". These marks are permanent: they correspond in cells to the first category of control of transcription mentioned above, for example, the conformational state of the chromatin. A second category of marks that do not appear on charts are those that mark, for example, a recent wreck. These must be recognised by sailors only by their presence on the water. This category corresponds to the chromatin marking also referred to above, which is written and deleted as appropriate by the phenotypic state. Transcriptional regulation at multiple levels thus serves to limit the combinatorial possibilities of gene products in the system.

The second analogy is what I call the *supermarket analogy*. I imagine the situation taking place in the cell is rather equivalent to the shelves of a supermarket being stocked from "behind the counter" with *only* the goods that will be required by customers. The equivalent of this process in the cell is transcription. I imagine the shelves to be deep and the customers only having access to the very front most section where the immediate precursors of active products are stored. The progression of the post-transcriptional steps I see in terms of a migration from the back of the shelf (mRNA) towards the front (pre-active protein). What this implies is that the production of transcripts (at the back of the shelf) will not necessarily be a good guide to the presence of active gene products being used and indeed the evidence shows this to be the case [19], even in bacteria [20]. It is useful to refer back to the Kashiwagi et al experiment [6] which can be interpreted as follows: when effectively deprived of nutrients the cell responds by transcribing all its available gene products akin to filling the shelves with all of the available products and in effect waiting to see which products the shoppers would select, this being the optimal attractor state.

Interaction with the environment

Interaction of the cell, as a system, with the environment in which it is embedded is one of the most important features of the independent attractor model. In the original justification for developing the model, namely, trying to explain radiation induced genomic instability, we are dealing with the issue of how the cell interacts with environmental sources of radiation. In contrast to the conventional way of considering interaction with the environment, namely the acquisition of new mutations, the response of the system is mediated by *process*, rather than *material*, dysfunction. Cells have an impressive battery of processes aimed at detecting and repairing damage to the genomic DNA before the cell goes into division. These processes, which we must regard as having been evolutionarily conditioned, because modern cells have overcome stresses in their evolutionary past, still have limits to their capacity to respond to stress. These limits are reflected in the independent attractor model in the values for the permissible ranges of gene product activity, **r**, and if these are not complied with (above or below) then an attractor/phenotype transition[3] occurs and that is deemed to be the first step into genomic instability. Now I want to introduce the concept of the *home* attractor [3]. A cell that is a component of a stably replicating species is one that by

[3] This assumes that other system attractors are plentiful. The case that this is probably so is made in reference [26]. Mostly these will be attractors that have not been "occupied" in the evolutionary past of the cell and therefore are "unconditioned". In germ cells these attractors could be the initial phenotypes for new species.

definition has optimised the replication of its genomic DNA. By optimised I mean that it has acquired the best available integrity together with a relatively high degree of robustness against further attractor transitions, the former reflected in the position in the state space and the latter by the values of **r**. The attractor of such a cell is referred to as the *home* attractor (see figure 3) and any alternative attractors within the state space available to the cell are termed *variant* attractors. The genomic instability phenotype is, therefore, represented by a variant attractor and by definition this attractor is less optimised than its predecessor and hence its increased tendency to produce genomic damage [10, 21]. Thus, stress on the processes that maintain the integrity of the genome and not the actual damage to the DNA, is what *causes* genomic instability.

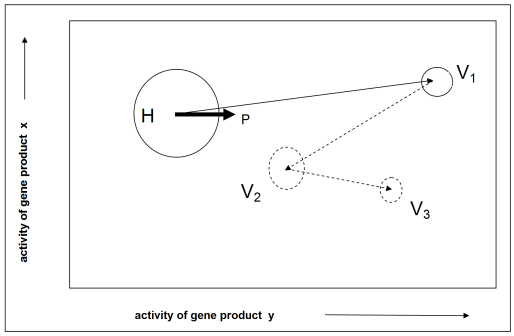

Figure 3: Represents a "slice" through the state space for coordinates for the activity of gene products x and y. H is the home attractor, namely that of the evolutionarily conditioned cell of a stably replicating species, the diameter representing the robustness of the attractor, related to **r**, the permissible range of activity and P is a perturbation that causes the value of **r** for the gene product y to be exceeded. Thus, the H attractor collapses and a new variant attractor V_1 is adopted. V_1, since it has not been evolutionarily conditioned, is less optimally located in the state space and less robust and, therefore, the system is prone to accruing damage and to further migration to other variant attractors as indicated by the dotted lines. Migration between variant attractors is the hall mark of genomic instability and indeed cells rendered unstable show a greater diversity of gene expression than normal cells [22].

Plausibility in terms of origin of life theories

The origin of the universe has been of consuming interest to cosmologists and there is a reasonable degree of consensus around "big bang" type theories, however, there is virtually no consensus on the origin of life within that universe [23]. Well before the discovery of the structure of DNA the Russian scientist Alexander Oparin proposed a metabolism-first theory involving oily droplets with aqueous cores suspended in a primordial soup of small molecules and undergoing polymerisation reactions within the droplets. This model was further developed by Freeman Dyson who produced a "toy model" of the physical chemical processes by which this might be happening [24]. This is a two-stage model in which *metabolising* but physically dividing, entities precede life and subsequently gain the ability to *replicate* according to a template. Evidence for meteorites carrying the building blocks of nucleic acids, in particular the Murchison meteorite, show that they would have been available on Earth at the time of the origin of life [25]. This model, far-fetched as it sounds, would be reasonably consistent with the independent attractor model and somewhat less far-fetched than alternative replication-first models.

Logical plausibility

I have advanced the argument [26], to a large extent based upon the arguments of Robert Rosen [27], that the conventional genetic regulatory network model contains a fatal logical impredicativity which implies that to code for all the functions of the cell and its *regulation*, would require an infinite length of DNA coding. I am not a mathematician or logician and so I cannot definitively say that that is true. However, all those who would maintain that the cell is not regulated

as a Turing machine are I think on the same side of the argument as I am: there does however appear to be weighty opposition to this view, not least by David Deutsch [28]. Rosen argues that in a natural system, as well as a *syntactic* component a second *semantic* component is required to overcome the impredicativity: the system must have an interactive environment – something a Turing machine does not have. Furthermore, these two components must have *independent* information sources. One possible candidate for the second (non-DNA sequence coding) component is chromatin marking [17], however, the chief objection to this is that so far no one has determined from where the information to locate the marks on the chromatin is derived. Without this knowledge it is not possible to confirm the independence of such marking from the genotype. Other arguments, critical of chromatin marking as a primary regulator, are advanced by, for example, Huang [11] and Deal [29, 30]. In any case chromatin marking can only directly affect transcription. In the independent attractor model the *syntactic* component can be seen as the interactions of the proteins according to the rules of engagement and the *semantic* component, the sequences coding for gene products on the genomic DNA. Therefore, the genotype (coding information) is located in the environment of the cell (in multicellular organisms it is shared by all cells) while in physical terms the DNA is part of the system (as it interacts with other system components). Therefore, if there is any "programme" in the regulation of the cell it is the self-organising syntactic component. Thus, the model is structured as is a natural language with the *grammar* constituted by the rules and a *vocabulary* by the coding sequences with the phenotype expressing *meaning*. This is a very plausible structure for a natural system.

Conclusions

The combined evidence from the phenomenon of radiation induced genomic instability and the challenges to the conventional genetic regulatory model, it seems to me, *force* us to consider an epigenetic cell regulatory model; whether the independent attractor model is the correct one is, of course, not clear but it is a candidate and it has a number of features which I have not had time to go into which give it plausibility. For example, seen from the perspective of that model the theory of punctuated evolution [30] can be rationalised.

I fully recognise that the model invokes processes for which we have no hard empirical evidence except that proteins are "sticky" and do form quaternary complexes spontaneously within the cell, for example, the transcription pre-initiation complex and ribosomes. There is much we don't know about how proteins behave in non-equilibrium environments and because of the thermodynamic openness of the cell this is precisely the environment in which they are functioning. The physicist Robert Laughlin proposed in a paper in PNAS [31] that the size range of proteins, the mesosphere, is one of the least understood areas of physics. Schrödinger, in his lectures, entitled "*What is life*?", insisted that life depended upon a new physics which we have yet to discover. That proteins were an essential cellular component considerably pre-dates the discovery of DNA but only now are the full implications of the discovery of disordered domains in proteins being explored [12].

If there is a "smoking gun" in favour of the independent attractor model as an alternative to genetic regulation I think

the Nakajima et al [7] experiment to reconstitute the cyanobacterium's circadian rhythm *in vitro* with just three proteins and ATP is a good candidate. Circadian rhythm must be one of the earliest functions acquired by cells and is found almost universally. One might speculate that in cyanobacteria it is a relic of proto-life prior to the adoption of nucleic acids as templates for replication, i. e., before transcription was available to the cell.

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