

What kind of a thing is the genome?

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Introduction

A little over a decade ago the mammoth task of sequencing the human genome was commenced. A few years ago the first results started to come in and it was with some surprise that researchers learned there were only about as third as many genes as there were proteins produced by them. More recently genomes of other species have been sequenced with the equally surprising result that the differences between these sequences and those of the human are not very marked. For example, the sequence of the genome of the chimpanzee differs in less than two per cent of its bases from that of the human genome. It can be argued that the sequencing of the genome has raised more questions than it has answered.

The driving force for the sequencing effort was the so-called central dogma. This states that there is a deterministic relationship between the genomic sequence and the biological activity of the proteins that the sequence codes for. Some of us have always thought that this was a rather simplistic view and we have been proved right.

Even more recently attention has been drawn to the so-called epigenetic features of the genome, specifically the way genes are deployed to produce the phenotype of the cell, that is, its outward nature. Essentially, the central dogma stated that the genomic sequence alone determined the phenotype; it is now clear that something else must be involved.

Clearly there is more to the way the genome operates than has hitherto been recognised. One of the features of genome that is little remarked upon is its extraordinary stability. If Darwin is to be believed then those of us living today are directly linked to the very first life forms to appear on the planet by a continuous chain of self replicating organisms at the heart of which is the genome. To be sure it has evolved and increased in its complexity but it has its origins in something that materialised 3.8 billion years ago.

When I lived in Rome I used to take refuge from the incessant traffic noise in the cemetery for foreigners in Trastevere. Buried there is the young English poet, John Keats. He died some two hundred years ago and so I suppose the inscription on his gravestone was carved then. Now it is nearly illegible due to erosion of the stone. That which is carved in stone is not so permanent. The famous inscription, "here lies one whose life is writ on water", may give us a clue to other forms of stability that have more permanence. Indeed the parallel evoked by this inscription is apt to our discussion because the medium upon which we might say "life is writ" is DNA and that is chemically quite unstable. In every cell of our bodies the bases in the DNA are being replaced at the rate of about 100 every minute because they have become damaged. The genetic code for our very existence is constantly falling apart and being rebuilt. Here is stability based on dynamics.



The things around us are there to be seen because they are stable and they can derive that stability from only two sources, namely the state of equilibrium and dynamic steady states.

Equilibrium is the lowest available energy state. Stable states do not need to exist only at equilibrium; they can be “tethered” to equilibrium, that is, spontaneously attracted to equilibrium but transiently activated by some source of energy. A working clockwork clock is such a tethered object. When it is “wound up” it has the energy to drive the cogs and hands stored in its spring but it is always making its way to equilibrium when the energy stored in the spring is exhausted and the clock stops. Winding it up restores it to a working clock and it can be maintained as such, that is, without reaching equilibrium, indefinitely as long as the spring is kept energised.

That is a very different stability from that associated with dynamic steady states. An everyday example of such a system is a whirlpool in a river. Such whirlpools can be very stable and possibly there are many that have been in existence for even thousands of years. We know of one that has lasted more than 130 years and we know about it because it was an object of curiosity to astronomers. It is the red spot on Jupiter. This is an atmospheric whirlpool of swirling clouds. Whirlpools never occur in still water; they require the flow of water (energy) to give them the stability. They also require an appropriate environment. Whirlpools do not occur in deep water flowing between parallel, smooth and straight banks; they require an environment to interact with, such as a river bed, irregular banks, rocks or bridge piers obstructing the flow. These objects set up counter flows which to some degree oppose the primary flow leading to the formation of dynamic steady states and the dynamically stabilized objects associated with them. Essentially dynamic steady states store energy therefore they are far from equilibrium. They can also be self assembling; if the conditions for their formation are in place they form themselves. If they reach equilibrium they cease to exist although the potential for them to be re-energised and reassemble is there it may not always be possible as their existence may depend upon their history, they can be evolved objects, objects with a history that also has to be replicated for them to come into existence. Whirlpools are among the simplest of these kinds of object and they serve here only in an allegorical sense. Another such object with which all are familiar is the candle. A lighted candle shows an extraordinary stability (in terms of the constant output of light) which relies on

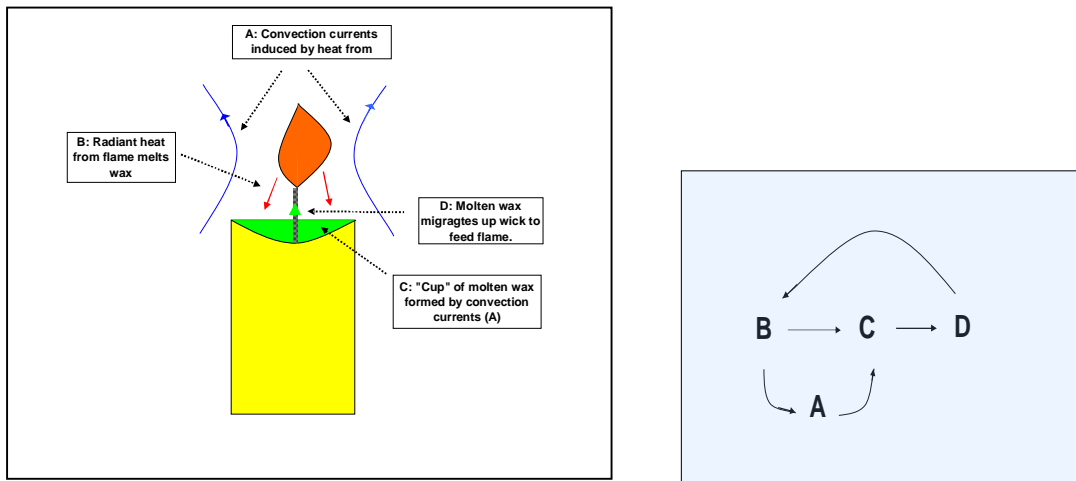


Fig 1: Schematic representation of the dynamical aspects of the candle and illustration of the closed loop nature of the processes driving it.

several dynamic processes; a flow of molten wax up the wick, heat from the flame melting wax at the top of the candle, convection of the air induced by the heat from the flame to cool the rim of

the candle and form a cup for the molten wax, etc. (see Fig 1). The successful candle relies on the optimum physical properties of its components, wax, wick etc. that interact one with the other to produce a constant light output. It is the consequence of several dynamic steady states and there is no "control centre" and in that sense the candle is self-organising, given of course the initial conditions. What we see in the living genome is the dynamic steady state of spontaneous damage of DNA due to hydrolysis and oxidation pitted against the cell's capacity to detect that damage and repair it. It is a dynamic steady state fundamental to the life process and it is central to the stability of the genome.

Ionising radiation destabilises the genome

Ionising radiation can damage DNA by causing chemical modification of its components, most notably the bases. If a base is altered or lost it causes mutation of the genomic sequence, a consequence that is most often damaging, potentially, for example, leading to cancer. The chemical phase of the damage process is very short in comparison to the biological processes such as transcription of the sequence into gene products or the replication cycle of the genome. The conventional dogma to explain the action of radiation assumes that before the cell has to replicate itself such damage can be detected and repaired. If this is fully successful then there will be no further consequences but if not then any residual damage will be replicated at the first cell division and, providing the offspring cell is viable, at all subsequent divisions. In other words the damage becomes fixed and where the damage is to a somatic cell it can (if the appropriate genes are affected) influence the growth behaviour of subsequent generations, potentially leading to cancer. If it is a germ cell that is damaged then if the damage is passed to the next generation it will affect all cells in that organism and potentially give rise to hereditary disease, depending again on which genes are affected.

In the early 1990s an effect in irradiated cells in culture was noted, namely that after irradiation the surviving cells underwent several apparently normal cell divisions but after a time started to exhibit abnormalities. In this case the abnormality was in the chromosomes in which so called aberrations occurred. The experiment studied the damage in a clone of cells all derived from a single irradiated cell so the phenomenon was called non clonal aberration. As damage could be exhibited after several normal cell divisions the phenomenon did not fit the existing dogma and the authors termed it genomic instability.

An interesting feature was that it occurred after small doses of radiation and this turns out to be very important in understanding what is happening. One of the first theories of radiation action was so called target theory. Radiation induced damage is randomly and very locally distributed, rather like bullets from a scattergun. Typically energy is deposited in volumes initially of dimensions comparable to the diameter of the DNA duplex, i.e., 3 nm. If the bullets are fired towards a target with a detector on it the size of the target can be determined by the average number of bullets needed to get one hit on the target. When we talk of the target in the cell we may mean a specific sequence of DNA, a gene for example, or a chromosome or the whole genome. It will take many more bullets on average to hit a gene than to hit a chromosome or the genome, at any place within it. The target experimentally determined for genomic instability induced by radiation is essentially the whole genome – it means it does not matter where it is hit. For this reason genomic instability has been termed a non-targeted effect, in contrast to the conventional effects of radiation where it is assumed specific genes (targets) have to be damaged.

The key question raised by the non-clonal aberrations was "where is the damage that is replicating in the cells that exhibit no damage but which will subsequently exhibit chromosomal aberrations?" Of course the conventional dogma has no answer for this and most radiobiologists regard the mechanism of untargeted effects as unknown.

As the target is not specific to a part of the genome we can regard the instability as a generic response of the genome. The generic responses of the genome to damage are detection of damage and its repair plus some other actions like arresting the cell cycle to allow the repair to take place. In other words what the cell does when it is damaged is change the patterns of expressed genes to undertake the response processes. In short, it affects that dynamic steady state that was identified as crucial to the stability of the genome. Why should this matter?

Dynamical systems theory

Dynamical systems are difficult to conceptualise for several reasons. One is that they are critically dependent on their environment so they cannot be studied out of context. Secondly, they are usually what we call emergent, that is, they exist in a hierarchical structure and depend on the physical properties of the levels below them. Fig. 2 (below) shows the hierarchical structure of living organisms. Working from the bottom up we see that atoms combine into molecules, molecules to macromolecules, etc.. At each stage new properties emerge, for example a two parts to one mixture of hydrogen and oxygen gases has entirely different properties to water, a molecule with two hydrogen atoms and one oxygen; one is explosive the other not for example! The genome is a complex of macromolecules (DNA, RNA, protein etc.) and what is being proposed here is that the dynamic properties of the genome emerge at this level and that its stability depends on the physico-chemical interaction of the gene products active at any point in time in the genome. Damage to the genomic sequence entails changing this mix by up or down regulating gene products.

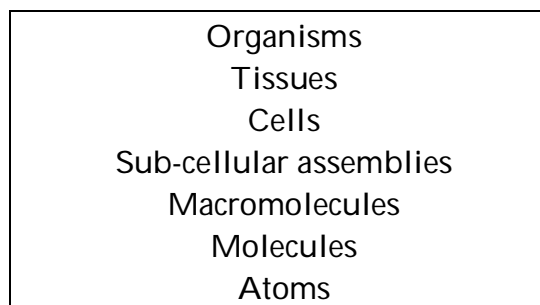


Fig. 2: Illustrating the hierarchical nature of living systems

Dynamical systems of this type have very specific properties one of which is that stable states are sited at attractors within what we call a state space (see Box). As in the case of a point in the room where you are sitting, which can be uniquely specified by three coordinates, a point in a high (n) dimensional state space can be uniquely defined by n coordinates. In this case the coordinates relate to the potential gene products that the genotype can generate and the maximum extent of activity they can produce. Thus defined such a state space encompasses all the possible states in terms of gene product mix that are possible for a given genotype. There is however a very significant constraint; only a fraction of the state space can be occupied in a stable way; it is so to speak "quantised" with attractors at points of stability, all other domains can only be occupied transitorily. Thus the system can make transitions between attractors but will only be stable at attractors.

Box: State space and attractors:

State space can be regarded as “thinking tool” to help in conceptualising complex dynamical systems. Normally we think of “space” in the sense of volume in three dimensions, say x, y and z called the coordinates. Any point in that space is represented by a unique set of values for x, y and z. If the space is a cube with unit length side then the point at the centre of the cube has the coordinates (0.5, 0.5, 0.5). If the point moves within the space then a trajectory can be mapped out in terms of a sequence of coordinates at time intervals. State space is an elaboration of this everyday concept in which the number of dimensions can be increased to any appropriate value. In the case of the genome that appropriate value would be the number of gene products that the genotype could produce, in the case of the human genome about 100,000. Of course it is not possible to envisage what that would look like in physical terms but that does not matter. The point is that what we call the “state” of the dynamical system is a single point within that state space and any movements of that state can be envisaged as a trajectory within the state space.

In the case of the genome each gene product can be seen as a dimension calibrated up the maximum activity of that product that can be expressed. Within the high dimensional state space formed every state that the genome can adopt is included.

For a state to be stable it will be located at an attractor. An attractor could be a fixed point, a limit cycle or some other less orderly structure within a confined domain within the state space. Attractors in the genomic state space seem likely to fall in this latter category. Returning to the physical space analogy we started with consider a room with two light bulbs, one lit and a fly. The fly will be found buzzing around in a domain around the lighted bulb; the fly is in an attractor. If that bulb is extinguished and the other one lit that will become the attractor for the fly. If both bulbs are lit there will be two attractors in the system and the fly might be in either and cross between them.

State spaces don't necessarily have attractors but those for complex dynamical systems do. In the case of the genome they are important because they give rise to the phenotypic properties of the cell housing the genome.

When radiation damages the genomic sequence the expression of genes for the detection and repair of that damage perturbs the attractor at which the genome is sited potentially causing it to adopt another or variant attractor. It is this step which gives rise to genomic instability; it is a quantum leap from what will be called the “home” attractor to a new or variant attractor.

The home attractor is that at which the normally stable genome is conducting activities such as the faithful replication of the DNA code, its transcription to mRNA and eventually active protein gene products as well as repairing damage that occurs spontaneously due to hydrolysis and oxidation. These might be called “housekeeping” activities but they are far from mundane, they are what have made it possible for the thread of life to stretch back 3.8 billion years. In evolutionary terms maintenance of the integrity of the genotype must be of high priority and so it might be concluded that the home attractor has been subject to “conditioning” in order to optimise its performance; variant attractors are thus likely to be inferior if they work at all (if they don't they will not be seen as the genome will not replicate) and lead to errors in repair, transcription and translation of the code and thus the damage seen in genomically unstable cells.

Is there any evidence for attractors?

Although attractors have been discussed in the context of biological function it was only in 2005 that the first experimental evidence of an attractor was obtained. In the dynamical model of the genome the process of differentiation by which cells change from, for example, stem cells to the terminally differentiated functional cells can be seen as a transition from one attractor to another. The bone marrow stem cell system, that provides the functional blood cells, for example, undergoes this differentiation process constantly as the terminally differentiated cells die after a few days of activity. One of the cell types is called a neutrophil and these cells have precursors that can be stimulated into differentiation *in vitro* by at least two separate agents. By measuring the changes in gene expression after two groups of cells were so stimulated by different agents it was shown that although both groups arrived to the same point, the terminally differentiated neutrophil, the gene expression “routes” (measured serially for some 7 thousand genes) were

markedly different: there was no such thing as a predetermined differentiation pathway as is traditionally assumed but rather an undefined transition from one state (attractor) to another.

In another experiment unirradiated (control) and irradiated (assumed to be genomically unstable) cells, were grown as single clones and their gene expression profiles measured at intervals. In both cases the gene expression patterns diversified, that is, became more heterogeneous, but the irradiated cells the more so. A pair wise comparison showed that the heterogeneity was greatest in the irradiated cells. This result is consistent with there being a tendency in both control and irradiated groups to adopt variant attractors with increasing numbers of cell divisions but for unstable cells to do so significantly more readily.

Very recent results on mice bred from a mating between an irradiated father and unirradiated mother show evidence of a form of instability called tandem repeat mutation. Tandem repeats are non-coding DNA sequences equivalent to that used in humans for paternity testing. That radiation induces this instability in germ cells has been known for some time – what is new is that these mutations are observed in the somatic cells of the offspring mice and that these cells are more prone to mutations and further damage to their DNA than cells of offspring without a radiation history. Thus, irradiation of the paternal genome produced an effect that was inherited in the offspring as a global instability affecting all the cells in the new organism. It is extremely difficult to envisage how this would happen in terms of the conventional dogma.

These results may not be incontrovertible evidence for dynamically mediated stability but they are certainly consistent with it.

Properties of the state space

The state space contains attractors but these must be seen as part of an “architecture” that is a property of the state space and one that is also dictated by the genotype. It is established that the genes coded into the genotype do not act independently of one another; they are networked. This has been shown again using measurement of gene expression patterns to see which genes seem to be expressed together. Interestingly the network uncovered is of a specific type called “scale free”. Scale free networks are commonly self assembled and are characterised by having a few genes highly connected to others and the majority connected to only a few other genes (see Fig. 3) This gives them robustness, certainly a feature of living systems but they are also sensitive, as are living systems. This combination of robustness and sensitivity is unusual; it is as if there was something with the qualities of an F1 motor car combined with those of a steam traction engine. This combination is exactly what is found in living systems. Consider for example a professional pianist and the extraordinary dexterity that enables him/her to translate notes on the page into musical sound. He/she will survive and perform in a wide range of conditions, can be fed at irregular intervals on a wide range of fuels, can tolerate irregular sleep patterns etc..

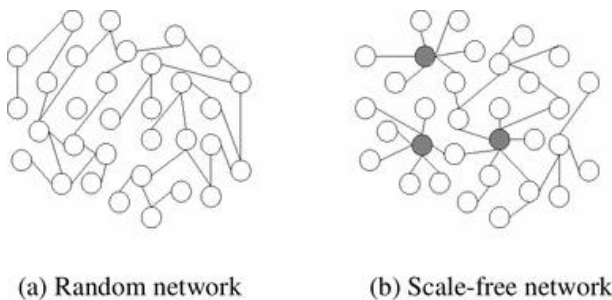


Fig. 3: Illustration of different network conformations

At this point it is necessary to make a point of caution. The state space of the human genome has 100,000 dimensions and typically a high dimensional attractor might involve say more than a 1000 of these dimensions. Such an attractor is clearly a complex entity. When say a stem cell differentiates to a neutrophil it may undergo several cell divisions in the process. Certain dimensions in the attractor dealing with the housekeeping during differentiation do not change while others, which endow the cell with the properties of a neutrophil do. The attractor concept is therefore complex and relatively ill defined but never the less I believe it is a useful thinking tool.

What these gene to gene interactions do is create an architecture embedded in the state space that guides free genomes, i.e., those not in attractors, through the state space until an attractor is encountered. For example, consider a genome triggered from its attractor and set free. It can move freely in certain directions facilitated by the gene to gene interactions (they can be imagined to create in essence a kind of "gravity") but not in others. It is still not clear what it is that defines "up" and "down" in this model but we have to assume there is an "up" and a "down" otherwise processes such as development and differentiation could not take place spontaneously.

There is however a distinction to be drawn between planned and unplanned transitions within the state space. The Nobel prize winning geneticist Barbara McClintock noted many years ago in her studies on the genetics of maize that the genome was constantly being challenged by its environment and sometimes it responded in a predictable way (to challenges it had evolved to respond to) and sometimes in an unpredictable way (to x-rays for example). What would appear to be happening here is that state space architecture can evolve to deal with environmental challenges in an orderly manner but if that is not the case a much more open ended outcome will result. Mostly it must be expected to be detrimental but it may also be part of the process that allows organisms to respond to environmental changes, i.e. evolve.

Epigenetics

Earlier on I mentioned the realisation that something termed epigenetics was increasingly recognised as being important. Until recently the word epigenetic was used to mean anything that influenced phenotype that was not related to the genotype, or genomic sequence. Now its meaning has been associated with the control of gene expression and the mechanisms by which genes are suppressed or activated to produce their gene product. The mechanism of these processes is being increasingly understood in terms of methylation of the DNA or its associated histones (together DNA histones and other proteins comprise the chromatin which is the stuff of the genome) and the structure of chromatin either around the gene sequence or around sequences that control genes.

The fact that there are more than 200 terminally differentiated cellular phenotypes in the human, all with the same genotype, testifies to the importance of the epigenetic state of the genome. These phenotypes are generated by selective use of the gene products generated from the genotype and this in turn, according to the current dogma, is determined by the methylation status or structure of the relevant chromatin. In the dynamic model of the genome it is the position in the state space of the occupied attractor that determines the epigenetic state.

Therefore we can view the process of differentiation, which is in effect the transition between two phenotypes, as either a transition from one attractor to another in the state space or as a complex sequence of methylations, demethylations and structural changes in selective parts of the chromatin. The situation is complicated by the phenomenon of imprinting where alleles of one parental origin are silenced leaving the expression solely from the genes deriving from the other parent. This type of methylation has to be permanent. For example, in females one of the x-

chromosomes is totally imprinted. According then to the current dogma in the process of differentiation complex methylation changes take place in some domains while remaining undisturbed in other domains.

The process of differentiation is also often accompanied by clonal expansion, that is, starting from a single stem cell numerous terminally differentiated cells are formed. This is, for example, the case with spermatogenesis in male germ cells and with the formation of blood and lymphatic cells which derive from bone marrow stem cells. In such a process numerous mitoses take place and at each one the epigenetic state of the mitosing cell is "remembered". This is essential as differentiation may require several intermediate cell phenotypes. It implies in the current dogma that methylation and chromatin structural features are also replicated. In the dynamic model the attractor at mitosis is inherited by the newly replicated genome as the process proceeds through several intermediate attractors defining the intermediate phenotypes.

The situation concerning inheritance along the germ line is more complicated (see Fig. 4). Following the fusion of the sperm and egg to form the zygote, the single cell from which all the cells that will form the new organism derive, the genome must be put into what is called a

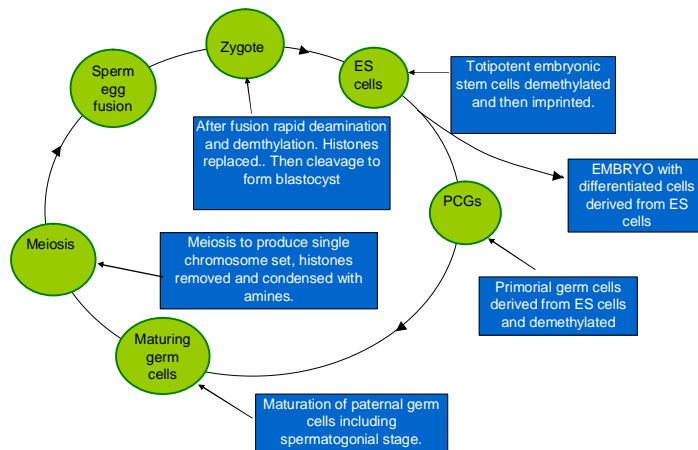


Fig 4: The transgenerational germ cell cycle in mammals.

totipotent state. Thus from immediately after fusion and for the next few cell divisions, in mammals, there is a genome wide demethylation. At this stage, prior to the formation of the blastocyst, there are essentially two genomes, paternal and maternal, sharing the same cell and to a large degree in the earliest stages, behaving independently. As cleavage (the early cell divisions) takes place these genomes come into synchrony. The synchronisation of dynamical systems is a well known phenomenon. The cell divisions at this time give rise to two categories of cells, the inner cell mass (ICM) surrounded by the trophectoderm. The ICM are totipotent cells called embryonic stem cells and they develop into the embryo whereas the trophectoderm cells develop into the placenta. Embryonic stem cells also, early on, give rise to primordial germ cells (PCGs) which develop into the germ cells of the new organism.

The current dogma says that because of all this demethylation that epigenetic characteristics cannot be inherited in the germ line. There is a historical perspective here in that the French contemporary of Darwin, Lamarck, had developed the notorious theory of the inheritance of acquired characteristics. It is notorious more for social than scientific reasons yet it has created a state of denial regarding epigenetic germ line inheritance among the scientific community

causing a number of examples where explicit “exception clauses” precede discussion of epigenetics and inheritance. However, there are clear exceptions to this rule one being the occasional failure to demethylate specific genes and the other being the inheritance of the instability phenotype. The second is of considerable interest to this discussion.

Mice carrying the pink eyed mutation, p^{m} , which gives a light coat colour, may acquire dark spots if, during embryogenesis, the mutation reverts in some cells. The dark spots are in general larger if the reversion takes place early in development. If the male parent has been subjected to irradiation some six weeks before mating, at the spermatogonial stage of sperm maturation, the offspring mice tend to have larger and more frequent dark spots than the controls without an irradiated parent. What has been inherited is the epigenetic tendency to reverse the mutation. If a chimera of embryonic cells from a mating of an irradiated father and unirradiated mother is formed with embryonic cells from an unirradiated mating, the cells originating from the parents with a radiation history are found to have a reduced proliferative capacity. The inherited effect is an epigenetic one of failure to proliferate appropriately. If the offspring of these chimera are mated with unirradiated females the effect persists into the next generation. Finally the offspring of matings between irradiated males (spermatogonial stage) and unirradiated females have a markedly increased sensitivity to cancer induction by known carcinogens. Again the inherited effect is the propensity to succumb to cancer induction.

The common factor in all these examples is an inherited effect related to the housekeeping functions of the genome. It is significant that it is irradiation of the male parent that gives rise to the epigenetic effects. In addition to its rapid demethylation after fusion, after meiosis and prior to packing into the sperm the paternal genome undergoes the removal of all histones and is condensed with amines. On fusion it is deaminated and it gathers new histones from the egg cytoplasm. In other words all traces of methylation and chromatin structure modifications are destroyed and yet the effect is retained, just as at mitosis. It seems this has again to be the inheritance of a variant attractor induced in the male parent’s germ cells prior to mating.

There is also a problem in seeing the methylation status or chromatin structure as a means of determining transitions from one phenotype to another. These features control gene expression and not directly the active gene product mix in the genome. For example, mRNA and proteins can be transcribed and stored in an inactive form for future use, proteins can be “chaperoned” between active and inactive forms and active proteins can be degraded by other gene products. Thus, although the pattern of gene expression is related to the mix of active gene products it is not a direct or one to one relationship; gene expression is a surrogate but no more for the critically important gene product mix.

Implications of the dynamic model

Epigenetics will become an increasingly important aspect of biology which will have to be integrated into the underlying theoretical framework. Much progress remains to be made. We can talk in terms of language and music by way of analogy but not much more. We can equate the genotype with the vocabulary of a language and the epigenetic component with the grammar. We can talk of orchestras playing a nearly infinite variety of music on a finite set of instruments. We can even get into the kitchen and talk of a whole range of bakery products made from a few ingredients. They are good and useful analogies but they don’t, at least to me, seem to open new avenues of research. As is now apparently proposed there will be an even more daunting task than sequencing the genome if the approach, as advocated in the journal *Nature*, of recording the methylation status of cells in all their states is actually implemented.

On the other hand phenotype determined by the dynamic state as defined by position in the state space does open opportunities for further research in so far as mapping the state space at least around certain key attractors is a feasible aim. The problem can also be tackled by investigating network structures and gene to gene interactions. The dynamical concept also can provide a framework for a conceptual basis for epigenetic phenomena.

Another implication is that there is a source of variation, so far I believe largely ignored, in the network structure of the genome. Gene to gene interaction determines the structure of the state space architecture and in that the attractors are embedded. The attractors are determinants of cellular phenotype. Consider the home attractor which can be regarded as providing the "stability phenotype". It entails a combination of gene products acting in concert to provide the optimum conditions for the maintenance of the integrity of the genomic sequence including through mitosis. In principle it can be conditioned in a number of ways. Firstly the efficiency of the processes it oversees can be increased by fine tuning the gene product mix, that is, modifying the gene to gene interactions, Secondly, its resistance to irreversible perturbation can be increased by modification of the state space architecture around it increasing the basin of attraction, again a modification of the state space architecture. Also as the genome cannot be propagated unless it is able to develop from a zygote to a fully grown adult and mate, the process of development can be conditioned by wider ranging modifications to the state space architecture. Development can be seen as a special case of differentiation where numerous differentiation events (trajectories through the state space architecture) take place in a highly coordinated fashion to develop the form and functions of the new individual; a kind of avalanche of coordinated events. These three types of process would constitute adaptation in evolutionary terms. There is, however, a big difference between this kind of adaptation and that based on upon variation derived from genotypic sources which must be gradual. Epigenetically mediated adaptation, because it is based on a "quantised" state space, can and must make "jumps", specifically the contribution made by several gene products to a particular phenotypic feature can be changed in a single transition for one attractor to another.

Seen from this perspective a single genotype may provide, through epigenetic variation, numerous whole organism phenotypes simply by deploying a limited range of cellular phenotypes with different developmental programmes. Indeed, it would surely be entirely possible to make several species from a single master genotype on the basis of the rules governing gene to gene interaction. Thus, looking for the "essential" element of humanness that distinguishes us from chimpanzees in the DNA base sequence might be seen as somewhat fruitless.

It is increasingly being recognised that epigenetic factors play an important role in disease. Cancer, because of its association with mutations is generally regarded to be initiated by a specific mutation, for example colorectal cancer by the truncation of the APC gene. In truth the early stages of cancer are impossible to study as the disease is widely believed to start with a mutation in and the consequent modification of the growth characteristics of a single cell. It is not until a cell mass of about 1 cm diameter had accrued that the disease will be diagnosed and by that time the character of the originating cells is obliterated. Direct support for the mutational theory is therefore weak. As I have previously proposed carcinogenesis could start with an epigenetic event similar to that which is observed for genomic instability. The genome, freed from its home attractor by a perturbation, migrates to a variant attractor where its housekeeping is less efficient and starts to accrue genotypic damage. This, in principle, can lead to modification of the genotype and thus the state space architecture and further migration in a co-modifying state space. Malignancy is a distinct if ill defined phenotype that would be associated with a particular domain or domains, of the state space.

Support for such a concept comes from the fact that a few cancers are solely epigenetic in character, that is, they have a genotype identical to the normal cell from which they derive and in fact can be de-malignantised by implantation into normal tissue. An epigenetic origin of cancer would have considerable practical implications. On the basis of the current dogma, the mutational theory, only genotoxic agents should be considered as potentially carcinogenic whereas if it is an epigenetic phenomenon any factor that can influence the state of the genome is potentially carcinogenic. Here radiobiology throws more light on biology in general. Shortly after the discovery of genomic instability another related effect was discovered, namely the bystander effect. This entails the initiation of effects almost identical to those deriving from genomic instability in cells that have themselves not experienced any ionising events but which have been in the vicinity of cells that have. It is established that the pseudo radiation effects are mediated by chemical signalling from the irradiated cells. Thus, damage to the genotype *per se* is not necessary for instability to be induced in a genome.

Conclusions

Departure from the dogma that prevails in cell and molecular biology, namely that *albeit* tacitly, the genome is assumed to be an object tethered to equilibrium and periodically activated to read and process genotypic information, to adopt the view that it is fundamentally a self assembled, complex, adaptive and thermodynamically open dynamic entity, reveals some explanatory power in terms of established biological observation and evidence. The fundamental nature of the differences between these, what I earlier called clock type and whirlpool type objects, cannot be overstated. The one cannot be "mapped" onto the other; they are largely incommensurable. In trying to explain these ideas to a colleague I have been asked to provide some "hooks" similar to those that his concepts were hanging on but I found that very difficult. It seems that there is a conceptual gulf to be crossed before most of those immersed in the practice of biological research can take a critical position in relation to the dynamical model. Yet they not me, have the wherewithal to provide the necessary critical assessment.

The sequencing of the genome has revealed a complexity underlying biology that was barely comprehended a few years ago. The question to be addressed now is will this complexity yield to a research agenda based on what has worked so far, namely essentially the clock model of the genome and reductionism, or is an entirely new approach required? You might legitimately ask if things have worked up to now what would be the justification for changing to a radically different approach now which you say is incompatible with the traditional model. It has to be acknowledged that cell and molecular biology has made very remarkable progress with the clock model but it is possible that within a dynamically stabilised entity clock like processes occur embedded in attractors. Thus, some aspects of biology succumb to the clock/reductive approach. However, few would argue with the claim that living systems are adaptive and many would agree that the genome is an adaptive entity. It is difficult to see how there can be much confidence in the results from a reductive approach in these circumstances. Therefore the case for reviewing the approach to biology can be made regardless of the model adopted to account for stability.

Another aspect concerns the wider debate about evolution, the origins of life and conflicts with theology. Clock type objects have the stamp of design on them whereas dynamically stabilised objects can be self assembling and self organising. Historically cities, economies, the World Wide Web and the INTERNET are examples of dynamic systems that have largely self assembled in the sense that in most cases the initial conditions have been created and a "spark" has set them off but there is nothing built into the system to control them, they have to a large degree their own life. For example researchers now study the ways in which the INTERNET organises the flow of data traffic; that is determined by the system from rules, e.g. "POP" and "STMP", which are

negotiated at individual servers. The INTERNET infrastructure has grown at a prodigious rate in the last decade simply by individuals connecting computers to it. There is no central control deciding who can and who cannot join. The great British physicist Michael Faraday was fascinated by the humble candle even while he was making great discoveries with electromagnetics. He started the tradition at the Royal Institution of lectures on science for children and he lectured himself on the "*Chemical History of the Candle*". Incidentally, at a time when our politicians seem naturally to graduate to knighthoods and the House of Lords it is notable no honours were awarded to Faraday until 1995 when a £20 note was issued showing him giving one of his lectures for children. Despite the title of his lecture it is Faraday's observations of the physics of the candle that are most remarkable. In the first lecture he stated "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 a candle." As stated above the stability of light output from the candle is based on a complex of dynamic steady states without any physical "control centre" and given the right conditions it is self-organising, as Faraday stated "I can not imagine a more beautiful example than the condition of adjustment under which a candle makes one part subserve to the other to the very end of its action." According to Faraday there was a natural precursor to the candle in branches of wood found in Irish bogs; these burned at one end due to oils contained in their porous structure resulting in a "natural candle". It is clear that complex entities can evolve from self-assembled and self-organised objects: the argument that "if there is a watch, there is a watch-maker" applies to things in the "clock" category but not necessarily to things in the "whirlpool" category.

Having reached this point I am conscious that there is at least one serious omission from this discussion and that is the work of the British geneticist CH Waddington sadly deceased. He was discussing essentially these ideas back in the 1940s. He would, I suspect, be fascinated to observe how stubbornly the cell and molecular biology community have stuck with the clock model of the cell and I suspect he might regard this lecture as a "Janet and John" equivalent for biology; nevertheless I fully acknowledge his profound influence on my thinking. His last book "*Tools for Thought*" published in 1977, after his death, he introduced the concept of the "Conventional Wisdom of the Dominant Group" for which he proposed the acronym "COWDUNG". This was in the context that science has to be founded in a philosophical environment and that the then prevailing philosophy of reductionism was inappropriate. Waddington is also credited with coining the term epigenetic which he used to describe the "interactions of genes with their environment, which bring the phenotype into being".

So what kind of a thing is the genome? In much the same way as most people do not associate the television set with the metals, semiconductors, glass and plastic from which the object is made but rather with what is shown on the screen, it would be sensible, as Waddington proposes, to focus scientific attention on what the genome does; a "process" centred view rather than a "thing" view. The first and foremost thing that it does is mediate change; from a zygote to an adult, from a slime mould to a human, from a normal cell to a malignant cell. However, processes are much more difficult to study than things, the first of many difficulties being that of conceptualisation. State space does provide a conceptual framework for the genome but it entails regarding it as a dynamical entity and embracing the concept of attractors and much besides that are in essence not amenable to the still prevailing scientific philosophy, reductionism. So there is a philosophical challenge here, which may already be being met but if not it should be.

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