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DISCUSSION

The epigenome and top-down causation

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Genes store heritable information, but actual gene expression often depends on many so-called epigenetic factors, both physical and chemical, external to DNA. Epigenetic changes can be both reversible and heritable. The genome is associated with a physical object (DNA) with a specific location, whereas the epigenome is a global, systemic, entity. Furthermore, genomic information is tied to specific coded molecular sequences stored in DNA. Although epigenomic information can be associated with certain non-DNA molecular sequences, it is mostly not. Therefore, there does not seem to be a stored 'epigenetic programme' in the information-theoretic sense. Instead, epigenomic control is—to a large extent—an emergent self-organizing phenomenon, and the real-time operation of the epigenetic 'project' lies in the realm of nonlinear bifurcations, interlocking feedback loops, distributed networks, top-down causation and other concepts familiar from the complex systems theory. Lying at the heart of vital eukaryotic processes are chromatin structure, organization and dynamics. Epigenetics provides striking examples of how bottom-up genetic and top-down epigenetic causation intermingle. The fundamental question then arises of how causal efficacy should be attributed to biological information. A proposal is made to implement explicit downward causation by coupling information directly to the dynamics of chromatin, thus permitting the coevolution of dynamical laws and states, and opening up a new sector of dynamical systems theory that promises to display rich self-organizing and self-complexifying behaviour.

Keywords: epigenetics; emergence; causality

1. THE GENOME AS A PHYSICAL OBJECT

> One can best feel in dealing with living things how primitive physics still is.
>
> Albert Einstein [1, p. 34]

> Although studies of the *epigenome* are in early stages, the idea that environmental events can be permanently registered by our cells is a fascinating one that presents an important challenge to the next generation of biological scientists.
>
> Alberts *et al.* [2, p. 473]

A landmark event in the history of biology was the identification of the DNA molecule that embeds the heritable genetic database of all known forms of life. This discovery had great practical importance, but no less conceptual significance. The concept of inheritance is fundamentally about symbolically stored and transmitted information, whereas a molecule is a physical object: in modern parlance, DNA is hardware, while the genetic data it contains are software. Thus, the genome—a subset of DNA—represents the intersection of the informational and the physical. When speaking informally about genetics, scientists often conflate the informational and the physical, the hardware and the software, just as neuroscientists will sometimes carelessly flip from mind-talk to brain-talk. But while this loose terminology might facilitate practical progress in the discipline, it papers over a huge crack in the conceptual basis of life.

It is often commented that, after all the fuss and effort to sequence the human genome, the results have turned out to be somewhat underwhelming. One of the surprises was the relatively small number of genes that humans possess—perhaps as few as 22 000. It was already evident at the start of the project, however, that cataloguing genes *per se* was of limited value in explaining life's processes, because there is no way that even a billion bits of information can, on their own, specify the entire structure and organization of an organism, such as the human body, which contains exponentially more information than does the genome that is supposedly coding for it. Consider, for example, the brain, with its 10^{12} neurons and perhaps 10^{16} synaptic connections. Clearly, the brain's wiring diagram could not be

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accommodated in the human genome alone. Similar remarks apply to the layout of the vascular and lymphatic systems.

The foregoing mathematical mismatch has a simple and well-known resolution. First, the genome is not some sort of blueprint for an organism, as is sometimes claimed. A blueprint has a one-to-one correspondence between the symbolic representation and the actual object. Rather, a genome is an *algorithm* for building an organism, and an algorithm differs fundamentally from a blueprint. Now, algorithmic information theory proves that in a closed system, the output of an algorithm cannot contain more bits of information than is present in the input data and the algorithm itself (see [3]). However, the genetic algorithm does not operate as a closed system. A defining characteristic of a living organism is that it is an open system: there is a continual throughput of matter and free energy from the environment, and an export of entropy. Thus, a large amount of information contained in a cell derives from its biological environment and a large amount of information in an organism derives from its ecological environment. To return to the neurological example, human babies are not born with their brains hard-wired by genetics. The detailed wiring of the brain develops and changes over years in response to the experiences of the child, e.g. to external sense data. So, genetic information is augmented by environmental information: genes may constrain the development of an organism, but they do not alone determine it.

Secondly, it is important to understand that genes are not simply 'there'. They are effective only if activated or 'expressed'—switched on, to express it informally. Thus, a given gene can exist in one of the two states, on or off, which—in a trivial sense—leads to exponentially more information being stored in the system (since a set of N genes can have 2^N distinct states). Because genes can implement changes that lead to other genes being switched on or off, a genome is not a linear programme. The entire set of genes forms a dynamical network affected both by internal links and external environmental factors. The term *epigenetics* has been coined to denote this higher, extra-DNA, level of activity and control. It was introduced originally by Waddington [4] to address the fact that all somatic cells in a eukaryotic organism possess identical DNA, yet cells differentiate during development into many distinctive cell types (liver, kidney, brain, skin, etc.) as a result of additional factors that, at the time he wrote, were largely mysterious. Today, the subject of epigenetics is burgeoning and many of the mechanisms of epigenetic action have now been elucidated [5]. In a nutshell, genetics deals with what genomes are and epigenetics deals with what they do.

Epigenetic changes can come about because of chemical signals received from other genes, or from both chemical and physical signals originating in other cells, organs or the external environment. These signals may serve to switch genes on or off using molecular markers or the physical rearrangement of DNA (see below for further details). Crucially, epigenetic changes may be heritable, but they are nevertheless reversible (in contrast to genetic changes), and indeed may be both promoted and reversed by environmental factors. In some cases, the mechanisms of epigenetic heritability are understood at the molecular level [6–9]. It has been widely supposed that epigenetic markers are efficiently erased in germ cells, so that the next generation of organism begins with an epigenetic *tabula rasa*. However, there are some known examples of transgenerational, or gametic, epigenetic inheritance in which epigenetic changes are transmitted to offspring [10] in a manner containing an echo (perhaps unwelcome) of Lamarckism [11]. The best-known examples are in plants and insects, although there are cases reported in mammals too, specifically rats and mice [12]. Claims for transgenerational epigenetic inheritance in humans [13] have, however, been greeted with scepticism [14].

Epigenetics can seem hard to understand, or even mysterious, because so much of our scientific intuition is based on linear quasi-isolated causal chains and reductionist descriptions. In biology, it is usually impossible to trace a simple thread of causation and to neglect length and time scales very different from those characterizing the process of interest. For example, changes in an organelle such as a mitochondrion may have knock-on effects down at the gene level and up through the cell level to the entire organism and its environment, and vice versa. There is thus a web of causation, both upward and downward in length scale, with complex feedback loops leading to many possible stable and unstable states. Generally, an explanation for a biological process will entail both upward causation—such as when a gene is switched on and makes a protein that affects cell and organismal behaviour—and downward causation—when a change in the environment triggers a response all the way down to the gene level. Because epigenetics lies—in some sense—in the middle domain, between gene and cell, distinguishing causation from mere correlation can be very difficult. Thus, although it may be tempting to regard a certain epigenetic molecular marker as the *cause* of an epigenetic change, it may in fact be merely a 'cog in the machine' [15]. The necessity to consider organisms as systems subject to both upward and downward causation complicates causal reasoning and presents a challenge to physical scientists used to thinking of step-by-step cause and effect. The subject of systems biology attempts to get to grips with this fundamental and unavoidable characteristic of life (For a review see [16]).

Downward causation used in the straightforward sense of the system affecting a gene is not in itself necessarily a profound concept. Consider, for example, the tryptophan repressor used by *Escherichia coli*. These bacteria can make the important amino acid tryptophan with the help of five enzymes. The five genes that code for the five enzymes are located side by side on the DNA. If a bacterium gets enough tryptophan from its environment (e.g. the gut of a host organism), it shuts down its own production in response to this environmental chemical signal. The details have been fully worked out (see [17]). Specifically, a repressor protein already present in the cell can block transcription of the five tryptophan genes, and thus the production of the enzymes, by binding to a coded site on the DNA near the genes, which compromises the gene read-out mechanism (involving a molecule of RNA). But the repressor will not bind as described unless

it possesses the right shape. And it achieves that potent conformation only when two molecules of tryptophan stick to it. So in the presence of abundant tryptophan, lots of potent repressor proteins are available to shut down the cell's own tryptophan production. Similarly, when tryptophan is in short supply, the cell's genes get switched back on. There are many known repressor and activator proteins responsible for gene switching by similar sorts of mechanisms. Eukaryotes are much more complicated than prokaryotes, however, and have evolved a variety of correspondingly more complex gene regulation mechanisms that are able to integrate and respond to not just one but a multiplicity of signals. From hereon, the discussion will be limited to eukaryotes.

2. KEY EPIGENETIC PROCESSES

Although epigenetics is an emerging and still incompletely understood discipline, some basic ideas have become well established (for a recent review, see [18]). The first priority has been to identify the important epigenetic variables. The epigenetic correlates of biological properties can be both physical and chemical. Eukaryotic DNA does not exist as a simple open strand; rather it is wrapped around molecular frames called nucleosomes, made of several histone molecules. The resulting structure is called chromatin, and it makes up the chromosomes. Each human cell contains about two metres of DNA; so to accommodate it within the nucleus involves a very high degree of chromatin compactification. The three-dimensional architecture of chromatin is crucial to the functioning of the cell, as I shall shortly explain.

Genes may be switched off not only by proteins binding to DNA, but also by various small molecules being attached to specific points on the DNA. For example, the methyl group is often used to effectively silence a gene by being attached to GC sites. The pattern of methylation on a genome can be copied and inherited by the daughter cell, ensuring that the same genes are active in parent and daughter cells of the same type. This is one example of epigenetic inheritance. Other epigenetic mechanisms involve various post-translational modifications of proteins. The simple picture in which a gene codes for a protein that rolls off the ribosome production line, folds neatly, and goes about its business is a gross simplification. Many freshly minted proteins are accosted by enzymes that modify their chemical and physical forms by attaching small molecules to them. For example, histones, which go to form nucleosomes, have little tails attached, which can be modified in this manner, leading to thousands of different variations in the tail patterning of each nucleosome. The modification of specific histone tails is associated with (though does not necessarily cause) altered chromatin structure and behaviour [15]. Given the multiplicity of available histone tail structures (not to mention the existence of variant types of histones themselves), and the important epigenetic correlates of these modifications, some molecular biologists have suggested that there may be a histone code operating alongside the genetic code, constituting a complementary, non-DNA-based, digital information processing system [19]. Mostly, however, epigenetic information, in contrast to genetic information, does not seem to be in coded digital form.

In order for genetic instructions to be read out of DNA, the read-out machinery needs to gain physical access to the gene concerned. This is difficult if the gene is buried deep within a highly compactified structure. Chromatin is therefore incessantly unravelling and re-packing sections of itself to expose specific genes needing transcription at any given time to meet the multifarious demands of the cell. Genetic signals originating in DNA, and their biological consequences, thus depend on the three-dimensional organization of chromatin. A graphic illustration of the importance of chromatin's physical structure is given by cancer cells, in which the chromatin can become drastically and noticeably rearranged within the nucleus, a gross abnormality that correlates with oncogenes being expressed and tumour suppressor genes being switched off [20]. A complex physical system, involving a network of micro-tubules and other mechanical paraphernalia, helps implement the structural rearrangement of chromatin [21]. Some chromatin architecture can also be inherited, providing yet another form of epigenetic cell memory. Silencing of genes by physically packing them away seems to be a crucial feature of eukaryotic gene regulation and control.

Chromatin remains poorly understood, in spite of textbook diagrams rather precisely depicting its packaging and structure. It is not just the complexity that is problematic for study, but the mesoscopic scale of the system. DNA is well studied using atomic force microscopy and other precision techniques, while whole chromosomes can be imaged in a light microscope. But the realm in between is largely uncharted territory and difficult to access experimentally [22]. Chromatin is a highly dynamic, heterogeneous, organized, information-rich, soft, mesoscopic state of matter unlike anything else known in science, and currently beyond the reach of many standard laboratory technologies. More to the point as far as this article is concerned, chromatin marks the intersection of upward and downward causation, because its structure and behaviour are influenced both by the genes it contains and by the macroscopic forces acting on it from the rest of the cell and the cell's environment.

There are many other examples of epigenetics at work. Recently, evidence has emerged that the geometrical arrangement and spacing of nucleosomes along the chromatin strands represent an important aspect of chromatin structure and epigenetic control [23]. Then there is the entire world of microtubules, which help rearrange chromatin, organize mitosis, facilitate cell motility, channel proteins and fulfil many other functions [21]. Another fascinating phenomenon is mechano-transduction, where the physical properties of a cell's environment, such as the hardness or stickiness of a surface, or sheer stresses in the surrounding medium, can influence gene expression [24]. Embryogenesis provides the most striking example of epigenetics at work. In the early-stage embryo, a ball of identical pluripotent cells differentiates into many cell types and organs in response to a network of physical and chemical environmental signals, mostly still ill-understood (see [25]).

Many excellent reviews of the field of epigenetics may be found in the literature (see for example [5]).

The remarkable discoveries summarized briefly in this section provoke the question of how the 'epigenetic agenda' is stored, propagated and implemented. It is to that central question that I now turn.

3. THE EPIGENOME AS A VIRTUAL OBJECT

One may loosely define the 'epigenome' as standing in the same relation to epigenetics as the genome is to genetics, forming a sort of shadow information system that complements the genomic information system. But it would be a mistake to regard the epigenome and the genome as on a similar physical footing; the two represent completely different conceptual entities. The epigenome is exponentially larger (in informational terms) than the genome. As already remarked, epigenetic changes, while they may be heritable, are nevertheless reversible, enabling the environment—including the extracellular environment—to contribute information to the epigenome. There is also a key distinction between the way the epigenome and the environment interact and the way that the genome and its environment interact. The environment exerts a selective filter on the genome from one generation to the next, in the familiar manner of Darwinian evolution. That is, genetic mutations may be selected for or against by the environment, *on a time scale determined by the generation time*. By contrast, the environment can affect epigenetics over *chemical* time scales (in effect, in real time). So we look to the genome to explain the story of evolution over billions of years, but to the epigenome to explain the specific complex structure and the behaviour of a cell or an organism and its ability to adapt and respond to its environment, *constrained by but not completely explained by* its inherited genes.

But if the genes are not calling all of the shots, what, precisely, is? Consider the example of post-translational modification of histones by certain enzymes. These busy enzymes—the humble foot soldiers of life—are of course simply doing what molecules have to do. They carry out orders using the laws of physics and engage in purely local interactions. If they find themselves up against the right protein in the right state, they modify it through perfectly normal physical interactions. But life can be understood only by seeing the big picture, that is, the way in which an individual post-translational modification event conforms to an overall plan or strategy for the cell as a whole, a strategy involving countless other molecules. In a real army, each foot soldier's orders are part of coherent strategy worked out and promulgated by headquarters. And headquarters is *a real place*, with a geographical address, where thinking, planning beings such as major generals, with an overall vision of who does what, direct the battle. That is how it works with genomics. We can point to a DNA molecule and say 'There is the genome!' Information (e.g. the instruction, 'make protein X!') flows outward (and upward in the length scale of its impact) from spatially localized segments of a specific one-dimensional structure—the ultimate source of genetic information. However, we will look in vain for any particular physical object within the cell that we can identify as 'the epigenome.' In the case of epigenetics, *there is no physical headquarters*, no localized commanding officers issuing orders, no geographical nerve centre where the epigenomic 'programme' is stored and from where epigenomic instructions emanate to help run the cell. The epigenome is not to be found at a place and the ultimate information source of epigenetics cannot be located anywhere specifically; rather, it is distributed throughout the cell. To be sure, the epigenome is *manifested* in particular structures (histone tails, nucleosome patterns, methylation patterns, chromatin packing . . .), but it does not *originate* there. The epigenome is everywhere and nowhere; it is a global, systemic entity. Expressed more starkly, *the epigenome is a virtual object*. Given that it calls many, if not most, of the biological shots, its non-existence as a specific physical entity is deeply significant.

A popular response among biologists to the question 'Where is the epigenome?' is that it is in fact nothing but the genome, since the exponential combinatorics referred to earlier are built precisely from the switching on and off of genes. For example, in his lucid critique of the field of epigenetics, Ptashne [26] identifies the key puzzle for the specific case of nucleosome modification: 'one way nucleosome modifiers are sometimes said to regulate genes is by "opening or closing the chromatin structure", thereby allowing (or preventing) access of the transcriptional machinery to the DNA. Such a view is problematical on the face of it: how would the nucleosome modifiers "know" which genes to pack or unpack unless instructed by a specific DNA binding recruiter?' Precisely: how could they know? So how is the all-important molecular recruitment process supervised? According to Ptashne, 'Histone modifiers can play roles in gene expression, but they (as well as enzymes that trigger DNA methylation, in some cases at least) must be recruited to genes by specific DNA binding proteins.' The binding proteins, which regulate the switching of genes, are in turn manufactured in response to the instructions of other genes. The circularity of this reductionist argument will be evident. If it is decided in advance that DNA is the sole 'master controller' of the nucleosome modification—if DNA is the only database that 'knows', to paraphrase Ptashne—then one need do no more than follow the protein trail back to DNA. While this conclusion may or may not turn out to be correct in the case of nucleosome modifications specifically, it obviously cannot be the story for the entire epigenetic agenda in general. To claim so would be analogous to the fallacy of saying that as a million plays can be built from a few thousand English words, we need look no further than the dictionary to 'explain' the works of Shakespeare. Undeniably the genome provides the words, but the epigenome writes the play! For those readers who prefer non-anthropomorphic analogies, one might say that countless different snowflakes can be built from a set of identical ice crystals, but although the basic features such as the hexagonal symmetry of all snowflakes may be explained in terms of the symmetry properties of the constituent crystals, the information specifying the specific filigree adornment of the 'arms'

on any given snowflake is not contained in the ice crystals, but is attributable to the environment.

The foregoing reasoning notwithstanding, it is indubitably the case that *some* gene switching is attributable to the activities of other genes (a good example being the so-called homeobox). But that is far from saying that *all* epigenetic activity is nothing but a manifestation of gene activity; that is, that epigenetics is merely an epiphenomenon. In accordance with the emergence theme of this volume, and the need to avoid falling fall into the trap of 'nothing-buttery', a clear conceptual distinction between genome and epigenome needs to be maintained.

4. THE EMERGENCE OF SEMANTICS

The convergence of hardware and software in DNA is not of itself an especially profound fact. After all, a compact disc is a physical object that encodes information. Or, to take a simpler example, an electron's spin may be in one of the two states—up or down—which may be used to represent one bit of information. In other words, the identification of information with specific states of matter is familiar to physicists. However, genomic information has an altogether different character than the spin direction of an electron. The distinction concerns not the quantification, but the *nature* of biological information. Any configuration of objects—for example, leaves on the forest floor or raindrop marks on the ground—can be said to contain information inasmuch as it would require a certain number of bits to describe or specify that configuration. Likewise, the configuration of A, C, G and T nucleotide bases in a DNA sequence represents digital information. But the information in the genome is not just a collection of 'any old bits'. A biologist will characterize a gene as *a set of instructions*; for example, for a ribosome to build a particular protein. Fallen leaves and raindrops are not instructing anything to do anything.

In the realm of human discourse, the concept of 'instruction' implies that the information being exchanged has *semantic content*. That is to say, it *means* something. Of course, a person or a robot may be programmed to blindly implement instructions, but in that case, the meaning is implicit in the design of the system/programme. (A famous example that demonstrates the latter point is John Serle's 'Chinese room' [27].) At some level, instructions are *implementable* only if someone (or something) involved can *interpret* them. At the level of genetic instructions, the foregoing terminology of 'meaning' and 'interpretation', although an evocative analogy, is surely too anthropocentric, and a better description is to say that genetic information is 'contextual'. A gene is no more than a random sequence of base pairs when DNA is taken in isolation. It becomes 'instructional' only in the context of a molecular milieu that can 'interpret' the sequence and act upon it (e.g. make a protein). This molecular milieu includes the ribosome, various RNAs and enzymes that collectively cooperate to implement the instructions. It also includes, implicitly, the entire biosphere and genetic history of the organism, because the meshing of DNA instructions to molecular milieu has been created and honed by billions of years of evolution. Thus, 'context' here is both explicitly and implicitly a global concept, whereas the bits of information in the DNA are obviously localized objects. Crucially, biological information is both digital and encoded; it has to be decoded and translated before it is implemented. The existence of a coded digital semantic (or, if preferred, contextual) information channel is a fundamental defining characteristic that separates living from non-living systems.

5. SPONTANEOUS SELF-ORGANIZATION VERSUS INSTRUCTED ORGANIZATION

Some inanimate physical and chemical systems spontaneously self-organize and can display 'lifelike' behaviour. A famous example is the so-called Belousov–Zhabatinski (B–Z) reaction (see [28]). Here, a simple chemical mixture when forced far from thermodynamic equilibrium spontaneously grows patterns such as spirals. The patterns can be satisfactorily explained in terms of nonlinear reaction dynamics. Now compare the B–Z patterns with the case of a bacterial colony in a Petri dish, responding to physical and chemical stimuli (e.g. a food source) by reorganizing its distribution. Are the patterns that the colony adopts to be explained (not merely described) along the lines of a simple nonlinear differential equation of the type used to explain the B–Z reaction? Clearly not, for there is a key distinction. Molecules in the B–Z reaction are inert, merely responding to local forces. They may be said to 'cooperate' after a fashion, but at the level of passively responding to chemical gradients and thermodynamic forces. By contract, bacteria are *active agents* that *harness* physical forces to carry out a pre-programmed agenda. They may do this by cooperating with other bacteria, *not* spontaneously, but in a *controlled* manner. Bacteria respond when chemical gradients trigger complex internal processes that may involve the controlled, programmed release of energy and their motility may be against the gradients along which simple 'dumb molecules' might be conveyed. Of course, it may be possible to approximately describe mathematically the behaviour of bacterial colonies in a descriptive, phenomenological sense, in the same manner as one may model stock market movements mathematically. But description is not the same as explanation.

In spite of these clear fundamental differences, could it nevertheless be the case that the exceptional organized nature of living matter is merely 'more of the same' spontaneous pattern-forming phenomena that appear in the B–Z reaction—that is, chemical self-organization writ large? After all, some basic developmental and cellular functions undoubtedly may be attributed to simple physical and chemical self-organization. For example, the spontaneous self-assembly of cellular bodies such as nucleosomes and even ribosomes from their components is straightforward enough. Might all of epigenetics be no more than a synergistic superposition of very many self-assembling structures and self-organizing chemical cycles—so many that the specifics get lost in the enormous complexity? Many biologists explicitly or implicitly adopt precisely

such a reductionist explanation. The problem, however, is that it gets us no further forward in explaining life's remarkable properties. Even if it is the case that, *in principle*, living matter may be reduced to the physics of intermolecular interactions alone, a fully satisfying account of an organism needs to include both bottom-up and top-down causation.

How might top-down causation be incorporated into our description of epigenetics? A possible way forward has been suggested by Goldenfeld & Woese [29], who also regard life as an emergent phenomenon, and ask, 'How is it that matter self-organizes into hierarchies that are capable of generating feedback loops that connect multiple levels of organization and are evolvable?' They suggest that somehow life must be an inevitable consequence of far-from-equilibrium physics, but note that the physical laws that govern such systems are at this stage unknown. The key missing ingredient, they posit, is what they call 'self-reference'.

> The rules that govern the time evolution of the system are encoded in abstractions, the most obvious of which is the genome itself. As the system evolves in time, the genome itself can be altered; thus, the governing rules are themselves changed. From a computer science perspective, one might say that the physical world can be thought of as being modelled by two distinct components: the program and the data. But in the biological world, the program is the data, and vice versa. For example, the genome encodes the information which governs the response of an organism to its physical and biological environment. At the same time, this environment actually shapes genomes, through gene transfer processes and phenotype selection. Thus, we encounter a situation where the dynamics must be self-referential: The update rules change during the time evolution of the system, and the way in which they change is a function of the state and thus the history of the system.
>
> Goldenfeld & Woese [29, p. 387]

Their definition of self-reference is thus a form of top-down causation, implemented by coupling the *states* of the system to the *dynamical laws*. Goldenfeld & Woese [29] illustrate their proposal with the application of game theory to biology, in which the rules of the game change according to the state of play. In the context of the present paper, a more fitting procedure along these same lines is to couple the *information content* of biological states to the dynamics of the system. Consider the specific example of chromatin. It would entail augmenting the normal terms referring to local forces contained in the Hamiltonian for chromatin with additional (presumably small) *non-local* terms representing functional (i.e. semantic or contextual) information. By coupling the mechanical and informational dynamics in this manner, the dynamical laws describing chromatin behaviour would become time-dependent and change according to the informational state of the system. Information would then possess direct, albeit subtle, traction over matter and permit epigenetic control to be exercised directly on the chromatin itself.

Attributing causal efficacy to information ('software') at the molecular level ('hardware') is no mere technical modification, but represents a decisive break with one of the founding tenets of physical science. Since the time of Newton, physicists have maintained a distinctive asymmetry between laws and physical states. The laws of physics have always been regarded as immutable, whereas the states of a physical system may change with time. Thus, laws determine how states evolve, but there is no 'back reaction' of states on laws. One might say that the laws are indifferent to the states, and the Hamiltonian is independent of time. But if informational terms are introduced into the Hamiltonian, permitting the dynamics of the system to depend on certain changing *states*, namely those containing biologically functional information, then such a theory explicitly couples laws and states, and introduces time dependence into the dynamical laws. Although such a proposal represents a radical step, it has the virtue of immediately opening up a largely unexplored regime in which distinctively new forms of self-organizing emergent behaviour are surely to be expected. An attempt by this author to introduce a similar coupling between laws and states in cosmology likewise opens up promising new realms to be explored [30].

There is an interesting historical analogy with the foregoing proposal. Quantum mechanics introduced a new and a shocking view of causation into fundamental physics. Einstein famously balked at indeterminism, but was content to accept quantum mechanics as a phenomenological convenience for the purposes of practical calculation. However, he insisted that there was a deeper layer of (complicated) hidden variables beyond our ken that, if understood, would restore deterministic causality. Most physicists, in contradistinction to Einstein, prefer to accept that the nature of causality in the quantum realm is fundamentally different, and that indeterminism is truly intrinsic to the system. Likewise one could, in the spirit of Einstein, regard epigenetics as a product of complicated hidden variables, manifesting themselves in a surprisingly organized manner in the dynamical behaviour of chromatin. A simpler viewpoint, however, would be to regard the proposed 'information terms' in the dynamical equations, not merely as a phenomenological convenience, but as a truly fundamental change in the nature of causality, irreducible to a system of hidden variables. Conceptually, that would herald an even more radical shift in the nature of causality than the transition from classical to quantum mechanics.

6. CONCLUSION

It is obvious that living organisms behave in a manner quite unlike other complex physical systems, and science faces the challenge of accounting for the remarkable properties of living matter. Putting one's finger on precisely what distinguishes life from non-life is notoriously hard, but concepts such as autonomy, agency and behaviour come to mind. Simple systems such as projectiles respond passively to physical forces acting on them, but living systems are able to *harness* forces to carry out an internal agenda, often pre-programmed genetically (or

epigenetically). To use the jargon, they are more than the sum of their parts. Thus, they provide striking examples of emergent behaviour, and for this reason they have exemplified much the decades-old debate between proponents of reductionism and emergence. The growing realization that many of life's remarkable properties may be catergorized under the label 'epigenetics' provides an opportunity to sharpen that debate. Chromatin is an information-rich, highly-dynamic, mesoscopic system that lies at the heart of eukaryotic biology and captures most of what is baffling about living matter.

This paper sets out a case that the epigenome is a useful concept, but should be regarded a virtual object (in contra-distinction to the genome), as there is no identifiable 'command-and-control' centre, or instructions set or programme, etched into a physical system, from which epigenetic control ultimately emanates. The epigenome exerts its influence instead via downward causation in the sense that global, or systemic, properties of the organism exercise local control, down to the level of genes. It is conceivable that an account of top-down epigenetic causation might be possible in terms of hidden dynamical variables. Such an account would represent a relatively un-contentious form of weak emergence. A more radical, strongly emergent description would entail introducing an explicit coupling between dynamical laws and information-rich states, thus endowing higher level entities, such as contextual information, with *direct* causal efficacy on matter alongside intermolecular forces. Although such a proposal represents a decisive break with the normal formulation of the theory of dynamical systems, a rich variety of self-organizing emergent behaviour is likely. So far, theories of this sort remain largely unexplored.

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