Genes, brains, and unpredictability: Developments in the sciences and reflections on what it means to be alive*

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The most dramatic statement of the reductionist approach in the biological sciences is the 'astonishing hypothesis' of Francis Crick that something as central to our sense of self, namely the human soul, is in effect 'no more than the behaviour of a vast assembly of nerve cells and their associated molecules'. Recent advances such as the sequencing of entire genomes (the human genome being a well-publicized example) or the elucidation of some of the neuronal mechanisms associated with memory, for instance, appear to support this point of view, that we can eventually possess the recipe for human individuality. This essay contends that the essential limitation of such a programme stems not from the remaining problems of working out the details, but from the fact that living systems are fundamentally complex. Drawing on the ideas of deterministic chaos and complexity theory, it is proposed that while the broad contours of the connection between biological functioning, genetic information and the organization of its nervous system will be accessible, the unique developmental trajectory of any organism – that which constitutes the essence of individuality and confers a notion of being alive – will remain beyond the realm of precise scientific prediction.

IN our never-ending quest to understand more about the relationship of man with the rest of the universe, spectacular advances in modern science have made it possible to ask increasingly detailed questions about the essence of what it is to be human. On the one hand, the process of unravelling the DNA of any organism and deducing the sequence of nucleotides that make up this long and complicated molecule has become a routine task, routine enough to be automated to the point where it can be carried out by robots, and fast enough that the entire genome of any organism can be sequenced within a few years at the most. On the other hand, increasingly sophisticated experiments and techniques have made it possible to probe brain function in increasing detail, to the extent that a map – howsoever primitive – of the brain and its functions is slowly emerging[1].

What does this hold for the future? Will relentless scientific onslaught on such problems eventually, as this picture seems to suggest, give a completely deterministic description of any 'living' organism? Although ultimately we are interested in describing humans, we can start with less ambitious goals: can we hope to capture the essence of what it means to say, that any organism, however primitive, is alive?

It seems unlikely, given the complexity of the problem. But it is not unlikely for the obvious reason that getting a complete description of something as complex as a living creature is difficult. As already alluded to, there have been significant advances in understanding the brain (human or other), tremendous progress in sequencing DNA in order to get at the genetic structure, and so on. The unlikelihood lies in the essential unpredictability of complex systems[2]. Mathematical developments in the study and exploration of nonlinear phenomena and studies in the theory of chaos[3] since the 1960s have contributed to a major paradigmatic shift in the physical sciences. The discovery that completely deterministic systems can show dynamical behaviour as 'unpredictable as a coin toss' has had profound consequences on the way in which any number of physical phenomena have been viewed and analysed.

The issues that have been raised by these advances, namely the successful completion of genome projects, the brilliant breakthroughs in neurobiology research and the revolution of chaos theory, strike at the roots of some of the fundamental questions that have occupied human thought for centuries. There is a *zeitgeist* bringing

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together a number of different strands of thought so that we seem nearer the goal of understanding the questions themselves. In the process, we may be close to some of the answers. These will not be complete, but the offer of any answer, however partial and however incomplete, on what it means to be human is one that must be accepted and explored, as must the concomitant necessity to re-evaluate the reductionist programme in the natural sciences.

Genome projects: Finding all the genes

The announcement of the (essential) completion of the sequencing of the human genome is both a scientific event of great significance and an event of great importance. That a group of scientists and entrepreneurs could, within the span of a few years, completely unravel the structure of the DNA of any individual is a *tour de force*, among the highest scientific achievements of man.

What exactly has been done? It requires some background in order to fully appreciate the significance of the Human Genome Project, or any other genome project.

One of the major advances in biology in the last century has been in deciphering the importance of the DNA molecule and the laws of inheritance. It has been a long journey from Mendel onwards, a journey that painstakingly crossed a number of milestones, starting from the idea of the ‘gene’, through the discoveries of chromosomes, the DNA molecule, its structure and the genetic code[4].

We are still learning the details, but the major facts are largely known. In essence, they are that each organism, be it a mammal or a bacterium, has within each of its cells, a DNA molecule which carries all the information required for its functioning. The information lies encoded in the structure of the DNA molecule, which is a double-stranded polymeric entity composed of four different kinds of molecular subunits, adenine, thymine, guanine and cytosine, denoted A, T, G and C. The size of the DNA molecule and the order in which these subunits are placed determine the function, the biochemistry and therefore the biology of the organism. How big is the DNA molecule? It is more useful to characterize the size of the DNA in terms of the number of subunits comprising it and since the molecule is a double helix, as was discovered by Watson and Crick, it is actually enough to know the sequence of one half of it: one strand of the double helix of DNA determines the other half, the other strand, by complementarity (A hydrogen bonds with T, C with G). On the molecule itself, the information is carried on certain portions of the DNA whose function it is to carry out any number of tasks such as the synthesis of proteins, the initiation of reactions and other tasks involving regulation within the cell or for groups of cells.

Each organism is unique. It is unique in its DNA. However, we have all – all life on this planet, that is – evolved from a single event that took place around 3.5 or so billion years ago. That event of creation laid the foundations for all life forms on earth, which therefore share a common genetic code and a common evolutionary history. In this history, the DNA molecule has played a central role, as the replication of the DNA molecule allows for both deliberate and accidental errors, and mutations which are internal catalysts for evolution. Another important catalyst for evolution comes from the physical environment, which, as we observe, continuously changes, putting forward a continuously changing set of challenges to any organism which may evolve in order to adapt and must adapt in order to survive.

The DNA of a human – the human genome – contains 6 billion or so bases, namely it consists of a long series of the letters A, T, G and C placed in a particular order. Does this make man? At one level it does, because the 3 billion letters on one strand of the DNA contain all the information needed to make the individual.

What has been done so far is to get a very detailed map of this molecule, so that almost all the regions containing the genes are known in great detail. Spectacular advances in chemistry and molecular biology have made this almost a matter of routine. Since one now knows the complete list of the 3 billion letters one after the other, the next task is to find all the genes. For a number of other organisms, especially yeast and several bacteria, this task has been accomplished in totality. For the human genome this task is somewhat more complicated, but it has, in essence, been done.

What of it, then? The prospect that every single gene on our DNA or on that of any other organism’s DNA can be known is one that has fueled the hope that eventually we will be able to understand an organism from the most fundamental level upwards. This is the sense in which I wish, in this essay, to explore what it means to be human, or more generally, what it means for any organism to be alive.

Are we more than the sum of our genes?

Finding the genes on the DNA is one part of the task of decoding the DNA[5]. Finding out what exactly the genes do is much more involved. As we realize now, a given trait is not always the result of a single gene and groups of genes need to act in concert to produce so called ‘genetic’ effects. Indeed, rarely is a single gene responsible for any characteristic in any organism, which, by its very nature, is an entity of enormous complexity. (In a sense, we were fortunate that Mendel chose to study those traits in peas wherein there is a nearly one-to-one correlation to genes.)

Today it is believed that not more than 40,000 genes are all that are involved in determining the function of an organism as large and as complex as man. For a bacterium it can be much fewer: some have just around 1000 genes in all. While it is generally true that the more ‘advanced’ the organism, the more the number of genes that are required for it to function, the reverse is not necessarily true, so the relationship between the complexity of an organism, length of genome and number of genes is a complicated one.

One of the big targets of the genome projects is to try to identify the gene or the set of genes that is responsible for a given medical condition, say diabetes or asthma or cancer. Already the genes that cause certain kinds of cancers or other diseases such as Huntington’s disease or the predisposition to Alzheimer’s, etc. have been ‘identified’. The hope that by discovering the genetic cause of a disease one can find a cure for it provides a very strong impetus for such studies.

But is there more that one can expect from genome projects? Are there genes for other aspects of our behaviour? Can we hope to understand not just the genes that may cause specific diseases or conditions, but also genes that may determine different behaviours in organisms as complex as us?

What indeed do we mean when we say that one organism is more complex than another? Or that one thing is more complex than another? Complexity, most simply defined, is measured by how much it takes to fully describe an object: the more complex something is, the more you can say about it[6]. Even with this admittedly limited notion of complexity, it is clear that humans are more complex than any other organism on the planet. The distinction usually takes the form of enumerating what it is that humans do which sets us apart from other living things – some of these are language, emotion, philosophy, a sense of religion and culture. There is evidence that we are not the only beings with some of these attributes, but we are likely to be the only ones with all of them developed as highly.

One other feature of complex systems is the phenomenon of emergence: the whole has properties that the parts need not have[2]. Emergence is a collective phenomenon. Consciousness is an example: it is a property of the human brain, but an individual cell that goes into making up the brain is not, in any sense, conscious. Simpler examples can be found. A molecule of water is not a liquid, but a collection[7] of molecules of water has this property. Thus emergence is at once both simple and profound, and most significantly, it is an important attribute of complex systems.

The question thus becomes: Are all these attributes that we take to define the human condition dependent, in any direct and determinable way, on the genes we possess? And therefore then, are these a consequence of the DNA in our cells? In a trivial way, the answer is, of course, yes. The DNA must determine everything since it contains the blueprint for all that goes into making us. But the question is directed more specifically: How is this thought, this memory, this action, governed by this set of genes? Or is it? We are a very long way away from a comprehensive answer to any of these questions. These are among the most profound that can be posed (Who are we? How did we come here? Where are we going?), but in some limited spheres, some crucial experiments are being carried out to determine the physical basis – if determinable – of particular emotions.

The astonishing hypothesis

The most explicit statement in support of this level of reductionism is that by Francis Crick who, in 1990, advanced what he calls ‘the astonishing hypothesis’[8]. Crick is concerned with that most ephemeral of human qualities, the soul. The main thesis, Crick states, is that ‘You, your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more that the behaviour of a vast assembly of nerve cells and their associated molecules’.

The idea of the soul, that there is more to us than just a complex interaction between molecules, is central to the mind–body problem. How does one understand the emergence of consciousness above and beyond the billions of cells that make up a human brain? Must there not be more to a being human than biochemistry?

Apparently, from some points of view, at least, not. Crick’s astonishing hypothesis is remarkable not just because this is a daring idea. It forces one to examine, to the extent that current knowledge allows; just how much of brain function is presently understood and how much, it can be inferred by extrapolation, can be understood. Many of the experiments described by Crick relate to visual perception and while they are not near explaining awareness, they give some indication of the level of effort that will be needed to understand the visual system completely. The inescapable conclusion, however, is that this will, eventually, be within the realm of the possible.

What is the immediate consequence of this chain of reasoning? If a ‘complete’ understanding of visual awareness is possible, then, presumably, so is essentially every other sensory awareness. By slow degrees, therefore, by more and more experimentation, it should be possible to get to the molecular basis of each emotion. To what extent is this an accurate estimation of what is possible?

The role of selection

It is necessary to appreciate that evolution may have played a role in the process. Is the nature of human thought a consequence of the way in which our brains have developed? This is a question that has occupied many seminal thinkers and in particular some physical scientists who have attempted to analyse the nature of scientific thought.

For instance, in 1921, Einstein, while discussing the significance of mathematics in the development of scientific thought, remarked[9] '. . . an enigma presents itself which in all ages has agitated inquiring minds. How can it be that mathematics, being after all a product of human thought that is independent of experience, is so admirably appropriate to the objects of reality? Is human reason, then, without experience, merely by taking thought, able to fathom the properties of real things'?

Fifteen years later, he went on to say[10], 'The very fact that the totality of our sense experiences is such that by means of thinking . . . it can be put in order, this fact is one which leaves us in awe, but which we shall never understand. One may say "the eternal mystery of the world is its comprehensibility" (Kant)'.

Has evolution shaped us for reasoning? Would there have been some form of Darwinian selection that gave an advantage to those with the ability, or at any rate, the trait that would lead eventually to the ability, to make a model of reality in the brain? This evolutionary advantage, amplified over time, has led to the human brain that has great skill in describing the world. At the same time, then, the brain has also retained all those features that helped it along the path and gave selective advantage and among these could be those attributes of the human mind that we find so difficult to describe and define – creativity, imagination, emotion, philosophy and religiosity, for instance. Therefore, argues Hamming[11] in an insightful article on the effectiveness of mathematical thought, 'We can cope with thinking about the world (only) when it is of comparable size to ourselves and our raw unaided senses . . . . Evolution, so far, may possibly have blocked us from being able to think in some directions; there could be unthinkable thoughts'.

What about other, thinkable, thoughts? If evolution has ensured the development of the human brain with its billions of interconnected neurons to be capable of mathematical thought, are there other aspects of consciousness that are similarly the product of evolution? Indeed, perhaps the sense of soul has also conferred evolutionary advantage, bringing us to this stage of humanness. To a limited extent some recent experiments give indication that this may be so.

Religion, memory and brain function

Regardless of whether (or how) consciousness is an emergent property, one aspect of human behaviour merits some discussion, namely, the pervasive practice of religion[12]. It is a fact that religious experience and religious feeling is central to what one may term the human condition. There is no culture, however primitive, which does not have some manifestation of it, and in less primitive cultures, traditional religions have been replaced by other communal activities. In a sentence, religion may be necessary for human evolution.

This point of view has been bolstered by experiments[13] carried out by Ramachandran and his research team, on what they term a God module in the human brain. This could underpin an evolutionary instinct to believe in religion. 'There may be dedicated neural machinery in the temporal lobes concerned with religion, which may have evolved to impose order and stability on society.'

It is well known that any thought process or emotion is correlated with specific neuronal activity. The temporal lobe connection to artistic creativity has been known for some time; patients with temporal lobe epilepsy often manifest a characteristic obsession with philosophical issues and become excessively religious[14]. Similarly, recent experiments on memory, for instance, where magnetic resonance imaging of the brain is used in real time, go even further. They correlate specific mental activities with specific regions in the brain. Thus every thought, it is suggested, can ultimately be traced back to a specific sequence of activity of a specific set of neurons. There are, admittedly, billions of these which are interconnected in a complex co-dependent web, but nevertheless, the problem of thought is reducible, in some sense, to the behaviour of a complex network, each unit of which one can understand in as much detail as one wishes[15].

On the matter of memory, significant progress has been made in understanding the mechanisms of memory at the neuron level. It is now believed that memory is encoded in the brain as a spatio-temporal pattern of activity in the neural network and stored by modifying the connections between the neurons themselves. Recall involves retracing the pathways through the network, involving specific molecules, activation of different molecular networks, and even perhaps, most unexpectedly, it may involve the DNA. Neural networks may be modified by the rapid activation of many genes.

Will a similar deterministic description of consciousness also become possible?

The nonlinearity of almost everything: Deterministic chaos

A major paradigmatic shift, the so-called third revolution in physics, in the latter part of the last century, has been the discovery of deterministic chaos[3]. This is the realization that very simple (but nonlinear) systems have the potential to display dynamical behaviour as complicated as one can imagine. It is not possible to give a full description of chaos theory here, but the implications of the theory are profound enough to warrant being described. These have become summarized as the 'butterfly effect', namely the possibility of systems being so unpredictable that the quality of a prediction is sensitive to effects as unimaginably small as that of a butterfly flapping its wings thousands of miles away. Nonlinearity makes it possible for small effects to get magnified exponentially rapidly, so that the very small translates into the very large very quickly.

The generality of the arguments, which are ultimately mathematical in nature, makes chaos theory applicable to a wide variety of disciplines. What are its implications? When applied, for instance, to systems such as the weather, chaos theory says that accurate prediction is not possible beyond a certain time frame. When applied in other contexts, it often gives a rationale for the intrinsic unpredictability of certain phenomena and gives an escape from the certainty of Laplacian determinism by which it is claimed that the past and future of the universe can be predicted by an ideal observer who knows the positions and velocities of all the particles and the laws governing their motions. Chaos theory says that for nonlinear systems this is in general impossible because the smallest error in specifying the positions and velocities would, in the presence of chaos, magnify so rapidly as to make all predictions meaningless. The only requirement is that there be chaotic dynamics in the nonlinear system; our present understanding is that indeed, chaotic dynamics is abundant, in the sense that most nonlinear systems will have the potential to show chaos. Indeed, the more complicated the system, the more likely this becomes and in systems as complex as those we are considering here, like the brain or a cell, for instance, it is a certainty that the system will, in all senses of the word, be chaotic.

Having chaos does not preclude all forms of prediction, however. The property of complex systems to have attractors, namely a set of states to which the system eventually settles, allows for some level of prediction. The motion on attractors can be chaotic, in which case these are termed strange attractors: the chaos makes precise prediction impossible, but the existence of attractors makes it possible to give some idea of what behaviour will obtain.

Studies of models of many cellular processes, their chemistry and biochemistry show the presence of chaotic dynamics and attractors. There is also evidence that brain activity, as evidenced by EEG signals, may show deterministic chaos. Experimentation in this area is still in its infancy, but the methods of chaos theory have found some application in these studies and they suggest that there may be complex attractors that describe the dynamics of electrical signals in the brain. This observation is consistent with current models of neuronal activity. Any mathematical model of neural networks has a dynamics that is chaotic, showing extreme sensitivity to perturbations.

Synthesis

If a completely deterministic description of any living organism was possible, one somewhat disturbing consequence would be the necessity to re-evaluate some of our beliefs about what it means to be alive or what makes us human. A concept which is central to this is that of free-will[16], that our consciousness allows us to determine our actions rather than that our actions are merely the outcome of the inexorable laws of motion of the several billions of atoms and molecules that constitute our being. Where, for instance, is there any scope for choice, creativity or argument?

Full determinism appears to go hand in hand with complete predictability, at least in principle. But experience, be it with humans or with other species, shows that one of the main features of a ‘living’ organism is that there are aspects to its behaviour that are only approximately predictable.

I believe that a reductionist approach to biology is ultimately untenable for a variety of reasons, but the principal one is this. If every gene were to be known (and in principle they all will be), if every biochemical network in every cell were to be known (and, again, they can eventually all be determined), if every neuron in the brain could be described in as much detail as possible with all its connections, as deterministic as the resulting system is, it will be chaotic[3]. The unpredictability of the detailed behaviour of a system as complex as a living organism is itself an emergent property.

This is in contrast to our knowledge, say, about the structure of atoms and molecules, which are described by the laws of quantum mechanics. The quantum theory, which is intrinsically non-deterministic, has built into its structure the uncertainty principle. Yet this theory is capable of precise predictions, which can agree with the results of experiments to an astonishing level of accuracy. Shortly after the solution of the Schrödinger equation for the simplest atom, namely hydrogen, Dirac remarked, in 1929, that ‘The fundamental laws necessary for the mathematical treatment of large parts of physics and the whole of chemistry are thus fully known, and the difficulty lies only in the fact that application of these laws leads to equations that are too complex to be solved’. He was correct in a gross sense, because once the right equation is known, all that remains is to solve it, however difficult and intractable that might be. But as he also mentioned, this was not going to be easy. Even today, with the computational power that is currently available, accurate calculations for all but the smallest molecules are intractable. In a deeper sense, he was wrong because several features of the real world cannot be embodied within something as microscopic as the Schrödinger equation, collective behaviour and emergent properties being among them. Yet, the complexity that he refers to is nothing like the complexity of systems such as those we are discussing here. Complex atoms or molecules are difficult to describe exactly because of the sheer computational difficulty, although the underlying equations are linear. Owing to the intrinsic nonlinearity, the level of complexity of a living organism is entirely in a different class.

What then of the soul or what it means to be human? While it may be true that all human genes will be discovered very shortly and that we will gradually acquire more and more knowledge about the circuitry of the brain in all its detail, the sheer complexity of this 'system' which has inbuilt dynamical chaos necessarily precludes complete description. This is not only true for us, but also, in a fundamental way, even for the lowest organisms. In this sense, unpredictability is both the consequence, as well as the defining quality of what it means to be alive.

1. Blakemore, C., *Mechanics of the Mind*, Cambridge University Press, Cambridge, 1977.
2. Waldrop, M. M., *Complexity*, Simon and Schuster, New York, 1992.
3. Gleick, J., *Chaos: Making a New Science*, Viking, New York, 1987.
4. See, for example, Watson, J. *et al.*, *Molecular Biology of the Gene*, *Complete Volume 4/e*, Benjamin-Cummings, New York, 1987.
5. For a pedagogical review, see Tiwari, S., Bhattacharya, S., Bhattacharya, A. and Ramaswamy, R., *Curr. Sci.*, 1996, **71**, 12–24.
6. Informal description attributed to Parisi, G., in a talk by Virasoro, M., 1996.
7. The question of how many molecules of water can have the property of being 'liquid' is a tricky one. One or two is too few, but a few tens or hundreds may be enough. Here I mean more like an Avogadro number, of the order of 10^{23} or so, as in a glass of water.
8. Crick, F., *The Astonishing Hypothesis*, Simon and Schuster, London, 1994.
9. In an address to the Prussian Academy of Science in Berlin on 27 January 1921.
10. Einstein, A., *Physics and Reality*, reprinted in Einstein, A., *Out of My Later Years*, Citadel, Secaucus, NJ, 1956, p. 61.
11. Hamming, R. W., *Am. Math. Mon*., 1980, 87.
12. There are many common points between science and religion. Central to the quest that either discipline entails is a search for what is perceived as the ultimate 'truth'. However, as Eddington stated nearly 70 years ago, 'We have no creed in science, but we are not lukewarm in our beliefs. The belief is not that all the knowledge of the universe that we hold so enthusiastically will survive the letter; but a sureness that we are on the road. If our so-called facts are changing shadows, they are shadows cast by the light of constant truth.'
13. The actual experiments that were carried out were as follows: Ramachandran and his colleagues studied highly religious volunteers and those whose religious beliefs were not known. The subjects were shown a list of 40 words, which included sexual, violent, religious and 'neutral' terms. Responses were measured to track the amount of communication between parts of the brain. The non-religious group showed sweaty palm activity (a gauge for arousal and an indirect way of measuring certain neural activities) when presented with sexual terms. Patients with Temporal Lobe Epilepsy (TLE), though, were disproportionately aroused by the religious words, leading the Ramachandran team to conclude that human beings may have evolved specialized circuitry in the brain for the purpose of mediating religious experiences, and that the TLEs are at the extreme end of the spectrum. The experiments further point to a specific location in the brain – the temporal lobe – where this activity takes place. Some details are to be found in Ramachandran, V. S. and Blakeslee, Sandra *Phantoms in the Brain: Probing the Mysteries of the Human Mind*, Quill, New York, 1998.
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