Genes Without Prominence

Keith Baverstock

Keith Baverstock is a physical chemist currently working on the public health follow-up to the Fukushima accident.

The cell is a complex dynamic system in which macromolecules such as DNA and the various proteins interact within a free energy flux provided by nutrients. Its phenotypes can be represented by quasi-stable attractors embedded in a multi-dimensional state space whose dimensions are defined by the activities of the cell's constituent proteins.[1]

This is the basis for the dynamical model of the cell.

The current molecular genetic or machine model of the cell, on the other hand, is predicated on the work of Gregor Mendel and Charles Darwin. Mendel framed the laws of inheritance on the basis of his experimental work on pea plants. The first law states that inheritance is a discrete and not a blending process: crossing purple and white flowered varieties produces some offspring with white and some with purple flowers, but generally not intermediately colored offspring.[2] Mendel concluded that whatever was inherited had a material or particulate nature; it could be segregated.[3]

According to the machine cell model, those particles are genes or sequences of nucleobases in the genomic DNA. They constitute Mendel's units of inheritance. Gene sequences are transcribed, via messenger RNA, to proteins, which are folded linear strings of amino acids called peptides. The interactions between proteins are responsible for phenotypic traits. This assumption relies on two general principles affirmed by Francis Crick in 1958, namely the sequence hypothesis and the central dogma.[4] The sequence hypothesis asserts that the sequence of bases in the genomic DNA determines the sequence of amino acids in the peptide *and* the three-dimensional structure of the folded peptide. The central dogma states that the sequence hypothesis represents a flow of information from DNA to the proteins and rules out a flow in reverse.

In 1961, the American biologist Christian Anfinsen demonstrated that when the enzyme ribonuclease was denatured, it lost its activity, but regained it on re-naturing. Anfinsen concluded from the kinetics of re-naturation that the amino acid sequence of the peptide determined how the peptide folded.[5] He did not cite Crick's 1958 paper or the sequence hypothesis, although he had

apparently read the first and confirmed the second.

The central dogma and the sequence hypothesis proved to be wonderful heuristic tools with which to conduct bench work in molecular biology.

The machine model recognizes cells to be highly regulated entities; genes are responsible for that regulation through gene regulatory networks (GRNs).[6] Gene sequences provide *all* the information needed to build and regulate the cell.

Both a naturalist and an experimentalist, Darwin observed that breeding populations exhibit natural variations. Limited resources mean a struggle for existence. Individuals become better and better adapted to their environments. This process is responsible for both small adaptive improvements and dramatic changes. Darwin insisted evolution was, in both cases, gradual, and predicted that intermediate forms between species should be found both in the fossil record and in existing populations. Today, these ideas are part of the modern evolutionary synthesis, a term coined by Julian Huxley in 1942.[7] Like the central dogma, it has been subject to controversy, despite its early designation as the set of principles under which *all* of biology is conducted.[8]

The modern synthesis, we now understand, does not explain trans-generational epigenetic inheritance, consciousness, and niche construction.9 It is possible that the concept of the gene and the claim that evolution depends on genetic diversity may both need to be modified or replaced.

This essay is a step towards describing biology as a science founded on the laws of physics. It is a step in the right direction.

Paradigmatic Instability

The human genome was sequenced in 2001. Francis Collins, leader of the International Human Genome Sequencing Consortium and current Director of the US National Institutes of Health, claimed in 1999 that knowing the sequence would lead

> to previously unimaginable insights, and from there to the common good [including] a new understanding of genetic contributions to human disease and the development of rational strategies for minimizing or preventing disease phenotypes altogether.[10]

These benefits have not materialized. Only for rare conditions has DNA sequence been related to disease. Where common diseases are concerned, the failure to account for the genetic variation of complex traits in terms of abnormal alleles is widely acknowledged.[11] This is the problem of missing heritability.

Then there is the phenomenon of genomic instability induced by ionizing radiation. The default assumption of radiobiology is that if a cell with damage to its DNA survives cell division, damage will be stably replicated in all subsequent generations. A 1992 experiment showed that, in some cases, cells that survive radiation exposure become unstable and acquire damage spontaneously in subsequent generations.[12]

Genomic instability was first observed in 1976 by the Swedish geneticist K. G. Lüning.[13] He exposed male mice (F0) to 239Pu and scored their offspring (F1) for intra-uterine death, caused by a dominant lethal mutation. Surviving male offspring, however, also produced intra-uterine death in their offspring (F2). A dominant lethal mutation had skipped a generation.

More recently, irradiated round worms (*Caenorhabditis elegans*) were shown after several generations to exhibit significant differences in gene expression when compared to non-irradiated controls.[14] The gene expression in the irradiated population was more heterogeneous, indicative of stochastic diversification of phenotype, the same result seen in genomically-unstable human cells.[15]

Genomic instability has been observed for several phenotypic endpoints and is inducible by several environmental agents in addition to radiation.[16] It is a real biological phenomenon, not an experimental artifact.

Darwin recognized that neither the fossil record nor the evidence from extant organisms supported a gradual view of evolution.[17] Many distinguished biologists, including Thomas Huxley, William Bateson, Hugo de Vries, Richard Goldschmidt, and Stephen Jay Gould, have questioned gradualism. More recently, Denis Noble has questioned the modern synthesis of evolution.[18] There is important experimental evidence that is inconsistent with the principles underpinning the machine model of the cell.[19]

A new approach is required.

Thermodynamics

Twenty years before Darwin published *On the Origin of Species*, Edward Blyth made an important point:

> [A]mong animals which procure their food by means of their agility, strength, or delicacy of sense, the one best organized must always obtain the greatest quantity; and must, therefore, become physically the strongest, and be thus enabled, by routing its opponents, to transmit its superior qualities to a greater number of offspring.[20]

Food is free energy that metabolic processes convert to work and entropy. Free energy utilization is governed by the second law of thermodynamics. By 1900, when biologists were first aware of the implications of the work of both Darwin and Mendel, Ludwig Boltzmann had already formulated the molecular interpretation of entropy.[21] Since then, it has been commonplace to understand the second law of thermodynamics as suggesting that increasing entropy *inevitably* implies increasing disorder.

Evolution demonstrates the reverse. Organisms evolve to become more ordered and complex, rather than less. Erwin Schrödinger thus suggested that life feeds on negative entropy by exporting entropy to its environment.[22] In extending this idea, Roger Penrose argued that high-energy solar photons are a form of low-entropy energy. Life degrades them into low-energy, high-entropy photons that are radiated back to space at night.[23] But empirical evidence shows that the more mature an ecosystem, the lower its black body temperature.[24]

The physicist Arto Annila, focusing on energy carriers, rather than energy itself, has considered systems open to energy exchanges with their surroundings and with chemically-interacting components.[25] In energy-rich surroundings, as free energy is consumed and entropy increases, the system evolves towards diversity via its chemical reactions, occupying higher and higher energy levels. Increasingly complex chemical compounds are formed as the kinetics of the chemical reactions move the system to more probable states.[26]

Increasing entropy does not inevitably lead to increasing disorder. In 1900, Henri Bénard demonstrated what is now called Rayleigh–Bénard convection, a clear empirical demonstration of increased entropy appearing as order in the form of structured Bénard cells.[27] Increased entropy and disorder need not be synonymous. Evolution and the second law are compatible.

Nature has long been known to follow Pierre Louis Maupertuis's principle of least action.[28] In the context of energy consumption, this means that disequilibria in free energy will be leveled as efficiently as local conditions allow.[29] In evolutionary terms, any improvement to an organism's metabolic efficiency will be advantageous, and if transmitted to the next generation will lead to the evolution of increasingly more efficient organisms.[30]

Efficiency of energy transduction then is the basis for natural selection, not genetic diversity.

What would be the cellular phenotype of a complex system? The question requires an answer in terms of dynamical system theory, a discipline deployed to describe the long-term behavior of such systems in mathematical terms.[31] In dynamical system theory, an attractor is a stationary state of a system toward which those states that are within a basin of attraction converge. Although this makes an attractor stable under small perturbations, larger perturbations can push the system to a variant attractor. There is no continuum of stable states between attractors. Transitions are true saltations: jumps or switches.

Gradualism is not an option.

In the case of a cell, the system is defined by the interactions among proteins, which can be represented by a state space in varying dimensions. A typical human cell is able to express a few thousand active proteins. Its state space would thus have a few thousand dimensions, each corresponding to the activity of one protein. Active proteins are governed by rules of engagement that determine their involvement in the attractor.

The attractor is formally defined by relations in predicate (or first order) logic in terms of the activities of the participating gene products, the proteins p_k.[32] Whether or not a given protein is engaged in the attractor depends on rules specifying its maximum and minimum activities. These encompass the range, r, of activities, m, required at any given time t. For two proteins p_1 and p_2 if the activity of p_1 lies within its specified range at time t_1, then the activity of p_2 will lie within *its* specified range at t_2, on the condition that $t_2 > t_1$. If the condition set by a given rule cannot be met, the attractor collapses and a variant attractor may be adopted.

Notice that:

- The gene products, or proteins, are governed by the attractor.

- The attractor evolves irreversibly in time; the system ages.
- The attractor is a non-holonomic entity; its present state is contingent on its history.[33]

For any gene product there are typically several rules of engagement. A gene product can be engaged with several other gene products. A perturbation of any one gene product thus has the potential to perturb all those with which it is engaged. If perturbations lead to the adoption of a variant attractor, the transition can induce a substantial phenotypic jump, several traits gained or lost simultaneously.

This has important implications for evolution.

The Unit of Inheritance

Attractors can be regarded as ordered, non-holonomic profiles of active proteins evolving according to the rules of engagement. Out of these profiles emerge the regulation and phenotype of the cell. If, on cell division, this profile is shared between the two resultant cells, they will both inherit the attractor. Mendel's unit of inheritance is a process in protein chemistry that takes place in the cytoplasm and not the nucleus of the cell. Attractor states are discrete and can be segregated. They conform to Mendel's analysis of inheritance.

Some years ago, the mathematical biologist Robert Rosen concluded that living systems are complex systems that are closed to efficient causes.[34] They are systems capable of self-regulation. Machines, on the other hand, are systems open to efficient causes. Such systems can be reduced to their component parts and reassembled. Complex systems that yield emergent properties cannot.[35] Only the dynamic cell model satisfies Rosen's conditions for living systems.

The gene is not what regulates the cell, it is not responsible for the organism's phenotype, and it is not Mendel's unit of inheritance.

What role, then, does it play?[36]

DNA is essential to the functioning of the cell. A great many resources are devoted to maintaining its integrity. DNA serves as an inert database to enable the cell to provide its progeny with necessary peptides. These are the starting materials that when folded and activated become the cell's work horses.[37]

Although the peptides are intermediates between messenger RNA (mRNA)

and the protein, Crick paid them scant attention.[38] Anfinsen confirmed Crick's sequence hypothesis, but the folding process in his experiments was far too slow to be the mechanism operating in the cell.[39] What Anfinsen *did* show is that the proteins acquire information when the peptide folds. The folding process consumes free energy. The information measures the entropy of the process and it is not necessarily related to the information in the DNA.

Genes play practically no role in the properties of the cellular phenotype.

John Ellis has long urged protein chemists to conduct their experiments under conditions closer to those prevailing in the cell.[40] This is, of course, what the great Hans Krebs argued as early as 1962.[41] Anfinsen's experiments could not have been representative of what was taking place in the cell. Little progress in elucidating the structure of proteins in the cellular environment has been made.[42]

Genomic Instability

In 1984, Barbara McClintock noted

> There are "shocks" that the genome must face repeatedly, and for which it is prepared to respond with a programmed manner. Examples are the "heat shock" responses in eukaryotic organisms and the "SOS" responses in bacteria. ... But there are also responses of genomes to unanticipated challenges that are not so precisely programmed. The genome is unprepared for these shocks. Nevertheless they are sensed, and the genome responds in a discernable but initially unforeseen manner.[43]

James Shapiro, a student of McClintock, has also argued the case for the cell being able to modify its genome, at all scales, from point mutations to major chromosomal rearrangements and whole genome duplications.[44] Suppose that as a result of cellular stress a specific protein cannot function within its required range. The attractor collapses and the system makes an arbitrary transition to a variant attractor. Because of the high dimensionality of the system, this phenotypic transition is irreversible. Once displaced from its initial attractor, the new phenotype is more prone to attractor collapse and, thus, further phenotypic transitions.[45]

Genomic instability is irreversible. In germ cells, it can be transmitted to future generations; in somatic cells, it is capable of inducing the same effects as mutations. The cell regulates itself, often by acting on its own DNA. This reg-

ulation represents a violation of the central dogma.[46] Circular causality is an essential feature of a living organism and is one of the features that distinguish what is alive from what is not.[47]

The cellular phenotype is an emergent property of the cell. Emergence has proved a controversial concept, but simple chemical reactions provide examples. A mixture of nitrogen and hydrogen molecules at room temperature is clearly different from the product of the energy-induced reaction that forms ammonia.[48]

In the same way, the consequences of introducing or modifying genes may not be predictable or reversible given the highly interactive nature of the proteins engaged in the attractor and the non-holonomic nature of the cell phenotype.

The Key to Life

Proteins and protein chemistry are, therefore, central to the functioning of organisms. Proteins are a multifunctional class of compounds of nearly unlimited variety; their properties can be modulated by the environment. Their chemistry takes place largely in the cytoplasm. In the machine cell model, chemical regulation is provided through a gene regulatory network.[49]

There are several empirical problems with this paradigm.[50] The cytoplasm of eukaryotic cells houses numerous partially-folded proteins that are fully functional when induced to fold.[51] In 1890, the German chemist Emil Fischer introduced the lock-and-key concept to explain the specificity of enzymes. This was adapted to the machine model of the cell, an enzyme uniquely recognizing a DNA binding site and triggering the transcription of a specific gene sequence.

Very little is known about the structure of proteins in the crowded environment of the cytoplasm.[52] Two processes must be involved: self-organization and computation.

Self-organization occurs when the entropy generated by free energy dissipation appears as order rather than disorder. How a system behaves in this respect depends on context. Consider the flocking of birds. Here, a large numbers of birds behave in an orchestrated way. Flocking can be described from the outside by the specific rules of engagement followed by each individual. It is doubtful that any of the birds are calculating their position by an appeal to external rules of engagement. In all probability, adopting a specific position relative to other birds is the most energy-efficient way to fly. The birds are slip

streaming.

Either these rules, or the non-linear dynamics of the system, create order out of potential disorder.[53] Similarly, one can interpret the protein interaction maps that have been constructed from cell lysates as systems in which proteins behave according to a set of rules.[54]

Some proteins catalyze reactions, but many, as Dennis Bray has observed, govern the transfer and processing of information.

> Because of their high degree of interconnection, systems of interacting proteins act as neural networks trained by evolution to respond appropriately to patterns of extracellular stimuli.[55]

Even primitive microbes exhibit purposeful behavior, such as quorum sensing, chemotaxis, and phototaxis.[56] Consider the slime mould *Physarum polycephalum* grown under warm, humid conditions. The tips show a marked reduction in growth when the temperature is lowered and the humidity reduced. Having reduced their growth under these conditions, the plasmodia continued to reduce their growth in their absence.[57] Other experiments with the mould strongly suggest the ability to trade off risk for benefit.[58] Even more remarkable are the army ants, *Eciton*, which can form living bridges over obstacles that hinder foraging ants. These bridges reduce the number of army ants available for foraging, but under experimental conditions, army ants have been observed to move their bridges in order to optimize foraging.[59]

František Baluška cites other examples of neurobiological phenomena across the microbial world and in plants that can only be attributed to information processing.[60] He makes the case that consciousness and cognition are undeniable and essential features of life. And, whatever else they may be, attractors are also computational units of the cell.[61]

Dynamical versus Machine Models

Is there an empirical test to discriminate unequivocally between the dynamic and machine cell models? The answer is probably not. However, so far it has not proved possible to explain genomic instability in terms of molecular genetics; inheritance of genomic instability is non-Mendelian.[62] This is a strong argument against the machine cell model.

Malignant tissue exhibits both genomic instability and mutations.[63] The same

is true of cells in atherosclerotic tissue.[64] Disease endpoints provide few clues about their origins. On the other hand, a number of hereditary conditions associated with radiation exposure can definitely be attributed to mutations.[65] Radiation would appear capable of damaging cells by inducing both genomic instability and mutations.

In 1974, Richard Lewontin pointed to a paradox that has been inherent in experimental genetics since Mendel's time: in terms of traits, what is interesting is not measurable, and what is measurable is not interesting.[66] Genetics is based on measurements of well-defined traits, like flower color, but geneticists have tended to ignore more complex traits, such as those emerging from several interacting proteins.

Is the success of molecular genetics based on an unwarranted generalization of a series of special cases?

Genomic instability is induced by radiation much more effectively than mutations, and at much lower doses.[67] An enzyme is not an ordinary chemical, Rosen correctly observed.[68] Much of the structure of a protein forms a scaffold, which holds a few critical amino acids in a specific formation. Most amino acid substitutions in the scaffold are unlikely to affect the protein's activity. The cell is refractory to mutations.

Suppose that a gene codes for a specific peptide; the peptide then folds to a protein governing a particular trait. A mutation rendering the protein inactive, the mutation and the trait find themselves associated, but not necessarily causally. Consider again Mendel's pea plants. In the purple-flowered variety, a transcription factor switches on the expression of anthrocyanin. A single base substitution that renders the transcription factor inactive produces the white-flowered variety.[69] All that can be said is that that protein no longer has the information necessary to induce the color.

Diseases such as cancer, schizophrenia, and type II diabetes are usually regarded as due either to environmental causes or faulty genes. If they are heritable, the assumption is that they are genetic. Since 2001, with the completion of the sequencing of the human genome, it has been possible to test the latter hypothesis.

It has comprehensively failed.

Even before 2001, identical twin studies showed that common cancers have a minimal genetic component.[70] More recently, the results of a very large study

of schizophrenia patients demonstrated that, at best, less than four per cent of the disease risk is genetic.[71] Kenneth Kendler, reviewing thirty years of research, has concluded that "efforts to ground a categorical biomedical model of schizophrenia in Mendelian genetics have failed."[72]

If the cell is treated as a complex system with a quasi-stable phenotype, it is clear that genomic instability and not genetic change underpins most environmentally induced disease. Treating it as genetic will not help to develop the "rational strategies for minimizing or preventing disease phenotypes altogether" that Francis Collins predicted.[73]

The Origin of Life

There are two theories about the origin of life: replication-first or metabolism-first. The replication-first hypothesis, which invokes an RNA world, is the more widely accepted.[74] RNA has, like DNA, the capacity to store sequence information, but it can also exhibit catalytic activity, thus behaving like a protein.[75] The metabolism-first is often dismissed because proteins are necessary for transcription from DNA and DNA is necessary for the existence of proteins. For this reason, the origin of life is often regarded as a chicken and egg problem.

Through the chemical polymerization of small molecules, just possibly, proto-life evolved in oily droplets suspended in the oceans.[76] I suggest the protein-only proto-life preceded life as we now know it. Due to stress on droplet membranes, droplets could divide but not replicate.

The adult tardigrade, a small animal whose somatic cells do not divide after hatching, so rendering its DNA inactive, has extraordinary resistance to environmental stress, including ionizing radiation, and for practical purposes can be regarded as a protein-only multicellular organism.[77]

Protein-only proto-life is viable.

At a later stage, amino acid sequences might have been read back into RNA and then DNA.[78] A plausible mechanism for reverse translation has been proposed.[79] Reverse transcriptase is able to convert mRNA to DNA. Reverse translation and reverse transcription are legitimate cellular processes.

Building on the work of Mendel and Darwin, Ronald Fisher published *The Genetical Theory of Natural Selection* in 1930.[80] Fisher's first law of natural selec-

tion was that the rate of increase of fitness of any organism is proportional to its genetic variance. This law, operating on Mendel's particulate units of inheritance, is the foundation of the modern evolutionary synthesis. Speciation occurs when breeding populations adapt to environmental change over many generations, or new mutations arise, introducing new variation.

A population of *Escherichia coli*, subject to a glucose nutrient that limited growth, was regularly sampled over 40,000 cell generations to assess relative fitness. Mutation rates were determined by DNA sequencing. Up to 20,000 generations, mutations increased linearly, at the rate of about two per 1,000 generations. Relative fitness, on the other hand, rose dramatically in the first 1,000 generations to some 80% of the fitness recovered at 20,000 generations. Thereafter it increased linearly at a much reduced rate of 1.5% per 1000 generations.[81] Beyond 20,000 generations, the cells became hypermutable.

This experimental result is not explicable in terms of the modern evolutionary synthesis.

Testing to see how a bacterium responds to previously un-encountered environmental conditions, Akiko Kashiwagi et al. equipped an *E. coli* bacterium with a plasmid containing two operons enabling the cell to exploit two nutrient sources.[82] Each operon suppressed the other if deployed. Fluorescent assays indicated which operon was active. When confronted by a major environmental change, the cell, the authors assume, has to find and adopt a new signal transduction route using natural selection. In this case, the bacterium was given the solution that natural selection might have found, but no signal transduction route. On switching the bacteria from one nutrient source to the other, metabolic activity initially dropped dramatically, but after an hour or so increased again, signaling that the alternative nutrient was being metabolized. The authors concluded that the bacterium was able to select between attractors each adapted to the appropriate nutrient conditions much more rapidly than conventional theory would predict.

There is no role for natural selection here.

For at least its first two billion years, life consisted of prokaryotes, with a very limited capability to form multicellular structures. These life forms had qualities of the kind generally attributable to neurological activity. Without them, the organisms would have been helpless in a hostile environment. The same must have been true for the preceding proto-life forms.[83]

Simply encoding peptide sequences in DNA would not have been enough to

bring about such a profound property. Neurological activity is a product of protein chemistry. It is notable that all life forms can be rendered unconscious by the same anesthetics that work on humans.[84]

Life Without Genes

Mauno Rönkkö has developed a virtual ecosystem based on information-bearing particles.[85] Each particle—whether a speck of the soil, grass, rain, a worm or beetle, or a scent emitted by grass—carries information that enables it to interact with other particles in highly specific time-dependent ways. Running the full sequence of particle interactions animates the organisms in the ecosystem. In principle, cells in multicellular organisms could carry such information in their phenotypes. That information specifies associations with other cells, and from it emerges the organism's form.[86] Diversity in biological form can, therefore, be seen as a result of variation in cellular phenotype, derived from protein chemistry.

The evolution of function, according to the modern evolutionary synthesis, has been controversial. Richard Dawkins has argued that no matter how improbable a trait, there are gradual changes leading up to it.[87] In the dynamical model, gradualism is not a constraint. Genomic instability is a process in which the cell can experiment with diverse traits already inherent in its peptides, and which can be modified by spontaneous mutation as well as by the cellular phenotype.

Natural selection is based on the ability of an organism to extract free energy from its environment. An acquired ability to detect light or sound will preferentially be passed to future generations if these properties increase how efficiently energy is extracted. Thus, a genomically-unstable organism can improve an imperfect function by seeking variant protein chemistry within its own state space. The Kashiwagi experiment and the long term culture of *E. coli* provide evidence that this is so.

Since the publication of *On the Origin of Species*, many distinguished biologists have proposed mechanisms for non-gradual evolution. Gould and Niles Eldredge have proposed that evolution is characterized by long periods of equilibrium punctuated by relatively short periods of rapid phenotypic change.[88] Gould was influenced by the discovery of a diverse range of fossil forms in the Burgess Shale in Canada, formed some 505 million years ago in the Cambrian period.[89] Some of the basic forms that exist today, such as bilateralia, are present in those fossils; what is more, the Burgess Shale preserved the fossils of

soft-bodied organisms as well.

Punctuations in the fossil record might represent periods of genomic instability initiated by stress on an organism poorly adapted to a changing environment. The organism might have lost a nutrient source, the environment may have changed for the worse, or a new predator may have appeared. Genomic instability in the punctuation phase of an organism's evolution could thus be the basis of speciation.

Development has traditionally been explained as the expression of specific genes that have acquired positional information. The origin of this information is not completely clear, but may be related to gradients of certain chemical morphogens. Morphogen concentrations in the cell switch the differentiation processes on or off, and ultimately give rise to the many different cell types.

In the dynamical cell model, development is regulated by cellular phenotypes. Alan Turing outlined the mathematical basis for development through self-organization in terms of a reaction–diffusion model.[90] In Turing's model, cells release ligands, or morphogens, that bind to receptors on other cells, in order to enhance or repress their own release.[91] Testing this model has proved difficult. Little is known of the morphogens involved. But it has been verified in an artificial cell system comprised of emulsion droplets that represent cells.[92]

Consider now the ecosystem. All organisms evolve in the context of an ecosystem and each influences the other. Evolution is not a passive process. In the words of Annila, "everything depends on everything else," and outcomes are therefore non-linear.

Evolution is often seen as a struggle for survival among species. Darwin's third chapter in the *Origin* is, after all, entitled "Struggle for Existence."[93] But if a stable ecosystem is an attractor state, as I would propose, predation cannot be on the only guarantor of its stability.[94] A steady state between competitive and cooperative behavior is inescapable. Cooperation in nature is sometimes called symbiosis. African acacias, for example, are able to produce tannin. Tannin is toxic to mammals such as kudus and giraffes. Overgrazed acacia trees release ethylene, a plant hormone that stimulates trees downwind to produce protective tannin.[95]

The South African bird, the honeyguide, seems to cooperate with other species by showing them the location of bee colonies. Once the nest is broken open and the honey retrieved, the honeyguide can feed on the exposed beeswax. Beeswax is a potent free energy source, but honeyguides are almost unique in

being able to metabolize it.

According to Claire Spottiswoode, the honeyguide is also a highly virulent brood parasite.[96] Honeyguide chicks are reared by a species that neither cooperates with partners nor consumes beeswax. Spottiswoode questions whether the chicks' extreme violence best serves their interests. Perhaps the cooperative behavior that makes beeswax available in the ecosystem was a relatively late evolutionary development. The ability to utilize beeswax may have been an even later development. Not every trait necessarily has an explanation in terms of evolutionary theory or the struggle for existence.

But there is another interesting issue here: how do honeyguide chicks know how to behave in partnership? How do they know that beeswax is good to eat? They apparently are not taught by their parents, who abandon them as soon as the egg is laid.

It is a puzzle to Spottiswoode as well.[97]

Conclusion

The concept of the gene as the material element embodied in chromosomes that causes the cellular phenotype, regulates the cell, and constitutes Mendel's units of inheritance dates back to the mid-1920s, and research led by Thomas Hunt Morgan. At the same time, Hermann Muller showed that X-rays could mutate fruit fly genes:

> It has been found quite conclusively that treatment of the sperm with relatively heavy doses of X-rays induces the occurrence of true "gene mutations" in a high proportion of the treated germ cells.[98]

According to Jan Sapp, by the end of the 1920s, Muller and Morgan together had ensured the institutional dominance of genetics based on the governance of the cell by genes residing in the nucleus.[99] Fisher published his theory of natural selection in 1930. At the same time, Bénard had demonstrated directly that increasing entropy could appear as order in an open system, and Alexander Oparin had published his proposal for a metabolism-first origin of life.

When the structure of DNA was unraveled and information in the form of a base sequence code revealed, it was but a short and apparently irresistible step to the conclusion that genes were DNA base sequences.[100] The sequencing of the human genome has revealed the failure of the strategy launched nearly 100

years ago by Morgan and Muller; the majority of common heritable physical diseases cannot be accounted for in terms of genetic variance.

The sequence hypothesis and the central dogma, were, as Crick admitted in 1970, brash hypotheses.[101] The uncritical acceptance of these principles has been detrimental to biology. The infatuation with DNA has obscured the fact that there are deep, unexplored issues in protein chemistry: they need the attention of curious and innovative minds.[102]

1. What follows is based on three peer-reviewed papers: Arto Annila and Keith Baverstock "Genes without prominence: a reappraisal of the foundations of biology" *Journal of the Royal Society Interface* 11, no. 20131017 (2014), doi:10.1098/rsif.2013.1017; Keith Baverstock and Mauno Rönkkö, "The Evolutionary Origin of Form and Function" *Journal of Physiology* 592 (2014): 2,261–65; Andrei Karotki and Keith Baverstock, "What mechanisms underlie genomic instability?" Cell and Molecular Life Sciences 69 (2012): 3,351–60.

2. This is true of the first generation from a cross. In the second and later generations, intermediate forms can occur. However, the fact that the original form, as well as the intermediate forms, can occur indicates that the intermediate form is not due to blending. The unit of inheritance must have particulate character.

3. "This development [of the organism by cell formation] proceeds in accordance with a constant law, which is grounded in the material constitution and arrangement of the elements which achieved vivifying union in the cell." J. Gregor Mendel, "Versuche über Pflanzenhybriden," *Verhandlungen des naturforschenden Vereines in Brünn 4 Abhandlungen* (1866): 3–47, quoted in in Robert Olby, "Mendel, Mendelism and Genetics," MendelWeb, 1997.

4. Francis Crick, "On Protein Synthesis," *Symposia of the Society for Experimental Biology* 12 (1958): 138–63. The central dogma immediately became the subject of much further commentary and debate, but as Crick noted, the sequence hypothesis was "rather widely held." Crick defended the central dogma in 1970, but with less absolute certainty than might be associated with dogma; in fact, he seems to demote it to the status of a mere working hypothesis: "Although the details of the classification [of information transfer from DNA to mRNA to protein] are plausible, our knowledge of molecular biology, even in one cell—let alone for all the organisms in nature—is still far too incomplete to allow us to assert dogmatically that it is correct." Francis Crick, "Central Dogma of Molecular Biology," *Nature* 227 (1970): 562. Nevertheless, the central dogma became canonized in textbooks, classrooms, and institutions.

5. Christian Anfinsen, Edgar Haber, Michael Sela, and Frederick White Jr., "The Kinetics of Formation of Native Ribonuclease during Oxidation of the Reduced Polypeptide Chain," *Proceedings of the National Academy of Sciences of the United States of America* 47 (1961): 1,309–14.

6. Eric Davidson "Genomics, 'Discovery Science', Systems Biology, and Causal Explanation: What Really Works?" *Perspectives in Biology and Medicine* 58 (2015): 165–81.

7. Julian Huxley, *Evolution: the Modern Synthesis* (New York: Harper, 1942).

8. Massimo Pigliucci and Leonard Finkelman, "The Extended (Evolutionary) Synthesis Debate: Where Science Meets Philosophy," *BioScience* 64 (2014): 511–16.

9. Regarding trans-generational epigenetic inheritance, see for example: BBC, "The Ghost in Your Genes," *Dailymotion* video, March 3, 2014. A study based on historical records of an isolated community in Sweden going back several generations revealed life experiences, for example starvation, of grandparents can influence an individual's health. This phenomenon is termed epigenetics. Gene expression is controlled, it is generally assumed, by "marks" attached to the genomic DNA, or histone proteins closely associated with the DNA. A more fundamental meaning of the term epigenetics is "over and above" genetics, meaning the control of gene expression without implicating a specific mechanism. Epigenetics is not incorporated in the modern synthesis.

   Regarding consciousness, some form of this along with the ability to make decisions based on information gleaned from the environment (cognition) is a prerequisite for living systems to survive in a hostile environment. Unconsciousness can be induced in all organisms using the same anesthetics that work for human beings. The processes of inducing unconsciousness or regaining consciousness are so fast they cannot involve DNA. This important aspect of organisms is ignored in the modern evolutionary synthesis.

   Niche construction theory (NCT) is challenging mainstream evolutionary theory which maintains that evolution is a largely passive process in which organism phenotypes are selected on the basis of their propensity to replicate. NCT maintains that organisms modify their abiotic surroundings to influence their survival. While NCT is a relatively new proposal, Darwin, who had a lifelong interest in worms, noted that they were in effect modifying their environments (for example, reducing soft rock to soil and making soil more productive for plant growth) thus increasing the supply of organic detritus upon which they fed. Charles Darwin, *The Formation of Vegetable Mould through the Action of Worms, with Observations on their Habits* (London, UK: John Murray, 1881). See also Gillian Barker and John Odling-Smee, "Integrating Ecology and Evolution: Niche Construction and Ecological Engineering," in *Entangled Life, History, Philosophy and Theory of the Life Sciences*, vol. 4, ed. Gillian Barker, Eric Desjardins, and Trevor Pierce, (Dordrecht: Springer Science C Business Media, 2014), 187–211.

10. Francis Collins, "Shattuck Lecture: Medical and Societal Consequences of the Human Genome Project," *New England Journal of Medicine* 341 (1999): 28.

11. See the survey of twin studies designed to determine the likely value of techniques, such as Genome-Wide Association Studies (GWAS), in predicting future common health disorders: Nicholas Roberts, Joshua Vogelstein, Giovanni Parmigiani, Kenneth Kinzler,

Bert Vogelstein, and Victor Velcuescu, "The Predictive Capacity of Personal Genome Sequencing," *Science Translational Medicine*, April 2, 2012. The authors conclude:

> Our analyses indicate that: (i) for 23 of the 24 diseases, the majority of individuals will receive negative test results, (ii) these negative test results will, in general, not be very informative, as the risk of developing 19 of the 24 diseases in those who test negative will still be, at minimum, 50 – 80% of that in the general population.

In other words, on the basis of empirical evidence from people with either near-identical genome sequences (identical twins) or people with a 50% similarity in DNA sequence (non-identical twins), genetic profiling is unlikely to yield positive results for the man in the street. It is true that much of the strength of this analysis relies on data for cancer and the evidence here strongly indicates that cancer is not a genetic disease. However, Claudia Chaufan and Jay Joseph ("The 'Missing Heritability' of Common Disorders: Should Health Researchers Care?" *International Journal of Health Services* 43 (2013): 281–303) point out that "heritability" is an attribute of traits in a population, not in individuals. Furthermore, estimates of heritability rely on a controversial application of twin studies. See Roar Fosse, Jay Joseph, and Ken Richardson, "A Critical Assessment of the Equal-Environment Assumption of the Twin Method for Schizophrenia," *Frontiers in Psychology* 6 (2015): 62. Such estimates therefore say nothing about an offspring's chance on inheriting a parental trait. Therefore high heritability, as measured by twin studies, should not be taken as an indication that the genomic DNA sequence of an individual is causal in common physiological diseases (or for that matter, psychiatric disease, educational attainment, IQ, political affiliation or, self reported tiredness, see: Jonathan Leo, "The Search for Schizophrenia Genes," *Issues in Science and Technology* 32, no. 2 (2016); Cornelius Rietveld at al., "GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment," *Science* 340, no. 6139 (2013); M. F. Gosso, et al., "The SNAP-25 Gene is Associated with Cognitive Ability: Evidence from a Family-Based Study in Two Independent Dutch Cohorts," *Molecular Psychiatry* 11, no. 9 (2006): 878–86; Daniel Benjamin et al., "The Genetic Architecture of Economic and Political Preferences," *Proceedings of the National Academies of Science* 109, no. 21 (2012): 8,026–31; Vincent Deary et al., "Genetic Contributions to Self-Reported Tiredness," bioRxiv: 10.1101/047290). The absence of GWAS-type studies reporting strong correlations between such traits and genomic sequence abnormalities is better interpreted as evidence for a lack of genetically-based disease.

12. Munira Kadhim, D. A. Macdonald, D. T. Goodhead, S. A. Lorimore, S. J. Marsden, and Eric Wright, "Transmission of Chromosomal Instability after Plutonium Alpha-Particle Irradiation," *Nature* 355, no. 6,362 (1992): 738–40.

13. K. G. Luning, H. Frölén, and A. Nilsson, "Genetic effects of 239PU salt injections in male mice," *Mutation Research Fundamental and Molecular Mechanisms of Mutagenesis* 34 (1976): 539–42.

14. Katriina Huumonen et al., "Radiation-Induced Genomic Instability in Caenorhabditis elegans," *Mutation Research* 748 (2012): 36–41.

15. Susann Fält et al., "Long-Term Global Gene Expression Patterns in Irradiated Human Lymphocytes," *Carcinogenesis* 24 (2003): 1,837–45.

16. Andrei Karotki and Keith Baverstock, "What Mechanisms/Processes Underlie Radiation-Induced Genomic Instability?" *Cellular and Molecular Life Sciences* 69 (2012): 3,351–60.

17. In Chapter 9 of *On the Origin of Species*, Darwin says of the fossil record that it was: "the most obvious and gravest objection which can be urged against my theory." Charles Darwin, *On the Origin of Species* (London, UK: John Murray, 1859), 292. However, he also recognized that it might be expected to be incomplete even if his theory was correct.

18. Denis Noble, "Neo-Darwinism, the Modern Synthesis and Selfish Genes: Are They of Use in Physiology?" *Journal of Physiology* 589 (2011): 1007–15.

19. For example: Akiro Kashiwagi et al., "Adaptive response of a gene network to environmental changes by fitness-induced attractor selection," *PLOS ONE* 1 (2006): p.e49.; Jeffrey Barrick et al., "Genome Evolution and Adaptation in a Long-Term Experiment with *Escherichia coli*," *Nature* 461, no. 7268 (2009): 1243–47.

20. Edward Blyth, "An Attempt to Classify the 'Varieties' of Animals, with Observations on the Marked Seasonal and Other Changes Which Naturally Take Place in Various British Species, and Which Do Not Constitute Varieties," *The Magazine of Natural History* 8 (1835): 46.

21. However, Boltzmann himself recognized that life sought entropy: "The general struggle for existence of animate beings is therefore not a struggle for raw materials—these, for organisms, are air, water, and soil, all abundantly available—nor for energy which exists in plenty in any body in the form of heat (albeit unfortunately not transformable), but a struggle for entropy, which becomes available through the transition of energy from the hot sun to the cold earth." Ludwig Boltzmann, in *Theoretical Physics and Philosophical Problems: Selected Writings*, ed. Brian McGinness (Amsterdam: Kluwer Academic, 1974).

22. Erwin Schrödinger, *What is Life?* (Cambridge: Cambridge University Press, 1944).

23. Roger Penrose, *Cycles of Time: An Extraordinary New View of the Universe* (London: Bodley Head, 2010).

24. Eric Schneider and James Kay, "Order from Disorder: the Thermodynamics of Complexity in Biology," in *What is Life? The Next Fifty Years*, ed. Michael Murphy and Luke O'Neill. (Cambridge: Cambridge University Press, 1995), 161–74; Eric Schneider and James Kay, "Life as a Manifestation of the Second Law of Thermodynamics," *Mathematical Computing and Modelling* 19, no. 6–8 (1994): 25–48; Eric Schneider and Dorian Sagan, *Into the Cool: Energy Flow, Thermodynamics, and Life* (University of Chicago Press, Chicago, 2005). As ecosystems mature they degrade more of the incident energy from the sun, that is, the net solar flux incoming, minus the net long-wave outgoing flux, is maximized. The latter, measured as black body temperature by satellites and aircraft, is reduced with increasing ecosystem maturity (see table 16.2 in Schneider and Sagan). This is empirical evidence which contradicts the alleged need to export entropy (assuming it is disorder) in order to lower the internal entropy of an evolving open system as proposed for example by Prigogine: Grégoire Nicolis and Ilya Prigogine, *Exploring Complexity: an Introduction* (New York: W. H. Freeman and Company, 1989), and seemingly universally adopted since.

25. Arto Annila, "Natural Thermodynamics," *Physica A* 444 (2016): 843–52.

26. When entropy is derived from probability, it is understood to be a measure of bound and free energy per the average energy, not a measure of disorder. Order and disorder are merely mechanistic manifestations of the least-time free energy consumption. Order is no end in itself; the orderly processes of life appear in order to serve the least-time free energy consumption. Thus, the definition of entropy obtained by Annila completely reverses the conclusions Boltzmann reached more than 100 years earlier.

    Arto Annila and Keith Baverstock "Discourse on Order vs Disorder," *Communicative and Integrative Biology*, In Press.

27. For a description of Bénard's experiment, see: *Wikipedia*, "Rayleigh–Bénard Convection." Fluid is heated evenly from below and cooled at the top surface. Initially the thermal gradient is dissipated by conduction, with the consequence that disorder is generated as entropy. However above a critical thermal gradient organized (Rayleigh–Bénard) convection in the form of hexagonal cells of rising warm fluid and falling cool fluid occurs, accelerating the rate of heat dissipation. As free energy is more rapidly consumed under Rayleigh–Bénard convection, the entropy of the system must have increased and that increase is due to an ordered dissipative structure. So the entropy of the system is increased and so is the order.

28. Pierre Louis Maupertuis "Les loix du mouvement et du repos déduites d'un principe metaphysique," *Histoire de l'Académie Royale des Sciences et des Belles-Lettres de Berlin* (1746): 267–94.

29. A similar approach to the "least action" approach is taken for example by Eric Schneider and Dorian Sagan, *Into the Cool: Energy Flow, Thermodynamics, and Life* (Chicago: University of Chicago Press, 2005). The authors note that as systems are moved away from thermodynamic equilibrium they utilize all avenues to reestablish equilibrium.

30. The term "metabolic efficiency" covers a wide range of possibilities from metabolic processes at the chemical level to, for example, longer legs to enable faster running and, therefore, the more efficient capture of prey.

31. Anatole Katok and Boris Hasselblatt, *Introduction to the Modern Theory of Dynamical Systems* (Cambridge: Cambridge University Press, 1997). Dynamical systems theory (DST) was preceded by general system theory (GST): Ludwig von Bertalanffy, *General System Theory* (New York: George Brazillier, 1969). GST is based on the principle of equifinality, the process by which a final state of a system is achieved from a number of different initial conditions and routes. This principle is fundamental to the concept of an attractor state.

32. Keith Baverstock and Mauno Rönkkö, "Epigenetic Regulation of the Mammalian Cell," *PLOS One* 3, no. 6 (2008), doi:10.1371/journal.pone.0002290.

33. *Wikipedia*, "Nonholonomic System."

34. Robert Rosen studied relational biology under Nicolas Rashevsky at the School of Mathematical Biology at the University of Chicago. In 1960, the geneticist Richard Lewontin, appointed Dean of Biological Sciences, closed the Rashevsky school and in 1964 Rosen

moved through a variety of academic appointments ending up at Dalhousie University, Halifax, Nova Scotia, where he died in 1998. Ironically, writing about his decision to close the Rashevsky school in the *New York Review of Books* in 2003, Lewontin says that Rashevsky "failed to take into account the conviction of most biologists that real organisms were complex systems." Of course, in Rosen's terms, geneticists are convinced that organisms are simple systems, i.e., machines. Rosen summarized relational biology as "throwing away the matter and concentrating on the interactions." Rosen was a prolific author on many subjects and much under-appreciated by biologists.

Regarding complex systems, see Robert Rosen, *Life Itself: a Comprehensive Inquiry into the Nature, Origin and Fabrication of Life: Complexity in Ecological Systems* (New York: Columbia University Press, 1991). Category theory is a branch of mathematics in which processes can be abstracted and mapped: *Wikipedia*, "Category Theory." Theoretical biologist and former student of Rosen, Aloisius Louie, says category theory is the natural language of theoretical biology.

35. Philip Anderson, "More is Different," *Science* 177 (1972): 393–96.

36. Interestingly, Linus Pauling and Robert Corley described the role of DNA in much the same way as it is invoked in the dynamical cell model, in 1953:

> [T]he nucleic acids, as constituents of living organisms, are comparable in importance to proteins. There is evidence that they are involved in the processes of cell division and growth, they participate in the transmission of hereditary characteristics, and that they are important constituents of viruses.

Robert Corey and Linus Pauling, "A Proposed Structure for the Nucleic Acids," *Proceedings of the National Academies of Science* 39 (1953): 84-97.

37. H. Frederik Nijhout, "Metaphors and the role of genes in development," *Bioessays* 12 (1990): 441–46.

38. See "Ideas on Protein Syntesis (Oct. 1956)," and Francis Crick, "Central Dogma of Molecular Biology," *Nature* 227 (1970): 561–63. Peptides are linear, i.e., unbranched, biologically inactive or very low activity, chains of amino acids and are the direct product of translation from mRNA. They fold or are folded into three-dimensional (tertiary) structures, proteins, in the cell cytoplasm.

39. Christian Anfinsen, Edgar Haber, Michael Sela, and Frederick White Jr., "The Kinetics of Formation of Native Ribonuclease during Oxidation of the Reduced Polypeptide Chain," *Proceedings of the National Academy of Sciences of the United States of America* 47 (1961): 1,309–14. Anfinsen based his conclusion that folding was dictated by amino acid sequence on the kinetics of the re-naturation, or refolding, process in which he followed the increasing ribonuclease activity after the denaturing conditions were removed. In effect he was observing the peptide fold by trial and error until the native structure, the lowest energy state, was reached. In comparison to the speed with which peptides are known to fold in the cellular environment, fractions of a second to a few seconds, this process was very slow, taking 200 minutes to achieve recovery of 50% of the initial ribonuclease activity. What this experiment shows is that only this native structure, out of many other possible structures visited in the trial and error process, provides the spe-

cific activity associated with the ribonuclease enzyme: only the native structure carries the necessary information. If it is the case that the amino acid sequence determines the structure of the protein then it could be said that the information in the genetic code, which specified the amino acid sequence of the peptide, was in some way transferred to the protein. However, if the much faster folding of peptides in the cellular environment does not yield the native structure, an eventuality that is overwhelmingly probable, then the "thread" of information continuity is broken and the information carried by the protein is not that in the DNA sequence: the DNA sequence cannot be responsible for the phenotype.

40. Private communication.

41. Hans Krebs, "Enzymic Activity and Cellular Structure," in *Horizons in Biochemistry*, eds. Michael Kasha and Bernard Pullman (New York, 1962), 291–96.

42. Alan Minton, "How Can Biochemical Reactions within Cells Differ From Those in Test Tubes?" *Journal of Cell Science* 119 (2006): 2,863–69.

43. Barbara McClintock, "The Significance of Responses of the Genome to Challenge," *Science* 226, no. 4,676 (1984): 792–801.

44. James Shapiro, "Physiology of the Read-Write Genome," *Journal of Physiology* 592 (2014): 2,319–41.

45. Two properties of the attractor are of particular significance, namely stability (defined as the ability to replicate the genotype with integrity) and robustness (resilience to perturbation). In a stable species it is assumed that these properties have been optimized through evolutionary conditioning. (Keith Baverstock, "Radiation-induced Genomic Instability: A Paradigm-Breaking Phenomenon and its Relevance to Environmentally Induced Cancer," *Mutation Research* 454 (2000): 89-109.) To emphasize the uniqueness of the attractors representing the phenotypes of cells of established species they have been termed "home" attractors and unconditioned attractors adopted as a result of stochastic perturbation of attractors are termed "variant" attractors. Thus, genomic instability can be seen as the transition from a home to a variant attractor with the concomitant mutator phenotype (due to less than optimum stability) and greater propensity to be perturbed to other variant attractors as experimentally demonstrated by Fält et al. (Susann Fält et al., "Long-term Global Gene Expression Patterns in Irradiated Human Lymphocytes," *Carcinogenesis* 24 (2003): 1,823-45.) In this sense the genomically unstable phenotype can be regarded as an "incomplete" phenotype as once it is released from the home attractor it relatively readily migrates between variant attractors." Keith Baverstock, "A Comparison of Two Cell Regulatory Models Entailing High Dimensional Attractors Representing Phenotype," *Progress in Biophysics and Molecular Biology* 106 (2011): 443–49.

46. It can also be argued, based on Kurt Gödel's incompleteness theorem, that a single source of information alone cannot be responsible for yielding phenotype. See Keith Baverstock, "A Comparison of Two Cell Regulatory Models Entailing High Dimensional Attractors Representing Phenotype," *Progress in Biophysics and Molecular Biology* 106 (2011): 443–49.

47. If this looks like self-defeating circularity, reflect on the fact that if there is no external

creator of life, life must have initiated itself.

48. Tuomas Pernu, and Arto Annila, "Natural Emergence," *Complexity* 17 (2012): 44–47; Arto Annila, "Natural Thermodynamics," *Physica A: Statistical Mechanics and its Applications* (2015), doi:10.1016/j.physa.2015.10.105.

49. Roy Britten and Eric Davidson, "Gene Regulation for Higher Cells: a Theory," *Science* 165 (1969): 349–57.

50. Keith Baverstock, "A Comparison of Two Cell Regulatory Models Entailing High Dimensional Attractors Representing Phenotype," *Progress in Biophysics and Molecular Biology* 106 (2011): 443–49; Karl Niklas, Sarah Bondos, A. Keith Dunker, and Stuart Newman, "Rethinking Gene Regulatory Networks in Light of Alternative Splicing, Intrinsically Disordered Protein Domains, and Post-Translational Modifications," *Frontiers in Cell and Developmental Biology* 3 (2015): 8.

51. Vladimir Uversky, "Natively Unfolded Proteins: a Point Where Biology Waits for Physics," *Protein Science* 11 (2002): 739–56; Kenji Sugase, H. Jane Dyson, and Peter Wright, "Mechanism of Coupled Folding and Binding of an Intrinsically Disordered Protein," *Nature* 447, no. 7147 (2007): 1021–25; Karl Niklas et al., "Rethinking Gene Regulatory Networks in Light of Alternative Splicing, Intrinsically Disordered Protein Domains, and Post-Translational Modifications," *Frontiers in Cell Development Biology* 3 (2015): 8.

52. Alan Minton, "How Can Biochemical Reactions within Cells Differ From Those in Test Tubes?" *Journal of Cell Science* 119 (2006): 2,863–69.

53. See Alwyn Scott, *The Nonlinear Universe: Chaos, Emergence, Life* (Berlin: Springer, 2007).

54. Nils Johnsson, "Analyzing Protein-Protein Interactions in the Post-Interactomic Era. Are We Ready for the Endgame?" *Biochemical and Biophysical Research Communications* 445 (2014): 739–45.

55. Dennis Bray, "Protein Molecules as Computational Elements in Living Cells," *Nature* 376 (1995): 307.

56. Nils Schuergers et al., "Cyanobacteria use Micro-Optics to Sense Light Direction," *eLife* 5, no. e12650 (2016), doi:10.7554/eLife.12620.

57. Tetsu Saigusa et al., "Amoebae Anticipate Periodic Events," *Physical Review Letters* 100, no. 018101 (2008). Specifically if the cooler and drier conditions are imposed for ten minutes at intervals of one hour, three times, the plasmodium will reduce its growth rate for ten minutes at hourly intervals over the following two to three hours in the absence of cooling.

58. Toshiyuki Nakagaki et al., "Minimum-Risk Path Finding by an Adaptive Amoebal Network," *Physical Review Letters* 99, no. 068104 (2007). Light is toxic to these organisms so when grown such that they connect to two diametrically-opposite food sources in a rectangular agar plate which is half illuminated, the plasmodia minimize occupancy of the illuminated region of the plate.

59. Chris Reid, et al., "Army Ants Dynamically Adjust Living Bridges in Response to a Cost-Benefit Trade-Off," *Proceedings of the National Academy of Sciences of the United*

States of America 112, no. 49 (2015): 15,113–18. In field experiments, a variable width gap was inserted in the path of foraging ants bringing food to the colony. Up to a point longer bridges would be built to shorten the foraging route. A trade-off between using ants to make a bridge and foraging was observed to the benefit of the colony as a whole.

60. Frantisek Baluska and Stefano Mancuso, "Deep Evolutionary Origins of Neurobiology: Turning the Essence of 'Neural' Upside-Down," *Communicative & Integrative Biology* 2 (2009): 60–65.

61. An attractor can be seen as something akin to a multichannel parallel computer with exchange of information between channels in real time, i.e., far removed from simple algorithmic computation.

62. Andrei Karotki and Keith Baverstock, "What mechanisms/processes underlie radiation-induced genomic instability?" *Cellular and Molecular Life Sciences* 69, 20 (2012): 3,351–60.

63. Jason Bielas et al., "Human Cancers Express a Mutator Phenotype," *Proceedings of the National Academy of Sciences* 103 (2006): 18,238–42.

64. Maria Grazia Andreassi and Nicoletta Botto, "Genetic instability DNA damage and atherosclerosis," *Cell Cycle* 2–3 (2003): 224–27.

65. Keith Baverstock and Andrei Karotki, "Towards a Unifying Theory of Late Stochastic Effects of Ionizing Radiation," *Mutation Research* 718, no. 1–2 (2011): 1–9.

66. Richard Lewontin, *The Genetic Basis of Evolutionary Change* (New York: Columbia University Press, 1976), xiii.

67. There is a related effect to genomic instability called the bystander effect. Here unirradiated cells in the neighborhood of an irradiated cell can exhibit effects as if they had been irradiated. This effect is thought to be mediated through cell-to-cell communication. It is not addressed in this essay.

68. Robert Rosen, *Life Itself: a Comprehensive Inquiry into the Nature, Origin and Fabrication of Life: Complexity in Ecological Systems* (New York: Columbia University Press, 1991).

69. Roger Hellens et al., "Identification of Mendel's White Flower Character," *PLOS ONE* (2010), doi:10.1371/journal.pone.0013230.

70. Paul Lichtenstein, Niels Holm, Pia Verkasalo, Anastasia Iliadou, Jaakko Kaprio, Markku Koskenvuo, Eero Pukkala, Axel Skytthe, and Kari Hemminki, "Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland," *New England Journal of Medicine* 343, no. 2 (2000): 78–85. Data are provided for identical and non-identical twins. If a disease is genetic it is expected that concordance (both twins suffering the disease) will be high. If it is not genetic any concordance will be due to shared environmental factors. Using only the data for identical twins it is clear that for most cancers concordance is around 10% or less. This could be due to a) chance, b) shared environment, or c) a genetic component, or a combination of all three. Whichever, there is no evidence of a marked genetic component.

71. Schizophrenia Working Group, "Biological insights from108 schizophrenia-associated

genetic loci," *Nature* 511 (2014): 421–27.

72. Kenneth Kendler, "A joint history of the nature of genetic variation and the nature of schizophrenia," *Molecular Psychiatry* 20 (2014): 77.

73. Francis Collins, "Shattuck Lecture: Medical and Societal Consequences of the Human Genome Project," *New England Journal of Medicine* 341 (1999): 28.

74. Thomas Cech, "The RNA Worlds in Context" *Cold Spring Harbor Perspectives in Biology* 4 (2011): a006742.

75. There are several problems with the hypothesis. See Harold Bernhardt, "The RNA World Hypothesis: The Worst Theory of the Early Evolution of Life (Except for all the others)," *Biology Direct* (2012): 7–23.

76. This was proposed by Alexander Oparin in 1926 and elaborated by Freeman Dyson. See Alexander Oparin, *The Origin of Life* (New York: Dover, 1952); Freeman Dyson, "A Model for the Origin of Life," *Journal of Molecular Evolution* 18 (1982): 344–50.

77. See *Wikipedia*, "Tardigrade." Tardigrades have been demonstrated to have extraordinary resistance to ionizing radiation, tolerating doses up to 5000 Gy. (Daiki Horikawa "Radiation tolerance in the tardigrade Milnesium tardigradum" *International Journal of Radiation Biology* 82 (2006) 843–848). An unusual feature of these creatures is that after hatching from the egg the somatic cells do not undergo replication and thus their DNA, which is usually considered to be crucial for the survival of radiation insults, is dormant with respect to somatic cell replication during adult life. Irradiated individuals can lay eggs, but these do not hatch. Furthermore, the extraordinary resistance does not apply to the early stages of development in the egg, where cell division will be occurring until shortly before hatching. (Ingemar Jönsson et al., "Tolerance to gamma-irradiation in eggs of the tardigrade *Richtersius coronifer* depends on stage of development," *Journal of Liminology 72* (2013): 73–79). Thus, it is plausible to suggest that hatched Tardigrades are in effect an example of a "protein-only" form of multicellular life.

78. Reverse transcription (mRNA to DNA) is an established biological feature in contrast to reverse translation (peptide to RNA). However, there is no insuperable barrier to the process. The tRNA counterparts to the amino acids in the peptide would bind, and polymerization to mRNA would then follow. Such a process would have no role in modern cells.

79. Norman Cook, "The Case for Reverse Translation," *Journal of Theoretical Biology* 64, no. 1 (1977): 113–35; Masayuki Nashimoto, "The RNA/protein symmetry hypothesis: experimental support for reverse translation of primitive proteins," Journal of Theorical Biology 209 (2001): 181–87.

80. Ronald Fisher, *The Genetical Theory of Natural Selection* (Oxford: The Clarendon Press, 1930).

81. Jeffrey Barrick et al., "Genome Evolution and Adaptation in a Long-Term Experiment with *Escherichia coli*," *Nature* 461, no. 7268 (2009): 1,243–47.

82. Akiro Kashiwagi et al., "Adaptive Response of a Gene Network to Environmental Chang-

es by Fitness-Induced Attractor Selection". *PLOS ONE* 1, no 1 (2006) , doi: 10.1371/journal.pone.0000049.

83. This statement could of course be challenged. I make it on the grounds that the primary difference between proto-life and true life is the adoption of DNA as a data base for peptide sequences and as a template in the cell division process. In humans, anesthetics that cause us to lose consciousness act so quickly that one cannot conceive that DNA is involved in the process. Thus, I assume consciousness predates the origin of true life. This, therefore, implies that in some way consciousness is underpinned by protein chemistry. If the phenomenon of life is an emergent property of protein chemistry, and consciousness is an essential property of life, the last sentence is not unreasonable even if unexpected. The specific nature of emergent properties often depends on context. Bénard cells, discussed above, are a case in point: to form they require a broad, but relatively shallow fluid layer. However, depending on the depth and composition of the fluid, the convection cells can appear as hexagons, or other geometrical forms. Another case in point is the soliton, a wave of extraordinary stability first observed on the Grand Union Canal in 1845. In water, solitons form readily in long narrow troughs of shallow water. In theory their stability can be such that they have an infinite life in contrast to normal waves in deeper water and unconstrained, which disperse. Additionally, solitons have other extraordinary and counterintuitive properties, as described in a Wikipedia entry. This is another reason to heed Krebs's advice and study proteins in their natural environment: their chemistry may yield quite unexpected properties.

84. James Sonner, "A hypothesis on the origin and evolution of the response to inhaled anesthetics," *Anesthics & Analgesia* 107 (2008): 849–54. Sonner hypothesizes that anaesthesia arises from the effects of certain chemicals on cellular ion channels and not on an adaptation of the nervous system.

85. Mauno Rönkkö, "An Artificial Ecosystem: Emergent Dynamics and Lifelike Properties," *Artificial Life* 13, no. 2 (2007): 159–87.

86. Keith Baverstock and Mauno Rönkkö, "The Evolutionary Origin of Form and Function," *The Journal of Physiology* 592, no. 11 (2014): 2,261–65.

87. Richard Dawkins, *Climbing Mount Improbable* (London: W. W. Norton & Company Ltd., 1996)

88. Stephen Jay Gould, *The Structure of Evolutionary Theory* (Cambridge: Belknap, 2002), 146–154; Stephen Jay Gould and Niles Eldredge, "Punctuated Equilibrium Comes of Age," *Nature* 366 (1993): 223–27.

89. Described in detail in Stephen Jay Gould, *Wonderful Life: the Burgess Shale and the Nature of History* (London: Vintage, 2000).

90. Alan Turing, "The Chemical Basis of Morphogenesis," *Philosophical Transactions of the Royal Society B: Biological Sciences* 237, no. 641 (1952): 37–72.

91. Shigeru Kondo and Takashi Miura, "Reaction-Diffusion Model as a Framework for Understanding Biological Pattern Formation," *Science* 329, no. 5999 (2010): 1,616–20.

92. Nathan Tompkins et al., "Testing Turing's Theory of Morphogenesis in Chemical Cells,"

Proceedings of the National Academy of Sciences of the United States of America 111, no. 12 (2014): 4,397–402.

93. Charles Darwin, "Struggle for Existence," in *On the Origin of Species by Means of Natural Selection: Or, The Preservation of Favoured Races in the Struggle for Life* (London: John Murray, 1859).

94. Darwin noted the "proportional numbers" of species occupying an ecosystem. In Chapter 3 of the *Origin* he writes about heath land near Farnham in Surrey:

> Here there are extensive heaths, with a few clumps of old Scotch firs on the distant hill-tops: within the last ten years large spaces have been enclosed, and self-sown firs are now springing up in multitudes, so close together that all cannot live. When I ascertained that these young trees had not been sown or planted, I was so much surprised at their numbers that I went to several points of view, whence I could examine hundreds of acres of the unenclosed heath, and literally I could not see a single Scotch fir, except the old planted clumps. But on looking closely between the stems of the heath, I found a multitude of seedlings and little trees, which had been perpetually browsed down by the cattle. In one square yard, at a point some hundred yards distant from one of the old clumps, I counted thirty-two little trees; and one of them, with twenty-six rings of growth, had during many years tried to raise its head above the stems of the heath, and had failed. No wonder that, as soon as the land was enclosed, it became thickly clothed with vigorously growing young firs. Yet the heath was so extremely barren and so extensive that no one would ever have imagined that cattle would have so closely and effectually searched it for food.

Charles Darwin, *On the Origin of Species* (London, UK: John Murray, 1859), 82. A heath land ecosystem is transformed to what would eventually mature into a forest ecosystem simply by excluding a single key species. In the enclosed areas biodiversity would initially decline rapidly, and then, gradually, a new range of species would grow in. However, predicting what will evolve will not necessarily be possible because it will depend on which new species take up residence first and how they may modify the ecosystem's resources.

This is confirmed by an "experiment" on the atoll Fangataufa where the French nuclear test took place between 1966 and 1970, eliminating the gastropod community on the reefs. Comparing the ecosystems on flat reefs and steeply inclined reefs before and after the tests showed that on the former, repopulation in the 30 years after the tests led to distinctly different communities and, on the latter, similar communities. The authors conclude that on flat reefs that can be occupied by a wide range of gastropod species the process of re-growth was randomly determined, whereas on the steeply sloping reefs, where only a few species were capable of surviving the much harsher conditions, re-growth was environmentally determined and of much poorer quality. Pierre Legendre and Bernard Salvat, "Thirty-year recovery of mollusc communities after nuclear experimentations on Fangataufa atoll (Tuamotu, French Polynesia)," *Proceedings of the Royal Society B* 282 (2015): 20150750.

95. Sylvia Hughes, "Antelope Activate the Acacia's Alarm System," New Scientist, 29 September 1990; also see: Seamineral.com, "If Plants Could Kill They Probably Would: Part 1," 2014.

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99. Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (New York: Oxford University Press, 1987), xvi.

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