Biological Complexity

Harry Cook and Hank D. Bestman

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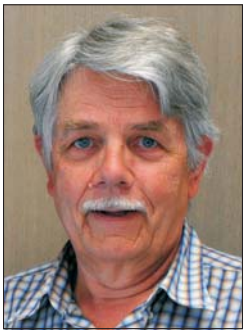

Hank D. Bestman

Complexity is often defined in the language of mathematics, computers, or information theory. We examine biological complexity as it occurs in the cytoplasm's relation to nuclear function, and in the case of epigenetics. In the nineteenth and twentieth centuries, the pendulum swings between appreciation of biological holism and complexity, and reductionism. During the second half of the twentieth century, complexity gains a new appreciation and emerges as a field of study in its own right. We propose a description of biological complexity that includes the functional dynamics of the various structural components of biological organisms and their levels of functioning, with the higher levels imposing boundaries on the lower levels. We suggest that this complexity reveals the wisdom of the Creator.

What is complexity? That is a complex question! That is, the answers are complex, and they depend on whom you ask. In this article, we will discuss biological complexity, using the relation between nucleus and cytoplasm, and epigenetics as examples. We will provide a brief history of biological complexity and describe the difficulties in defining complexity, in general, and biological complexity, in particular. Then we will propose a characterization of what constitutes biological complexity. In keeping with common parlance, we use "complex" and "complicated" (and their accompanying nouns) more or less interchangeably. As we go along, it will become clear that "complexity" is also a topic that has given rise to distinct views about the nature of biology and the entities it studies.

Cellular Complexity: The Gene-Centered Approach

The nucleus of the cell stands out. With standard histological techniques, the nucleus is much more noticeable than the outline of the cytoplasm. The chromosomes in meiosis and mitosis present a fascinating vista of structure and function. The genetic ratios observed by Gregor Mendel are intimately related to the activities of the chromosomes in meiosis. The establishment of nucleic acid as the carrier of heredity, then the discovery of the structure of DNA, and, finally, its roles in inheritance and protein synthesis present us with a fascinating journey of discovery. With this emphasis on the nucleus and nucleic acids, the role of the cytoplasm in various functions is often underestimated, but it is gaining attention at present. In this section, we attempt to describe a holistic view of cell functions as they pertain to cellular complexity.

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Mendel and his rediscoverers worked in continental Europe; however, the new subdiscipline of genetics was especially influential and successful in the Anglo-Saxon world. The contributions of William Bateson in England, and of Thomas Hunt Morgan in the United States, are particularly significant. Bateson was an established and respected British biologist when he heard of Mendel's work, and of its rediscovery. He coined the word "genetics" and, together with Reginald Punnett, worked vigorously to establish genetics as a field of study in Britain.[1] Mendelian genetics progressed rapidly in the few years between its rediscovery and the publication of one of Bateson's major works in 1909.[2] Bateson translated Mendel's pioneering article into English, and he broadened Mendel's theory to include more organisms, including animals. Through his work, along with that of others, genetics developed into a discipline that was separate from the study of reproduction in general. Bateson also kept in mind the importance of the whole organism and the connection between genes and embryological development.[3]

Morgan, the American geneticist, continued the trend established by Bateson, and contributed much to our understanding of genetics. Switching from embryology to the new science of genetics, he adopted the fruit fly, *Drosophila melanogaster,* as his research organism. This was a brilliant choice, and a great number of key discoveries, such as mutation, linkage, sex linkage, crossing over, and the giant chromosomes, followed. This work did much to supply a biological basis for Mendel's laws. Morgan trained several graduate students who became accomplished geneticists in their own right; Alfred H. Sturtevant, Calvin Bridges, and H. J. Muller stand out.[4] Like Bateson, Morgan began his biological career as an embryologist; his impressive findings in heredity hastened the separation of genetics from other fields of study in reproduction. Throughout his life, he retained his interest in embryology, but when he was engaged in his work in genetics, he deemed the relationship between genetic factors and their effects to be of secondary importance. In 1926, he stated that "the sorting out of the characters in successive generations can be explained … without reference to the way in which the gene affects the developmental process."[5]

In a perceptive discussion, Evelyn Fox Keller discusses the "nuclear monopoly" and the disregard for developmental processes which bring about the effects of genes; she speaks of "the discourse of gene action."[6] That is, many geneticists were content to speak of gene action without knowing the mechanisms by which these actions were achieved. Keller cites Morgan's comments, relevant to the topic of this article:

> It is clear that whatever the cytoplasm contributes to development is almost entirely under the influence of the genes carried by the chromosome, and therefore may in a sense said to be indifferent.[7]

Not all cell biologists agreed with this statement by Morgan; Jan Sapp reviewed the early biological literature that stresses the role of the cytoplasm.[8] Embryologists, who continued to remind cell biologists of the importance of the cytoplasm, stressed that all cells of an early-stage embryo receive the same hereditary information, and that it is the cytoplasm that gives the impetus for the early differentiation of cells. Even Morgan reminded biologists,

> The implication in most genetic interpretation is that all the genes are acting all the time in the same way. This would leave unexplained why some cells of the embryo develop in one way, some in another, if the genes are the only agents in the results.[9]

Thus, embryologists were emphatic in pointing out the role of the zygotic cytoplasm, and the complex interaction between nucleus and cytoplasm.[10]

In continental Europe, biologists were less enamored by the Mendelian paradigm and more reticent to ignore the role of the cytoplasm and the mechanisms that linked genes and their effects. Paul Weindling describes the various ways in which German biologists of the late eighteenth and early nineteenth centuries used their excellent microscopes and cytological skills to study the roles of the cytoplasm.[11] Keller states,

> The nucleus was the domain in which American genetics staked its unique strengths, associated with American interests (and prowess), whereas the cytoplasm was associated with European, especially German, interests and prowess.[12]

In a chapter entitled "Challenging the Nuclear Monopoly of the Cell in Germany," Sapp discusses this topic, emphasizing that many German biologists

saw the importance of the new genetics but, at the same time, espoused more holistic views, and that they studied the entire cell, including the role of the cytoplasm.[13]

Because the sperm possesses little or no cytoplasm whereas the egg contributes almost all of the cytoplasm of the zygote, Keller suggests that the indifference toward the role of the cytoplasm of embryos is also due to a gender bias. The role of the cytoplasmic dowry, as it has been called, has too often been ignored. Yet, it is also remarkable that many of the embryologists, investigating the role of the cytoplasm, maternal effects, and the field of embryology generally, were women.[14]

With the discovery of the structure of DNA in 1953, the attention fell, once again, on the nucleus of the cell. James Watson and Francis Crick opened their one-page letter to *Nature* with these well-known lines, "We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest." Near the end of the paper they add, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."[15] Within twenty years, the nature of the genetic code, the role of the several RNAs and the ribosomes, and the control of protein synthesis by DNA, via RNA, were elucidated.[16]

In 1958, Crick published a fascinating paper which outlined the triumphs and challenges of molecular biology at the time.[17] He recognized the sequence of nucleotides in the DNA of the nucleus to be the code for the incorporation of twenty basic amino acids into protein chains. RNA was seen to be a key in this incorporation, which occurred in the cytoplasm, and he also stated that there was more than one type of RNA. The DNA code was not yet known at this time, and Crick launched several hypotheses about the nature of the code: it would have to be a triplet code, but that still allowed for several possibilities.[18] He also formulated, in the text of the paper, but not in its present succinct form, the Central Dogma: that DNA controls the synthesis of RNA, and RNA that of proteins, and that this order cannot be reversed. He was emphatic that information could not pass from proteins to nucleic acids. Considering what was known about these matters at the time, Crick's hypothesis must be considered a stroke of genius. He professed that he was not aware of the absolutist connotations of the word "dogma," and that he used it in the sense of "grand hypothesis."[19] The nature of the genetic code and mechanisms of protein synthesis were worked out not long afterwards, in the mid-1960s.

Howard Temin's and David Baltimore's discovery of RNA retroviruses and the enzyme, reverse transcriptase, for which they received a Nobel Prize in 1975 (sharing it with Renato Dulbecco), appeared to contradict the Central Dogma, because in these viruses, the first step, in which the RNA of the virus directs the synthesis of a daughter DNA, goes against the flow of the dogma.[20] In spite of these findings, Crick, in 1970, reiterated the Central Dogma, emphasized its value and applications in molecular biology, and gave it the familiar short form that we recognize so well: DNA → RNA → Protein.[21] This formulation, while appearing to reemphasize the nuclear dogma, also hints at the importance the cytoplasm will be shown to have. Recombinant DNA technology would again emphasize the importance of DNA in bacteria,[22] and, later, of DNA in the nucleus in plants and animals. Successful application of this technology in higher organisms would, however, depend on a thorough understanding of the role of RNAs and protein synthesis in the cytoplasm, and of cell function in general.

Sequencing of DNA, although laborious at first, was aided by the development of the polymerase chain reaction[23] and improved sequencing techniques and equipment. These developments were paralleled by the identification and characterization of genes for human traits and illnesses, and optimism about the treatment of some diseases seemed, at times, little more than a ploy for increased research funding. In 1992, Richard C. Lewontin expressed his reservations:

> According to the vision, we will locate on the human chromosomes all the defective genes that plague us, and then from the sequence of the DNA we will deduce the causal story of the disease and generate a therapy. Indeed, a great many defective genes have already been roughly mapped onto chromosomes and, with the use of molecular techniques, a few have been very closely located and, for even fewer, some sequence information has been obtained. But causal stories are lacking and therapies do not yet exist; nor is it clear, when

> actual cases are considered, how therapies will flow from a knowledge of DNA sequences.[24]

Some of Lewontin's critique is still relevant today.

It is clear that the next step to be taken would be the sequencing of the human genome. It was spoken of as the Holy Grail of molecular biology.[25] The project started in 1990 under the leadership of James D. Watson, and its progress gained speed as sequencing equipment improved. Craig Venter, working at a private firm, Celera Genomics, used different techniques ("the shotgun approach") to establish his version of the genome.[26]

The joint announcement of the completion of a first draft of the human genome, on Monday, June 26, 2000, was a momentous occasion. The presence of President Bill Clinton, and his role in bringing the principals of the public and private sequencing institutes together, certainly made it that. Francis Collins, who had become the head of the Human Genome Project, and Venter had agreed to bridge the differences between the public and private approaches to enable the joint announcement to be made.[27] Collins has described various aspects of his life, his work, and his views in two books.[28]

We have described the importance of the nucleus, of genes, and of DNA, and have also described the tendency in the biological establishment to isolate their role from other cell functions and to overemphasize their importance. This tendency has been strengthened by the dominance of gene-centered approaches to the study of animal and human behavior, such as sociobiology, behavioral ecology, and evolutionary psychology.[29]

Cellular Complexity: The Cytoplasm Strikes Back

The simplicity of "a gene for this and a gene for that" would soon be shaken by the sheer complexity of genetic mechanisms within the cell. "Life is Complicated" proclaims the title of a recent article by Erika Check Hayden.[30] In the article, she describes, among other things, that "web-like networks" better portray the multiple pathways between many genes and their products and effects. She illustrates this with one protein, p53, which can bind to and inhibit a DNA site, can bind to thousands of RNA sites, and, due to a process called alternate splicing, can take nine different forms. These web-like networks can be so complicated in some cases that they have been referred to as "hairballs."[31]

This complexity of gene-effect relationships is examined and highlighted by Evelyn Fox Keller in *The Century of the Gene*.[32] In her book, Keller lauds the Human Genome project because it has changed our concept of the gene and our ideas about genetics and protein synthesis. In the early days of genetics, "gene action" was assumed to take place without need of explanation; when this action was investigated in laboratories all over the world, the complexity of the processes was found to be astounding.[33] DNA was found to be of several kinds: coding, regulating, and some was labeled, perhaps prematurely, as "junk."[34] Split genes, alternative splicing, genes coding for several proteins, depending on how they were "read," and post-transcriptional modification, added to the complexity. Single proteins were found to have several functions, depending on regulatory mechanisms. When it came to hereditary illnesses, some were found to have simple genetic causes, whereas the explanation for others was said to lie in the distant future.[35] Keller states that "the function of the structural gene depends not only on its sequence but, as well, on its genetic context, on the chromosomal structure in which it is embedded …, and on its developmentally specific cytoplasmic and nuclear context."[36] She also reexamines the complexity of how a "genetic program" shapes the developing embryo. Keller concludes that the classic image of the gene will be difficult to replace, because its replacement will shatter a popular icon.[37] Furthermore, "gene talk" is an effective tool for persuasion, for funding applications, and for marketing gene-based products.[38]

A critique of Keller's views from proponents of a more traditional gene-centered view was not long in coming.[39] However, for our purposes, it is important to note that both sides of the debate would be quick to agree that the relationship between DNA and the proteins produced in the cell is an extremely complicated one; it involves many nuclear and cytoplasmic processes. Knowledge of cellular complexity is of the utmost importance in order for various biotechnologies and cell and tissue culture techniques to be successful.

The beautiful structure of membranous organelles in eukaryotic cells (cells with nuclear and other

intercellular membranes) was a source of wonder and fascination when transmission electron microscopes came into common use in the middle of the previous century. Excellent high-resolution pictures of mitochondria, chloroplasts, and Golgi bodies, published by Don W. Fawcett, heightened this sense of wonder.[40] Discovered in 1890 by Richard Altmann and named in 1898 by Karl Benda,[41] mitochondria are now known to provide energy in a form usable by the cell for all kinds of processes.

The implications of the discovery that mitochondria contain DNA are discussed in detail by Nick Lane.[42] Each of the many mitochondria in a eukaryotic cell contains several circular strands of DNA; these circular strands resemble the configuration of bacterial DNA. This mitochondrial DNA was found to code for some of the proteins that function in mitochondria. They are maternally inherited because ova, but not sperm, pass on mitochondria to the zygote.[43] In a paper and a book, Lynn Margulis suggests that mitochondria are derived from a symbiotic union of a unicellular organism and a prokaryote in a process she called endosymbiosis.[44] This would explain the similarity between bacterial and mitochondrial DNA.

In green organisms, chloroplasts, the site of photosynthesis, have also been found to contain DNA. In 1905, Konstantin Mereschkowski postulated that chloroplasts arose by cells incorporating green photosynthetic unicellular organisms.[45] Margulis included chloroplasts in her theory mentioned above. Similar to mitochondrial DNA, chloroplasmic DNA also codes for proteins that are inherent to the function of the organelle, in this case, the chloroplast.

Cytoplasmic DNA, particularly mitochondrial DNAs, have provided fascinating insights into human evolution, and into cellular function.[46] Important for the topic of this article is that it is also a crack in the wall of the "nuclear monopoly," and another demonstration of the importance of the cytoplasm in hereditary mechanisms of the cell.

The whole cell, nucleus (or the circular chromosome in prokaryotes) and cytoplasm, carries out many metabolic and reproductive tasks. DNA is of the utmost importance in these activities, but, as we hope we have demonstrated, the picture of DNA as a simple one-to-one code for protein synthesis is no longer tenable or prevalent among cell biologists. The multifarious activities of the cytoplasm are the subject of intense study.[47] This complexity is leading cell biologists to more holistic views of the cell.

Epigenetic Inheritance

Epigenetic inheritance, a topic that is receiving much attention in biological literature, is our second illustration of biological complexity. When discussing cellular differentiation in the embryo, we noted that it was caused by cytoplasmic factors, most of which were derived from the egg. When it is passed from one cell generation to another, this differentiation has been called an "epigenetic inheritance system."[48] Epigenetic changes are "heritable variants that are not due to changes in DNA sequence."[49] Eva Jablonka and Marion J. Lamb have discussed various epigenetic phenomena in a recent book.[50] These mechanisms are not dependent on the primary sequences of DNA, and they do not replace the genetic mechanisms that are commonly described in genetics textbooks.

The addition of methyl groups to specific cytosine bases in DNA prevents the production of messenger RNA ("transcription") in the nucleus. This "silencing" of genes increases when the methylation is more extensive. The methylation is heritable, i.e., it is passed on in an organism from one generation of cells to another. The types of DNA that are methylated have been identified to some extent, and the methylation process has also been linked to some kinds of cancer.[51] New sequencing methods can now detect the presence of methylation in DNA.

Modification of histones represents another epigenetic mechanism. Chromosomes are made up of DNA, and of proteins largely consisting of histones. These histones can be modified by acetylation, deacetylation, or methylation, or they can be modified in other ways.[52] These changes can increase or decrease transcription and they can be passed on from one cell generation to the next, thus creating another epigenetic mechanism.[53]

RNAs, from 21 to 24 nucleotides long, can also function in epigenetic mechanisms. Such RNAs "span all eukaryotic kingdoms in their distribution … They … serve as molecular signposts to identify targets of silencing: retroviruses, retrotransposons, aberrantly expressed genes, and normal

developmental loci."[54] The source of these RNAs has been studied, and they, too, are now considered to be part of the epigenetic machinery of the cell.

Epigenetic mechanisms are varied. The ones we have described interact with each other, and there are other mechanisms, assumed to be epigenetic, that are not included in our short survey. Because they are acquired characteristics that are passed from one cell generation to another, they are often described as Lamarckian patterns of inheritance.[55]

Other Complexities

In a discussion of the complexity of the living cell, which they term "BioComplexity," Bruggeman, Westerhoff, and Boogerd point to the usefulness of reductionistic and nonreductionistic approaches in the study of the cell.[56] They suggest that the complexity of the living cell should not be ignored, and that recognition of this complexity has brought new life to the discussion of systems biology and emergence. The complexity of biological phenomena is receiving renewed attention, and there is an increasing awareness of the incompleteness of molecular and reductionist explanations in biology, as valuable as these may be in their own right.

There are other levels of functioning within biology that manifest complexity. Biology textbooks routinely describe several levels of such functioning, such as organelles, cells, tissues, organs and organ systems, organisms, populations, communities, ecosystems, and the biosphere.[57] These levels manifest their own complexities, complexities that are biological in nature; they cannot be reduced to chemical or physical phenomena, many theoreticians of biology suggest. Such complexities as the regulation of hormone levels, the intricacies of animal behavior, and the control of population sizes all need to have their own place in biology in order to do justice to the integrity of creation and the design of the Creator.[58]

Biological Complexity and Its Theoretical Background

The topic of complexity often transcends biological discussions and touches upon other disciplines and philosophy. The huge changes which occurred in Darwin's century have to be seen in a broader context in which reductionism was present at times and holism at other times. Reaction to the reductionism of Enlightenment thinking of the previous century was thorough. While the Enlightenment emphasized scepticism and exalted reason and science, romanticism in biology (or "natural philosophy," as Erik Nordenskiöld and others call it[59]) accentuated imagination over observation, and showed a fascination with vital forces and a predilection to spin overarching speculative theories. Arthur Lovejoy states:

> The God of the seventeenth century, like its gardeners, always geometrized; the God of Romanticism was one in whose universe things grew wild and without trimming and in all the rich diversity of their natural shapes.[60]

It is safe to say that accepting complexity was not a problem for romantic biologists.

One of romanticism's most accomplished representatives, Johannes Peter Müller, had many interests. In an early paper, he speculated about numbers and identities in biology, a speculative work which he later tried to destroy. He then continued the work of Goethe and Purkinje on sensory perception; this affected his mental well-being. Later in his life, he studied nerves, muscles, and other organ systems, and carried out marine research. Müller illustrates that researchers could move from the purest speculation at the height of romanticism to biological laboratory work that we still find in our textbooks today. Nordenskiöld suggests that Müller's "mental disease involved the downfall of natural philosophy in Germany."[61]

One overarching theory that gained currency in the romantic age, idealism in biology, suggests that basic building plans, "archetypes" for some, are structural laws or types for plants or animals, or large basic groups of plants or animals.[62] This pattern of thinking also left its mark on North American biology, perhaps most markedly through the lectures and writings of J. Louis R. Agassiz. This prominent Swiss biologist accepted a position at Harvard University, where he promoted idealistic thinking in morphology and classification. For Agassiz, types or forms are created; there are timeless designs for taxa, including species. Agassiz would encounter a capable opponent in Asa Gray, eminent Christian botanist and friend of Charles Darwin. Gray suggested that God steered natural selection by providing favorable mutations to the process. He debated common descent with Louis Agassiz in writing and in public discussions.[63]

While Agassiz held on to these views until his death, it can nevertheless be said that after these debates, idealistic notions of organismal structure and design were on the wane in the mainstream of North American biology. Darwin, due to illness or personality, was wont to have other people fight his theoretical battles for him. Thomas H. Huxley and Ernst H.P.A. Haeckel, both combative persons, were only too happy to oblige;[64] they did much to spread Darwin's nonessentialist, nonidealist views.

Darwin's ideas filled the void left by the romantics, or, it could be said, they were the last nail in their coffin. As we think about holism and biological complexity, we recognize that Darwin's views in *The Origin* were not reductionist or physicalist regarding biological phenomena. In the closing paragraph of the first edition of *The Origin of Species*, Darwin seems to favor a biological origin of organisms:

> There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.

In an 1871 letter to his friend, Joseph Hooker, Darwin states a more physicalist view:

> It is often said that all the conditions for the first production of a living organism are now present, which could ever have been present. But if (and oh what a big if) we could conceive in some warm little pond with all sorts of ammonia and phosphoric salts, - light, heat, electricity &c. present, that a protein compound was chemically formed, ready to undergo still more complex changes, at the present day such matter wd be instantly devoured, or absorbed, which would not have been the case before living creatures were formed.[65]

Thus, as is often the case with Darwin, he gives us two points of view, in this case, a nonphysicalist and a physicalist view. Wavering between two opinions is typical of Darwin's way of thinking.[66] In his extensive use of biological examples in *The Origin*, Darwin shows appreciation for biological complexity on several levels.

The pendulum between reductionist and holistic views swung again in the second half of the twentieth century. Molecular genetics and molecular approaches in such specializations as physiology, microbiology, and even classification would make many contributions, but would also lead, in some cases, to reductionism and physicalism. It is against these reductionist trends in biology that complexity thinking reacted. The great theoretician of American biology, Ernst Mayr, states,

> The claim of an autonomy of the science of living organisms … has been rather unpopular with many physical scientists and philosophers of the physical sciences. They have reacted by asserting that the seeming autonomy of the world of life does not really exist, but that all the theories of biology can, at least in principle, be reduced to theories of physics. This, they claim, restores the unity of science.[67]

Mayr then gives a helpful description of three different meanings or categories of "reductionism." He adds,

> This discussion of reductionism can be summarized by saying that the analysis of systems is a valuable method, but that attempts at a "reduction" of purely biological phenomena or concepts to laws of the physical sciences has rarely, if ever, led to any advance in our understanding. Reduction is at best a vacuous, but more often a thoroughly misleading and futile, approach. This futility is particularly well illustrated by the phenomenon of emergence.[68]

Precisely! We hope to discuss emergence, and the related topics of levels of complexity and hierarchies in a separate paper in preparation, while one of us (HB) is writing a paper on systems biology.

Complexity: An Emerging Discipline Today

As is to be expected, "complexity" is often used in its everyday meaning to describe biological phenomena, and, indeed, many complexities in biology readily come to mind. It is an interesting topic, therefore, to explore, what it is that defines complexity science. Complexity as a field of study is covered by a number of journals, and the Santa Fe Institute, in Santa Fe, New Mexico, is dedicated to the study of complexity in various guises. The institute recently sponsored a symposium on complexity and published the proceedings.[69] In an introduction to the volume, cosmologist/physicist Paul Davies states, "The study of complexity is hampered by the lack of a generally accepted definition."[70]

Peter Corning comments, "Unfortunately, the Templeton/Santa Fe symposium participants were partial to the definitions that have been developed by physicists, computer scientists, and information theorists, but this is ultimately an unsatisfactory approach to defining biological complexity." He further comments on the nature of complexity:

> What in fact does the word "complexity" connote? One of the leaders in the complexity field, Seth Lloyd of MIT, took the trouble to compile a list of some three dozen ways in which the term is used in scientific discourse. However, this exercise produced no blinding insight. When asked to define complexity, Lloyd [replied]: 'I can't define it for you, but I know it when I see it.' Rather than trying to define the properties that are commonly associated with the term, I would suggest that complexity often (not always) implies the following attributes: (1) a complex phenomenon consists of many parts (or items, or units, or individuals); (2) there are many relationships/interactions among the parts; and (3) the parts produce combined effects (synergies) that are not easily predicted and may often be novel, unexpected, even surprising.[71]

Some of the characteristics that Corning mentions will be addressed in our description of complexity.

As Corning states, some authors propose that the intricacies of complexity can be mastered with the use of computers or mathematics. For example, while Heinz R. Pagels, in an early book on complexity, recognizes a host and variety of complexities, he nevertheless suggests that the coupled capacity of computers and of human reason can help us understand the vast complexities that surround us in science and in daily life.[72] More recently, yet pursuing a similar path, Melanie Mitchell described the lack of agreement about defining complexity and its associated problems and stressed the importance of mathematics, computers, modeling, simulation, and networks in describing and studying complexity. Using computational techniques and modeling, Luis Rocha develops his theory of adaptivity and applies it to a variety of biological systems.[73] Similarly, C. S. Holling, studying diverse populations and ecosystems, uses modeling to develop his idea of resilience in ecological systems.[74] The characteristic of resilience may be applied to biological systems at other levels and to systems not discussed in this article. Without detracting from the work of these thinkers, and in agreement with Corning, we would suggest that the definition of complexity in single-celled organisms, in plants, in animals, and, indeed, in human life, requires descriptors that do justice to their separate and emergent levels of complexity.

Barbara J. Crowe, in a book that applies "complexity science" to her field of music therapy, is more definite when discussing the characteristics of complexity theory. Contrary to "empirical" (i.e., reductionist) science, as she calls it, complexity science provides helpful insights into her field, she suggests. She relates complexity to chaos theory (and the order that can emerge from chaos), unpredictability, nonlinearity, and wholeness. She concludes, "Complexity is about the real world."[75]

Although it has been difficult or impossible for thinkers to agree upon a definition of complexity in general, we will propose a description of complexity in biological structures and phenomena. This description will consist of two parts: (1) the inherent structure of living organisms, including the dynamic processes in, and related to, biological organisms, and (2) the concepts of wholeness (holism) and levels of functioning as they apply to the biological world.

The structure of cellular organelles, cells, organs, unicellular organisms, plants, and animals—the list could be made longer—is a significant part of biological complexity. We have illustrated this in the first part of our article, dealing with the relationship between nucleus and cytoplasm, and with epigenetic inheritance. In the cell, organelles, such as mitochondria, chloroplasts, and the structures involved in genetic mechanisms, are now well understood, and are known to "interact in space and time."[76] They are in a "perpetual state of transformation." Olaf Wolkenhauer and Allan Muir discuss the functional dynamics of cells—both unicellular organisms and cells that are components of organisms—mentioning the intricacies of the cell cycle, the "self-fabrication" of cells, metabolism, cell-signaling, and gene expression.[77] Thus, the structures within the cell and the dynamic processes in which they are involved are a noteworthy component of biological complexity.

When one examines multicellular organisms, plants or animals, the functions mentioned above still play a role, but we also encounter the structures and processes involved in homeostasis, sexual or asexual reproduction, and embryonic development,

growth, and differentiation (we do not distinguish between plants and animals at this time). Other complexities are notable when one examines organs, populations, and ecosystems. We conclude that at all levels of complexity studied within the discipline of biology, we find structures and processes that are an integral part of biological complexity, a part that cannot be expressed in the language of mathematics, statistics, or the computer.

A second characteristic of biotic complexity is that entities such as cells, organs, organisms, and populations, present themselves on several levels within the biological purview, as we mention above. Mayr states that in biology one deals with

> constitutive hierarchies, like the series macromolecule, cellular organelle, cell, tissue, organ, and so forth. In such a hierarchy the members of a lower level, let us say tissues, are combined into new units (organs) that have unitary functions and emergent properties. The formation of constitutive hierarchies is one of the most characteristic properties of living organisms. At each level there are different problems, different questions to be asked, and different theories to be formulated.[78]

We would add that as one moves from molecules to cells, a qualitative boundary is crossed that is different from the boundaries between the other levels of the part-whole hierarchy that Mayr mentions. We will discuss this topic more fully in a paper that we are preparing on emergence theory. Recognition of levels of functioning above the physical level is in direct opposition to the reductionism that we have mentioned above.

This "multileveledness," as it is sometimes designated,[79] has significant implications. Mayr states, "[N]ew and previously unpredictable characters emerge at higher levels of complexity in hierarchical systems."[80] For example, the behavior of stampeding bison cannot be predicted by studying their cells or organs. Studies at every level will reveal new kinds of structures, phenomena, and processes with new laws to govern them. In our paper on emergence, we will need to distinguish between various hierarchies: part-whole hierarchies, and hierarchies in levels of functioning and levels of structure.

Furthermore, the configurations and processes of a given lower level will be constrained and limited by the uses to which they are put in the level(s) above. For example, although there are many possible nucleotide sequences in a DNA molecule of a given length, only some of these sequences occur in DNA that functions in a particular living organism. Thus, Küppers states that a higher level can impose "boundary conditions" upon a lower level.[81]

Conclusions

Our discussion of the role of the cytoplasm and nucleus in the cell, and of epigenesis, illustrates the idea of complexity as it is used by scientists. These phenomena display complexity of structure and process, and they draw on functions at the physical level (e.g., DNA) and several levels of complexity within biology. The recognition of, and emphasis on, the complexities of biological phenomena and structures is a holistic response to the reductionism displayed by some molecular biologists in the second half of the twentieth century. We suggested that this kind of complexity should be defined or described in biological terms, and we gave two detailed examples.

Complexity leads into a discussion of systems biology and emergence, two topics we hope to return to later. Recognition of complexity and emergence should gain currency among Christian thinkers as they seek to do justice to created reality. The resurgence of discussions of complexity has led to an increased openness to theistic points of view.[82] A holistic view of biological processes and structures acknowledges the complexity in creation, a complexity that reveals the wisdom of the Creator.

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Notes

[1]Lindley Darden, "William Bateson and the Promise of Mendelism," *Journal of the History of Biology*10 (1977): 87–106.
[2]William Bateson, *Mendel's Principles of Heredity* (Cambridge: Cambridge University Press, 1909).
[3]Darden, "William Bateson," 98; Stuart Newman, "William Bateson's Physicalist Ideas," in *From Embryology to Evo-Devo: A History of Developmental Evolution,* ed. Manfred D. Laublicher and Jane Maienschein (Cambridge, MA: MIT Press, 2007), 83–107.
[4]Garland E. Allen, *Thomas Hunt Morgan: The Man and His Science* (Princeton: Princeton University Press, 1978); John A. Moore, "Science as a Way of Knowing—III Genetics, Proceedings, Symposium at the Annual Meeting of the

American Society of Zoologists" (Baltimore, MD: 1985), 583–747; Peter J. Bowler, *The Mendelian Revolution: The Emergence of Hereditarian Concepts in Modern Science and Society* (London: The Athlone Press, 2001), 130–7.

[5]Thomas Hunt Morgan, *The Theory of the Gene* (New Haven, CT: Yale University Press, 1926; reprint, New York: Garland Publishing, 1988), 26.

[6]Evelyn Fox Keller, *Refiguring Life: Metaphors of Twentieth-Century Biology* (New York: Columbia University Press, 1995), 3–35.

[7]Thomas Hunt Morgan, "Mendelian Heredity in Relation to Cytology," in *General Cytology*, ed. E. V. Cowdry (Chicago: University of Chicago Press, 1924), 691–734; cited from Keller, *Refiguring Life,* 7.

[8]Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (New York: Oxford University Press, 1987), 3–31. See also James Griesemer, "Tracking Organic Processes: Representations and Research Styles in Classical Embryology and Genetics," in *From Embryology to Evo-Devo,* ed. Laublicher and Maienschein, 375–433.

[9]Thomas Hunt Morgan, *Embryology and Genetics* (New York: Columbia University Press, 1934), 9; cited from Keller, *Refiguring Life,* 14; Griesemer, "Tracking Organic Processes," adds that Morgan's intention was not to ignore the role of the cytoplasm, but, rather, to "clarify and negotiate shared understanding and cooperation among diverging specialties—a task of unification, not segregation."

[10]Eric H. Davidson, *Gene Activity in Early Development* (New York: Academic Press, 1968); Scott F. Gilbert, "Induction and the Origins of Developmental Genetics," in *A Conceptual History of Modern Embryology*, Developmental Biology: A Comprehensive Synthesis, vol. 7, ed. Scott F. Gilbert (New York: Plenum Press, 1991), 181–206; Jan Sapp, "Concepts of Organization," in *Conceptual History*, ed. Gilbert, 229–58.

[11]Paul Weindling, "Darwinism in Germany," in *The Darwinian Heritage*, ed. David Kohn (Princeton, NJ: Princeton University Press, 1985), 683–730.

[12]Keller, *Refiguring Life,* 36.

[13]Jan Sapp, *Beyond the Gene,* 54–86. See also Jonathan Harwood, *Styles of Scientific Thought: The German Genetics Community 1900–1933* (Chicago, IL: University of Chicago Press, 1993) 61–84, 315–50.

[14]Evelyn Fox Keller, "Developmental Biology as a Feminist Cause?" *Osiris* 12 (1995): 16–28; Keller, *Refiguring Life,* 38–40.

[15]J. D. Watson and F. H. C. Crick, "Molecular Structure of Nucleic Acids," *Nature* 271 (1953): 737–8.

[16]Franklin H. Portugal and Jack S. Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance* (Cambridge, MA: MIT Press, 1977); Lois N. Magner, *A History of the Life Sciences*, 3d ed. (New York: Marcel Dekker, 2002), 417–69.

[17]Francis H. C. Crick, "On Protein Synthesis," in *The Biological Replication of Macromolecules*, Symposia of the Society for Experimental Biology, vol. 12 (Cambridge: Cambridge University Press, 1958), 138–63.

[18]Lily E. Kay, in *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford, CA: Stanford University Press, 2000), wrote a detailed and insightful description of the history and nature of the genetic code. The role of RNA, which receives attention in chapters 4 and 5, emphasizes one of the important processes that occur in the cytoplasm.

[19]Francis Crick, *What Mad Pursuit: A Personal View of Scientific Discovery* (New York: Basic Books, 1988), 109.

[20]David Baltimore, "Viral RNA-Dependent DNA Polymerase," *Nature* 226 (1970): 1209–11; Howard Temin, "RNA-Dependent DNA Polymerase in Virions of Rous Sarcoma Virus," *Nature* 226 (1970): 1211–13.

[21]Francis Crick, "Central Dogma of Molecular Biology," *Nature* 227 (1970): 561–3.

[22]Clifford Grobstein, "The Recombinant-DNA Debate," *Scientific American* 237, no. 1 (1977): 22–33; Harry Cook, "The Biology Business," *Journal of the American Scientific Affiliation* 34, (1982): 129–34.

[23]Kary B. Mullis, François Ferré, and Richard A. Gibbs, eds., *The Polymerase Chain Reaction* (Boston, MA: Birkhäuser, 1994).

[24]R. C. Lewontin, "The Dream of the Human Genome," *The New York Review of Books* (28 May 1992), 31–40.

[25]For a good discussion of the origin and the use of the term, see Lewontin, "The Dream of the Human Genome."

[26]J. Craig Venter, *A Life Decoded: My Genome, My Life* (New York: Viking, 2007).

[27]"On the great day, happily, all the rivalries were swept aside by everyone's feeling of being part of an historic achievement" (Venter, *A Life Decoded,* 311).

[28]Francis S. Collins, *The Language of God: A Scientist Presents Evidence for Belief* (New York: Free Press, 2006); *The Language of Life: DNA and the Revolution in Personalized Medicine* (New York: HarperCollins, 2010).

[29]Edward O. Wilson, *Sociobiology: The New Synthesis* (Cambridge, MA: Belknap Press of Harvard University Press, 1975). A book that has been foundational in behavioral ecology and that has gone through four editions, from 1978 to 1997, is John R. Krebs and Nicholas B. Davies, eds., *Behavioural Ecology: An Evolutionary Approach*, 4th ed. (Oxford: Blackwell Science Ltd, 1997); all four editions of this book have been edited by the same two persons, and each contains chapters that were written especially for that edition. For a thorough outline and critique of evolutionary psychology, see David J. Buller, *Adapting Minds: Evolutionary Psychology and the Persistent Quest for Human Nature* (Cambridge, MA: MIT Press, 2005). A voluminous literature critiques these three subdisciplines.

[30]Erica Check Hayden, "Life Is Complicated," *Nature* 464 (2010): 664–7.

[31]See, e.g., Arthur D. Lander, "The Edges of Understanding," *BMC Biology* 8, no. 40 (2010): 1–4.

[32]Evelyn Fox Keller, *The Century of the Gene* (Cambridge, MA: Harvard University Press, 2000).

[33]Keller, *Century of the Gene,* 5, 45–72

[34]Ibid., 55–9; W. Wayt Gibbs discussed the important role that "non-coding DNA" is being shown to have in "The Unseen Genome: Gems Among the Junk," *Scientific American* 289 (2003): 46–53.

[35]Keller, *Century of the Gene,* 66–9

[36]Ibid., 72.

[37]Ibid., 136–7.

[38]Ibid., 143.

[39]Jerry A. Coyne, "The Gene Is Dead; Long Live the Gene," *Nature* 408 (2000): 26–7; Sean B. Carroll, "Communication Breakdown?" *Science* 291 (2001): 1264–65.

[40]Don W. Fawcett, *An Atlas of Fine Structure: The Cell, Its Organelles and Inclusions* (Philadelphia, PA: W.B. Saunders Company, 1966).

[41]We are indebted for these historical details to Jan Lever, *Geïntegreerde Biologie* (Utrecht: Oosthoek, 1973), 94–5.
[42]Nick Lane, *Power, Sex, Suicide: Mitochondria and the Meaning of Life* (Oxford: Oxford University Press, 2005), 242–57.
[43]Ibid., 242–6.
[44]Lynn Sagan, "On the Origin of Mitosing Cells," *Journal of Theoretical Biology* 14, no. 3 (1967): 255–74 (Margulis was married to astronomer Carl Sagan at the time of publication); Lynn Margulis, *Origin of Eukaryotic Cells* (New Haven, CT: Yale University Press, 1970).
[45]See William Martin and Klaus V. Kowallik, "Annotated English Translation of Meresckowski's 1905 Paper 'Über Natur und Ursprung der Chromatophoren im Pflanzenreiche,'" *European Journal of Phycology* 34 (1999): 287–95.
[46]Lane, *Power, Sex, Suicide.*
[47]It is noteworthy that Craig Venter recently produced a "synthetic cell" by synthesizing the genome of a bacterium but supplying the cytoplasm of an existing bacterial species. Elizabeth Pennisi, "Synthetic Genome Brings New Life to Bacterium," *Science* 328 (2010): 958–9.
[48]Eva Jablonka and Marion J. Lamb, *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life* (Cambridge, MA: MIT Press, 2005), 113.
[49]J. Bruce Walsh, "The Emperor's New Genes," *Evolution* 50 (1996): 2115–8.
[50]Jablonka and Lamb, *Evolution in Four Dimensions,* 113–46. See also Thaler Roman, Eva Aumüller, Carolin Berner, and Alexander G. Haslberger, "Interaction of Hereditary and Epigenetic Mechanisms in the Regulation of Gene Expression," in *Epigenetics and Human Health: Linking Hereditary, Environmental and Nutritional Aspects,* ed. Alexander G. Haslberger and Sabine Gressler (Weinheim: Wiley-VCH, 2010), 13–34.
[51]Ryan A. Rapp and Jonathan F. Wendel, "Epigenetics and Plant Evolution," *New Phytologist* 168 (2005): 81–91.
[52]Ibid.
[53]Jablonka and Lamb, *Evolution in Four Dimensions,* 126–8.
[54]Rapp and Wendel, "Epigenetics and Plant Evolution."
[55]Eva Jablonka and Marion J. Lamb, *Epigenetic Inheritance and Evolution: The Lamarckian Dimension* (Oxford: Oxford University Press, 1995). For a description of Lamarckism, see Harry Cook and Hank D. Bestman, "A Persistent View: Lamarckian Thought in Early Evolutionary Theories and in Modern Biology," *Perspectives on Science and Christian Faith* 52 (2000): 86–96.
[56]F. J. Bruggeman, H. V. Westerhoff, and F. C. Boogerd, "BioComplexity: A Pluralist Research Strategy Is Necessary for a Mechanistic Explanation of the 'Live' State," *Philosophical Psychology* 15 (2002): 411–40; Hiroaki Kitano, ed., *Foundations of Systems Biology* (Cambridge, MA: MIT Press, 2001).
[57]Neil A. Campbell et al., *Biology*, 8th ed. (San Francisco, CA: Pearson Benjamin Cummings, 2008), 4–5.
[58]Creation reveals the will of the Creator; it fulfills his purposes. Isaiah 28:23–29 professes that growing crops is possible because farmers understand the intricacies of the nature of various crop plants; this, too, is based on the wisdom of the Creator. See also Brian J. Walsh and J. Richard Middleton, *The Transforming Vision: Shaping a Christian World View* (Downers Grove, IL: InterVarsity Press, 1984), 41–56; Jacob Klapwijk, *Purpose in the Living World? Creation and Emergent Evolution* (Cambridge: Cambridge University Press, 2008).
[59]Erik Nordenskiöld, *The History of Biology: A Survey* (New York: Alfred A Knopf, 1932), 286–98.
[60]Arthur O. Lovejoy, *The Great Chain of Being: A Study of the History of an Idea* (New York: Harper and Row, 1936), 16.
[61]Nordenskiöld, *The History of Biology: A Survey*, 384.
[62]See Ernst Mayr, "Agassiz, Darwin, and Evolution," *Harvard Library Bulletin* 13 (1985):165–94. Mayr calls this biological viewpoint "essentialism" in *The Growth of Biological Thought* (Cambridge, MA: Harvard University Press, 1982), 38.
[63]Edward Lurie, "Agassiz and the Idea of Evolution," *Victorian Studies* 3 (Sept. 1959): 87–108; Edward Lurie, *Louis Agassiz: A Life in Science* (Chicago, IL: University of Chicago Press, 1960), 252–302.
[64]Adrian Desmond and James Moore, *Darwin: The Life of a Tormented Evolutionist* (New York: Warner Books, 1991).
[65]Quoted from Janet Browne, *Charles Darwin: The Power of Place* (Princeton, NJ: Princeton University Press, 2002), 392–3. The abbreviations are Darwin's.
[66]Harry Cook and John R. Wood, "Looking at Nature through Other Eyes: God's Governance of Nature in the Religion-Science Debate," *Christian Scholar's Review* 39 (2010): 411–40.
[67]Mayr, *The Growth of Biological Thought,* 59.
[68]Ibid., 63.
[69]Niels Henrik Gregersen, ed., *From Complexity to Life: On the Emergence of Life and Meaning* (Oxford: Oxford University Press, 2003).
[70]Paul Davies, "Introduction: Toward an Emergentist Worldview" in Gregersen, *From Complexity to Life*, 3–16.
[71]Peter A. Corning, "Book Review Essay" of *Technological Forecasting and Social Change* (2004) www.complexsystems.org/essays/ReviewComplexity.htm (last accessed May 28, 2011).
[72]Heinz R. Pagels, *The Dreams of Reason: The Computer and the Rise of the Sciences of Complexity* (New York: Bantam Books, 1989).
[73]See http://informatics.indiana.edu/rocha/lr_form.html (last accessed June 21, 2011).
[74]C. S. Holling, "Resilience and Stability of Ecological Systems," *Annual Review of Ecology and Systematics* 4 (1973): 1–23; Garry Peterson, Craig R. Allen, and C. S. Holling, "Ecological Resilience, Biodiversity, and Scale," *Ecosystems* 1 (1998): 6–18.
[75]Barbara J. Crowe, *Music and Soulmaking: Toward a New Theory of Music Therapy* (Lanham, MD: Scarecrow Press, 2004), 25–50.
[76]Olaf Wolkenhauer and Allan Muir, "The Complexity of Cell-Biological Systems," www.sbi.uni-rostock.de/fileadmin/user_upload/Olaf/SBI_staff_Olaf_ComplexityofBiologicalSystems.pdf (last accessed June 1, 2011).
[77]Wolkenhauer and Muir, "Complexity."
[78]Mayr, *The Growth of Biological Thought,* 65.
[79]Wolkenhauer and Muir, "Complexity."
[80]Mayr, *The Growth of Biological Thought,* 64.
[81]Bernd-Olaf Küppers, "Understanding Complexity," in *Chaos and Complexity: Scientific Perspectives on Divine Action*, ed. R. J. Russell, N. Murphy, and A. Peacocke (Berkeley CA: Center for Theology and the Natural Sciences, 1995), 93–105.
[82]Niels Henrik Gregerson, "From Anthropic Design to Self-Organized Complexity," in *From Complexity to Life: On the Emergence of Life and Meaning*, ed. Niels Henrik Gregerson (Oxford: Oxford University Press, 2003), 206–34.