

Complementarity in Biological Systems: A Complexity View

Niels Bohr and Max Delbruck believed that complementarity—such as wave–particle duality—was not limited to the quantum realm, but had correlates in the study of living things. Biological complementarity would indicate that no single technique or perspective allows comprehensive viewing of all of a biological entity's complete qualities and behaviors; instead, complementary perspectives, necessarily and irrevocably excluding all others at the moment an experimental approach is selected, would be necessary to understand the whole. Systems biology and complexity theory reveal that, as in the quantum realm, experimental observations themselves limit our capacity to understand a biological system completely because of scale-dependent “horizons of knowledge,” a form of biological complementarity as predicted by Bohr and Delbruck. Specifically, observational selection is inherently, irreducibly coupled to observed biological systems as in the quantum realm. These nested systems, beginning with biomolecules in aqueous solution all the way up to the global ecosystem itself, are understood as a seamless whole operating simultaneously and complementarily at various levels. This selection of an observational stance is inseparable from descriptions of biology indicates—in accordance with views of thinkers such as von Neumann, Wigner, and Stapp—that even at levels of scale governed by classical physics, at biological scales, observational choice remains inextricably woven into the establishment, in the observational moment, of the present conditions of existence. These conceptual shifts will not only have theoretical impact, but may point the way to new, successful therapeutic interventions, medically (at the scale of organisms) or environmentally/economically (at a global scale). © 2013 Wiley Periodicals, Inc. Complexity 18: 11–20, 2013

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1. INTRODUCTION

Niels Bohr, the “father of quantum mechanics,” in *Causality and Complementarity*, wrote: “Thus the existence of life itself would have to be regarded in biology, both as regards the possibilities of observation and of definition, as no more subject to analysis than the existence of the quantum of action in atomic physics [1].” In this and similar statements made throughout his life, Bohr indicated an impression with intuitive, scientific and formally philosophical roots, that the complementarity predicted and observed in quantum mechanical investigations—such as the wave–particle duality of light and all quanta—was not limited to the quantum realm, but was a more broadly applicable (perhaps universal)

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concept, which should have correlates in the study of living things [2, 3]. Complementarity in life would indicate that no single technique or perspective allows the comprehensive view of all of a biological entity's complete qualities and behaviors; instead, complementary perspectives, which necessarily and irrevocably exclude all others at the moment an experimental approach is selected, are necessary to understand the whole.

He was not alone in this sentiment. For example, Nobel laureate Max Delbrück was originally a student of physics, but under urgings from Bohr he began to study biology to better identify the nature of biological complementarity [2, 3]. Delbrück's impetus to study bacteriophages, which led to his Nobel prize, originally came from his and Bohr's sense that biological complementarity might best be viewed where experiments revealed contradictory or incomplete findings. Whether viruses were or were not alive seemed a place to start. However, despite how extraordinarily fruitful an area of investigation this turned out to be, it failed to point directly toward a form of biological complementarity.

Aside from a few historians or philosophers of science [2–6], interest in the notion of biological complementarity largely faded away in subsequent decades. Just as quantum mechanical complementarity became apparent when experimental procedures revealed apparent contradictions, biological complementarity had to await the necessary experimental and conceptual advances for it to be recognized. Here, we argue that the ascent of complexity theory, on the one hand, and of systems biology, on the other hand, now reveal important forms of biological complementarity. These concepts, moreover, may have profound impact for experimental design and theoretical implications for harnessing the behaviors of biological systems, advancing biology to its next stage of development.

2. COMPLEXITY OF BIOLOGICAL SYSTEMS

Systems biology is arguably the biology of the 21st Century, though for most scientists and physicians this still does not mean more than computational crunching of enormous data sets generated by genomics, proteomics, metabolomics, and so on. The real task and novelty of systems biology is that it is the reverse of reductionism: all the myriad bits of data obtained by taking biological structures apart are now to be reassembled to better understand the living whole: hence, *holism* as opposed to reductionism.

But this holistic enterprise is clearly not merely the same as putting a watch back together after having taken it apart. Biological systems are far more dynamic, indeed, *alive*. The implications of this shift, from reductionism to holism, are still not yet widely appreciated, but have profound implications for the biological sciences and, perhaps, beyond. In fact, they have implications for the very nature of science itself.

At the same time, most people working in complexity theory and related fields, while championing this broader approach to systems biology, have their own application bias: most often the basic research focuses on the mathematical forms for describing complex systems and/or computational modeling of specific systems. Generalizable principles that link the mathematics of seemingly unrelated phenomena sometimes emerge from such studies, but the methodology, data, and results are often highly specific to the system under study.

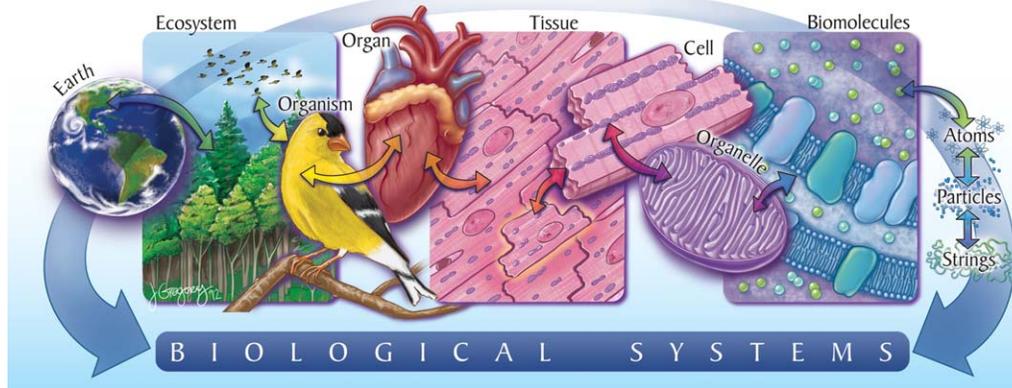
However, with this kind of focus on the details of individual systems, broader implications for understanding that biological systems are always, in fact, systems of systems (of systems...) may be under appreciated. The enormous computational power required for modeling multitier self-organizing systems and their emergent

properties, across more than two adjacent levels of scale, makes broader study difficult, and ultimately it is not even clear that increasingly higher computations will converge onto new knowledge of biological systems. This difficulty, though, should not prevent exploration of general principles of biological “systems of systems” that are implied by the principles of complexity theory as we wish to explore in this essay.

In fact, complexity analysis illuminates these changes by providing a framework to understand how the small bits and pieces self-assemble into larger, biological structures. In brief, complexity describes how interacting agents in biological systems (at least) self-organize into larger scale structures which display *emergent* properties not easily predicted from the characteristics of the individual agents at the lower level of scale or contained in them [7–11]. The whole is more than the sum of the parts.

A simple set of factors promotes the likelihood of emergent self-organization, particularly of *adaptive* self-organization—in which the community of interacting individuals changes the modes of self-organization to adapt to a changing environment—that is the hallmark of life. We argue that this applies to the very existence itself of living entities *and* their environments, as no life can be found devoid of an environment with which it interacts and within which it exists. As such, this organization must ultimately apply to the entire global ecosystem itself. Below we list these factors but also point out how they must break down:

- There must be significant numbers of interacting agents (three birds do not form a flock, two people do not form a village) and the complexity of the system and its potential adaptive strategies increase with increasing numbers (a village is not a city, is not a megalopolis).

FIGURE 1

Hierarchies of complexity and biological complementarity. All biological systems at all levels of scale derive from self-organization of smaller interacting agents. The self-organization leads from lower levels of scale, through increasing complexity of “systems of systems,” to higher levels of scale. At each level of scale, different horizons of knowledge set in. Thus, for example, whether something appears to be a *unitary entity* or *thing* at one level of scale (e.g., a bird at our everyday observational scale) or a *phenomenon* arising from interacting smaller things (e.g., the cells of the bird, the molecules of the cells, etc.) at a lower level of scale depends on the scale of observation. This is the basis for a form of biological complementarity as foreseen by Niels Bohr. The nature of the system depends on a selected observational stance of an investigator, simultaneously revealing details present at the selected scale of observation while obscuring features seen at lower or higher levels of scale than the one selected.

- There must be an overall balance of homeostatic, negative feedback loops (positive feedback loops may be present, but do not predominate).
- The individual agents do not partake of global sensing, but respond primarily to local cues derived from the local environment (including other agents within the local environment). This may be analogous to nonlocality issues arising in entangled quantum systems, where local realism breaks down and is replaced by global non-locality [12–15].
- There must be limited randomness or “quenched disorder” in the system: too much yields no capacity to self-organize, too little does not allow for exploration of new organizational strategies in response to changing conditions. Nevertheless, it is the inherent randomness, as in quantum systems, which provides the creative freedom to adapt.

Single cells can interact with each other and fulfill the second through

fourth criteria described above [10, 11, 16]. When there are sufficient numbers of them to do so, they organize into communities the way ants, birds, people, and the wider diversity of other living beings organize into communities such as, for example, ant colonies, flocks of birds, cities or cultures, and ecosystems, respectively. Some of these cellular colonies achieve such a high level of sustained interactivity that we call them multicellular organisms, though some life forms, such as slime molds, hold an intermediate ground: sometimes a dispersed colony, sometimes a sustained body [42].

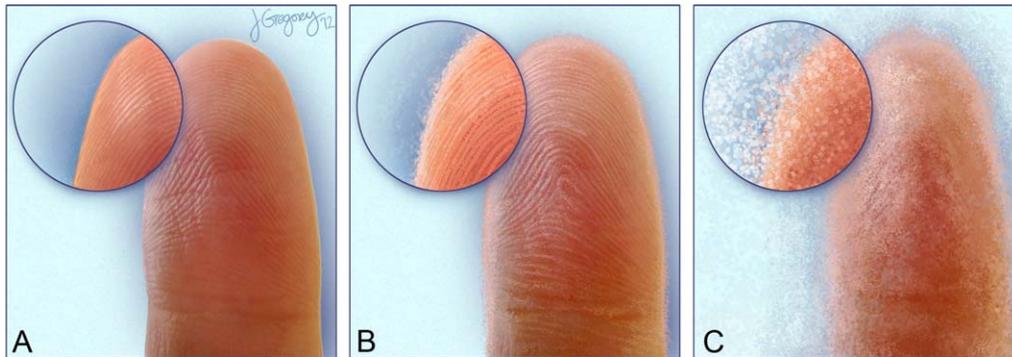
3. BIOLOGICAL COMPLEMENTARITY: CELL THEORY DETHRONED

This brief description highlights an interesting, but little discussed implication of a true systems biology approach: biological systems can be described as nested or overlapping levels of organization whose definition depends on the scale of observation

(Figure 1). In this sense, they are not absolute, in analogy to quantum properties which take on specific values upon acts of observation. What appears to be a unitary (however mobile) entity at one level of scale (a flock of birds, a school of fish, and a green grass prairie) resolves at a lower scale into interacting component organisms; in turn, each animal or plant, when observed at the microscopic scale, dissolves into interacting, self-organizing cells. Our own bodies are, of course, no different: we are individuals or we are a colony of single cells, some of which contain our own genetic material, but most of which are a very diverse collection of bacteria [8, 17] (Figure 2).

Thus, whether something appears as a unitary thing or an intricate, interactive dance of smaller things depends on the scale of observation. Furthermore, this dependence on scale of observation has a corollary: the view from one perspective necessarily obscures the ability to describe and

FIGURE 2



Holistic versus reductionist perception. Common reductionist inclinations can lead to an underdeveloped view of complementarity as merely reflecting ever more spatially restricted views as one moves downward through levels of scale (Figure 1); rather, the entire biological entity under examination comprises all the superimposed components and processes at all levels of scale simultaneously, mutually affecting each other, in a holistic overlay. We may tentatively suggest analogy between this macroscale holism and the *superposition* of all quantum mechanical possibilities in the uncollapsed wave function prior to observation. Discerning the relevant views at each level of scale is constrained by applicable horizons of knowledge. As with light wave/particle duality, though light is the totality of the complementary views, any single view excludes the others in the moment of experimental observation. Thus, if the reader looks at his/her own finger at the every day scale, it looks like an anatomic structure bounded by skin and having defined features like a fingerprint, apparently determined by human genetic inheritance (A). However, simultaneous with that view, at the microscopic level the functional, living human finger is not bounded by the skin layer: it is a less well-bounded community of interacting cells, human (e.g., squamocytes that are sloughed into the environment as they die) and bacterial (e.g., that breakdown cellular debris to produce lubricants for skin at the joint folds [41]) (B). Also, simultaneously, the finger is a collection of atoms and (bio)molecules in aqueous solution, being exchanged as a cloud-like phenomenon with the environment through physiologic processes like respiration and perspiration (C). Analysis could, of course, be extended downward into the quantum realm. Thus, the fully functional finger arises from all levels of scale, each influencing those above and below, simultaneously and holistically. Complementarity indicates both that the totality cannot be investigated comprehensively, all at once, and that the nature of biological boundaries (and therefore the nature of the biological subject) changes with different observational stances.

assess relevant features that manifest at other levels of scale, above and below, though of course such features garnered by observations at other levels of scale can certainly inform our understanding of any particular scale. Thus, we come to the tantalizing similarity to the role of the observer in quantum systems. This observation dependence is precisely a form of complementarity hinted at, though imprecisely conceptualized, by Bohr, Delbruck, and their colleagues [1–3]. In other words, as one approaches the observational limit, complementarity must be evoked to allow a more complete description of the components under observation.

The centrality of classical cell theory, as the foundational doctrine of Western biology and medicine, is the first victim of the recognition of biological complementarity. Classical biol-

ogy implicitly assumed that there is a biological reality independently of the observational situation setup to reveal that reality. This is simply not true. The ancient philosophical debate as to whether a body is an endlessly divisible fluid continuum or made of a finite number of indivisible subunits was settled when the microscope revealed empty boxes, like the *cells* of monks or prisoners, devoid of furniture. As empty cells could not be further subdivided, the cell became the defining unit of life. But is it?

We can go down a further level of scale, to nanometer lengths, and recognize that cells also have no defined, unitary, inherent existence, but—just as flocks resolve into birds, and bodies into cells—cells also dissolve from view, resolving into the interactive, self-organizing dance of atoms and molecules afloat in aqueous solution [18–

21]. Thus, an alternate, equally verifiable, and potentially powerful model of the body—a classical *fluid theory*, perhaps—is born [17, 18]. Such a fluid theory may be useful to explain biological phenomena that remain unexplained by cell theory. For example, acupuncture, for which no anatomic correlates to meridians and acupoints have been identified. If one cannot explain acupuncture in terms of anatomy, how can one explain it in terms of the building blocks of anatomy, namely cells? As yet, no one has made substantial progress in such efforts. However, that a fluid model of acupuncture might be more powerfully descriptive is seen in the work of Yang and colleagues [22], who recently showed that the initiation and propagation of acoustic waves through tissue is related to the location of acupoints and meridians.

We note here that in the quantum theoretical framework of modern physics, atoms themselves are not the ultimate building blocks of the universe, composed themselves of elementary particles (protons, neutrons, and electrons, protons and neutrons in turn made of more fundamental particles, quarks, etc.), interacting with other particles and with photons, and so on, in hierarchies of interactions [23, 24]. We do not know yet what quantum field theory of particles will turn out to be valid, beyond the so-called “standard model,” supersymmetry, supergravity, or string theories, but in most physicists’ view, all particles should reduce into (the yet unverified) strings, which are just vibrations of the unified field. In quantum field theory, elementary particles continue to be dissolved into more fundamental particles, until the Planck level of scale, where space-time itself breaks down. As such, both in biological systems and in quantum systems, it is the *process of interactions* that is central, which can be more closely described in terms of fluidity, rather than *hard, unchanging* physical objects. If strings are the ultimate structures of a vibrating field, what does this tell us about quantum, molecular, and cell biology?

4. BOUNDARY SELECTION, UNCERTAINTY, AND INCOMPLETENESS

Studying how complex systems work requires determining the rules or *axioms* that govern the interactions between agents and between them and their local environments within the system. Computational modeling of systems based on these axioms then generates a virtual living system that may or may not mirror the real-time living system being studied, depending on how accurately the virtual system captures the rules of interaction in the living system [8–11, 16, 25, 26]. If the virtual self-organization looks nothing like that of the real world system, then

several kinds of adjustments can be made, including (but not limited to) re-evaluation of the axioms describing interactions, changing the number of interacting agents, or varying the degree of quenched disorder in the system.

Implicit in this analytic process is the establishment of boundaries between those agents and environmental features that are to be included in the defined system and those that are excluded. Inevitably, there will be selection of agents and an environment that define the system observationally in the natural world or experimentally (e.g., individual cells in culture, intact tissues, or organs maintained *ex vivo*, whole organisms in small, model environments, aboriginal communities visited by anthropologists) and this selection necessarily excludes others.

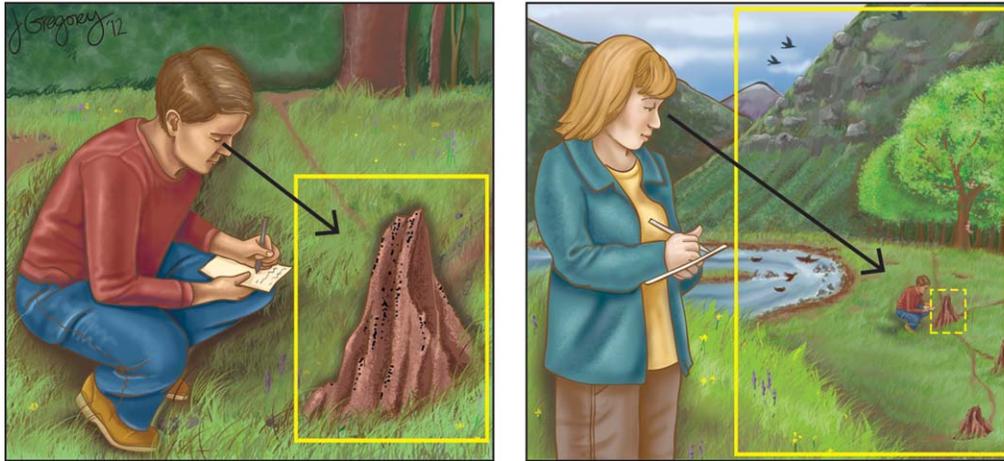
Thus, modeling of complex systems in all but the case of modeling the entirety of a living system across all levels of scale (a provisional example, for our current purposes, being a complete modeling, say, of all life on earth), are steps toward holism, but are also still reductionist as selection of boundaries for observation/experimentation are unavoidable. This is where the whole conundrum lies, the parts-whole complementarity [12, 15]. Kafatos et al. [12, 13] refers to the levels where complementarity sets in, as these levels are approached, as *horizons of knowledge*. These are determined by physical constants (such as quantum complementarities at the atomic scales determined by Planck’s constant), coupling complementary pairs such as momentum and position.

This inherent reductionism—even during systems biologic attempts at holism—yields an inherent *uncertainty* in all our descriptions of biological systems related to the necessary incompleteness (perhaps in a Gödelian sense) of our models. Like Heisenberg’s uncertainty in the quantum realm, this biological uncertainty can-

not be overcome by better, novel technologies not yet invented. Like quantum uncertainty, *any attempt to study a system will necessarily change the nature of the system being studied, either by experimentally/physically abstracting it from its larger context or by conceptually isolating it from some of its inputs by drawing restrictive boundaries around the system in the process of modeling.*

Bohr himself pointed out that studying a biological organism, for example, by breaking it up into parts, changes its nature, as compared to a similar organism not being tampered with (i.e., *in vitro* vs. *in vivo*). In the case of cell biology, Potten and Loeffler [27] first described “cellular uncertainty” stating: “One of the major difficulties in considering stem cells is that they are defined in terms of their functional capabilities which can be assessed only by testing the abilities of the cells, which itself may alter their characteristics during the assay procedure: a situation similar to the uncertainty principle in physics.” Theise and Krause [17, 28, 29] came to similar conclusions, also through studying adult stem cells, though recognizing that the uncertainty is not limited to stem cells, alone. They stated the principle thus: “any attempt to analyze a cell necessarily alters the nature of the cell at the time of isolation, thereby altering outcomes of subsequent differentiation events.” This uncertainty can be reduced, but not eliminated, in part because of the unavoidability of boundary selection, but also, in part, because of the inherent quenched disorder in all systems.

Moreover, the issues of boundary selection reach an even higher level of urgency when we realize that the selection process is usually performed to exclude the observer from the observed system, but this is the heart of the issue: all biological systems, as complex systems, are exquisitely sensitive to any perturbation, however

FIGURE 3

Boundary selection of nonlinear systems: inseparability of observer and observed. All biological systems are complex, nonlinear systems; as such, they are exquisitely sensitive to small changes in starting conditions or small perturbations. Thus, while any experimental evaluation of a biological system involves an investigational observer setting boundary conditions around that system, separating the observer from the observed and thereby seemingly preserving the division between them (Left: an entomologist studying an ant colony), they are also—necessarily—a coupled system that can be observed from yet a higher level with boundaries that enclose the lower level observer with the observed (Right: an ecologist studying an ecosystem). The view of the ecologist highlights the conditional nature of the entomologist's “observational boundary”: despite the entomologist's boundary selection, one can see that he is in fact is now coupled with the ecosystem in which he studies the colony, disrupting other coupled systems: other ant colonies, flora near the ant colony, birds, and mammals that might interact with the colony, and so on. Thus, in direct analogy to the observational problems in the quantum realm, there is inherent experimental uncertainty and the act of observation always modifies the biological system under study.

minor—the act of investigation necessarily implicates the observer in altering the studied system to some degree, whether it be by interfering with microenvironments of cells at the microscopic level [17, 18, 28] to inserting the observer into the ecosystem at a macroscale (Figure 3). The mathematics of nonlinear chaotic or complex systems defines this exquisite sensitivity to initial starting conditions—the oft quoted flap of the butterfly wing in the southern hemisphere potentially leading to hurricane formation in the northern hemisphere [30].

The use of double-blinded, placebo-controlled trials for studying therapeutic interventions is an example of how these issues of uncertainty and boundary conditions can be addressed in biological studies. The observing, treating clinician in any study may influence the outcomes of therapeutic interventions through very

subtle changes in behavior or language. Use of a double-blinded placebo assures that this intertwining of observer (study clinician) and observed (patient/subject) is accounted for in measuring study outcomes. Thus, such studies are an example where traditional 20th Century approaches already take these current, larger concerns into consideration and come up with solutions that are robust and clarifying. What is needed is for all studies of biological systems to consider similar controls for their experiments, if possible. Thus, one possible solution is for versions of double-blinded placebo-controlled studies to be considered for molecular biology, cell biology, tissue biology, ecology, and so on.

This complexity-based analysis of biological systems overlaps significantly with the field of developmental systems theory (DST), a “fellow traveler” to the considerations herein (DST founda-

tional thinker Susan Oyama, personal communication) which initially studied and described the processes of organism development such as in animals where it would describe the conceptual and theoretical aspects of embryonic and fetal development [31]. DST enhanced our understanding of the development of organisms by moving beyond the merely genetic regulation of events by showing how these are enmeshed of a broad web of mechanisms that include epigenetics at the molecular level and, more radically, mechanisms at levels of scale beyond the merely molecular. It did so by creating a more generalized view of “inheritance,” describing how aspects outside the body or bodies giving rise to new life could also be inherited, yet outside of genetic/epigenetic processes.

Hence, in what should not be a surprise, development in the womb is subject to the physiochemical

properties of the maternal environment. Once one starts to move outside of the genes and their transcriptional machinery into the body (a change in scale, in part), there is no logical reason to stop there. One must then consider the environment in which the coupled maternal-fetal system finds itself and one cannot end the analysis at birth. A simple example would be how the physical structure of a community's environment (e.g., the physical structure of a beaver dam or of a wasp nest) is in fact also inherited, further conditioning the development of subsequent generations. Expanding further outward, one then must describe inheritance of "culture" that also significantly impacts on the development of individuals and of the living community as a whole. DST thus conceptually encompasses not just embryologic and fetal development, per se, but is inclusive also of the entire lifespan of the organism, the community of organisms, and the emergence of all biology at all levels of scale, including, ultimately, the global ecosystem itself [31].

Here are two examples of how selection of boundaries can impact on our methodologies for biological investigation, the likelihood of success of such studies, and the possibility for their practical application.

- Adult stem cells can be studied in culture and much can be usefully discerned about their internal physiological processes and how these can specifically, dynamically respond to carefully calibrated factors in their microenvironment [32]. However, isolated cells in culture, even when culture conditions are finely tuned to mimic the environment of the cell in its normative, in-tissue niche, are not being subjected to the dynamic interplay present in the intact niche.

Thus, one may study stem cells in isolation or in purified communities, but greater accuracy in modeling of stem cell behaviors requires including

the cell:cell and cell:matrix interactions within the body's intact niche, including aspects as diverse as inflammatory cell inputs (with all the diverse cell types of the immune system, particularly when disease/injury activates the niche), innervation, blood flow, stiffness of the microenvironment, cytokine/chemokine gradients, chemical gradients (such as bile salts in the liver stem cell niche), myofibroblasts, physical contact with differentiated progeny of stem cells, and so on. [33].

That the immediate environment of the niche itself, modeled in this more complex fashion is still incomplete, however, rapidly becomes apparent when one takes an observational step further outward. The innervation inputs come from the central nervous system from the brain, inflammatory, and hematopoietic cells come from the marrow, spleen, thymus, blood flow is conditioned by functioning of the heart, hormonal regulation of the niche reaches the niche from all sorts of other organ systems, and so on. [34]

- A common pathophysiologic change in the aging human esophagus—Barrett's esophagus—is the replacement of the normal squamous lining epithelium by intestinal-type, mucin-producing, columnar epithelium in response to reflux of gastric juices into the lower esophagus. The clinical importance is that this shift is a step toward malignancy. Recently, Yang et al. [35] have demonstrated that there is a simultaneous shift in the composition of the baseline bacterial flora of this region of the esophagus. As this report's authors point out, it remains uncertain whether the shift in flora is a response to the shift in epithelial lining on the one hand or a primary cause of the shift on the other hand.

Thus, the alteration in the human tissue is a dynamic interplay between the human cells and the nonhuman cells in the region. If one just models

the human esophageal lining, one will miss the contribution of the flora. If one models only the bacterial flora, one may miss the impact of the epithelial responsiveness to the environment. Both such reductive modeling attempts will undoubtedly help garner interesting insights into the pathobiology of Barrett's esophagus, but some things will be missed. However, modeling the two communities—the human and the nonhuman—as one larger, interlocked, highly coupled community will be still more accurate, more complete, and more revealing of the human disease [36]. Such an approach is likelier to achieve the practical goal of better treatment of the disease and prevention of the subsequent development of cancer that sometimes follows.

In both these examples, it becomes clear not only that conceptual change is required for scientific understanding to achieve a greater level of completeness, but, moreover, there is urgency to such an expansive enterprise because fields such as regenerative medicine and prevention of cancer in many instances will depend on it. These are not trivial aims or outcomes.

These limitations, however, should not be thought of as dire for any of the established fields of biological investigation and should not be taken as undermining the successes of prior research. Past reductionist approaches or those which are more systems oriented, but do not take into account the issues raised by boundary selection, are not invalidated any more than prior physics theories and findings were undermined by quantum uncertainty; Einstein was dismayed about God playing dice, but his dismay was foolhardy. The acceptance of quantum uncertainty and related concepts led to even greater success than he and his peers could have imagined, recently being crowned by the probable discovery of the Higgs boson. As in physics, the prior findings were not

completely invalidated, but they were better contextualized and further understood as *approximations* of how things work. Likewise, while attitudinal adjustments in the biological sciences may be required, in all likelihood this will herald still greater success, built on those discoveries that derived from the more limited, previous methodologies.

As we further explore the application of a generalized principle of complementarity to biological systems, we reach the conclusion that a new science is needed, where complementary constructs apply at all levels and all fields of knowledge. As an example, to make progress in global climate change, one should not just examine the physical Earth as a system (or even as a system of systems) but consider its interactions with human systems, affecting the global climate and being affected by it. Different degrees and levels of complementarities can be quickly identified. In another example, the economic system (as a system of systems), works at global, regional, and local levels, whereas it must stand apart and in complementary relationship to the actions and decisions of individuals. Such ideas are beyond the scope of this essay but hint at fundamental applications of generalized complementarity frameworks.

Also, these understandings of complementarity and their relationship to complexity are not necessarily distinct from the previously expressed concepts of biological complementarity pointed to by Howard Pattee. He stated that “biological systems need both [rate dependent] structural and [rate independent] informational concepts from their description” and suggested that such biological structure and information were an aspect of biological complementarity [4–6]. This is not in contradiction to what is presented herein, given that different forms of complementarity (or complementary relationships) may be present in biology as they are in quantum

physics. But it is also possible to see in Pattee’s formulation a variant statement of the same principles suggested here, namely that the informational aspects of biology (e.g., genetic code) are manifested at higher levels of scale than the structural features that encode the information (e.g., sequences of base pairs). We therefore see no contradiction between the biological complementarity recognized by Pattee and our own concepts; indeed, they may be intimately related.

5. SUMMARY

Niels Bohr intuited that the complementarity that was inherent in experimental investigations of the quantum realm, and which has been shown to be an irreducible aspect of the nature of the universe rather than merely an artifact of our technological limitations, was a reflection of a more universal complementarity, one that must necessarily be reflected in biological systems. The failure to robustly identify this complementarity until now perhaps was a result of the necessity of holistic, rather than purely reductive approaches to studying biology. Despite the success of the biologic and medical enterprises of the reductionist era, the newer, systems biologic approaches now reveal that, as in the quantum realm, selection of experimental process approach itself inherently limits our capacity to understand a biological system completely as it does in the quantum realm.

Quantum physicists surmised that these conceptual limitations were fundamental to the nature of the quantum world and that no technology could accomplish the feat of complete, simultaneous descriptions of all aspects of quantum phenomena. This complementarity—that one description based on one experimental point of view necessarily excludes some features discerned by a different experi-

mental point of view—is now clearly present in biological systems as well. We hereby raise the possibility that selection of an observational stance is inseparable from descriptions of biology and the impact of our minds’ actions through such observational selection may be inherently and irreducibly coupled to the observed biology just as it is in the quantum realm. Moreover, the nonlinearity of such systems, with their exquisite sensitivity to starting conditions, means that boundaries between observer and observed are artificial constructs, necessary for experimental design, but inescapably affecting both observer and observed as they do in the quantum level.

Kafatos and Nadeau [12] have shown that virtually most, if not all, fields of study depend on the workings of complementarity, which itself becomes a foundational principle for the universe. How this concept may illuminate a still more universal principle of complementarity that would encompass both quantum and biologic processes is beyond the scope of this article. Implications of biologic complementarity, however, may be quite broad. Previous descriptions of biological or even universal “part-whole complementarity” are not different from the complexity theory-derived perspective presented here, but, in fact, are here simply specified with greater precision. Thus, as in prior writings, these concepts may have important implications for the development of a theory of consciousness and how “mind”, expressed through observational activity, is a pervasive aspect of the universe at all levels of scale (“panpsychism”) rather than something that simply arises when a portion of the universe (such as a living cell or a brain) becomes sufficiently complex for it to emerge (“emergentism”) [37]. It is interesting to note that Roy and Kafatos applied complementarity to the cerebellum’s response and perception functions.

Such complementarities in brain science would clearly impact understanding the nature of mind and consciousness in general, setting the ground for exploring further connections between neuroscience and quantum physics [38].

Furthermore, given the importance of axiomatic modeling for the understanding of biology in a systems, holistic approach, it may also be important to consider the implications of the Incompleteness Theorems of Kurt Gödel [39, 40]. Applying Gödel's thinking to computational modeling of biology may affirm that biologic complementarity and uncertainty, like those of the quantum realm, are not technology dependent, but inherent.

6. CONCLUSIONS

These caveats aside, it is clear from even this preliminary description of biologic complementarity that systems biology is not simply the pursuit of statistical methods and computational power for analysis of large data sets. We are on the threshold of a profound paradigm shift that will have practical as well as theoretical implications for

harnessing the behaviors of biological systems:

The future science of biology will be understood as describing systems of systems, working together in complementary relationships similar to the situation applicable to microphysics. As limits of knowledge or horizons of knowledge are approached, through the application of nonlinearity in complexity theory, complementarity will be viewed as a fundamental cornerstone and necessity of the workings of life itself. The individual organism and its environment comprise systems of systems, starting from biomolecules in aqueous solution to organelles and to cells, then to tissues, organs, and bodies, all the way up to the global ecosystem itself and perhaps beyond, and will be understood as a seamless whole operating at various levels, all being aspects of the fundamental complementarity and inescapable (however subtle) intertwining of observer and observed.

It would be important to explore relationships between complementary biological variables and establish

principles equivalent to the uncertainty principle and associated biological "constants" (in analogy to Planck's constant). These conceptual shifts will not only have theoretical impact, but may point the way to new, successful therapeutic interventions, whether medically in the healing of bodies (at this and lower levels of scale) or environmentally/economically for healing our ailing planet (at a global scale). Understanding and accepting the coupling of observer to the observed in biology and how this shapes our understanding of biology—both the limitations and the potential implied by biological complementarity—may profoundly reshape our understanding of what it is to be human and what it means to be part of a living, biological universe.

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