Infection and Immunity

Reductionistic and Holistic Science

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Infect. Immun. **2011, 79(4):1401. DOI: 10.1128/IAI.01343-10.**
Published Ahead of Print 14 February 2011.

INFECTION AND IMMUNITY, Apr. 2011, p. 1401–1404 Vol. 79, No. 4
0019-9567/11/$12.00 doi:10.1128/IAI.01343-10

EDITORIAL

Reductionistic and Holistic Science[▽]

A reductionistic approach to science, epitomized by molecular biology, is often contrasted with the holistic approach of systems biology. However, molecular biology and systems biology are actually interdependent and complementary ways in which to study and make sense of complex phenomena.

"Reductionism is one of those things, like sin, that is only mentioned by people who are against it."
—Richard Dawkins (14)

Few scientists will voluntarily characterize their work as reductionistic. Yet, reductionism is at the philosophical heart of the molecular biology revolution. Holistic science, the opposite of reductionistic science, has also acquired a bad name, perhaps due to an unfortunate association of the word "holistic" with new age pseudoscience. However, fortunately there is an increasingly popular euphemism that lacks the pejorative connotations of holism for scientists—"systems biology." Since its debut a decade ago (23, 29), "systems biology" has appeared as a medical subject heading (MeSH) in PubMed more than 3,000 times. A fundamental tenet of systems biology is that cellular and organismal constituents are interconnected, so that their structure and dynamics must be examined in intact cells and organisms rather than as isolated parts. We recall that the late author Douglas Adams created a fictional detective named Dirk Gently who described his methods as "holistic" because he relied on the "fundamental interconnectedness of all things" to solve crimes (1). Gently used this to justify a large expense account, arguing that each of his personal expenses, like a beach holiday in the Bahamas, must be related to an ongoing investigation at some level. Although funding agencies are not likely to accept holistic accounting practices, holistic approaches have become increasingly popular in microbiology, sometimes advocated as superior to reductionistic ones (42). Researchers often adopt holistic or reductionistic approaches to study a problem without justifying their choice or explaining the advantages and limitations of such an approach. In this essay, we consider the dichotomy between holistic and reductionistic approaches to science and their implications for microbiology. First, however, a few definitions are in order.

Types of reductionism. "Reductionism" can have epistemological, ontological, and methodological meanings (34). Epistemological reductionism addresses the relationship between one scientific discipline and another and is defined as "the idea that the knowledge about one scientific domain can be reduced to another body of scientific knowledge" (7). For instance, can one, as Crick proposed, "explain all biology in terms of physics and chemistry" (12)? Certainly different scientific disciplines are interrelated and share fundamental principles, but discrete disciplines continue to exist because phenomena are best understood at one level or another. In fact, it can be argued that in practice disciplines such as physics and biology are epistemologically discontinuous, for science currently lacks a grand theory that allows us to connect such disparate phenomena as quantum mechanical states and the songs of birds. Epidemiology may be related to molecular biology, which in turn is related to chemistry and ultimately to physics, but the investigation of an ongoing cholera epidemic cannot be effectively carried out at the level of a molecule of cholera toxin or the quantum state of an electron around a single carbon atom within the toxin B subunit. In fact, the revolution in modern physics that replaced such bedrock assumptions of classical physics as continuity, separability, and determinism with discontinuity, entanglement, and the uncertainty principle has raised serious doubts about whether epistemological reduction can ever be realized. Exploring the epistemic relationships between different disciplines might be grist in the mill for a philosopher of science but does not seem a particularly fruitful endeavor for a working scientist.

Ontological reductionism presents an even thornier issue. Ontological reductionism is defined as "the idea that each particular biological system is constituted by nothing but molecules and their interactions" (7), in other words, the centuries-old debate about whether physical matter is the only reality in nature. Instances in which esoteric mathematical knowledge has later been found to be perfectly suited for describing newly discovered physical phenomena have prompted contemplation of the "unreasonable effectiveness of mathematics" in describing the physical world and raised deep philosophical questions about the possibility of a Platonic reality beyond our measurements and senses (44). Now, though, we find ourselves squarely within the realm of philosophy and feeling increasingly uncomfortable as we tiptoe gingerly through metaphysics.

The third category, methodological reductionism, describes the idea that complex systems or phenomena can be understood by the analysis of their simpler components. Methodological reduction is often traced back to Bacon, who in the early 17th century proposed that principles derived from specific cases might be applied to make general predictions (5, 21). Descartes soon afterward suggested that one should "divide each difficulty into as many parts as is feasible and necessary to resolve it" (16). As a contemporary example, a reductionistic approach would be to use a reporter fusion to the *ctxA* cholera toxin gene in order to identify environmental conditions responsible for regulating toxin production during infection (17). The experimenter would argue that regulation is most likely to occur at the level of transcription and that a simplified *in vitro* reporter system reduces the number of complicating experimental variables and facilitates analysis. An advocate of a more holistic approach could posit that cholera toxin gene expression is better studied during infection of a host and in the context of a genetic network of coregulated loci monitored over time (26, 32). In this example, reductionistic and holistic

[▽] Published ahead of print on 14 February 2011.

methodologies can be viewed as alternative approaches to understanding a complex system, with each providing useful, but limited, information. This essay focuses on the issue of methodological reductionism and leaves epistemological and ontological reductionism to the philosophers.

Molecular biology: a triumph of reductionism. If reductionistic methodology sounds familiar, that is because reductionism is implicit in much of molecular and cellular biology. Reductionism allows a microbiologist to explain that a bacterium fails to respond to therapy because it has acquired a gene encoding a beta-lactamase or that a patient exhibits enhanced susceptibility to infection because he has a mutant receptor for gamma interferon. Reductionism permits a microbiologist to screen *Salmonella* mutants for the ability to survive in cultured macrophages, knowing that this phenotype is predictive of the ability to cause mammalian infection (18). The successes of the reductionistic approach in biology during the latter half of the 20th century are undeniable, and yet limitations to methodological reductionism have been recognized. There are numerous examples of *in vitro* experimental observations made with isolated components of cells that are not directly applicable to the physiology of whole organisms. For example, mice deficient in Toll-like receptor 4 signaling are highly resistant to the effects of purified lipopolysaccharide but extremely susceptible to challenge with live bacteria (37, 48). The *Infection and Immunity* (IAI) Instructions to Authors state that "papers that utilize conserved microbial constituents (e.g., lipopolysaccharide, peptidoglycan) to stimulate immune responses, unless accompanied by experiments demonstrating relevance to the interaction between intact microbes and hosts or host cells," are not within the scope of the journal. This is a tacit recognition of differences between pathogenic microbes and their parts and of the journal's preference for understanding the biology of whole organisms.

Emergence of systems biology. The last decade has witnessed a backlash against the reductionism of molecular biology. The philosophical antecedents of holism can be traced back to Aristotle, who is said to have pithily observed that "the whole is more than the sum of its parts." Smuts later coined the term "holism" as "a tendency in nature to form wholes that are greater than the sum of the parts through creative evolution" (46). Systems biology has increasingly been touted as a revolutionary alternative to molecular biology and a means to transcend its inherent reductionism (2, 22, 29). Theoretical biologists, like Stuart Kauffman, have emphasized the ability of complex systems to give rise to emergent novel properties that are not predictable from the examination of individual components (6, 28). A humbling example is provided by the inability of detailed knowledge about the molecular structure of water to predict surface tension, a macroscopic phenomenon reflecting emergent behavior among water molecules. The issue of emergence imposes a theoretical limit on the knowledge available from reductionistic methodology. Systems biology has already had a transformative effect on microbiology. An emphasis on pathways, networks, and systems has given rise to powerful new bioinformatics and experimental methods. Genomic, microarray, and proteomic analyses are now commonplace in IAI (25, 35, 40). Systems approaches can be "top-down," starting from "-omics" data and seeking to derive underlying explanatory principles, or "bottom-up," starting with molecular properties and deriving models that can subsequently be tested and validated (8). The first approach begins with data collection and a description of phenomena, while the latter is more mechanism based, but both produce models of system behavior in response to perturbation that can be tested experimentally. The construction of synthetic regulatory circuits, the modeling of complex genetic and metabolic networks, and the measurement of transcriptional dynamics in single cells are just some of the new ways of analyzing complex phenomena that have invigorated microbiology (3, 11, 38, 39, 43). Systems biology approaches are particularly attractive for analyzing the exceedingly complex events that occur as a host encounters a pathogenic microbe or a vaccine (19, 26, 41).

Some limitations of reductionism may reflect current technological capabilities rather than inherent shortcomings of the approach. An early triumph for reductionism was the discovery that one could separate tobacco mosaic virus (TMV) into its RNA and coat protein components, which could then self-assemble when combined (30). However, in contrast to TMV, the self-assembly of more-complex structures is often impossible. This underscores the relationship between the inherent complexity of a system under study and the limits of methodological reductionism. However, the recent report that a complete functional genome can be inserted into bacterial protoplasm through advances in synthetic biology (20) demonstrates that technological advancements can greatly empower and validate reductionistic approaches. The limitations of reductionism are a moving boundary.

A false dichotomy. Methodological reductionism and holism are not truly opposed to each other (15). Each approach has its limitations. Reductionism may prevent scientists from recognizing important relationships between components or organisms in their natural settings, appreciating the evolutionary origins of processes and organisms, grasping probabilistic relationships underlying complicated and seemingly chaotic events, or perceiving heterogeneity and emergent multilevel properties of complex systems. Holism, on the other hand, is inherently more challenging due to the complexity of living organisms in their environment. Fundamental principles may be difficult to discern within complex systems due to confounding factors like redundancy and pleiotropy. Signal may be swamped by noise. The technology is seductive, but more data do not necessarily translate into more understanding. It is not yet certain whether current approaches to holism, such as systems biology, are adequate to cope with the challenges posed by emergent properties of complex biological systems. When fecklessly performed, systems biology may merely describe phenomena without providing explanation or mechanistic insight (9) or create virtual models that lack biological relevance.

It is difficult to imagine how a number of important scientific discoveries could have been made by any method other than a reductionistic approach. Without isolating DNA from other cellular constituents, Avery, Macleod, and McCarty could not have conclusively demonstrated that it alone was responsible for the transformation of the pneumococcus (4). Similarly, the power of reductionism was shown when a single *Yersinia* gene could confer upon *Escherichia coli* K-12 the ability to invade eukaryotic cells in tissue culture (24) or when the replacement of murine E-cadherin with its human counterpart rendered transgenic mice susceptible to oral challenge with *Listeria* (31). Likewise, there have been important observations for which a

holistic approach has been essential. The discoveries that high levels of expression are the predominant barrier to horizontal gene transfer (47) and that *Helicobacter pylori* contains an unexpectedly large number of small untranslated RNAs and transcriptional start sites within operons (45) are but two recent examples. Confidence in these findings is critically dependent upon the authors' ability to use holistic high-throughput methods to generate and analyze enormous datasets: the attempted subcloning of nearly 250,000 genes and the sequencing of hundreds of thousands of cDNAs.

It should be emphasized that a combination of reductionistic and holistic approaches can be synergistic. In one example from the pathogenesis field, a holistic cRNA microarray analysis revealed that the *RegIII*γ gene, encoding a C-type lectin, was strongly induced within intestinal Paneth cells following microbial colonization of germfree mice (10). The same lab subsequently went on to hypothesize that the RegIII lectin kills Gram-positive bacteria and demonstrated that it is able to bind the bacterial peptidoglycan carbohydrate backbone via a conserved (EPN) molecular motif, confirmed by site-specific mutagenesis of a single amino acid in the tripeptide (33). In another example, a holistic genome-wide RNA interference (RNAi) screen was first used to identify host factors important for influenza virus replication (27). When the screen suggested that viral replication was dependent on the cell cycle regulator p27, the investigators moved to a reductionistic approach and were able to demonstrate reduced influenza virus replication in a p27-deficient mouse *in vivo*.

Reductionism and holism are in fact interdependent and complementary. Reductionism is most useful if observations made in a simplified system allow accurate predictions, or at least the generation of hypotheses, to be made when returning to the complex natural world. However, interpreting observations from holistic studies may require mechanistic insights gained from earlier reductionistic work or may generate hypotheses that are amenable to testing through reductionistic experimental approaches. Ironically, Kitano noted that systems biology became possible only once advances in molecular biology allowed the emergence of genomic analysis and high-throughput measurements (29). We conclude that one approach is not necessarily better than another. Observations made in test tubes that have no correlates in the real world may not be very useful biology, but the mere creation of large datasets without interpretation, or holistic cartoon models that fail to achieve concordance with empirical reality, is also of little value.

The way forward. How can these alternative ways of doing science be reconciled? Investigators employing a reductionistic approach should attempt to test the predictive power of their observations in a more complex setting. For example, a biochemical study of protein-protein interactions should obtain evidence that such interactions and their consequences occur in an intact cell. An *in vitro* study of microbial resistance to a stress condition could be enhanced by experiments to determine whether the mechanism applies to interactions with host cells in which the particular stress occurs. A study showing the behavior of a microbe infecting host cells in tissue culture might be fruitfully expanded to include a *bona fide* infection of an animal host. Similarly, investigators should attempt to determine the degree to which reductionist findings are generalizable to other systems. An immunological study that shows the importance of a certain response in mice should be tested in other animal models or, where possible, in humans to ascertain whether general conclusions can be drawn. System-wide models, whether describing interactions of genes, proteins, small molecules, or organisms, should be rigorously tested and refined against real-life observations. Attempts should be made to identify the general organizing principles that underlie complex phenomena (36), and areas of discordance between predicted and observed results must be forthrightly addressed.

The recent focus on systems biology in microbiology is not a revolution or even a true paradigm shift, in the sense that reductionistic and holistic methodological approaches have been coexisting and thriving for centuries. One can argue that Darwin's theory of evolution represents an early example in which many reductionist observations on finches and domesticated pigeons were synthesized into a system that unified all of biology. The real seismic event in the recent rise of system biology arguably has more to do with the introduction of computer technology that allowed inexpensive calculation and the storage of prodigious amounts of information than with new conceptual approaches. Nevertheless, there is no denying the revolutionary impact of holistic thinking on the field, both in calling attention to situations in which reductionistic approaches have been deficient and in the generation of new experimental approaches for the analysis of complex systems. Computer technology has permitted the development of sophisticated mathematical, engineering, and computational tools that have allowed new questions to be asked. The central dogma of molecular biology (DNA → mRNA → protein) may not have been overturned, but it certainly has been extended (DNA → mRNA → protein → protein interactions → pathways → networks → cells → tissues → organisms → populations → ecologies) (23).

Whether one's methodology is primarily reductionistic or holistic, it is wise to begin by considering the limitations of the approach. This will help to limit imprudent extrapolation and point the way for further experimentation. In the end, the test of both reductionistic and holistic paradigms is their ability to explain and make useful predictions about the real world. No one said it would be easy. As Douglas Adams said, "If you try and take a cat apart to see how it works, the first thing you have on your hands is a non-working cat. Life is a level of complexity that almost lies outside our vision" (13).

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