Fundamental issues in systems biology

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Summary
In the context of scientists' reflections on genomics, we examine some fundamental issues in the emerging postgenomic discipline of systems biology. Systems biology is best understood as consisting of two streams. One, which we shall call 'pragmatic systems biology', emphasises large-scale molecular interactions; the other, which we shall refer to as 'systems-theoretic biology', emphasises system principles. Both are committed to mathematical modelling, and both lack a clear account of what biological systems are. We discuss the underlying issues in identifying systems and how causality operates at different levels of organisation. We suggest that resolving such basic problems is a key task for successful systems biology, and that philosophers could contribute to its realisation. We conclude with an argument for more sociologically informed collaboration between scientists and philosophers. *BioEssays* 27: 1270–1276, 2005. © 2005 Wiley Periodicals, Inc.

Introduction

As genomics matures from a data-collecting enterprise to an explanatory science, and as those scientific endeavours take on disciplinary contours, a range of underlying issues are being explicitly and implicitly addressed by the scientists involved. These reflections are an important part of the way that a discipline constitutes itself as a field by setting out central problems and achievements alongside a history of conceptual and empirical precursors. One of the most widely discussed fields in emergent genomics is systems biology, and it raises several important questions that need to be resolved if the science is to advance. The issues that are most fundamental are how the systems that are the focus of systems biology are defined, and how those definitions affect the research agendas that arise from earlier scientific legacies.

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Preceding interpretations of genomics

The early days of genomics began with fairly simple conceptualisations that emphasised the shift from identifying genes to sequencing and mapping entire genomes.[1] As the data poured in and the field achieved wide recognition, these definitions were expanded to give greater emphasis to functional analyses.[2,3] Although much of the discussion of the status of genomes has been conducted via evaluations of the evolving metaphors in genomic discourse—from the ineptness of the blueprint metaphor to analogies with jazz scores and Theseus's ship[4–6]—there are also some excellent systematic discussions of genome conceptualisations.[7]

Two issues concerning the status of knowledge in genomics are frequently discussed. The first is that early genomics shared the reductionist aspirations of genetics, which led to a preoccupation with sequence structure and deterministic accounts of function.[3,8] Persistent (and prescient) demands for a more hierarchical and less simplistically deterministic understanding of molecular processes were voiced even in the early years of genomics.[9,10] These calls increased with the proliferation of sequence information and eventually combined with a second concern that genomic processes could usually be described only by qualitative statements such as 'Gene A inhibits Gene B'.[11–13] For many biologists, the real future of genomics lies in its dual potential for going beyond reductionism *and* for becoming a quantitative science. The developing anti-reductionist consensus—a distinct but by no means universal trend—requires a move from the dissection of things to the dynamics of processes, thus necessitating a trade-off between mechanistic detail and quantitative tractability.

Another central epistemological issue was explored by Roger Brent in his 2000 paper, 'Genomic biology'.[14] The article attributes the decline of hypothesis-driven research in biology to the growing influence of the data-driven or discovery approach of genomics (for objections to these categories, see Refs. 15–17) Although Brent believes many claims made on the basis of genomic observations may never be tested because of changed scientific standards, most commentators see the data-driven approach as a preliminary phase in the development of a true science in which experimentation and hypothesis testing eventually play pivotal roles.[12,18]

Many scientists talk about a genomics 'revolution' because of the dramatic changes that the field exhibits in technology, scientific practice, social organisation and biological understanding.[13,14,19,20] Although such changes have major implications for more general or philosophical understandings of science, professional philosophers have made only minor contributions to the issues that are peculiar to genomics. Most philosophical discussions of genomics conducted within the discipline of philosophy are, in fact, bioethical and concerned exclusively with human genomics, human nature and personal identity.[21] Scientists often perceive philosophers as distant observers who interpret episodes in science when they are already over. Regardless of whether this is a fair description or not, there is certainly a movement now for philosophers to engage with biological science at its cutting edge (for example Refs. 22,23).

Our argument in this paper is twofold. The first point is that the philosophical issues under discussion in the emerging genomics research programme of systems biology must be addressed in order for the science to achieve its stated goals. The second is that the resolution of such problems could be most effectively achieved by closer collaboration between scientists and philosophers.

Systems biology

As the Human Genome Project gathered momentum and its initial goal of a draft sequence drew closer, scientists and policy makers began increasingly to articulate visions of how technology-driven acquisitions of genomic knowledge could be transformed into explanatory accounts and strategies of intervention.[24] These ideas drew sustenance from earlier aspirations to understand complex biological organisation and its properties in ways that went beyond simple genetic determinism. The general area on which many of these ambitions and hopes converged is now what is called 'systems biology'. The overarching aim of systems biology is 'the ultimate goal of modern biology: to obtain a fundamental, comprehensive and systematic understanding of life'.[25] This understanding is sought not just in relation to humans (though human health is a focus of much systems biology), but for a wide range of organisms including microbes and plants. To achieve this goal, systems biologists intend to integrate and explain global DNA, RNA, protein and metabolite data by combining mathematical modelling and extensive computational analysis with large-scale experimental techniques.[26–31]

Not only is systems biology predicted generally to transform biological understanding and practice,[29,32] but its methods and concepts are anticipated to have important effects on other sciences such as physics, engineering, mathematics and social science.[33] Strong arguments are made that systems biology is more than just an extension of genomics and bioinformatics—it is indeed their necessary and 'natural' conclusion, but it is also something qualitatively different from what has already been achieved by the various 'omic' tools and findings.[34–36] A good question to ask, therefore, is whether systems biology sets itself apart from earlier genomics because of its object ('systems') or because of the way it does things ('systematically').

The objects of systems biology

Under the systems biology rubric are two different (but not mutually exclusive) understandings of 'system'. The first account is given by scientists who find it useful for various reasons (including access to funding) to refer to the interconnected phenomena that they study as 'systems'. The second definition comes from scientists who insist that systems principles are imperative to the successful development of systems biology. We could call the first group 'pragmatic systems biologists' and the second 'systems-theoretic biologists' (for a variety of similar divisions and somewhat different interpretations, see Table 1). The majority of today's systems biologists fall into the former category, united simply by an agreement that systems biology involves the study of interacting molecular phenomena through the integration of multilevel data and models.[40] For them, 'system' is a convenient but vague term that covers a range of detailed interactions with specifiable functions.[11,41] The main force behind the development of this science is the technology that enables increasingly comprehensive data to be collected and then collectively analysed.[42]

For hard-line systems-theoretic biologists, however, an ad hoc approach to systems is inadequate. It is crucial, they argue, 'to analyse systems as systems, and not as mere collections of parts' in order to understand the emergent properties of component interactions.[27,34,43] Systems are taken to constitute a fundamental ontological category, and differences between biological and human-made (engineered) systems are considered less important than their similarities.[34,44] Although this form of systems biology developed in response to the genomics 'revolution', it draws on much earlier systems theorists such as cyberneticists Norbert Wiener[45] and W. Ross Ashby,[46] general and organismal system theorist Ludwig von Bertalanffy,[47,48] mathematical biophysicists Nicolas Rashevsky[49] and Robert Rosen,[50] systems engineer Mihajlo Mesarović,[51] and (very occasionally) living systems theorist James Miller.[52] System definitions derived from these sources are very abstract and generalisable, usually no more specific than 'complex structures of *interdependent* and subordinate *components* whose relationships and properties are largely determined by their function in the whole'.[35] The use of universal systems definitions is more than a pledge of allegiance to general systems theory; they are proposed as the theoretical orientations through which biological data should be approached. However, it is widely recognised that theories such as Bertalanffy's are too abstract for today's systems biology.[53]

Table 1. Categorisations of systems biology

	Type One	Type Two
Haubelt et al., 2000[37]		
Label	*Biological systems biology*	*Systems-oriented biology*
Precursors	Reductionist molecular biology	Cybernetics; network theory in electronics; biochemical systems theory (BST) and metabolic control analysis (MCA); cell biology
Focus	Integration of data from different levels & sources	System functions and properties
Huang, 2003[11]		
Label	*Localists*	*Globalists*
Precursors	Classical molecular biology	General networks (physics perspective); Kauffman[38]
Focus	Large datasets of constituent parts; 'pathway-centric'	Deeper principles of complex systems; wholes
Levesque & Benfey, 2004[39]		
Label	*Panomicists*	*Dynamicists*
Precursors	Reductionist molecular biology; genomics	Systems theory
Focus	Components; reconstruction of networks from high-throughput data	Modelling networks as complex systems; applying principles of systems theory
Westerhoff & Palsson, 2004[36]		
Label	*Biology-rooted systems biology*	*Systems-rooted biology*
Precursors	Mainstream molecular biology; genomics	Non-equilibrium thermodynamics; self-organisation; BST & MCA
Focus	Pattern recognition and phenomenological modelling of macromolecular interactions	New functional states arising from simultaneous interactions of multiple molecules; fundamental principles and laws

Genomes-in-systems

Although systems are not closely defined by either stream of systems biology, it is helpful to see how these general notions of system are related to the way genomes are conceptualised. Although all systems biologists agree that genomes are not deterministic programmes, there does appear to be a difference of conceptual emphasis between pragmatic- systems and systems-theoretic accounts of genomes. For the former, genes and genomes still have a degree of causal and informational priority over other levels of molecules. They are given the status of precisely definable 'digital cores of information' that *drive* the interactions constituting systems.[26,33,54]

From the systems-theoretic perspective, the demotion of the genome goes further. Genomes in this framework do not explain anything: they 'merely' constitute some of the components on which higher-level system properties depend.[36,55] The study of genomes becomes simply an exploratory or first-level tool for the analysis of cells and tissues. This conception of genomes and genomics makes it clear that the primary objects of system-theoretical inquiry are higher-level processes and properties rather than the more concrete molecular bases of these phenomena.

Issues in the investigation of biological systems

For both sorts of systems biologists, what really matters is the modelling process and how it navigates between the demand for abstraction and the need for detail. Models or simplifying abstractions are designed to synthesise information and transform datasets into biological insight.[56,57] Biology has traditionally used 'mental models' in diagrammatic form or as natural language narratives, but their imprecision and limited scope makes them inadequate for charting and explaining complex molecular interactions and their emergent properties.[58–60] Mathematical modelling is not new to molecular biology, but systems biology is the first genomic discipline to rely so unreservedly on it.

Model tools and concepts are seldom drawn in any detail from systems predecessors—not even from highly favoured ones such as Rosen[61]—but from biochemical, electrical and systems engineering.[41,58,62–65] Once a model has been developed to an appropriate level of complexity, it can be run repeatedly by a computer and function as a high-throughput hypothesis tester.[58,60] Ultimately, the results of simulations must confront more traditional real-world experimentation, although the proportion of such tests reduces bench experimentation to a supplement or safeguard.

Rather than discussing in detail the sorts of modelling tools systems biologists use (a topic that will soon repay close philosophical scrutiny), we will look at some of the most general epistemological claims about the modelling process. Systems biologists classify modelling approaches into three categories: bottom-up, top-down, middle-out.[66–68] Bottom-up modelling starts with DNA and proteins, then works upwards to try and characterise higher-level processes; top-down approaches begin with high-level functions and then incorporate the details. Some modellers believe both have such serious practical and in-principle problems[67] that a 'middle-out' approach must be developed. Their proposal is to start somewhere in-between the top and bottom levels, then work out towards a hierarchy of models. Naturally enough, there is disagreement about where these levels begin. What some call the middle, others see as the bottom.[66]

The division of systems approaches into two streams is mirrored by modelling strategy. Pragmatic systems biology is most commonly characterised by a bottom-up (sometimes middle-out) approach, whereas systems-theoretic biology takes a top-down perspective and aims for 'fundamental principles and laws'.[36,44] Pragmatic bottom-up modelling is concerned with connecting molecular interactions and thus extends the approaches of early genomics. It might be considered a continuation of reductionist strategies, although any such admission is usually accompanied by plans to scale up to higher levels of process and modelling.[69] The general assumption is that systems, whatever they are, will appear 'naturally' from biological reality rather than be imposed by (artificial) theory. Systems-theoretic approaches, on the other hand, are launched from system principles and seek to establish a new tradition of non-reductionist but still molecular inquiry. Crucially, no systems biologist finds it satisfactory to restrict inquiry to one level, wherever it is begun. It is the aim of integrating different levels that presents the fundamental objection to a traditional reductive molecular approach.

Integration of approaches

The perceived need for systems biology to integrate levels of biological data is mirrored by an insistence on the integration of its constituent disciplines, methods and modes of inquiry—especially discovery and hypothesis-driven approaches, and more narrowly, wet and dry experimentation.[12,26,29,40,54,58,62] The common theme of all outlines of systems biology is integration, hence systems biology's other moniker of 'integrative biology'.[70,71] None of this discussion, however, goes much beyond endorsing such fusions.

One aspect of integration that is less touched on and potentially more contentious is the integration of pragmatic systems biology with systems-theoretic biology. How important is it for the success of systems biology that the two streams become one? This is not an issue for practical systems biologists, who mostly think 'the more the better' in regard to data and analysis of all kinds. They diagnose the non-fulfilment of earlier systems biology promises as a straightforward fault of inadequate molecular understandings and insufficient data.[37] Predictably, systems-theoretic biologists believe that primary research questions must be framed by systems concepts in order for a genuine and successful systems biology to develop.[11,35,36]

Crucial issues for systems biology

A major reason that these differences exist (and are unlikely to be remedied by different levels of models coming together) is because of the lack of a clear ontology of systems in either perspective. Both systems biologies are currently less about systems (in a theoretical sense) than about aspirations towards systematic and thoroughgoing approaches to the phenomena of interest. The field could, therefore, be described as an epistemological commitment to a general approach that foregrounds mathematical modelling in order to capture system dynamics and transcend piecemeal analyses of interconnected biochemical processes.

The key question for both systems biologies is not only 'what is a system?' but 'what biological units map onto those systems?' The former question is a central concern of the systems-theoretic approach, but the answers that it offers are of limited use without a demonstrably productive answer to the latter question. Cells are obvious candidates but the crucial properties that constitute them as such, and that might also constitute other objects as biological systems, remain to be determined. Although pragmatic systems biology has already met with considerable success, it does not want to be *terminally* pragmatic and must eventually generate enough theory to inform the integration of genomic and non-genomic levels of localised interactions. Theory need not mean universalisations extracted from the specific abstractions of systems luminaries such as Bertalanffy, however. The project of localising and defining biological systems can instead be developed within existing practice. This project could accomplish two things: it could make the new systems biology theoretically self-sustaining, and it might integrate the two streams of system approaches as they map system concepts onto biological hierarchies. In relation to concepts of genomes, for example, it is certainly conceivable that a pragmatic systems biology could be developed that accepts the full decentring of the genome envisaged by systems-theoretic approaches. A unified pragmatic and theoretic systems biology would take a step forward that is more than either a continuation of traditional genomic approaches or a revival of older systems terminology.

The primary task for such a science would be what could be identified as the third crucial question for systems biology: 'how are individual biological units and their behaviours altered, controlled or constrained by becoming components of the system?'[22] Systems biology of any persuasion has to demonstrate that when single components come together and form a system, they engage in novel behaviour and produce novel phenomena by the system itself constraining the components. Understanding this downward causation (or how causality operates at different levels of organisation) and the differences between units acting in aggregation and systematic organisation is the true and distinctive purpose of systems biology. A substantive answer to this question should cash out the definite but sometimes inchoate anti-reductionist intuitions prevalent in contemporary molecular biology. This last question, therefore, builds on the ontological issues to become an epistemological one that lies at the very heart of systems science.

Applications to a proposed system

One way to think about how these philosophical issues are connected and intimately tied to the science is by taking a quick look at another of the new genomics disciplines, metagenomics. Analyses of metagenomes, or composite genomes of microbial assemblages in particular habitats,[72,73] provide a new way at looking at in situ microbial communities and the relationships between genomes, organisms, populations and environments.[74–80] Although metagenomics is still at an early stage of constructing massive sequence inventories or gathering functional information,[81–84] the field could potentially lead to radical reappraisals of the nature of boundaries between biological entities and the organisation of life itself. At the very least, it challenges highly individualistic assumptions of biological and molecular interaction.[85,86]

The realisation of metagenomics as a true 'microbial systems science' in which ecosystems are systematically analysed as 'metaorganisms' or 'complex biological networks across multiple hierarchical levels'[31,74,87,88] will depend on finding the right levels of organisation to analyse. Even if some of the most provocative ontological problems raised by contested claims about horizontal gene transfer[89–91] are left aside, the study of metagenomes (and metaproteomes and metametabolomes) indicates that taking a system perspective requires ontological flexibility and epistemological openmindedness about where to focus the science. Non-system ways of thinking may limit the novelty of such science (it will default to the traditional study of lots of interacting molecules and organisms) while, on the other hand, allowing serious questions about the viability of system concepts for understanding such extended entities as ecosystems to be avoided. For the microbiologists who are thinking about microbial systems science, the test will be the identification of emergent causal properties of systems. This will require demonstrations that the behaviour of single components cannot be understood simply in terms of their intrinsic properties, but must be seen as simultaneously determined by features of the systems of which they are part.[92,93]

Other issues

As well as developing productive accounts of systems ontology and causality, there are a number of other philosophical questions to be asked and answered by systems biologists and observers of the field. One would be an analysis of the implications of the in silico emphasis of systems biology for traditional philosophies of experimentation. Although the logic of experimentation is closely related to the logic of modelling, the traditional boundaries between experiment and model are being challenged by systems biology. A closely connected concern is whether the validity of in silico testing can ever be comparable with that of in vivo tests, or whether in silico results have ultimately to be supported by 'real' experimental results. Although standards for testing might be shaped by the convenience, cheapness, and political advantages of side-stepping animal testing (an important systems biology aim), scientific as well as consumer scepticism about the transfer of in silico results to in vivo treatment will have to be anticipated, most obviously in applications to drug discovery.

A final issue is how the transfer to biology of systems engineering concepts and tools (such as robustness and circuit design) will affect biological concepts such as evolution and selection. While systems-theoretic proponents might perceive as straightforward and sensible the relegation of selection to the 'fine tuning' of structures based on design principles,[11,63] pragmatic systems biologists—who are more inclined to prioritise notions of contingency, tinkering and adaptation—will be more sceptical about allowing the conceptual framework of design to predominate.[69] If general design principles were to trump contingent selection, the science of biology could once again be conceived of as a search for laws rather than the investigation of historical outcomes of unknown generality. Systems biology thus encapsulates some of the oldest philosophical tensions in biology and perhaps can be interpreted as just their latest manifestation—an interpretation that must inevitably engender a degree of scepticism about the likelihood that systems biology will lead to their solution. All these questions barely touch upon the fact that the future of systems biology will be shaped as much by social factors as by scientific and philosophical ones, with different ways of thinking about systems evolving within a context of 'big biology' funding, industry expectations, and conflicts between diverse disciplinary cultures provoked by the interdisciplinary mandates inherent in systems biology.[26,94,95]

Conclusions

Although it is early days yet for understanding the philosophical issues in systems biology, identifying and conceptualising the systems central to each inquiry is clearly a basic philosophical issue integral to the success of the science. Understanding how cells, organisms and communities are to be understood in a hierarchy of dynamic processes is, of course, exactly the task systems biology has set itself and there are grounds for optimism that either stream of systems biology may provide important insights into this problem. However, since the history of systems biology has generally been one of failure, and because there are some key philosophical tensions that could seriously hamper the development of systems biology, it seems that making some special philosophical efforts in these crucial early days of systems biology would be worthwhile.

Programmatic outlines of systems biology are constantly rehearsing arguments for interdisciplinarity, and we think our analysis has shown that there are good reasons for those interdisciplinary efforts to include philosophers. Even though we have pointed out that philosophers haven't as yet been that interested in genomics for its own sake, the issues raised by systems biology are likely to make the idea of closer involvement with the science a very attractive proposition. Philosophical approaches such as developmental systems theory (DST),[96] which locates a deprioritised genome within a hierarchy of biological levels that include environments, would seem to have natural affinities with systems biology.[97] Systems biology in turn offers DST's currently critical abstractions a constructive grounding for future research orientations. The form and scope of any such philosophical–scientific collaboration would, of course, be dictated by particular research programmes and their needs, but we presume there would always be room for innovative thinking about how to proceed.

We would also emphasise that more questions need to be addressed than the key three issues of 'What is a system? What biological units map on to systems? How do systems constrain individual components?' As we already mentioned, a whole gamut of social and economic forces, including the restructuring of scientific roles in novel interdisciplinary and transdisciplinary contexts, are shaping the direction and content of systems biology. Although philosophers of science and scientists have often discounted or ignored such social factors, their evident impact on genomics has made such bracketing impossible. Scientists and philosophers will need to develop sociologically informed philosophies of systems biology in order to offer the most valuable guidance to scientific practice in a time of rapid change.

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