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science & society

Calculating life?

A sociological perspective on systems biology

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Systems biology is an excellent research topic for social scientists because systems biologists themselves are fascinated by the social organization of their field. Moreover, as systems biology is an emerging research area, studying it from a sociological perspective allows social scientists to observe how scientists develop new fields of inquiry and practice, and challenge existing institutional and disciplinary structures. This article presents the results of our study of systems biology and of how systems biologists perceive their own field.

We start by exploring the organization of knowledge production in systems biology, which is a research 'approach' that brings together biologists, physicists, engineers, mathematicians and computer scientists in novel interdisciplinary arrangements. We then look at how systems biology positions itself in relation to other types of biological inquiry, particularly molecular biology.

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Discussions of the distinctiveness of systems biology often address the goals of the field: some systems biologists aim to make biology as quantitative, rigorous and predictive as physics and engineering, with the overall objective of making living systems calculable and ultimately predictable; others argue that this aspiration is misplaced, and stress the contingency and unruliness of biology. We explore these tensions, and reflect on their sociological dimensions and their consequences for future interdisciplinary work in the life sciences.

This article presents results from our empirical research. We draw on more than 50 interviews with systems biologists from the USA, UK and Japan, as well as attendance at systems biology conferences and workshops, extended visits to laboratories and discussion groups with systems biologists. Although we refer to our respondents by their discipline of training, they all self-identify as doing systems biology.

Systems biology is usually described as an attempt to make sense of the vast amounts of data that have been generated by genome-sequencing projects and other molecular data-generating exercises. System biologists develop and use algorithms, software and mathematical models to analyse the data in order to produce dynamic *in silico* models of biological systems. Systems biologists either are, or have recruited to their enterprise, physicists, computer scientists, engineers and mathematicians.

As with many new research fields, there is as yet no consensus definition of systems biology. Systems biologists argue, however, that the novelty of their field arises from the kinds of computational technologies that are being used to study biological systems, which have made it possible to accumulate and analyse previously unprecedented levels of molecular data, and have allowed the integration of many different types of data. Our interviewees often said that systems biology is an 'approach', rather than a traditional research discipline. In fact, one of its key features is interdisciplinarity, which interviewees described as necessary to solve the problems that are being raised by the field.

It is notable that systems biologists articulate a division between the 'social' and 'scientific' elements of their field, and then openly discuss the value of the social aspects. This is in part because they work in a situation that differs significantly from the more common way of doing science in the past century. Instead of working within disciplinary boundaries, systems biologists see their research as transgressing these boundaries. They attempt to integrate not only data and technologies, but also disciplines and people. Scientists talk about how "the development of systems biology depends on the sociology" and how it is important to cultivate a social environment in which scientists with different expertise can work together productively.

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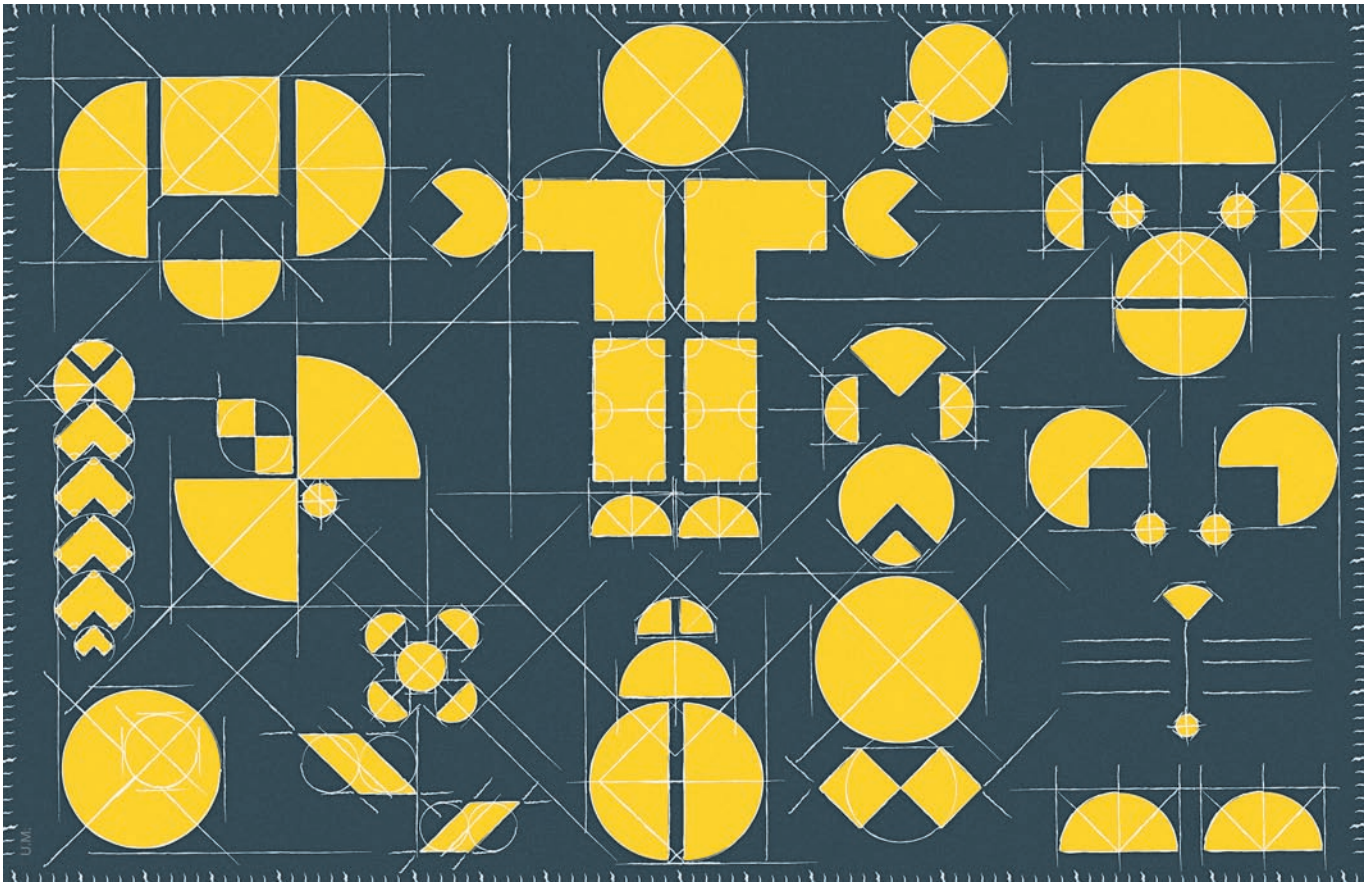
Another demonstration of the interconnectedness of the social and the scientific is the commonly expressed idea that systems biology has 'no walls'. This point is made in a metaphorical sense: systems biologists maintain that the field draws on expertise from whichever area is most useful or appropriate at the time because "ideas are everywhere", as one interviewee noted. Two senior researchers even thought that the disciplinary spread of systems biology could extend to the social sciences and humanities. The idea of 'no walls' also has currency in a literal sense because there are no walls between the laboratories at many systems biology institutes, in order to facilitate communication between researchers. New buildings have interdisciplinarity purposely built into the design, with social spaces where the 'wet' experimental people and the 'dry'



computational people can easily come across one another.

It is not easy to establish such new institutional arrangements. Leroy Hood, Director of the Institute for Systems Biology in Seattle (WA, USA), said that he had to fight against the constraints of academic bureaucracy to set up his new research institute (Agrawal, 1999). Similarly, Hiroaki Kitano, who established The Systems Biology Institute in Tokyo, Japan, built his institute outside the university system. This also meant, however, that he faced some difficulties related to working outside the usual academic networks. Another example is the development of an interdisciplinary systems biology centre in the UK, which required "an enormous struggle" according to a British biologist, because of vested interests and conservative colleagues.

Hood's view is that "new organizational structures were needed for the realization of a paradigm change" (Hood, 2008); so, it might be that one way in which systems biology can be distinguished from the life sciences that preceded it is by its organizational innovations. In its early days, molecular biology was the product of a confluence of scientists from several disciplines, including biology, physics and chemistry. This confluence became a discipline that later transformed most of biology. Whether something similar happens with systems biology remains to be seen. Nevertheless, even those who are reluctant to talk about 'paradigm change' in systems biology point out that its most notable aspects include its interdisciplinary nature, and the way in which it has brought in a new wave of physical scientists and mathematicians to study biological issues (Noble, 2007).

Many systems biologists have revolutionary ambitions for their field, which is often described by its proponents as a new way of doing science that will bring great changes. For example, one computer scientist said that "we [are] going to have to create a new way of thinking about biology that's going to be as great a revolution as the molecular revolution was". As it makes a point of distinguishing itself from previous research traditions, the question of whether systems biology constitutes a paradigm shift is often raised. Rather than discussing the merits of the arguments about paradigm shifts here, we look instead at how and when the language of paradigms is used by systems biologists.

The issue of whether systems biology constitutes a paradigm shift comes up most often in comparisons with molecular biology. In fact, Fred Boogerd and colleagues note that "practicing systems biologists are often hindered by paradigm battles with molecular biologists" (Boogerd *et al* 2007). A computer scientist highlighted the antagonism between the two fields by saying "it's still very much an 'us and them' thing between the molecular and the systems people". This is in a context where, until recently, "the mainstream was dominated by the reductionist molecular biology agenda". Against this background, it is perhaps not surprising that systems biologists often experience resistance from the 'old school' of molecular biology. Indeed, some interviewees argued that the antagonism towards systems biology from the proponents of previous paradigms is itself a sign of a paradigm shift.

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The most common way in which systems biologists distinguish their work from that of molecular biologists is by invoking the term 'reductionism', and arguing that systems biology adopts a more holistic approach. Interviewees said that systems biology studies the system as a whole, rather than individual molecules; this means that it is impossible to study a system in terms of a 'favourite molecule', which is a common characterization of how a molecular biologist proceeds. For example, systems biologists say that the normal research training process in molecular biology in the past was 'one gene, one PhD'.

Many systems biologists say that their field is not reductionist and is in fact a reaction to the essential failure of the reductionist agenda, particularly in terms of drug development, but also in terms of the failure of reductionist approaches to provide a satisfactory understanding of the operation of biological systems. One biologist put this point vividly by saying that systems biology is "the name of the crisis; it's the name of the fright that everyone's gone into about having all the pieces and still not knowing how biology works."

The relationship of systems biology to reductionism is not straightforward, however. Some systems biologists are explicit about their own reductionist objectives. One, for example, thinks that "the systems stuff's really a starting point for the reductionist biology." Some commentators also see systems biology as being firmly a part of the reductionist enterprise, and the field is even sometimes accused of being reductionism writ large (Huang, 2000). There is also the potential for a different type of reductionism in systems biology: the application of models from physics, mathematics and engineering to biological data (Fujimura, 2005). In fact, a UK policy-maker warned systems biologists at a conference that they must be careful not to replace molecular reductionist approaches with mathematical reductionist approaches.

Despite these concerns, the dominant discourse of systems biology is one of anti-reductionism. This is so pervasive that the Biotechnology and Biological Sciences Research Council (BBSRC; Swindon, UK), the largest funder of systems biology in the UK, felt the need to state that it "has not become anti-reductionist as a result of encouraging the uptake of systems biology approaches […] the molecular-level research it has funded—and continues to fund—is an important part of the picture" (BBSRC, 2006). Although it is not possible to distinguish molecular biology from systems biology clearly in terms of reductionism, systems biologists draw on this representation of molecular biology when they define their work in opposition to more 'traditional' forms of biological research.

Another way in which systems biology is distinguished from molecular biology is in its aspiration to make biology a more rigorous and quantitative discipline. For example, one interviewee maintained that the "intuition or naive understanding" of molecular biology will be replaced with the "rigid mathematical or computational understanding" that systems biology brings. A UK systems biologist has similarly written that "a key challenge for the future is to integrate analytical tools, technologies and theoretical rigour from the physical sciences, engineering and mathematics into the very fabric of bioscience research" (McCarthy, 2004). The aim to find foundational truths, laws or mathematical structures in biology was expressed by an ex-physicist, who said that he prefers to do science "from a quantitative, theoretical physics point of view" and is looking for "equivalent laws and theoretical structures in biology".

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A related feature of systems biology that is also found in the physical sciences and in engineering is the objective to be predictive. Some systems biologists say that their ultimate goal is to generate models *in silico* that will be able to predict the emergent properties of living systems. They think that once this happens, life "will become calculable" (Boogerd *et al*, 2007) and systems biology will have fulfilled its promise.

A research field that specifically aims to build biological systems that can be calculated, modelled and predicted is synthetic biology. Several interviewees discussed synthetic biology and its relationship to systems biology, and this comparison helps to illuminate further aspects of systems biology. The two can perhaps be most easily distinguished in terms of their different intentions. Whereas synthetic biology aims at construction, systems biology is directed towards understanding existing biological systems. However, this distinction is not clear cut. Steven Benner and Michael Sismour, for example, stress how a greater understanding of biological systems can be gained from synthetic approaches (Benner & Sismour, 2005), and others see synthetic biology as a way of testing the models in systems biology by trying to build them as functioning biological systems (Barrett *et al*, 2006). In this way, synthetic biology can be described as 'systems biology in reverse', although some see synthetic biology as a distinct field with autonomous aims (Endy, 2005).

A clear objective of synthetic biology is to make biology into an engineering discipline (Endy, 2005). As in systems biology, this is an attempt to make biology less qualitative and descriptive, and more quantitative and predictive (Lazebnik, 2002). Notably, in both systems biology and synthetic biology we see biologists trying to turn biology into a 'hard' science.

However, in both systems biology and synthetic biology there are those who think that this 'hard'-science approach will not lead to biological insight. Some scientists we interviewed who are working in systems biology think that the search for laws is misguided because, as one computer scientist argued, biology itself is more suited to the attitude of the naturalist than the mathematician. He explained that "[t]he naturalist is someone who places a great deal of attention [on] the oddity and the variety and multiplicity of the world as it is." He is sceptical of the idea that biology is written in the language of mathematics, and thinks that attempts to find foundational truths in biology are mistaken. Others agree that it is futile to seek the kind of generalized 'understanding' that would be gained from the discovery of general laws, saying that, though, systems biologists should think in terms of answering specific biological questions.

In synthetic biology, we see similar concerns about the application of principles from engineering. Adam Arkin and Daniel Fletcher, for example, have asked: "Can

we develop, or deal with, the lack of a coherent theoretical and physical foundation for living systems? Or is control of biology destined for the same fate as rainmaking?" (Arkin & Fletcher, 2006). Despite the attempts to integrate theoretical rigour "into the very fabric of bioscience research" (McCarthy, 2004), we might never reach a situation where we have an "Ohm's law of genes and proteins" (Pleiss, 2006). Some interviewees think that biological systems will not be fully susceptible to engineering goals.

…engineers are always looking for general principles, whereas biologists are far more interested in the outliers

These differences in aspiration reflect, to some extent, the differences between the disciplinary backgrounds of the people who are doing the research. For example, an engineer pointed out that, in his experience, engineers are always looking for general principles, whereas biologists are far more interested in the outliers. A computer scientist agreed that "the biologist is always interested in the particular and the oddity"; this is perhaps because biologists are used to working with "dirty, unruly living systems".

Possibly because of these interdisciplinary tensions, many systems biologists stress the centrality of biology to their work. For example, one biologist maintained that "the really key point is that systems biology is driven by biology." Another insisted that, in systems biology, "the questions are biology and the language is biology." Perhaps it is because systems biology, with its emphasis on computation and mathematics, is different from biology as traditionally practiced that these researchers want to emphasize their commitment to biological questions.

Also, although a great deal of emphasis in systems biology is placed on computational modelling, most systems biologists think that there is still—and will be for the foreseeable future—an essential role for 'wet' experiments that are carried out at the laboratory bench. As one respondent noted, "you've still got to do experiments to prove that you're correct." This is a demonstration of the point that it is hard for many biologists, particularly those trained in molecular biology, to accept the results of computational experiments without doing the 'real' biology (Calvert, 2007; Fujimura, 2003). A computer scientist working in systems biology expressed this sentiment, perhaps with some frustration, saying "I think that the traditional approach has been that if you don't do it in a lab with a test tube and a Bunsen burner, it's not science."

The importance of biology that is expressed here is also seen in the views of interviewees who think that systems biology is not a paradigmatic change, but rather an inevitable natural progression towards biological understanding. One policy-maker made this point by saying "I don't think systems biology is revolutionary as a direction or as a vision, it's just necessary," whereas a biologist expressed the view that "biology is not different, biology is just more complex."

Some interviewees think that systems biology is not a paradigmatic change, but rather an inevitable natural progression towards biological understanding

Yet, we have shown that in many ways biology is different. Systems biology attempts to integrate data and ideas from several disciplines in order to explore questions that have not been answered by any single one. This makes it different from molecular biology as it has been practiced during the past 30 years. Systems biology also differs from physiology in the twentieth century, not least because it uses new technologies and new forms of data. We have also shown that there are many sociologically and philosophically interesting features of systems biology, such as the efforts to characterize its practices in opposition to molecular biological reductionism and to frame its aspirations in terms of the 'rigour' of physics, mathematics and engineering. Systems biology brings together a range of different people with different ideas about the nature of biological understanding, and it transgresses the boundaries between different scientific disciplines. Whether these differences will eventually constitute a paradigmatic shift awaits an historical answer.

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doi:10.1038/embor.2009.151