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Calculating life? Duelling discourses in interdisciplinary systems biology

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ABSTRACT

A high profile context in which physics and biology meet today is in the new field of systems biology. Systems biology is a fascinating subject for sociological investigation because the demands of interdisciplinary collaboration have brought epistemological issues and debates front and centre in discussions amongst systems biologists in conference settings, in publications, and in laboratory coffee rooms. One could argue that systems biologists are conducting their own philosophy of science. This paper explores the epistemic aspirations of the field by drawing on interviews with scientists working in systems biology, attendance at systems biology conferences and workshops, and visits to systems biology laboratories. It examines the discourses of systems biologists, looking at how they position their work in relation to previous types of biological inquiry, particularly molecular biology. For example, they raise the issue of reductionism to distinguish systems biology from molecular biology. This comparison with molecular biology leads to discussions about the goals and aspirations of systems biology, including epistemic commitments to quantification, rigor and predictability. Some systems biologists aspire to make biology more similar to physics and engineering by making living systems calculable, modelable and ultimately predictable—a research programme that is perhaps taken to its most extreme form in systems biology's sister discipline: synthetic biology. Other systems biologists, however, do not think that the standards of the physical sciences are the standards by which we should measure the achievements of systems biology, and doubt whether such standards will ever be applicable to 'dirty, unruly living systems'. This paper explores these epistemic tensions and reflects on their sociological dimensions and their consequences for future work in the life sciences.

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1. Introduction

Systems biology is an approach to biology that brings together biologists, physicists, engineers, mathematicians, statisticians, and computer scientists. These interdisciplinary interactions are often accompanied by lively discussions about the epistemic aspirations of systems biology, because some systems biologists aim to make biology as quantitative and predictive as physics and engineering. But others argue that this aspiration is misplaced, and instead stress the multiplicity, contingency and unruliness of biology.

We start this paper by outlining the field of systems biology, and we show that it is often described as an 'approach', which is defined not only epistemically but also organizationally. We go on to show, however, that the most common way in which systems biologists differentiate their work from the molecular biology that has until recently dominated the biological sciences is in epistemic terms. For example, systems biologists discuss topics such as the role of hypotheses in their work, and they talk about their field's revolutionary aspirations, especially as compared to their view of molecular biology. Reductionism is one of the key issues drawn upon by systems biologists to distinguish their work from molecular biology, although the relationship of systems biology to reductionism is not clear-cut. Systems biology also aspires to replace the 'intuition' of molecular biology with 'rigour'. In this way the aspirations of physics and engineering are adopted by systems biology,

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including the desire to uncover laws and to predict the behaviour of biological systems. Predictability is closely linked to the idea of 'calculating life' which, for some systems biologists, is the ultimate aspiration of their field. This aspiration is taken even further in the field of *synthetic* biology, which aims to construct biological systems. However, some systems biologists are concerned that the epistemic value schemes of the physical sciences are not those that are most appropriate to biology. They maintain that because of the unruliness of living systems, 'proper biology' requires different practices and objectives. We show that these differences in epistemological aims are often the result of differences in disciplinary training, because scientists coming from different disciplines have different ideas about the aims of their research. For these reasons, we conclude by arguing that systems biology needs to embrace epistemic pluralism if it is to successfully pursue its interdisciplinary agenda.

All of the empirical material presented here comes from the perspective of systems biologists. Although we refer to our respondents by discipline of training, it should be borne in mind that these are all people who self-identify as engaged in systems biology. We draw on over 50 interviews with scientists working in systems biology in the US, the UK and Japan, attendance at systems biology conferences and workshops, extended stays in systems biology laboratories in the US and UK, two discussion groups with systems biologists, and email exchanges with interviewees. We also draw on the scientific, philosophical and sociological literature on systems biology.

2. What is systems biology?

Systems biology is represented by many of our respondents as an attempt to make sense of the vast amounts of data that have been generated by the genome sequencing projects and other large-scale molecular data-gathering exercises, by combining computer modelling with high-throughput 'omics' techniques (Auffray, Imbeaud, Roux-Rouquié, & Hood, 2003). Although there have been attempts to apply systems theory to biology in the past (notably Bertalanffy in the 1930s and Weiss in the 1950s), these were not successful in establishing a new field, and some have argued that this was because the mathematical models that were developed were too abstract to be applied to specific biological problems (Kitano, 2002). Today, in contrast, there is a great deal of molecular biological data available, and developments in computation and computer science have made it possible to apply mathematical models to complex biological systems (Ideker, Galitski, & Hood, 2001).

Physicists, computer scientists, engineers, mathematicians and biologists have begun to collaborate under the banner of systems biology to build dynamic *in silico* models of biological systems since the late 1990s, and it is now one of the funding priorities in Europe, the United States, and Japan (Reiss, 2005; US Department of Energy, 2005; World Technology Evaluation Centre, 2005). Many governments have prioritized systems biology in their budgets and a growing body of literature identifies itself as systems biology. In the last five years there has been a rapid rise in the numbers of international conferences, chairs, departments, institutes, and journals dedicated to systems biology (Fujimura, 2005; Powell, O'Malley, Müller-Wille, Calvert, & Dupré, 2007).

As with most new fields there is no consensus on the definition of systems biology. One rather cynical way of describing it is "physiology with advertising" (Biologist12). Systems biologists argue, however, that what is new about the field is the kinds of computational technologies that are being used to study biological systems, which have made it possible to accumulate previously unprecedented levels of molecular data, and which have allowed the *integration* of many different types of data.

When interviewees try to put their finger on what systems biology is they often say it is an 'approach'. One of them explains that what she means by an approach is "a set of beliefs or intuitions about what's important in an organism or in an understanding of an organism" (Computer scientist8), which involves moving beyond a molecular-level understanding and taking the cellular and environmental context into account. Systems biology is an approach in that it approaches problems that cannot currently be solved by a single discipline, as disciplines are currently constructed. Whether systems biology will become a discipline—and if it does, what kind of discipline it will become—remains to be seen. In the meantime, one of the key features of the systems biology approach is its *inter*disciplinarity, which is said to be unavoidable, because the skills of many disciplines are necessary to solve the problems that are being raised by the field.

2.1. Interconnectedness of the social and epistemic

What is particularly striking in systems biology discourses is that many definitions of the field merge the social and the epistemic. Systems biology is described as being integrative, not only of data and technologies, but also of disciplines and people. For example, a systems biology lab manager said that he thought there were two prongs to the definition of systems biology: the first prong is a technical definition, which involves high through-put methods and the use of computation and mathematics, but more interestingly, the second prong is a non-technical definition, which refers to interdisciplinary organisation, and which he thought would result in a new culture of interdisciplinary work (Biologist20). The importance of the social and organisational aspects of the field were made clear when interviewees put forward the idea of systems biology as being some kind of sociological experiment. For example, one stressed that the "development of systems biology depends on the sociology" (Biologist11). By this he meant that it was important to generate the appropriate social environment where scientists with different expertise could come together to work productively as a team.

Another demonstration of the interconnectedness of the social and the epistemic in the field is the commonly heard trope that systems biology has 'no walls'. This point is made in an epistemic and metaphorical sense when systems biologists maintain that the field has no walls because it draws on expertise from whichever area is most useful or appropriate at the time ("why not? Ideas are everywhere", as Biologist6 says). Two senior investigators even thought that systems biology's disciplinary spread could extend to the social sciences and humanities (Biologist9 and Biologist6). But the idea of 'no walls' also has currency in a literal and institutional sense, because there are no physical walls between the laboratories at many systems biology institutes, to facilitate communication and collaboration between researchers. One systems biology laboratory was specifically designed so that it was possible for the scientists to easily see each other working in the space, to encourage the idea that they were part of a larger community. An interviewee explained that this physical set-up was chosen because science is "all about seeing the greater picture" (Biologist19). He is using the word 'seeing' here to talk about *understanding* in science, but this understanding also requires the ability to literally see one's colleagues. These new buildings have interdisciplinarity purposely built into their design, and incorporate social spaces and 'streets' to encourage serendipitous interactions between 'wet' experimental and 'dry' computational researchers. They serve as reminders to researchers of other ways of thinking about and solving problems and reminders of opportunities to ask for help with issues that appear intractable.

It has not been easy to establish new interdisciplinary research organizations. One of the US's leading systems biologists, Leroy

Hood, said that in the initial stages of setting up his Institute for Systems Biology he had to fight against the orthodoxy and the constraints of academic bureaucracy (Agrawal, 1999). Similarly, the setting up of a large interdisciplinary systems biology centre in the UK with its own dedicated building required "an enormous struggle" (Biologist19). This is because, according to systems biologists, it was necessary to confront conservative colleagues with vested interests in the *status quo*. As one of them put it: "You must not under-estimate the importance of culture in blocking interdisciplinary advances" (Computer scientist5). In another US university, the decision to build an interdisciplinary research centre was top-down, initiated by university and funding administrators and initially opposed by most campus laboratory scientists. The building of new interdisciplinary structures is challenging for the existing disciplinary "fiefdoms" (Biologist19) and "silos" (Biologist9 and Biologist12) "where people feel protected and safe" (Biologist19) because they are not required to step outside of their "comfort zones" (Biologist7).

Hood maintains that "new organizational structures were needed for the realization of a paradigm change" (Hood, 2008, p. 11), making the point that the content of research is heavily influenced by the organizational and physical environment in which it takes place. These organisational innovations may be the most important way in which systems biology is different from the life sciences that preceded it (although it should be remembered that in its early days, molecular biology was also itself the product of a confluence of scientists from different disciplines, including physics and chemistry). Even those who are reluctant to talk about 'paradigm change' in systems biology do point out that one of systems biology's most notable aspects is its interdisciplinary nature and the way in which it represents a new wave of physical scientists and mathematicians coming to study biological issues (Noble, 2007).[1]

2.2. Systems biology as revolutionary?

It is not uncommon for systems biologists to talk about the revolutionary ambitions they have for their field. Systems biology is often described by its proponents as a "new way of doing science" (Biologist12), or a "different way to think about biology" (Computer scientist1), which will bring great changes. For example, a computer scientist says:

> "we're now 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" (Computer scientist1).

The novelty and legitimacy of systems biology can be gauged by the reactions the field provokes. Boogerd, Bruggeman, Hofmeyr, and Westerhoff (2007) point out that "many systems biologists are confronted in response to their papers or grant applications that the science they are doing or proposing is not quite proper, being insufficiently driven by minimal hypotheses" (p. 322). A biologist originally trained in molecular biology helps situate this comment by explaining that "during the 1980s and beyond there's been a fairly profound revolution in the way that science is done, where a lot of work is very empirical". By empirical, he means that "the hypothesis is constructed later as a way of integrating the parts" (Biologist12). This is very different from the idealised Popperian model that many scientists have used to represent how science proceeds, where a hypothesis is first formulated and then tested against the available data. Systems biologists, in contrast, will often generate hypotheses from the data (Biologist6). For example, a computer scientist says "of course, we have a perspective, but fundamentally we're going to let the data talk to us" (Computer scientist1).

A problem with 'letting the data talk' is that these scientists can have trouble getting grants and getting published because of their perceived lack of hypotheses.[2] In this manner, systems biology is commonly accused of being a mere 'fishing expedition' (see Kell & Oliver, 2004), which yields no real understanding of biological mechanisms.[3] A response to this criticism is: "you're fishing in a pond in which you know there is a jolly good fish to be caught, you know you have got some jolly good bait and you know correspondingly the chances of catching it are very high" (Computer scientist5). The point being made here is that valuable scientific work can be done, even in the absence of conventional hypotheses.

Of course, hypothesis-driven and data-driven approaches are not dichotomous, and have co-existed throughout the history of science (Glass & Hall, 2008). In our contemporary study, interviewees acknowledge the interplay between the two when they talk of an iterative cycle in systems biology, and of "principled hypothesis generation" based on data produced in well-designed experiments (Computer scientist5). Some systems biologists—for example, one who conducts viral engineering studies—run both wet lab experiments and dry lab computational data-driven experiments in a single laboratory. Other systems biologists work in collaboration with wet lab experimenters. Still others develop ideas for "fishing expeditions" from reading wet lab studies. Thus, in the actual science, as opposed to the rhetorics exchanged between systems biologists and molecular biologists, it is often difficult to separate hypothesis-drive and hypothesis-generating studies. Ideker et al. (2001) have also written that the integration of both discovery science and hypothesis-driven science "is one of the mandates of systems biology" (p. 344).

This is not to underplay the problems that systems biologists currently face in explicitly undertaking data-driven research, and the dominance that ideas about the importance of hypotheses can have in funding contexts (see O'Malley et al., 2009). Nevertheless, data-driven research, including quantitative genomics searches for medically relevant genetic markers or genes, has recently dominated genomics research and has also been criticized for the vast resources it has consumed (Fujimura, Rajagopalan, Ossorio, & Doksum, 2010). At this point, systems biology appears to be gaining research credibility and funds, but it is a question for future research as to whether this growth will continue along the lines of genomic studies or will be affected by "fishing expedition" attacks currently faced by genomics.

3. The comparison with molecular biology

Since systems biologists often distinguish their research from that of previous traditions, it is not surprising that there is much discussion of whether systems biology constitutes a paradigm shift. We will not discuss the merits of arguments about paradigm shifts here.[4] Our goal is to show how these systems biologists

[1] For a dedicated discussion of interdisciplinarity in systems biology, which addresses communication, disciplinary identity, training and academic reward structures, see Calvert (2010).

[2] In an acknowledgement one systems biologist thanks two UK funding agencies "for keeping alive nonhypothesis-dependent science during the dark days and now" (Westerhoff & Kell, 2007, p. 64).

[3] In the light of these criticisms, it is interesting that a survey of 100 papers by Rowbottom and R. M. Alexander (forthcoming) shows that scientists working in biomechanics will present their work as being hypothesis-driven even when it is not. None of the papers in their sample presented their research as an exploratory 'fishing trip'.

[4] Recall that Margaret Masterman counted at least 23 definitions of paradigm in Thomas Kuhn's (1962) introduction of the term into history and philosophy of science. The definition of paradigm shift is even more treacherous terrain, see Masterman (1970).

position their developing field with respect to other fields, so we examine how and when the language of paradigms is used by systems biologists. What follows is a characterization of molecular biology by some of the systems biologists we have interviewed. Although we acknowledge that molecular biology is more than is represented by these systems biologists, our point is that the rhetorics of difference from molecular biology are key to the researchers' epistemic and institutional construction of the systems biology approach.

As we saw with the discussion of hypotheses, the issue of whether systems biology marks a paradigm shift comes up most often in comparisons with molecular biology. In fact, Boogerd et al. (2007) note that "practicing systems biologists are often hindered by paradigm battles with molecular biologists" (p. 5). Some systems biologists even argue that molecular biology is a detour in the history of biology, and the antithesis of systems biology (Biologist18 and Computer scientist1). A computer scientist highlights 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" (Computer scientist5). This is in a context where, until very recently, "the mainstream was dominated by the reductionist molecular biology agenda" (Computer scientist5).

With this background it is perhaps not surprising that systems biologists often experience resistance to systems approaches from the "old school" (Computer scientist9) of molecular biology. Some interviewees even argue that a "phenotype" (Biologist11) of a paradigm shift is the antagonism that a new scientific movement gives rise to from proponents of previous paradigms. They talk about how emotional and political responses are common in discussions of the merits or otherwise of systems biology (Biologist11).

3.1. Holism versus reductionism in systems biology

Many systems biologists invoke the term 'reductionism' when they refer to molecular biology and argue that systems biology adopts a more holistic approach. They use terms like 'global' or the 'big picture' to describe their perspective. However, reductionism and holism are 'fighting words' in the history of biology. Philosophers of science and biologists have been engaged in debates about reductionism and holism for at least the last hundred years. Instead of trying to define the terms and debates in any final form, here we look at how the actors we interviewed used the terms. Generally, the debate is about methodological reductionism, because it concerns whether the appropriate level of focus is on parts or on wholes. Systems biologists use the term 'reductionism' to refer molecular biologists' attention to the parts of the organism, including DNA, RNA, and proteins, and their functions. Systems biologists argue that, in contrast, they are interested in understanding how parts are organized into systems, because, in their eyes, systems explain more than individual parts. Some systems biologists also discuss their focus as on the *interactions* among parts. Here again, one could argue that molecular biologists also focus on interactions, but primarily between parts of a smaller system as, for example, between a protein receptor and a segment of DNA. The focus of systems biologists is on larger scale systems.

Interviewees maintain that since systems biology studies systems as wholes, it is impossible to study them in terms of one's "favourite molecule" (Biologist15), which is a common portrayal of a molecular biologist's approach. From this perspective, molecular biology reduces biological complexity to the actions of molecules, especially the heroic action of particular molecules. This attitude explains what is often said about the strategy for success in molecular biology: "one gene one PhD" (Computer scientist8). One molecular biologist explained that he moved into systems biology because he wanted to avoid the inevitability of his future career path: "I could almost predict what the next 10 years was going to look like. You can just plug in a different molecule" (Biologist7). Systems biologists say that it is not surprising that this approach is pervasive because molecular biologists have been rewarded for at least the last 50 years for doing this type of research, and have managed to secure high profile publications and successful careers on the basis of this strategy (Computer scientist9).

In contrast to these studies of the actions of molecules, one of the central claims made by many systems biologists is that their field is not reductionist, and is in fact a reaction to "the essential failure of the reductionist agenda" (Computer scientist5), both medically in terms of drug development (Biologist11), and conceptually in terms providing a satisfactory understanding of the operation of biological systems. This perceived failure of reductionism to deliver explains why it has become a pejorative term for some systems biologists. An interviewee puts his concerns 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" (Biologist18). This comment is best understood in the context of the international human genome projects which left researchers with too few genes to account for the complexity of bodies, diseases, and therapeutics (Venter et al., 2001).

In this context, some systems biologists have become interested in emergent phenomena (Westerhoff & Kell, 2007). One graduate student even defines systems biology as "the study of emergent properties in science" (Physicist4). Emergence is another highly contested term, but it can be understood as a situation where the properties of a whole cannot be deduced from the knowledge of the properties of the components, because the components work differently together than they do apart (see Broad, 1925; Calvert, 2008). As one interviewee puts it: 'is the sum greater than the parts? If it's not, it's not systems biology' (Biologist18). With the introduction of concepts such as emergence we are given the impression that in systems biology analytic frames multiply and broaden far beyond the focus on individual molecular components, typical of molecular biology. Here again, we note that these systems biologists have constructed a particular view of 'molecular biology' that molecular biologists might not recognize, since many do study interactions among parts. Our point, however, is that molecular biologists focus primarily on parts and secondarily on their interactions, while systems biologists see their work as centrally concerned with interactions.

3.2. Reductionism writ large?

Despite these discussions of the failure of reductionism and the importance of emergent processes, many of the systems biologists we interviewed were explicit about their own (methodologically) reductionist objectives. One, for example, thinks that "the systems stuff's really a starting point for the reductionist biology" (Biologist13). Another echoes this point:

> "what we have got to emphasise is a molecular level analysis, so we need to be able to trace back emergent properties or life or biology, phenotypes, whatever we're looking at, to the molecular underpinnings" (Biologist7).

These systems biologists see their work as using systems approaches to find interesting signals and relationships that then have to be studied in a reductionist fashion using experimental molecular biological methods. For these researchers reductionism is clearly not a pejorative term. What we see here is a collaboration between molecular biology's detailed biochemical analysis of interactions among parts and two of systems biology's conceptual and methodological strengths: broad analysis of vast quantities of molecular data, and conceptual and computational models of emergent phenomena. Some commentators go further to argue that systems biology's version of holism is itself reductionist. They view systems biology as firmly part of the reductionist enterprise and accuse the field of being reductionism writ large. For example, one critic says of certain varieties of systems biology:

> "This is brute-force, geno-centric reductionism in the guise of entireness, rather than a novel integrative approach devoted to wholeness" (Huang, 2000, p. 471).

Some of our interviewees similarly saw systems biology as an acquisitive data-gathering exercise, whose main objective is to enumerate the components that make up biological systems, rather than form an understanding of the operation of these systems. A biologist criticises this data-gathering approach by pointing out that "you can measure the colours of everybody's T-shirts and everybody's date of birth and you know nothing about the world at all" (Biologist10, UK). Another makes a similar objection, asking: "would we have a better understanding of the behaviour of the universe if we count the stars?" (Biologist2, France). These objections to systems biology are obviously formulated in response to a narrow conception of systems biology that does not match the breadth of the field as we know it, just as molecular biology is broader than its representation in systems biology rhetorics. Nevertheless, they clearly demonstrate a perspective on systems biology's epistemics as being no better, and perhaps even worse, than molecular biology's reductionism. These examples show the different interpretations of systems biology that are being wielded in current duelling discourses.

There is, however, the potential for a different type of reductionism in systems biology. Some systems biologists adopt particular models borrowed from physics, statistics, computer science and engineering and apply them to biological data. These models oftentimes carry their own versions of reductionism, because they are based on assumptions about the character of biological systems, and they excise whatever cannot be translated into the appropriate technical terms (see Fujimura, 2005). A UK policy maker was wary of this type of reductionism in warning a systems biology conference that they must be careful they are not replacing *molecular* reductionist approaches with *mathematical* reductionist approaches (Policy maker2). The kinds of tacit knowledge that biologists have gained from years of learning about the details of historical development of biological systems could disappear when top-down physical, engineering and computer science models are used to select and shape biological data.

Despite these complexities and criticisms, the dominant discourse of systems biology is one of anti-reductionism. This discourse is so pervasive that the Biotechnological and Biological Sciences Research Council (BBSRC), the UK's largest funder of systems biology, felt the need to be explicit about its position on anti-reductionism:

> "BBSRC has not become anti-reductionist as a result of encouraging the uptake of systems biology approaches. BBSRC maintains a neutral position here ... and acknowledges that systems biology may involve bottom-up, top-down or middle-out approaches. It acknowledges that the molecular-level research it has funded—and continues to fund—is an important part of the picture" (BBSRC, 2006).

This statement is another demonstration of the tension between systems biology and molecular biology, and it shows a recognition by the BBSRC that there is concern that traditional molecular biological research will suffer in a climate that is favourable to systems biology. Although we have shown that it is not possible to distinguish molecular biology from systems biology clearly in terms of reductionism, we can see that the issue of reductionism is a live one which systems biologists draw upon when defining their work in opposition to what they represent as more traditional forms of biological research.

4. Epistemic aspirations

Systems biologists also distinguish their work from molecular biology by saying that they aspire to make biology into a more rigorous and quantitative discipline. For example, one interviewee maintains that the "intuition or naïve understanding" of molecular biology, will be replaced with the "rigid mathematical or computational understanding" that systems biology brings (Physicist3). This contrast highlights a central epistemic objective of some systems biologists. It also demonstrates that ideas about what it is to do science, and what good science should achieve, are articulated in systems biology in a strikingly self-conscious manner. Perhaps it is because systems biology is still trying to establish itself as a new field of science that we see systems biologists developing their own set of philosophical discussions about their work, by engaging in self-reflection and debate.

A UK systems biologist summarises the agenda of systems biology in writing 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, p. 936). A leading Japanese systems biologist similarly writes: "The discovery of fundamental, systems-level principles that underlie complex biological systems is a prime scientific goal in systems biology" (Kitano, 2004, p. 826). A visual demonstration of these objectives is the circuit diagrams that are the 'poster child' of systems biology (as well as its sister discipline synthetic biology); diagrams which blatantly draw on electronic engineering as their metaphor of choice (see Fujimura, 2005). If these epistemic aspirations are successful, we could see all biological research becoming more quantitative, relying more heavily on modelling, and importing the skills of those from other disciplines trained to deal with large amounts of data.

In these discussions it is implicit that physics, mathematics and engineering have achieved more than biology, and that biology would benefit by adopting their approaches. And we do see attempts to find laws and guiding principles in systems biology. For example, an ex-physicist, who is now a systems biologist, says that he prefers to do science "from a quantitative, theoretical physics point of view", which he says involves looking for "equivalent laws and theoretical structures in biology" (Physicist1). He acknowledges that biology currently lies "half-way between history and physics", but hopes that systems biology will bring biology closer to physics. Others, however, think that the kinds of laws that will be discovered in biology will be 'softer' than those of the harder sciences (Biologist15), because they will be more specific and more context-dependent. For example, a possible biological 'law' might be: "complex systems tend to organise themselves into what looks like structured complexity" (Computer scientist8). This points to a possible 'third way' for systems biology, between the laws of physics and the contingency and particularity of biology (Boogerd et al., 2007).

Prediction is another epistemic aspiration of systems biology that is found in the physical sciences and in engineering. The importance placed on prediction in the field is indicated by the title of the 10 year-vision of the UK's major funding council for systems biology (the BBSRC): "Towards Predictive Biology" (BBSRC, 2003), although discussions with systems biologists reveal that there are differences in how prediction is interpreted. One interviewee, for example, explained that when physicists produce a model that matches existing data, biologists will often be unimpressed because what is predicted is what is *already* known to them (Computer scientist4). We see that there are conflicting ideas here about whether predictions generated by models should accommodate previously known data or whether they should be predictions of something previously unexpected (see Musgrave, 1974; Rowbottom, 2008). Some systems biologists show that they adopt the latter interpretation when they say that their guiding aspiration is to generate models *in silico* which will be able to predict the emergent properties of living systems from the interactions of their components (Westerhoff & Kell, 2007). They think that once this happens, life "will become calculable" (Boogerd et al., 2007, p. 324), it will be possible to capture life in a computer model, and systems biology will have fulfilled its promise. The research programme that expresses this objective in perhaps its most extreme form is *synthetic* biology, which aims to construct novel biological systems (and redesign existing ones) that are calculable, modelable and predictable.

4.1. Comparing Systems Biology with Synthetic Biology

Several interviewees discussed synthetic biology and its similarities to and differences from systems biology. This contrast is useful because it throws light on the epistemic aspirations of systems biology. The two fields can be most easily distinguished in terms of their different intentions: synthetic biology aims at construction, whereas the objective of systems biology is to understand existing biological systems. However, this distinction does not hold in all instances. Some synthetic biologists, such as Benner and Sismour (2005), stress that synthetic approaches can lead to a greater understanding of biological systems, and others see synthetic biology as providing 'the acid test' (Systems Biology Conference, Edinburgh 2008) of the models in systems biology by trying to reverse engineer them as functioning biological systems (Barrett, Kim, Kim, Palsson, & Lee, 2006). In this way synthetic biology can be described as "systems biology in reverse" (Computer scientist9). Others see synthetic biology as "a reductionist approach to systems biology" (James Collins in Ferber, 2004, p. 158), because synthetic biology aspires to reduce the complexity of biological systems by developing discrete and substitutable parts. Some see synthetic biology as a distinct and autonomous field (Endy, 2005).

Systems biology largely takes its inspiration from physics (see Westerhoff & Kell, 2007), while a clearly stated aim of synthetic biology is to make biology into an engineering discipline (Andrianantoandro, Basu, Karig, & Weiss, 2006; Brent, 2004)[5], i.e. to apply the principles of standardisation, decoupling and abstraction to synthetic systems (see Endy, 2005). This attempt to make biology into engineering is, again, an attempt to make biology less qualitative and descriptive and more quantitative and predictive (Lazebnik, 2002). This, synthetic biologists hope, will "improve the efficiency, reliability and predictability of our biological designs" (Arkin, 2008, p. 774).

Our point here is not to discuss the merits of their arguments, or the differences or similarities between physics and engineering, but to point out that in both systems biology and synthetic biology we see an attempt to turn biology into something that, our interviewees' eyes, has greater epistemic credibility.

Some commentators such as Pottage and Sherman (2007) say that this push towards making biology more like physics and engineering comes from the aim to make the world more instrumentalizable and programmable. This echoes the views of historians and philosophers of science in the late 20th century that molecular biology was an experimentalist programme that would allow humans to better manipulate nature (e.g. Hacking, 1983; Haraway, 1981–1982; Kay, 2000; Keller, 2000, 2002).[6] Ironically, however, despite these concerns, molecular biology's efforts to transform a multi-faceted, contingent object such as cancer into a predictable and controllable object has instead produced a multitude of representations, explanations, and examples such that cancer genetics is at least as multi-faceted, complex, and contingent as pre-genetic representations of cancer (Fujimura, 1996). The same could turn out to be the outcome of both systems and synthetic biologies.

5. Dissenters

The issue of what kind of knowledge systems biology should aim to produce is discussed at length by systems biologists both individually and in group discussions at systems biology conferences and workshops. Researchers who call themselves systems biologists are developing their own set of philosophical definitions and debates about their work, again perhaps because systems biology is still trying to establish itself as a new field of science. This open discussion has provided us with dissenting views.

In both systems and synthetic biology there are some who do not embrace the attempt to make biology a predictable and controllable science. For example, one computer scientist argues that the search for laws is misguided, since he thinks that biology is much better suited to attitude of the 'naturalist' than the 'mathematician'. He explains:

> "The naturalist is someone who places a great deal of attention on to the oddity and the variety and multiplicity of the world as it is, rather than looking for first principles that you can deduce the nature of the world from" (Computer scientist2).

He is skeptical of the idea that biology is written in the language of mathematics, and thinks that "attempts to find foundational truths" in biology are mistaken (Computer scientist2). In his view, the kind of understanding biology gives is the kind of understanding gained from mapping a continent, i.e. from paying attention to the detail and the variety of the terrain. Other interviewees also concur with Keller (2007) when she says that what is fundamental in biology "is far more likely to be found in the accidental particularities of biological structure arising early in evolution, than in any abstract or general laws" (p. 120).

We see related challenges in synthetic biology to the adoption of principles from engineering. Arkin and Fletcher (2006), for example, ask some pertinent questions: "is the conventional paradigm of engineering appropriate for biology? 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?" Despite the attempts to integrate theoretical rigour "into the very fabric of bioscience research" (McCarthy, 2004, p. 936), some opine that we may never reach a situation where we have "Ohm's law of genes and proteins" (Pleiss, 2006, p. 738). Some synthetic biologists think that biological systems will not succumb to engineering goals, and that "the engineers will find out that the bacteria are just laughing at them" (Wimmer quoted in Breithaupt, 2006, p. 23).

These concerns and differences in epistemic aspiration reflect, to some extent, the disciplinary background of the person who is doing the biological research. For example, an engineer pointed out that in his experience in working in systems biology, engineers are always looking for general principles, whereas biologists are far more interested in the outliers (see also Rowbottom, in 2011). A computer scientist agreed, saying that coming from his

[5] Although, as we have seen, some systems biologists do explicitly adopt engineering principles (see Kitano, 2002).

[6] Haraway argues that cybernetics had at its base a structure meant to control and dominate, to achieve and affect power. She argues that cybernetics was fundamentally a discourse based on domination and hierarchy. These 'command-control systems' were 'ordered by the probabilistic rules of efficient language, work, information and energy' (Haraway, 1981–1982, p. 246).

disciplinary perspective it seems as if "the biologist is always interested in the particular and the oddity" (Computer scientist2). The computer scientist/engineer's aspiration for guiding principles is perhaps expressed in the statement "Life would be so much easier if we just had the source code", which was found posted on an office door at a systems biology centre, and which is perhaps an expression of frustration with the "dirty, unruly living systems" (Biologist17) that are the subject of systems biology.

Some systems biologists hope these disciplinary tensions will be reduced in the future, because they will be able to "train a new generation of people that think differently" (Biologist17). Many argue that training will have to become more conceptual (Biologist1), and that there will be a move from specialists to integrators (Policy maker1). The aim is that young systems biologists will be able to "find new ways of speaking and to be able to communicate across different conceptions of the world" (Computer scientist2). Here we see a recognition that institutional attempts must be made to deal with the epistemic pluralism of the field.

6. Centrality of biology

Leaders of the field of systems biology tend to emphasize their commitment to biological questions, perhaps because of the disciplinary diversity in the field, and because systems biology's *in silico* modelling and emphasis on computation and mathematics differs from biology as traditionally practiced. For example, a common refrain is that "systems biology is driven by biology" (Biologist1). An interviewee elaborates:

> "I think biologists need to drive systems biology, because if it's driven by computation or engineers, without a depth of training in biology, they lose that sense, they tend to treat molecules as nodes and edges without a sense of how they're performing their functions" (Biologist7).

Another senior scientist is keen to emphasise that in systems biology "the questions are biology and the language is biology" (Biologist17). The head of a systems biology institute insists that a mathematically trained scientist who comes into his institute has to be "happy to portray himself or herself [as some] sort of biologist" (Physicist3), and that without this kind of commitment then they should not be engaged in systems biology. In the light of this comment, it is interesting that a mathematician working in a UK systems biology centre described himself as "working for the biological problem" (Mathematician1).

It should also be noted that although there is an emphasis on computational modelling in systems biology, most systems biologists think there is still an essential role for 'wet' experiments, carried out at the laboratory bench rather than on a computer. They stand by the idea that truth can only be provided through wet science (Biologist16) since "you've still got to do experiments to prove that [your models are] correct" (Biologist13). Many biologists, particularly those trained in molecular biology, still find it difficult to accept the results of computational experiments without doing the 'real' wet biology experiments (see Calvert, 2007; Fujimura, 2003; Rowbottom, 2011). This may be because "wet and dry science differ in terms of what their proponents regard as 'proper science'" (Penders, Horstman, & Vos, 2007, p. 613). A computer scientist working in systems biology expresses this sentiment, with perhaps some frustration, by 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" (Computer scientist8).

The importance attached to biology is also seen in the views of interviewees who think that systems biology is simply an inevitable natural progression towards biological understanding, rather than a paradigm shift. One policy maker makes this point by saying: "I don't think systems biology is revolutionary as a direction or as a vision, it's just necessary" (Policy maker1). A US biologist also expresses the view that "biology is not different, biology is just more complex" (Biologist5), and a UK biologist says "I still prefer to think about it as biology, trying to do good biology, and trying to do biology which is adequate to the complexity of the system" (Biologist15). This necessarily involves drawing on the available "facilities, funds and technologies to answer complex biological questions" (Biologist15). In other words, researchers now have more information on the bits and pieces of the puzzle, and they now need to understand the connections among the bits and pieces, whether they are systems biologists or molecular biologists.

Even in an interdisciplinary context, these examples show that what remains central (and undefined) in systems biology is biology itself. This is because in systems *biology* the objective is to understand biological systems using epistemologies and technologies adopted, and adapted, from elsewhere. As this adoption and adaptation process continues, new questions emerge for systems biologists about what constitutes proper biological understanding, what a biological question is, and even what we should recognise as a biological object.

7. Conclusion and Discussion: Epistemic Aspirations and Interdisciplinary Collaboration

This paper has explored systems biologists' discourses on the epistemic aspirations of their field. These discourses show that the epistemic and the social are closely linked in the definition of systems biology. That is, researchers in the field view its interdisciplinary organisational arrangements as central to its epistemological difference and distance from molecular biology (at least, the molecular biology of the last 50 years).

This interdisciplinarity also translates, not into a coherent transdisciplinary epistemology, but instead to a multiplicity of epistemic aspirations within the field of systems biology, and a range of different ideas about the nature of understanding. For some, a goal is to make life calculable. Others questioned the assumption that the standards of the physical sciences are the standards by which they should measure the achievements of biology. Several interviewees stressed the importance of wet science and 'proper biology', and leaders of the field insisted that biology is central to the enterprise of systems biology.

These different epistemologies extend beyond how to treat biological objects to philosophical issues such as whether the Popperian model of science holds for systems biology. As we have shown, some maintain that the innovation of systems biology is that it produces hypotheses that are based on data, and on more data than can be held in the head of a single scientist, or even in the heads of a group of scientists. The argument is that systems biology replaces the 'intuition' of molecular biology with the 'rigour' of physics, mathematics and engineering. From the perspective of systems biology, computational tools provide new, perhaps less biased hypotheses than the hypotheses that some argue have driven mainstream biological research. In contrast, others denigratingly call this approach a 'fishing expedition'.

Systems biologists defend their methods by arguing that their approach is more holistic than the reductionism of (their understanding of) molecular biology, while critics question whether systems biology is instead an extension of molecular biology's reductionism, or even a new kind of reductionism.

In another self-reflective philosophical discussion, we showed how some respondents even suggested that the conflict between systems biology and molecular biology is an indication of a paradigm shift. It is too early to know whether and how the field of systems biology will normalize, as in the sense of Kuhn's 'normal science', despite all the prognostications. And it is not clear that any field fits Kuhn's 'normal science' model, except perhaps at a particular moment in time. The field may never shift and stabilize into a set of canonical epistemological aims and methods; it may always be constituted of a range of different approaches. It may split into several different fields. Or it may go through a series of stages, with different epistemological aims. What interests us is that these systems biologists use discussions of issues like 'paradigm shifts' to push particular epistemological agendas. These are not just philosophical discussions, they are also duelling rhetorical discourses between opposing epistemic aspirations.

Despite these duelling discourses, our interviewees insist that one of the key features of systems biology is its interdisciplinarity, because the skills of many disciplines are necessary to solve the problems that are being raised by the field. If so, these different epistemological values and commitments raise questions about immediate efforts to collaborate on biological problems. Physicists, statisticians, and engineers currently contribute technologies and methods that biologists welcome, however much they may resent the intrusion of these disciplinarians into their field. The former also acknowledge, if sometimes begrudgingly, that the biologists might know a thing or two about the biological systems they want to model. Thus, collaborations are being forged based on mutual benefit. The question is whether the different and sometimes oppositional epistemic aspirations expressed by those who call themselves systems biologists will make it difficult for collaboration to occur, much less a coherent field of study to be institutionalized.[7]

If we consider disciplines such as physics and biology to be different epistemic cultures (Knorr-Cetina, 1999) with different languages and 'forms of life' (as do Collins, Evans, & Gorman, 2007), then different disciplinary epistemic commitments could be major stumbling blocks to collaborations in systems biology. If they succeed, however, we will have another demonstration of how scientists from different epistemic cultures can communicate enough to work together. Galison (1997) found that instrumentalists, experimentalists, and theoreticians in high-energy physics collaborate, despite their differences in training, by focusing on the same problem. Treating physicists and engineers as coming from different 'cultures', he argues that these different groups managed to communicate well enough to work together through the development of intermediate languages that developed in 'trading zones' such as high energy physics research. Star and Griesemer (1989) similarly found that hunters and trappers, on the one hand, and naturalist biologists interested in taxonomical methods and evolutionary questions, on the other, could produce knowledge through boundary objects and boundary experts. In these cases, researchers managed to put particular technologies to work to promote collaboration amongst researchers with different epistemic aims, even with different professional aims. Nevertheless, in all these cases, collaboration required a great deal of negotiation and labour at the borders. It may be that differences between paradigms, epistemologies, or methods do not constitute incommensurable boundaries to collaboration. With enough desire, commitment, and labour, these differences may not only be surmounted, they may be productive.

However, differences in epistemic aims may provide a greater challenge than boundary objects can handle. Star and Griesemer's hunters and trappers had no investments in the epistemic or theoretical aims of the biologists, they merely had to fill out forms describing where and when they found their animals. The biologists did not have to convince the trappers of the existence of ecological 'life zones' in order to persuade them to fill out the forms. Managing the filling out of information sheets can be difficult, but perhaps not as difficult as managing different commitments to scientific theories and aims, as any academic can testify. Will systems biologists manage to work together even though they hold heterogeneous epistemic aspirations?

The field of bioinformatics is a recent example of an integration of computer science, statistics and biology where a new generation of students have been multiply trained. Bioinformaticians still tend to specialise in one of the three fields, but they know enough of the other fields to provide them with an understanding of the epistemics and methods. Similarly, communication across disciplines in systems biology could be made easier if members of the field have a greater awareness and appreciation of their different epistemic assumptions and values. It is the case that attempts are already being made to train young systems biologists who are "able to communicate across different conceptions of the world"—people who not only possess a range of different skills, but are also sensitised to the co-existence of different epistemic values. Awareness and appreciation are probably much more feasible goals than an integration of epistemic aims. These new trainees may help, in the long run, to create a new discipline or an integrated field of collaboration where researchers have shared commitments and expertise. In the meantime, however, incentives may be what persuade researchers currently holding different epistemic aspirations to work together through their differences. These incentives currently include new ideas and methods to address common problems, and, perhaps most importantly, research funding that is specifically allotted to interdisciplinary research.

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[7] What is surprising is that while the epistemic aims of any systems biologist generally tend towards his or her original disciplinary training, this is not a rule that always applies. There are physicists who love, and spend time learning, the unruly details of biological systems. There are biologists who want order.

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