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Chapter 5

Enactments of Systems Biology

Annamaria Carusi

Reader in Medical Humanities

University of Sheffield

How and why were you initially drawn to systems biology?

My first encounter with systems biology was through a course I was invited to teach on interdisciplinary research skills. The course was created for a doctoral training centre for students with a background in mathematics, physics, engineering or computer science to tackle modelling in the life sciences. The doctoral programme was called the Life Sciences Interface Doctoral Training programme, and I went into it with the idea of adapting philosophy of science concepts and principles for use as 'reflective levers' so that tacit assumptions concerning scientific method in these domains could be articulated. I did not have specific knowledge of biological sciences at the time. Shortly afterwards, but also concurrently for several years, I was involved in a project to study the social dynamics of e-science, and I chose the same area as a major case study. My observations of organisational and institutional features of computational and systems biology offered opportunities to study the epistemology of these domains in the practices of the scientists. I was particularly drawn to questions relating to the roles played by very different modes of visualisation in the different disciplines that are meant to be collaborating for a fully functional systems biology project, and the stories told by the visualisations about interdisciplinarity, the clashes of cultures and the pleasures and pains of collaboration. The visualisations also turned out to be good places to explore what was considered to be an observation and good enough evidence in the different disciplines; finally leading onto the ways that the field of biology is being reconstituted. The visualisations were a good entryway to the crucial role of modelling in systems biology; for me they were the interface that allowed me to glimpse the material, technological and organisational complexity of systems biology that has sustained my fascination.

How do you view the relation between philosophy and systems biology, and (how) can these fields inform each other?

Whereas stabilised sciences enact philosophy, systems biology is writing a new philosophical script for enactment. I am deriving my use of the term 'enact' here from Judith Butler's notion of performativity. Butler's concern is with the social and cultural constructions of gender and sexuality and so the immediate relevance of the term to science and philosophy is probably not crystal clear. However, please bear with me. Butler encourages us to distinguish between something that is acted (like an actor acts a role on the stage) and something which is enacted, which is far more diffuse and not deliberate or consciously thought out. To act according to one or other gender role is enacted, not acted: it is a way of acting, of performing, that is informed by sedimented conventions in the socio-cultural milieu. It takes something like drag to bring out or show up the performative aspect of gender. When science is 'business as usual' it enacts a philosophical framework which is a kind of sedimented convention of the field; the tasks and routines associated with that way of doing science enact an implicit philosophical framework – an epistemology of what counts as evidence and reasons for belief; an ontology regarding the constituents of the world as represented by that specific scientific domain; an ethics regarding its import to science, scientists and the wider social world. Systems biology is not science as usual, or it aspires not to be as it deploys technologies that conceptually reshape the research field in some quite radical ways. We might say that systems biology is the drag of biology (or computer science, or mathematics, engineering or the many other sub-disciplines that it involves), in the sense that it shows up the philosophical enactments of the sciences it rests upon. But in another sense, it is also writing a new philosophical script as it goes along.

Epistemologically, systems biology is highly socially and technologically mediated. Such mediation is not novel: but digital and computational technologies are not like other technological instruments and apparatus, and we have not yet fully conceptually assimilated the precise nature of those differences, neither with respect to the forms of social interactions afforded, nor with respect to the forms of scientific representation and intervention they allow. Computational science that involves modelling and simulation is epistemologically challenging in itself, but when we are dealing with physiological processes, there are further epistemological challenges concerning the knowledge process and outcomes of which methodological challenges are only the tip of the iceberg. Computational tools and technologies have also unsettled the ontology of biology, pushing into prominence questions about the components and levels of biology, about mechanisms and causes, and how – or whether - to draw the borders of systems.

Systems biology also shows up the social and ethical stakes of biology, right across the board. The ethical issues relating to data should systems biology successfully be scaled up to a systems medicine level, and make increasing demands upon patients and citizens to be data providers, will include the well-known issues of anonymity, confidentiality and, consent; however, there are other deeper questions in the very ethos of systems biology – another form of enactment, the values and virtues that inform how science is done. For example, systems biology sometimes lays claims to a form of community ethos associated with technologies for sharing and standardising data (Leonelli & Ankeny 2012); we do not yet know how deep this ethos goes, exactly how it is expressed, nor how it interacts with other aspects of the science (such as ownership and authorship). Another aspect of the ethos of the science, which has not been explored, is the implications for scientists themselves. Here I mean 'ethos' in a broader sense including also values entrenched in the mode of doing science, of being a scientist and the relationship to the domain studied implicit in it. The shift to mathematical and computational methods opens up some new ways of doing biology and of being a biologist, but also shuts down others: for example, the intimacy between biologist and organism described in Evelyn Keller's biography of Barbara McClintock (Keller 2003) becomes less defining of what it is to *be* a biologist, to experience biology, and this too is, I think, an aspect of the broad (or deep) ethos of systems biology that has a certain significance for the field of biology. Finally, on a social level, it is an important question how a systems biological reconfiguration of biology - especially if it succeeds in discrediting reductivism - may affect the ideological purposes to which biology is so often put.

In all of these ways, systems biology will be writing a philosophical script as it writes its scientific script. So it might be expected that philosophers - that is, professional philosophers - should be involved with it, to make sure that the script is a good one, a philosophically sound one. However, I am not so sure that this is necessarily the case. Professional academic philosophy needs to reinvent itself if it wants to *participate* in this process. There are other roles available to it besides participation such as commentary and analysis. But to participate in shaping the domain requires setting aside purely philosophical interests and motivations, and the process can sometimes be more conceptually messy than is normal in philosophy. Firstly, thinking of participation as the application of pre-existing philosophical definitions does not work very well, as they often do not fit the domain practices, unless by *a prioristic* stipulation, which is not useful. Secondly, often things are fairly indeterminate in this emerging domain and could still go in different directions. It is not always clear in advance whether concepts are used imprecisely or even 'messily' because of lack of expertise with philosophical concepts, or because there just is not a precise concept yet, it is emerging. 'Model', 'represent', 'validation', 'certainty', 'evidence', 'cause', 'mechanism', 'process', 'disease', and many others, are examples of terms that are rather indeterminate in the way they are used in practice, and which do not necessarily do better when pinned down to a definition that works well philosophically. The results are not always of interest to philosophy, especially not academic philosophy as currently defined in Anglo-American philosophy. The gains are in surprises and challenges to find ways of thinking philosophically about innovative scientific methods and techniques in ways that can feedback into the science, and which sometimes may also be of interest philosophically. Pragmatically, this also means working on ways of communicating philosophical thinking in scientific contexts; ethically, it means fully taking on board the responsibility that is implied by making an input. The roles of stinging gadfly or enabling midwife for processes that philosophy stands aside from are not really productive for the philosopher participant. And what is the motivation for being a participant? For me, it is the realisation that there is no set or determinate way that systems biology is, it is still fluid enough for participation to make a difference. So many things about the epistemology, ontology and ethics of systems biology are indeterminate, and could develop in different ways. How it turns out is important scientifically, socially and ethically. Philosopher participants stand a chance of contributing to this formation; still, I think this is a role that, for reasons ranging from disciplinary egos to disciplinary boundaries, we are not yet able fully to take on.

What do you consider the most neglected topics and/or contributions in late 20th Century (philosophy of) biology?

We know that there has been a shift to mathematical and computational techniques in biology that is reflected in the education of biologists; however this is not at all neutral with respect to what the biology of the future will be. By this I do not mean only that biological methods will be different: clearly also understandings of evidence and the concomitant epistemologies will also shift. But along with this there will be shifts in the conception of biological entities and processes. The question for philosophy of biology and systems biology is: what is gained and what is lost through these shifts? How can one do philosophy of biology that takes on board the implications of technologies for biology as a discipline and as a domain?

In his Notes on Nature, originally written in 1956-7 there is the following cryptic remark by Maurice Merleau-Ponty:

> It is not possible to speak of Nature without speaking of cybernetics. Maybe this is only an ultra-finalism without mechanism, but we cannot think Nature without taking account to ourselves that our idea of Nature is impregnated with artifice (Merleau-Ponty 2003, 86)

Like so many other intellectuals of his time, Merleau-Ponty was attempting to respond to the challenge of cybernetics, that peculiar mix of technological and scientific thinking that emerged in the 1940s. Even though he was critical of many of the claims made by and on behalf of cybernetics, this quotation shows him fully taking on board the profound rethinking of nature that cybernetics implied. Systems biology is very closely intertwined with computational methods, in fact some would say that they are inseparable and maybe identical – that is, that systems biology just is computational biology. However, there has not been reflection on the implications of this particular technological mode of investigating nature. So far, the reflections on modelling in biology have not considered what a profound shaping of the conception of the biological is brought about by the technologies of modelling, be they 'organic' or computational technologies. I do not mean by this that we should accept the claims bordering on technological determinism of a book such as *Fourth Paradigm: Data Intensive Scientific Discovery* (Hey et al., 2009); however, it does seem that the witnessing of such profound shifts as have been brought about by technologies for sequencing that made the genome project possible, and the range of computational tools and resources that have made systems biology possible in recent history should elicit more reflection on the part of philosophy of biology and of systems biology. Historians of science (such as Hans-Jörg Rheinberger, Peter Galison and Lorraine Daston) attend to the interconnections between technologies and science, and go on to draw epistemological inferences that have not been taken up and elaborated upon by mainstream philosophy of biology. Yet it seems to me that we must try to elaborate epistemologies and ontologies of biology that are able to address the roles of technologies. This is particularly important in view of the specific nature of computational technologies, which are not mechanistic instruments. As Merleau-Ponty noted for cybernetics, these technologies operate according to a profoundly different logic, and it is this that makes them peculiarly able to investigate the form of non-linear causality that is associated with systems biology: but is this itself one of the ways in which the nature of systems biology is 'impregnated by the artifice' of its computational methods? This is a question that needs reflection.

What have been the most significant advances in systems biology?

The development of the advanced computational technologies that got off the ground with the human genome project, and in particular the development of new statistical, mathematical, and computational techniques to make it possible to ask questions at a systems level and open different pathways of investigation, will stand to the credit of systems biology. Here once again, its fate and the way it will be viewed historically are bound up with its technologies. Just as systems biology has shown up the enactment of a philosophy (and sometimes many) in the biological sciences, it also shows up the profoundly social character of science. Here the advances in socio-technical infrastructure in systems biology are quite revolutionary for the science. For example, making knowledge and knowledge processes explicit is required for the integration of data that is characteristic of systems biology but at the very same time the computational infrastructure for doing this is a social infrastructure. The drive for ontologies to systematise knowledge in different domains has simultaneously resulted in platforms for communities to develop shared languages and vocabularies, and thereby identify themselves as communities with a shared stake in the development of these infrastructures and the future of their discipline. These socio-technical infrastructures that have sprung up around systems biology have reconfigured biological sciences in a deep and lasting way.

The fact that through these various socio-technological means, systems biology casts into doubt the central dogma of molecular biology, and proposes plausible alternatives to reductivism are hugely important for biology and for philosophy. Causality and levels will never be the same again, and that is a good thing. For me, the most important significance lies in what systems biology may be able to achieve on a socio-cultural level. Biological sciences play a hugely important role in shaping and legitimating ideologies concerning humans, animals, environment and the relations between them. The different forms of reductivism in biology have played out disastrously in the socio-cultural sphere, where we see an ever greater reliance on the most simplistic forms of natural determinism, that is fed by both methodological and ontological reductivism in science, ultimately resulting in a picture of the human and of society that is limited, skewed and simplistic. Even more importantly, it is a picture that is ideologically problematic, outsourcing so much of the life of humans and other animals to some inexorable 'natural' bottom-up linear causality. However it is not at all clear that systems biology will indeed fulfill the socio-cultural potential and loosen the grip of different forms of reductivism. One reason for this is that systems biology does present a more complex picture, which for that very reason is harder to communicate in the public domain. Something like 'the selfish gene' is eminently communicable: it contains within itself thousands of possible stories about how selfishness is exemplified in biology that will all be easily assimilable and apparently true to life – in both the biological and social sense. What are the systems stories that will do as well as the 'selfish gene'?

There is tremendous scope for systems biology to make important contributions to medicine and healthcare, not only promising better treatments, but perhaps also to change our relationship to health and disease. This in turn will be one of the places where the possible systems biology 'stories' will make a socio-cultural difference that could affect quite profoundly our experience of health and disease. Connected to human health is animal health and wellbeing and here systems biology may be on the cusp of making a hugely significant advance. If systems biology succeeds in replacing animal studies (models) with computational models, the shifts will be quite dramatic: not only in terms of the numbers of animals used in research, but in the conception of models in biomedical research (non-human animal, animal, computational), clinical trials, and ultimately in a reconfiguring of the ethical discourse around the use of non-human animal research models. But these are not actual advances yet, only promises. The next question calls attention to why we are not yet there.

What do you consider the most important problems in (philosophy of) systems biology and what are the prospects for progress in this respect?

The epistemology of computational modelling – specifically the form that it takes in systems biology – continues to be a challenge both to systems biology and its philosophy. Even though non-representationalist accounts of scientific models have been put forward in philosophy of modelling, it is unclear how they will actually work in systems biology. On the surface, they are very well suited for systems biology, as systems by their nature always point to the limits of representation, which closes off a system, or puts a border around it. This will always raise questions about the placement of the closure or border; it is a kind of performative self-questioning. That is good, it is better than pretending that the representational nature of something – like a model – is unproblematic. Except, of course, that the language of representation is still pervasive in the domain. What is the task of the philosopher-participant here: to try to eliminate talk of representation or to try to enlarge its meaning? The problem is more than one of terminology, but one of the conception of models (including computational models) that spills over into normative questions of the criteria whereby models are found to be acceptable, or, to use another term that is pervasive in the domain, validated. The conception of a validated model as one that represents a target domain by capturing or describing its features is a crucial limitation of the force of systems biology. Take the issue of original conditions that are often held to be required in order to arrive at absolute parameter values that will parameterise equations that are 'representations' of a process; what counts as the original conditions of an ever variable biological process? The very conception of the equations and the computational models yielded through the simulation of the equations, as representations, forces onto the domain a restriction, a border, that already skews it. However, we do not as yet have an alternative epistemic account of the validation of models. The 'models as tools' conception is a respectable alternative, but we do not yet have an account of what, in this domain, is a *good* tool. The reason for this is that, to date, systems biology has been conducted in a largely mathematical and computer science facing way, and has not sufficiently developed viable methodologies for robust experiment facing modelling. This is one of the greatest challenges facing systems biology, and especially, its development into systems medicine. In order to come to be trusted and used for medical purposes, systems biology must find a way of 'talking' to experiments. The conversations have to happen on the level of science and on the social level: that is, systems biologists have to overcome yet another interdisciplinary barrier and enter into real conversations with clinical and medical researchers, which depend on bringing their methodologies together. But so far, there has not yet been sufficient work done on the methodologies for this to happen, in particular, on how to go about making experiments and models comparable. Comparability cannot be taken for granted, in particular in face of the variability of biological systems. Variability has a different significance in biological and biomedical contexts, since in biology it may be safely dealt with through averages, depending on the specific research question, whereas in biomedicine, understanding and coping with variability is a central aspect of treatment.

If systems biology is characterised by its ability to think across levels and to produce multi-scale models, I believe that the underlying problem shared by systems biology and systems medicine, is the variability of biological systems across temporal and spatial scales (as described more fully in Carusi, 2014). There is a pressing need to develop techniques for measuring, modelling, simulating and analysing it; and for designing experimental systems that do not blackbox it, but instead let it play out so that it can figure in the models of systems biology. This is how the potential of systems biology may well be transformed into a systems medicine worthy of the name.

In considering the shift towards medical applications, in particular if notions such as the 'digital patient' are to be part of systems medicine, the crucial challenges are social, political and ethical. In biomedicine, issues of variability and validation have a social and ethical significance; while trusting a model in biology may have primarily epistemic importance, in biomedicine it has primarily pragmatic and ethical importance (in the sense of responsibility towards patients). Here, it is important not to limit ourselves to the language of impacts of science on society, but first and foremost to recognise that systems biology and systems medicine already have a socio-ethical character, and are already an expression of particular epistemic, ethical, and aesthetic values. How it plays out in healthcare, including how the patient is conceived and encouraged to identify her or himself is not just an external effect of the science, but already inscribed in it. The conception of data and model is critical, if systems medicine is going to depend on patients to be data producers, and is promising to generate patient-specific models. Here the epistemology and ethics of modelling come together, and the language of representation that is currently still so firmly entrenched in systems biology, or whatever alternatives are found for it, will certainly have a non-neutral effect on how patients are encouraged to position themselves and understand their own role in systems medicine.

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