Biology and the systems view

Is there a move towards systems approaches in the life sciences?

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For many people, the advent of systems biology seems to herald a new era of research that might finally usurp the traditional, reductionist approach that has sought to understand living beings through the study of their constituent parts. The systems approach, according to this stance, is a new way both to investigate the 'machine of life' and, at the same time, to appreciate the uniqueness of living organisms: the unforeseeable behaviour of the whole owing to so-called emergent phenomena (Gilbert & Sarkar, 2000; Noble, 2008).

Although systems biology is a rapidly growing field (Calvert, 2008), the question remains as to whether it represents a general trend in the life sciences, as theoreticians of biology diagnosed that it would be years ago (Sarkar, 2005; Keller 2005), or whether it is a less wide-reaching phenomenon. Here, I present and discuss findings from an analysis of publications in reproductive genetics that could help to resolve this question. These findings indicate that although several individual articles from this field embrace systems approaches in a broad sense, most publications actually deal with relatively simple models of cause–effect relationships. The study also revealed that the complexity of models correlates with the types of technique and equipment used in the laboratory.

Theoreticians studying the philosophy and history of molecular genetics and its epistemologies hold that molecular biology and genetics were largely inspired by the reductionist approach of the 1960s and 1970s, which stated that all living processes should be explicable on the basis of the molecules involved and their interactions. The 1980s, however, witnessed a move away from reductionism towards

a systems approach in genetics (Sarkar, 2005; Kay, 2000; Keller, 2002, 2005). Some have associated the beginning of this development with the advent of the information sciences and their influence on genetics as early as the 1950s (Kay, 2000; Blumenberg, 1983). Others comment that the Human Genome Project led to a stronger emphasis on epigenetics, which in turn ended the reductionist era and marked a move towards systems approaches in the life sciences (Keller, 2002).

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Although philosophers of science in general have not yet focused on the reproductive sciences and their epistemologies, a single study from the turn of the century also notes a shift from a reductionist approach to a systems approach in this field of research (Burren & Rieder, 2000). In their analysis of interviews with reproductive scientists in Switzerland and Germany, Susanne Burren and Katrin Rieder found two different lines of modelling among researchers: those whose research was focused on molecular mechanisms tended to disassemble and simplify in order to draw conclusions from animal models, whereas those whose work focused on human genetics in a predominantly clinical setting tended to describe causal actions, keeping in mind the effects on and of the whole organism. These researchers talked about the complexity of interactions between genes, hormones and organs, and

even included environmental factors such as pollution or stress in their hypotheses. Burren & Rieder described this as a systems approach and as an organismic description of biological phenomena, which implies the existence of emergent properties. In their study, as in many others, the terms organismic, emergence and (anti-)reductionism have many usages and meanings, which makes it necessary to clarify what is meant by them.

The idea of 'emergence' dates back as far as Aristotle (384–322 BC) and is certainly relevant to the application of systems approaches, which many believe will allow scientists to grasp life itself. Systems approaches describe "more than the function of the sum of the parts", which is the most popular definition of emergence, as noted by the English philosopher Charles Dunbar Broad (1887–1971): properties are emergent if they cannot be deduced from the behaviour of the individual components of a system (Broad, 1919, 1925). To illustrate emergent properties, water is often used as an example: even if we were to analyse the properties of single water molecules, we would not be able to deduce that wetness is a quality of water.

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The term emergence can generate both worry and excitement owing to the inclusion of the word 'more' in its definition: what

is the inexplicable ‘more’ that exceeds the sum of the parts, if not some metaphysical entity? This problem becomes more explicit when the terms ‘strong emergence’ and ‘weak emergence’ are applied (Boogerd

et al, 2005). Weak emergence means that the more, although not explicable at present, might be so later with the advent of advanced techniques. It specifies that whenever we change the properties of a system, there must

be a change in the properties of the parts of the system, whether we are able to track them down or not. Some philosophers describe this phenomenon as ‘supervenience’ (Lewis, 1986). Strong emergence means that there are properties of a system that will never be explicable by investigations of the basic level of observation because they cannot be deduced from its components, even in principle. Some philosophers, however, argue that it is difficult to maintain such a universal impossibility claim (Hoyningen-Huene, 1994; Nagel, 1979).

Sociologist of science Jane Calvert of the Economic and Social Research Council Centre for Social and Economic Research on Innovation in Genomics (Innogen Centre; University of Edinburgh, UK) has stressed, in relation to systems biology, that some biologists have a different idea of what emergence means, as they take the context of the system into account (Calvert, 2008; Powell & Dupre, 2009). For them, the issue would be whether the behaviour of a system is fully explainable by the properties of its parts and its environment.

The American biologist William Emerson Ritter (1856–1944) introduced the now widespread term ‘organicism’, which describes a theory that is built on the idea of emergence and viewing life as an organic whole, and rejects reductionism (Ritter, 1919). Organicism also rejects vitalism—which holds that a vital force, other than the sum of the parts, accounts for life—and argues that organisms show emergent properties (Stephan, 2005; Harrington, 2002). Reductionism is the opposite of—or, depending on your perspective, the counterpart to—emergence, and numerous vocal authors have questioned the sense of the reductionist approach in biology (Kitcher, 1984, 1999; Sarkar, 2005). Calvert (2008) has stated that “the dominant discourse in systems biology is one of anti-reduction”, whereas one of the most widely read reductionists, the American philosopher of biology Alexander Rosenberg (Duke University, Durham, NC, USA), has claimed that reductionism has largely—but wrongly—been discredited (Rosenberg, 1997, 2006; Rosenberg & Kaplan, 2005).

In fact, Rosenberg refers to a less frequently applied, specific syntactical approach, according to which only those explanations that can be reduced to physical laws are useful. Most philosophers of biology, however, have noted that this does not

reflect the reality of scientific work, and have therefore focused their interests on explanatory models. Alternatively, Scott Gilbert and Sahotra Sarkar (2000) have offered the following more open definition of reduction: “all complex entities (including proteins, cells, organisms, ecosystems) can be completely explained by the properties of their component parts”. Similarly, the American evolutionary biologist Ernst Mayr (1904–2005) described the reductionist approach as follows: “as soon as one has completed the inventory of each of [the components], it should be an easy task to explain also everything observed at the higher levels of organization” (Mayr, 1997, 2005).

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Many authors have described emergence as a historically introduced epistemology that is mainly endorsed by biologists in developmental studies and embryology. Mayr has even claimed that organicism was endorsed by many biologists throughout the twentieth century (Mayr, 1997), although publications on organicism actually had their heyday between 1920 and 1940 (Wheeler, 1936; Bergmann, 1944; Sumner, 1944), and largely disappeared thereafter. In fact, the philosopher of science John Dupré (University of Exeter, UK) has expressed doubts that such a claim of organicist primacy was ever true for molecular geneticists (Dupré, 1999).

Mayr's take on organicism proposed that emergence results from irreducibility. Gilbert, a developmental biologist at Swarthmore College (PA, USA), together with the philosopher Sarkar at the University of Texas (Austin, USA), tried to strengthen a version of organicism for heuristic purposes, which relies on context dependency. They defined organicism as a theory that describes “complex wholes as inherently greater than the sum of their parts in the sense that the properties of each part are dependent upon the context of the part within the whole in which they operate” (Gilbert & Sarkar, 2000). This ontological account turns into epistemology: “Thus, when we try to explain how the whole system behaves, we have to talk about the context of the whole and cannot get away talking only about the parts” (Gilbert & Sarkar, 2000). Furthermore, they argue that “the properties at one level

of complexity (for instance, tissues) cannot be ascribed directly to their component parts but arise only because of the interactions among the parts. [...] For instance, one cannot isolate a molecule and say that it has a temperature”. In favour of strong emergence, they argue against reduction, as it insufficiently explains phenotypes and is unable to predict development.

When different disciplines with different methodological systems, traditions of modelling and paradigms come together in a new field of research, these differences clearly influence the research work. Sociologist of Science Sarah Shostac from Brandeis University (Boston, MA, USA) has argued that, in the case of toxicogenomics, two main factors allowed toxicology and genomics to come together: strong public funding, and the use of the same statistical language and statistical modelling in both areas (Shostac, 2005). By contrast, and with regard to the disciplines that join the field of reproductive genetics, there is traditionally strong aversion by developmental biologists and embryologists to both classical and molecular genetics. The American geneticist and embryologist Thomas Hunt Morgan (1866–1945) strongly expressed this idea in his defence of developmental biology against genetics during the first decades of the twentieth century, as did Gilbert in the 1960s and 1970s (Mayr, 2005; Gilbert, 1996; Lorenzano, 1995).

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However, there is also the idea that systems accounts could help reductionist approaches, which could be seen as a move towards the integration of molecular genetics with reproductive biology. In this regard, Rosenberg has argued that the ‘computing’ of seemingly irreducible phenomena, such as the development of the embryo, might become possible through systems biology (Rosenberg, 1997). Even Gilbert & Sarkar end their defence of emergence with the idea that the advances of computing indicate that developmental biology would

have to “learn to reckon” (Gilbert & Sarkar, 2000). However, Calvert (2008) still finds confirmation in her interviews with systems biologists that they feel “hindered in their work by paradigm battles with molecular biologists” (Boogerd *et al*, 2007).

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So, we might expect that when molecular or genetic approaches come together with more ‘organicist’ approaches from developmental biology, gynaecology, cytology or embryology, they either do so under the umbrella of systems approaches—as the assumed general move towards systems approaches would indicate—or that the differences in paradigms and therefore modelling between them prevail. Both options should resonate in their publications. A systems approach might be even more likely, as the relationship between the nucleus, plasma and organism—and the intertwined role of each in heredity—builds the core of the research topic of reproductive genetics, comprising generativity and reproduction. The nature of this relationship has arisen throughout the history of biological research (López-Beltrán, 2007; Lorenzano, 1995; Delgado Echeverría, 2007; Korochkin 1981), and has most often led to harsh debates about reduction and emergence (Sarkar, 2005). Although classical and later molecular genetics dealt with heredity, its interrelation with higher organic structures was not their focus. With the advent of epigenetics and reproductive genetics, however, the relationship between the nucleus and the organism seems to have returned as an issue of embryology, developmental biology and cell biology (Delgado Echeverría, 2007; Jacob, 1993; Lorenzano, 1995; Horder *et al*, 1986).

Reproductive genetics is a new and growing field of research, which includes gynaecology, embryology, developmental biology and all other disciplines in the field of reproductive biology, as well as molecular biology and genetics. The aim is to gain knowledge that is pertinent to questions about fertility, infertility

and reproductive development, and their genetic causes. Its growth has been triggered by an increase in research funding from national and supranational agencies; one of the major starting points was the funding for “projects in reproductive genetics and epigenetics” by the US National Institute of Health and Child Development (NICHD; Bethesda, MD, USA) in 2000. In Europe, the professional societies of researchers involved in this field united their efforts in clinical practice and research policy (European Societies of Human Genetics and Human Reproduction and Embryology, 2006).

Apparently, this joint venture between different fields in reproductive biology and genetics or genomics was not as easy as the application of genomics and genetics to other disciplines, such as pharmacology. One major event in reproductive genetics is an annual workshop called ‘Frontiers in Reproduction’, which was first held in Cambridge (MA, USA) in 1998. A report from the 2001 symposium notably described the ‘oddity’ that reproductive sciences and genetics joined so late as follows: “Specialty meetings focused on the application of new genomic and proteomic technologies are increasingly common. One might romantically suppose that the genomics bandwagon ought to find no better propulsion system than the very engine to which the genome owes its immortality. And yet, ironically, the field of reproductive biology has been slower to incorporate post-genomic era approaches than many other biological disciplines” (Rocket, 2001).

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Did the participants in this new area develop a common paradigm and shared ways to model the interactions between the components that have shaped reproductive phenomena during the past years? Does the systems approach, as proposed by so many theoreticians, lend itself to such a common platform? To investigate these questions, we performed a qualitative epistemological analysis of journal articles that were produced by members of reproductive genetics institutes or that referred to reproductive

genetics. The initial analysis covered the period from 2006 to 2007 and included around 50 articles, which were analysed for the models that they applied.

The term ‘model’ in this context refers to descriptive explanatory models. Models have a pivotal role in scientific praxis, which has generated a growing number of methodological studies on models (Laubichler & Müller, 2006; De Chadarevian & Hopwood, 2004; Magnani & Nersessian, 2002). This rising interest in the central techniques of knowledge production has also led to mounting confusion about what counts as a model and how to classify them (Leonelli, 2006; Horan, 1988). Our working definition of a model is that it represents relevant features in a way that makes it easy to access for the reader. A model thereby eases the transport of complex descriptive or explanatory representations of phenomena—most often processes—over time, space and perhaps disciplinary boundaries. In the analysed journal articles, these models are non-mathematical sentences as well as diagrams.

Our analysis shows that there are two major groups of articles: about one-half of the studies apply genotyping and haplotyping to create maps of single base-pair mutations, and the other half describe findings from other methods such as hormone analysis, cellular research and transcriptome analysis. Our analysis also shows that there are three main types and grades of complexity of the explanations in these texts, which correlate with the types of question the authors set out to answer.

The genotyping and haplotyping studies of the first type show the lowest level of complexity. Their causal model is a direct, linear path from gene to phenotype. Researchers either search for specific traits by producing mutants or try to identify genetic factors that ‘cause’ some phenotypic effect. The research question here is not ‘how’ something happens, but ‘why’ some property appeared in a subject—which is translated into ‘what is the respective gene?’ The aim of these studies is not to look for mechanisms, but rather to explain phenotypic phenomena by identifying genetic factors (Furnes & Schimenti, 2007).

Studies of the second type show more complex explanations: they apply the same genotyping and haplotyping methods, but also look for mechanisms. Often, the gene for which the study looks is connected to a phenotypic trait, which itself is a factor for

another trait that is relevant to reproduction. In these cases, the causal chain consists of at least three members and might imply feedback loops, for instance, a gene that ‘encodes’ a hormone receptor that itself, when ‘out of function’, affects something else (Radpour *et al*, 2007). These studies present multi-causal explanations in their discussion sections.

Studies of the third type, with the highest complexity level in their explanatory models, include no representatives of genotyping and haplotyping methods. Rather, these studies embrace typical systems approaches. They include, for instance, endocrinological studies, which not only deal with complex, often overlapping, explanatory and descriptive models—frequently depicted in ‘bow-and-arrow’ diagrams—but also describe hormonal effects on DNA regulation (Drummond, 2006). Other studies with highly complex explanatory models look for interactions between different cell components and the embryo (El Shourbagy *et al*, 2006), or apply transcriptome analysis to different cells and tissues, so as to include the local situation or context of the cells in the analysis (Jelinski *et al*, 2007). In another example, the authors found a different count of chromosome 23 at different times in the same embryo, and discussed the phenomenon of ‘self-normalization’ in embryonic cells in the case of trisomy. In this instance, the cell seems to be able to correct its genetic material by ‘chromosomal demolition’, which implies interaction at all levels of the DNA material, chromosomes, nucleus and plasma (Coulam *et al*, 2007).

In summary, the systems approach does not prevail in all studies of reproductive genetics. By contrast, the relatively new techniques of genotyping and haplotyping seem to impose a relatively diagnostic approach with linear cause–effect models or—as the research question and method are mutually dependent—the choice of diagnostic questions implies this methodology and modelling. However, about a dozen of the studies do indeed apply some kind of systems approach. They can be identified on the basis of research questions and explanatory models, and they allow for emergence, at least in terms of horizontal emergence or at the level of context dependency and unpredictability. There is no indication that the different models of explanations are necessarily incompatible with each other. However, the diagnostic approach and research question do not seem to allow for systems models.

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