

WORKSHOP REPORT: PHILOSOPHICAL ISSUES IN SYSTEMS BIOLOGY

Egenis, University of Exeter, November 30th – December 1st, 2006

The rapid growth of systems biology over the last few years has opened up many opportunities for new, more integrated approaches to the molecular study of biological phenomena. The many complex scientific issues that are arising (or becoming more obvious) as systems biology develops are of interest not only for scientists and their funders but also for philosophers of science. Although philosophy of science in the first several decades of the twentieth century focused on physics, a strong body of philosophical inquiry into biological science has been growing since the 1960s. Systems biology represents a challenge and an opportunity to philosophy of biology in the way it brings together models, molecules and approaches to life – some of which may integrate philosophical insights into physics as well. Scientists involved in systems biology are also challenged philosophically by their own activities, as multiple levels of biological phenomena are brought together in abstract mathematical models, and traditional approaches to life questioned and made to accommodate new modes of inquiry.

These zones of intersection for philosophers and scientists are sometimes dealt with in the scientific literature and more occasionally, in dialogue between practitioners of both disciplines. One such example of the latter was a recent workshop on *Philosophical Issues in Systems Biology*, hosted by Egenis (ESRC Centre for Genomics in Society) at the University of Exeter, from November 30th to December 1st, 2006. The aim of this meeting was for philosophically minded systems biologists to engage with philosophers in discussion about key philosophy of science themes, most notably the concepts of emergence and self-organization. Several scientists were invited, five of whom came from continental Europe.¹ A number of them had read and responded in various ways to a paper in the journal *BioEssays* by two of the philosophers, John Dupré and Maureen O'Malley.² The electronic discussion that had resulted from the scientists' comments on this paper indicated that a workshop would be the forum that would best enable a deeper exploration of philosophical issues in systems biology. The twenty or so people who participated in the workshop¹ included philosophers and social scientists from Exeter, Bristol and Ghent, as well as the invited scientists.

The workshop structure³ consisted of several researchers describing their projects and philosophical ideas, which had been expanded on in their own

¹ See participant list at the end of the report. Olaf Wolkenhauer (Rostock) was also planning to attend, but circumstances eventually prevented his participation.

² O'Malley, M. A., and Dupré, J. (2005). Fundamental issues in systems biology. *BioEssays*, 27: 1270-1276.

³ See the Appendix for the programme.

pre-circulated papers.⁴ These key presentations were followed by commentaries from other participants and then general discussion. Two sessions focused on emergence, one on self-organization, and the final one on a variety of associated and supplementary issues.

Frank Bruggeman (University of Manchester/Amsterdam) opened the first session with an account of his and Fred Boogerd's (see below) collaboration with two philosophers of science, Bob Richardson (Cincinnati) and Achim Stephan (Osnabrück). The aim of this group had been to explore and develop philosophical definitions of emergence, operationalize the most pertinent one, and then see how valuable it was for scientific and philosophical practice. A paper⁵ resulting from this project set out an explanation of the emergence of systems properties by examining biochemical networks within a schema of emergence inspired by philosopher C. D. Broad (1929). It also integrated a reflection on Jaegwon Kim's 'vertical emergence' or irreducible non-mechanistically explicable properties, but rejected it for a novel formulation of 'horizontal emergence'. This concept is based on 'component properties', or the qualitatively novel behaviour of relationally dependent system parts while involved in non-linear interactions with other subsystems and influenced by the state of the system they constitute. Quantitative knowledge of the behaviour of component parts can be mathematically integrated in order to achieve an exact understanding of emergent system properties.

Bruggeman concluded that their schema was concerned with strong ontological emergence rather than a weak epistemological variant (see Bedau, 1997). Although the paper produced by the collaboration appears to be a valuable addition to the philosophical literature on emergence, Bruggeman was not convinced that the philosophical work was necessary for advancing the actual science (despite his agreement that reductionist philosophies probably did hamper the development of some lines of scientific inquiry). This observation caused considerable discussion amongst participants, especially from those who disagreed.

Alex Powell (Exeter) set out a brief overview of twentieth-century emergence concepts, elaborating on the weak (epistemological) and strong (ontological) distinction, and pointing to the vagueness of other terms in the emergence literature, especially 'properties' and 'levels'. He set up a list of desiderata for a concept of emergence that would be relevant and valuable for systems biology, thereby questioning Bruggeman's insight that such philosophical work might not be necessary for the science to develop. However, the diversity of the phenomena that have been described as emergent led him to caution that developing a unified yet illuminating account would not be a trivial undertaking.

The commentator on this session, John Dupré (Exeter), focused on the crucial issue of downwards causation to determine whether a concept of emergence

⁴ See the Appendix for a list of these readings

⁵ See reading list.

was strong or weak. Many philosophers do not like the notion of downwards causation (because of the implication that the behaviour of parts depends in some way on the future state of the system that emerges from parts) and it is scientifically difficult to establish. The discussion that followed his comments focused on the problems of defining systems and levels without a concrete scientific question in mind, and the subsequent necessity of a pluralistic approach to such ontologies (i.e.: for a given set of questions, there is a right way to think about levels and systems). Participants did not reach agreement about downward causation and its centrality to strong emergence, with biological examples being given both for (cell curvature as a determinant of molecular-level developmental processes) and against it (biochemical networks).

The second session, also focusing on emergence, began with Janine Guespin's (Rouen) discussion of the resistance of many biologists to concepts such as emergence, despite its arguable importance to the understanding of non-linear dynamic systems. She proposed that a different form of logic is required to understand such non-linear behaviour, and that a good candidate for such logic would be the dialectic – a mode of thinking capable of comprehending complex processes and also of resolving the apparent contradictions generated by trying to understand such systems with formal linear logic.

Fred Boogerd (Free University, Amsterdam) followed with an elaboration of the philosophical schema outlined by Frank Bruggeman, cashing it out in relation to the study of biochemical networks and metabolic control analysis. He emphasized the necessary pluralism of an approach to such systems and the iterative cycle of studying system behaviour *in silico* and *in vivo* (involving hypothesis generation, quantitative experiment and simulation). He concluded that such an approach had the potential in principle to achieve a complete mathematical description of cell behaviour and would thereby achieve a full mechanistic explanation of the 'live' state of the system.

Lenny Moss (Exeter) began his presentation with a general reflection on biological practice, suggesting that since its Aristotelean inception, the principal challenge of biology has been to account for how living beings can not only exhibit good design but can act dynamically so as to sustain their own existence ('final cause'). The scientific revolution, however, rendered the relationship of 'formal' to 'final' cause variable and contingent by allowing the abstraction of formal properties of living systems and their further generalization either through defining classes of mechanisms or through mathematical extrapolation, or both (e.g.: an enzyme can be characterized by a structural analysis of its catalytic interactions with a substrate, or quantitatively through enzyme kinetics). Moss argued that much actual biological practice now proceeds in a Kantian fashion, taking as given the facts of model organisms (including cells in culture) and attempting to explain their 'always-already ordered' structure. Such practice does not, however, explain how such ordered structure brought itself into being to begin with. In its strongest interpretation, systems biology can be seen as an effort to go

beyond this Kantian point of departure and derive or explain the apparent finality of life on the basis of formal first principles.

Moss then challenged the metaphysical premise that the potentialities of matter to attain more 'detached' and complex forms is finite and can be exhausted by scientific laws or generalizations. An alternative metaphysical premise, he argued, might be that nature explores greater levels of detachment (and complexity) and that its potential to do so can never be formally exhausted. Using this premise as a starting point would lead systems biology to localize its explanations of the properties of particular contingent possibility spaces (levels of detachment), rather than attempt to find the necessary and universal laws of all possibility.

The commentator for this diverse session, Samir Okasha (Bristol), viewed all the presentations through the lens of Darwin's theory of natural selection. Issues such as non-linearity, he argued, needed to be understood vis-à-vis adaptation, and he suggested that the concept of emergence might be disposed of with more empirical knowledge. The key question for final cause, he concluded, was good design. In other words, without Darwinian theory, material explanations of biological function or telos would not be legitimately biological.

The third session, nominally about self-organization theories and concepts, began with Charles Auffray's (Villejuif) distinction between Cartesian concepts (analytical, reductionist) and the 'conjunctive logic' of systemic modelling. Multiscale integration is the major challenge for systems biology, he argued, and a middle-out approach (as opposed to a top-down or bottom-up one) was the one most likely to realize systems biology's aims. Auffray turned to his work with physicist Laurent Nottale on scale relativity, which uses linear and non-linear scale laws to understand the behaviour of self-organizing biological structures. This approach, he argued, would enable the development of an integrative theory of life based on first principles (e.g.: Why are cells as they are? What are the fundamental principles underlying natural selection and making it a non-circular explanation?), as well as the integration of multiple levels of phenomena so crucial to systems biology. Inevitably, these achievements would have social applications and allow health trajectories to be plotted and monitored. Such new ways of thinking will not, however, replace classical inquiry but supplement and expand it.

Vic Norris (Rouen) focused his talk on the bacterial cell and how to understand it. He proposed that an understanding of what cell structures and processes are would require an understanding of 'hyperstructures' and 'competitive coherence'. Hyperstructures (assemblies of molecules that interact to perform a particular function) operate at a level that falls between the macromolecule and the cell. Competitive coherence involves the balance between the maintenance of continuity and the need for coherence with respect to internal and external conditions. Cells have to be understood via these concepts as members of populations exploring phenotype space via competitive coherence strategies (growing versus surviving, specializing versus diversifying). Emergence, therefore, is competitive coherence at work.

Jamie Stevens (Exeter) responded to these presentations with a general appeal for openmindedness and the willingness to simultaneously maintain old ways of doing biology while developing new approaches. He also cautioned that some systems, no matter how optimistic systems biologists are now, will ultimately prove to be intractable to such analyses.

The final session of the workshop was a diverse one, bringing together different questions and approaches before attempting to synthesize the main issues and conclusions of the workshop. Two short presentations (actually following the main presentation described below) addressed emergence in different ways. Jonathan Davies (Exeter) proposed that systems emergence could be best understood in terms of a contrast between localized and distributed causal explanations. Sally Wasmuth (Exeter) argued that strong emergence and downwards causation could be attributed to the visual system in humans and other animals. Both talks led to a discussion of the idea of 'distributed' causation or multicausality, and how it could be understood within frameworks such as hysteresis and global attractors.

The main presentation of this session broadened the scope of the workshop even further as Jane Calvert (Exeter) discussed the sociological roots of philosophies of systems biology. Drawing on interviews with systems biologists in the US (especially Leroy Hood's Institute of Systems Biology) and the UK (the BBSRC's Centres for Integrative Systems Biology), Calvert outlined key philosophical concerns of systems biologists. These included the concept of 'understanding' versus prediction and control, the role of hypotheses, the need for reductionism, the importance (or otherwise) of data comprehensiveness, and how interdisciplinarity could be most successfully achieved. She found that few of the scientists involved in systems biology identified themselves as systems biologists. Her report of this finding led to considerable discussion about how disciplinary identities are internalized and whether systems biology will eventually be perceived as a discipline *sui generis* or whether it will continue to be an intersection of disciplines. Other discussion covered the similarities and differences between terms such as systems biology, integrative biology, computational biology, theoretical biology and dynamic biology. 'Will whatever is called systems biology achieve its broad aims?', asked one participant, to which the consensus answer seemed to be 'Who knows? But now is the time to try it!'

The final minutes of the workshop were devoted to topics that had been left out of earlier discussion and plans for further work together. The inclusion of different approaches to systems biology, including synthetic biology, was considered important as was the incorporation of a greater diversity of philosophical themes and biological theories. A few steps towards facilitating ongoing discussion between practitioners of systems biology and philosophers were agreed on.

1. Circulation of workshop powerpoint presentations to all participants. ✓
2. Circulation of workshop report (an overview) to all participants. ✓
3. Participation of some workshop participants at the Biennial Meeting of the International Society for the Philosophy, History and Social Study of Biology,

to be held at the University of Exeter, July 2007. The hope is to hold a special session on systems biology with further discussion between philosophers and scientists. [Underway]

4. Set up a way to circulate amongst ourselves and others a 'network of terminology', which would clarify the way certain terms are used in different disciplines and how they might be useful in cross-disciplinary discussion. [Not sure how to get this going: Ideas anyone?]

5. Future workshops: To be announced as hosts become available.

APPENDICES : Participants, programme, reading list

Participants

Charles Auffray (Villejuif)
 Frank Bruggeman (Manchester/Free University, Amsterdam)
 Fred Boogerd (Free University, Amsterdam)
 Jane Calvert (Exeter)
 David Carslake (Exeter)
 Jonathan Davies (Exeter)
 Philippe Debacker (Ghent)
 John Dupré (Exeter)
 Janine Guespin (Rouen)
 Rod Hunt (Exeter)
 Lenny Moss (Exeter)
 Dan Nicholson (Exeter)
 Vic Norris (Rouen)
 Samir Okasha (Bristol)
 Maureen O'Malley (Exeter)
 Joris van Poucke (Ghent)
 Alex Powell (Exeter)
 Jon Rubin (Essex)
 Paula Saukko (Exeter)
 Jamie Stevens (Exeter)
 Sally Wasmuth (Exeter)

Programme

Thursday, November 30th

11.00 Early arrivals, registration and welcome, tea and coffee
 12.30-1.30 Lunch
 1.30-3.30 **Emergence and reductionism (1)**
 Frank Bruggeman: *Emergence in biology*
 Alex Powell: *Philosophies of emergence*
 Chair and respondent: John Dupré
 3.30-4.00 Coffee/tea break
 4.00-6.00 **Emergence and reductionism (2)**
 Janine Guespin: *The logic of dynamic non-linear systems*
 Fred Boogerd: *Biocomplexity*
 Lenny Moss: *Philosophical approaches to systems biology*
 Chair and respondent: Samir Okasha
 6.30-late Drinks, dinner and discussion at Café Paradiso, Barcelona Hotel
 (downtown Exeter)

Friday, December 1st

8.30-9.00 Tea and coffee
 9.00-11.00 **Self-organization**
 Charles Auffray: *Self-organized living systems*
 Victor Norris: *What is the bacterial cell?*
 Chair and respondent: Jamie Stevens

- 11.00-11.30 Tea and coffee
 11.30-1.30 **Broader issues and future directions**
 Jane Calvert: *Sociology of the philosophy of systems biology*
 Jonathan Davies: *Distribution + localization in biological systems*
 Sally Wasmuth: *Ontological emergence in the visual system*
 Chair and commentator: Maureen O'Malley
 1.30 Lunch and farewells

PRE-WORKSHOP READING LIST

Auffray, C., Imbeaud, S., Roux-Rouquié, M., and Hood, L. (2003). Self-organized living systems: Conjunction of a stable organization with chaotic fluctuations in biological space-time. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 361: 1125-1139.

Boogerd, F. C., Bruggeman, F. J., Richardson, R. C., Stephan, A., and Westerhoff, H. V. (2005). Emergence and its place in nature: A case study of biochemical networks. *Synthese*, 145: 131-64.

Bruggeman, F. J., Westerhoff, H. V., and Boogerd, F. C. (2002). BioComplexity: A pluralist research strategy is necessary for a mechanistic explanation of the 'live' state. *Philosophical Psychology*, 15: 411-440.

Guespin, J. (1998). Réductionnisme et globalisme en biologie. [Available on request from the author.]

Guespin-Michel, J., and Ripoll, C. (2000). La pluridisciplinarité dans les sciences de la vie : un nouvel obstacle épistémologique, la non linéarité. [Available on request from the author.]

Norris, V., Amar, P., Bernot, G., Delaune, A., Derue, C., et al. (2004). Questions for cell cyclists. *Journal of Biological Physics and Chemistry*, 4: 124-130.

Norris, V., Cabin, A., and Zemirline, A. (2005). Hypercomplexity. *Acta Biotheoretica*, 53: 313-330.

Philosophical papers on emergence.

Bedau, M. (1997). Weak emergence. *Nous*, 31: 375-399.

Cunningham, C. (2000). The re-emergence of emergence. *Philosophy of Science*, 68: S62-S75.

Klee, R. L. (1984). Micro-determinism and concepts of emergence, *Philosophy of Science*, 51: 44-63.

Silberstein, M., and McGeever, J. (1999). The search for ontological emergence. *The Philosophical Quarterly*, 49: 182-200.

Supplementary

Although Olaf Wolkenhauer was not able to attend the workshop, his papers were read for background because of their relevance to discussions at the workshop.

Wolkenhauer, O., and Mesarovic, M. (2005). Feedback dynamics and cell function: Why systems biology is called systems biology. *Molecular BioSystems* (Royal Society of Chemistry), 1: 14-16.

Wolkenhauer, O., and Hofmeyr, J. (in review). Cartesian closure is a necessary condition for self-organization in cell models. [Available from the author.]

Wolkenhauer, O., Mesarovic M., and Wellstead, P. (in press). A plea for more theory in molecular biology. In E. Butcher, P. Bringmann, and B. Weiss (Eds.), *Systems biology - Applications and perspectives*. Springer-Verlag. [Available on request from the author.]

Wolkenhauer, O. (2001). Systems biology: the reincarnation of systems theory applied in biology? *Briefings in Bioinformatics*, 2: 258-270.

Wolkenhauer, O., and Babuška, R. (2000). Fuzzy relational biology: A factor-space approach to genome analysis.
<http://www.csc.umist.ac.uk/fstb/hertford.pdf>

Wolkenhauer, O. (2000). A system-theoretic epistemology of genomics.
<http://www.sbi.uni-rostock.de/dokumente/change.pdf>