The conceptual challenge of Systems Biology

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Molecular biology continues to evolve at a rapid rate. Besides contributing to a massive increase of data on the building blocks of living organisms and to the development of technological tools to uncover these data, the widely adopted 'post-genomic' perspective increasingly challenges genetic reductionism and the reduction of biology to one subdiscipline or to physics. The perceived need for a more encompassing view of living organisms helps molecular biology to participate in both new biological disciplines such as Eco-Devo and Evo-Devo, and in trans-biological scientific departures such as Systems Biology.

Today, Systems Biology is widely promoted as a valid alternative to reductionism, as it interprets life in terms of complex systems in which genes trade places with the biochemical networks in which they reside. In this view, the marriage between molecular biology, computation and in silico modelling is proposed to bring biology from a qualitative and descriptive level to a quantitative and predictive level. A vital test case appears to be the integration of the diverse types of functional maps or '-omes' (e.g. genome, transcriptome, metabolome, proteome, interactome, phenome) in ways that elucidate biological properties and functions at the (sub)-cellular or organismal level. The efficiency of such an integration further is said to rely on the construction of a strong conceptual framework permitting interdisciplinary communication, infrastructures and publication channels into which scientific disciplines other than (molecular) biology can feed.

Although its leading spokesmen share these intuitions, Systems Biology harbours theoretical and practical differences, which will complicate its ambition to establish 'a new biology'. In this context, the symposium *Towards a Philosophy of Systems Biology*—held at the Vrije Universiteit of Amsterdam (VUA), the Netherlands, from 2 to 3 June 2005[1]—brought both systems biologists and philosophers of science together to debate on Systems Biology's philosophical foundations.

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The organizing committee, consisting of **Hans Westerhoff, Frank Bruggeman, Fred Boogerd** (all Department of Molecular Cell Physiology, VUA) and **Jan-Hendrik Hofmeyr** (Department of Biochemistry, Stellenbosch University, South Africa), expected these foundations to emerge from 'the non-linear interaction' between biology and sciences ranging 'from physics to ecology, from mathematics to medicine, and from sociology to chemistry'. Nonetheless, all scheduled scientists had strong affiliations with biochemistry, leaving room for one to speculate how different the exercise might have been if speakers from other scientific domains had been included.

With reference to analyses made in philosophy of science, Westerhoff provocatively opened the symposium by portraying (molecular) biology as being unscientific because of: (i) a failure to meet the standard criteria of physics and its inability to be reduced to physical or chemical theories, (ii) its imprecision in quantitatively testing hypotheses, (iii) its inaccessibility to experimentation and analysis because of an undefinedness of the involved factors and a lack of appropriate mathematics, and (iv) the inability to deal with emergent properties such as life itself. Systems Biology, in contrast, he claimed, could reshape biology into 'proper' science, sufficing the above criteria, while developing its own focus on molecular interactions and the organizational complexities hereof. Unfortunately, here the crucial theme of how to integrate the diverse '-omics' remained unexplored. Westerhoff's Systems Biology revolves more round the detection of those components that present themselves as easy targets for the manipulation and engineering of the system, thereby translating Systems Biology's 'paradigmatic shift' into a continuance of the Genome Projects. The bet seemed to be that complex biological systems still hold enough 'simplicity' to keep us going for the next decade.

Douglas Kell (University of Manchester, UK) countered philosophy of science's dismissal of induction by presenting it as an appropriate knowledge-generating method for data-rich but hypothesis-poor problems. As this situation actually suits Systems Biology, Kell favoured computational tools based on

[1]Cf. www.systembiology.net/philosophy/.

deduction *and* induction, iteratively intertwined with experimental and theoretical processes. Especially promoted were 'evolutionary computing' and 'machine learning', in which those models best fitting experimental data are selected and further varied to induce the generation of either new hypotheses or of one significantly fitting hypothesis that can be tested in the wet laboratory, leading to new discriminative data.

Robert Shulman, biochemist and biophysicist (Yale University, USA), retained the idea of grounding biology in physics. Contrary to Westerhoff, he argued that science goes from molecular mechanisms to conceptual frameworks, *not* vice versa. Shulman saw little practical advantage in defining systemic functions in terms of the 'holistic'—but also often intuitive and abstract—concepts introduced in Systems Biology.

Taking Shulman's criticism seriously, one should consider how far concepts such as 'self-organization' actually change our views and methods for studying living systems, especially when these ideas only vaguely correlate to a physical substrate or to concrete (bio)chemical hypotheses of empirically detected systemic functions. Conversely, when one retains a molecular language, can Systems Biology give word to biological systems as *wholes*? It certainly remains unclear where precisely the limits (if any) of reductionism are. Or why exactly this philosophical debate is recaptured in Systems Biology.

David Fell (Oxford Brookes University, UK) countered Shulman by showing how conceptual beliefs filter experimental observations. For instance, research on metabolic pathway flux, long dedicated to finding 'the one real' rate-limiting step, was based on the conceptual agreement on a 'first causal principle'. Only recently has it been accepted that causality can be distributed throughout such pathways, reviving the importance of (nested and sequential) feedback mechanisms. Fell connected this causality distribution to the 'paradox of non-essential genes', i.e. when 70% of the gene knock-outs in yeast produce no detectable phenotypic effect, the question is how to assign a function to a gene under these circumstances.

Regarding simulations, Fell wondered *which kind* of understanding a silicon cell may lead to. Indeed, our analog mode of cognitive understanding differs from the digital and mathematical rules reigning computational models. As control engineer **Olaf Wolkenhauer** (University of Rostock, Germany) later asked, will Systems Biology need a 'modelling of the modelling' to keep track of the explanations provided by these simulations? And if the derived hypotheses do not fit experimentally, where should one then change the model? Kell's computational fitness landscape here provides an interesting means to cope with the multitude of models that may arise after changing the original model.

Instead of stressing the characterization, storage and mining of data, Wolkenhauer linked Systems Biology to systems theory, i.e. the mathematical study of systemic properties of complex systems. He formulated the 'Central Dogma of Systems Biology' as the idea that biological function relies on feedback dynamics which cannot be appropriately visualized by two-dimensional static maps. Biochemical reactions should thus be presented as dynamical networks instead of graphical pathways. Still, such dynamic modelling experiences huge technical difficulties because of the large number of variables involved, the inherent non-linearity of the interactions, and the need to obtain quantitative time series data. Some modesty regarding the expectations for Systems Biology is in order.

Adapting Dobzhansky's famous dictum about the essentiality of evolutionary thinking, **Jan-Hendrik Hofmeyr** (University of Stellenbosch) stated that 'nothing in a biological system makes sense except in the light of the *context* in which this system resides', thereby placing proximate explanations of cellular processes once again at the heart of the matter. Hofmeyr characterizes living systems as featuring a 'persistence despite a continual decay of their molecular components and machinery and despite changes in context'. This led him to present a living system as a chemical factory of which the output is the factory itself. According to Hofmeyr, in living cells this 'circularity' is obtained by grace of the unassisted self-assembly of ribosomes, i.e. no additional information or energy is required. In trying to save Robert Rosen's formal description of circular causality in living systems, Hofmeyr's major stress thus was not on *context*, but on *autonomous* chemical, thermodynamical and kinetical processes by which biochemical networks develop and by which biological functions arise. Still, it seems more appropriate to stress both context and autonomy. Indeed, although ribosomes in vitro may self-assemble, in vivo (particularly in eukaryotic cells) the process relies on the organized structure of the nucleolus, which harbours diverse interacting components, such as catalytic RNA molecules, ribosomal proteins and chaperones, that presumably allow the assembly of ribosomes to occur at a faster rate.

A point made by scientists and philosophers alike was that if philosophy of science wants to contribute to the conceptual development of Systems Biology, it needs reorientation. Philosopher **William Bechtel** (University of California, USA), for instance, downplayed the importance of the philosophical debates on universal laws and theory reduction. Instead, he argued, the focus should be on mechanisms as providing functional explanations for biological phenomena without supplanting how the system as a whole works.

Also **Robert Richardson** (University of Cincinnati, USA) and **Achim Stephan** (Universität Osnabrück, Germany) argued that mechanical explanations transcend the reductionism–holism dualism by descriptively 'zooming in' on a particular part of the system, without losing track of the whole. In addition, biology need not look for universal laws, but for mechanisms bound to specific classes of organisms.

Similarly, as **Kenneth Schaffner** (George Washington University, USA) argued, Systems Biology needs to reflect on *when* and *how* mathematical modelling is most useful and *which level* of abstraction is appropriate with regard to the problem posed. For example, research on the motoric behaviour of *C. elegans* was aided more by a physiological account on neural networks than by an account on neural anatomy.

Although Richardson and Stephan showed how mechanistic thinking allows one to naturalistically redefine 'emergence' as 'when the available information about the mechanism's components and their relations in other types of organizations is not sufficient to account for the mechanism', it remains to be seen what this philosophical reorientation will signify for biology.

Another point made by the philosophers was that Systems Biology cannot hope to understand biological systems independently of their evolutionary history. This idea was not so much introduced in terms of neo-Darwinian ideas about natural selection and random mutation, as in terms of complexity and self-organization.

Alvaro Moreno (University of the Basque Country, Spain) argued in favour of a systemic view *à la* Maturana and Varela's autopoietic theory to account for life's basic property of self-organization in terms of three capacities: (i) self-maintenance (via boundary conditions and robustness), (ii) increase in complexity (or in the amount of different functional relations), and (iii) increase in autonomy (when the external conditions necessary for the system's viability are taken over and reconstructed). Based on these, the robustness of living systems can be explained as relying on local stable structures (modules) that create new internal–external distinctions in the system.

Adding a historical touch to the symposium, **Evelyn Fox Keller** (Massachusetts Institute of Technology, USA) reviewed how the concept of self-organization originally was seen by Immanuel Kant as challenging a mechanical understanding of biology. Cybernetics, chaos theory, network topology research and complexity theory made this concept more intelligible, but also dissociated it from its biological content and reference to intentionality or function. When accounting for the *origin* of biological function, both natural selection (itself relying on function) and Stuart Kauffman's strategy of tracing life's history to the first forms of spontaneous physical and chemical self-organization were seen by Keller as of little value. Instead, Herbert Simon's work on *evolution by composition* and *survival of the stable* was recommended by her for its interpretation of symbiosis as a novel functional form of stability. Keller argued in favor of seeing organic mechanisms as contributing to the persistence of this stability.

William Wimsatt (University of Chicago, USA) added that a study of the intertwined developmental and evolutionary history of organisms also may throw light on their current molecular characteristics. An 'eco-evo-devo' perspective, in his view, thus suits Systems Biology best.

In retrospect, this symposium prompts one to ask whether Systems Biology is genuinely looking for its own philosophical feet or rather is seeking justification for a self-proclaimed revolution. It *is* striking to see how molecular biology more and more gets depicted as data collecting of isolated molecules, as if none of the studies on the operon model, epigenetics or regulatory gene networks existed prior to Systems Biology.

Conceptually, Systems Biology shows a growing *liaison* (with its tensions and passions) between two discourses. While a 'mechanistic discourse' remains popular, the 'complexity discourse' is taken more seriously, as witnessed by the ease with which concepts like holism, self-organization, closure, non-linearity and causal distribution are considered as applicable to living systems. Nonetheless, further (interdisciplinary) research is needed to trace (i) the conceptual dynamics that will arise from the terminological choices currently made in Systems Biology, and (ii) how this will affect its practice.

In conclusion, it is exciting that the forthcoming symposium proceedings[2] will appear about simultaneously with the first edition of a Systems Biology's textbook[3]. Whereas the textbook necessarily has to position insights from other disciplines into a well-functioning Systems Biological view, *The Foundations of Systems Biology* holds the potential to provoke debate on some of the deeper issues involved and presents a challenge to scientists and philosophers to reflect further upon the taste of the wine that Systems Biology serves up.

[2]Proceedings appear in February 2006 as *The Foundations of Systems Biology* (Elsevier publishing), not to be confused with *Foundations of Systems Biology*, edited by Hiroaki Kitano (2001, MIT Press).

[3]To be published late 2006 by Humana Press. Cf. www.its.caltech.edu/~schoi/ for a tentative content.