Paradigm shifts versus fashion shifts?

Systems and synthetic biology as new epistemic entities in understanding and making 'life'

Thomas Potthast

Molecular biology and information technology (IT) have become two of the leading research fields and technologies of our time. Systems and synthetic biology therefore seem to be an almost perfect match: not only do these approaches blend biology and IT, but they also promise enormous potential benefits ranging from medical applications and energy production to completely new methods and systems of manufacturing. Systems biology represents a conceptual and data-driven move towards understanding and predicting molecular processes at higher levels of biological organization, including at the level of human beings. Synthetic biology redefines and expands the scope and power of applied biotechnology to design and create biological systems for all sorts of purposes. Not surprisingly, in the light of such an agenda, both research fields have been heralded, at the start of the new millennium, as new ways of doing biology.

Often, such developments and accompanying claims are associated with the idea of new paradigms in the sciences. However, both 'system' and 'synthesis' are far from being novel approaches in biology, at least on the conceptual level. So, is the buzz about systems and synthetic biology just that, a buzz, or are we seeing substantial shifts in paradigms and research programmes, as well as in laboratory and industrial practices?

At first glance, the question of whether systems biology is 'really' new and not just a quantitative change of degree, or whether synthetic biology 'really' does provide a completely new paradigm for biotechnology, might seem to be 'philosophical' in the malicious sense: who really cares about correct wording or

abstract categories? In fact, there are substantial implications, because the labelling of emerging fields in science has important consequences on several levels. Given the limits and the competitive nature of public and private funding, the order of the day is to sell research proposals with fancy—not to use the telling metaphor 'sexy'—terms in order to attract attention and, eventually, money. At the same time, there is a need for reliable information about the nature of new research fields, because it influences relationships with the general public. For gaining important insights, one can actually compare the current developments with the earlier discourse on the importance of the genome as the alleged "book of life" (Kay, 2000; Keller, 2002).

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More is needed than individual opinions about the novelty and significance of systems and synthetic biology. If we are facing a new paradigm, possible epistemological challenges for the life sciences have to be investigated. Moreover, there is a growing demand for societal debates on science policy goals, and possible benefits and potential dangers, particularly in regard to synthetic biology. If the goal of synthetic biologists is to "create life" (Benner, 2003), this claim requires the thorough deliberation of its theoretical, technical and symbolic foundations, and the respective consequences. This is precisely why science studies, social sciences, philosophy and history of science,

and ethics—which are, or should be, in all senses of this term, critical academic endeavours—are so important for discussing and deliberating on how these new research fields shape both science and society.

Before analysing whether systems and synthetic biology represent a paradigmatic shift in biology, I first discuss the various meanings and some implications of the notion of paradigms and related conceptual approaches, and then comment on the mutual interdependence and the links between systems and synthetic biology. What are the potentials and limits of combining them to build a new meta-approach for biology or forming distinct, new interdisciplinary and transdisciplinary realms? Do systems and synthetic biology just represent flip sides of the same coin of application-oriented science? I also comment on how scientists conceive and create this new field based on their epistemic backgrounds and strategic goals with regard to historical examples and recent developments. Identifying the intricate links between paradigm shifts and fashion shifts—rather than adopting a strict either/or view—seems to be a more productive way to understand and analyse the conceptual, practical and social dynamics of systems and synthetic biology, which are, ultimately, more a continuation and culmination of long-standing research programmes in biology than revolutionary new approaches.

The scientific notion of the word paradigm—from the Greek word '*paradeigma*', meaning 'example'—also relates to linguistic studies where it means a set of forms having a common root or stem. Thomas S. Kuhn (1922–1996), an American physicist, philosopher and historian, gave distinction to 'paradigm'

in the context of the history and philosophy of science in his influential book *The Structure of Scientific Revolutions* (Kuhn, 1962, 1970). The book itself is a paradigm of how the right wording at the right time—that is, ‘revolution’ in the political context of the early 1960s—can shape both society and science. Briefly speaking, Kuhn distinguished between normal progress of science and revolutionary phases, when a research field undergoes a ‘paradigm shift’. In normal phases, a paradigm is an accepted theoretical framework in which new theories and methods are developed. However, occasionally, scientific research enters a revolutionary phase during which the old paradigm is no longer suitable to explain new observations and ideas, and is being replaced by a new one—Kuhn named, for example, the general theory of relativity in response to observations that contradicted Newtonian physics.

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In essence, the key notions of a Kuhnian paradigm are that newly emerging paradigms indicate a crisis of the established ones. Notably, competing paradigms are incommensurable—that is, the new paradigm does not just expand on the old one but replaces it—and paradigms therefore change by revolutions only because many adherents of the old paradigm keep clinging to it and do not switch to the new one. Not surprisingly, Kuhn’s theory has attracted considerable criticism, often for conceptual reasons as the term paradigm can have many different notions: does it relate to a single concept or approach, to an important theory or to a whole discipline? In the case of systems biology, for instance, both bottom-up and top-down approaches have been identified as separate research paradigms. Moreover, the initial claims by Kuhn of the incommensurability of the old and new paradigm, and that paradigm changes only occur by revolutions, have also been contested both by historical case studies and by epistemological considerations. The most eloquent critique comes from Kuhn himself: “Paradigm

was a perfectly good word, until I messed it up” (Kuhn, 2000).

However, paradigms are far from going extinct. Although the term has been increasingly abandoned by the history and philosophy of science, it has begun a second career within the natural sciences and has led to many claims of new paradigms or paradigm shifts. As Kuhn only relates paradigms to ‘mature’ disciplines and not to novel pre-paradigmatic fields, it seems simply to be a good thing for a developing area of research to present a paradigm. Moreover, innovation and change, even revolutions, have positive connotations in the natural sciences. The inflationary use of the term paradigm today often denotes a new ‘fashion’ of doing things rather than a fundamentally new approach.

The fact that ‘paradigmatitis’ has become an infectious disease in discussions about new developments in the natural sciences also relates to different meanings of ‘revolution’. One could, for instance, indisputably describe the cracking of the genetic code as a revolutionary step forward for biology. Although it did not replace an existing paradigm, namely Darwin’s theory of evolution, it did create completely new possibilities for practically using this knowledge and for thinking about the essence of life. The same seems to hold true for systems and synthetic biology, both of which might ultimately create new forms of understanding by analysing and manipulating living systems in the way outlined above. If systems and synthetic biology become the new paradigms in biology, they will certainly marginalize other types of research due to competitive funding and career options, regardless of their alleged conceptual novelty.

In 1990, the German biologist Ernst Ludwig Winnacker stated that biology will only become a mature science akin to chemistry and physics when it enters the synthetic phase—which chemistry did more than 100 years ago (Winnacker, 1990). Molecular biology and *in silico* biology are even said to replace physics as “the ‘paradigmatic science’ of the twenty-first century” (Potthast, 2007).

Beyond notions of paradigms, other conceptual tools have been developed to analyse changes in the sciences. The Polish biologist Ludwik Fleck (1896–1961), from whom Kuhn got—among other notions—the idea of incommensurability, pointed out that science is not a monolith of shared

theories and practices, but a collection of different styles of thought and conceptual collectives that shape both theories and practices (Fleck, 1935). In this vein, one of the new properties of systems and synthetic biology is the merging of separate thought collectives by biologists, mathematicians, physicists, chemists, computer scientists and engineers.

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One interesting question is whether this results in a new way of organization and establishes robust new forms of cooperation. At the moment, it is not possible to give a clear answer because both systems biology and synthetic biology are still in the transition phase to whatever stable arrangements or networks of researchers will emerge. This observation matches a theory by the Hungarian mathematician and philosopher of science Imre Lakatos (1922–1974) who stated that research programmes have a stable ‘core’ and a flexible ‘periphery’, which do not undergo revolutions, but rather progressive shifts at the periphery (Lakatos, 1976). Biology would therefore retain its stable core of Darwin’s theory of evolution, while systems and synthetic biology would be at the rapidly changing periphery. In conclusion, it is not clear yet whether these new fields represent a paradigmatic shift similar to the general theory of relativity and quantum mechanics in physics. Generally, the frequent declaration of new paradigms seems to be mainly a strategy of selling science to funding agencies and the public, although it is still relevant to ask the question “What is new?” with regard to epistemology.

Systems and synthetic biology attempt to put into practice old ideas of creating life by adopting concepts, methods and tools from both IT and engineering. This approach goes beyond the current manipulation of existing living systems insofar as its ultimate goal is to create life ‘from scratch’, that is, from non-living matter, or by generating novel forms based on different materials than those commonly used in biology. In this teleological sense of making life by the

use of non-biological substrates, one might even declare systems and synthetic biology as a novel paradigmatic approach reaching much further than biology.

Recent publications about such philosophical aspects of systems biology (Bogeerdt *et al*, 2007) and synthetic biology (Boldt *et al*, 2009) indicate that making a clear separation between the two is not easy. As mentioned above, the latter appears to be the 'applied' branch of the first, which focuses more on theoretical and conceptual aspects; together, systems and synthetic biology comprise an attempt at a new meta-approach to biology.

Systems biology combines existing theoretical frameworks with data generated by genomics, proteomics and metabolomics: "Data without models merging with models without data" (Krohs & Callebaut, 2007). Ulrich Krohs and Werner Callebaut specifically name biochemical pathway modelling, biological cybernetics and '-omics' as the three roots of current systems biology. However, they criticize two main points: first, the epistemological goal of a 'realistic' representation of all metabolic processes is lacking in explanatory power, as the data will remain without physiological, functional interpretation; and second, there is no clear-cut definition of when the model is sufficiently detailed and complete—that is, when it is a realistic representation of the real object.

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This issue of methodological and ontological 'wholeness' has a long history, which I extend to the issue of whether systems biology has a shared theory of the specificity of biological systems in comparison to non-living systems. This is, in fact, the crucial point of all debates and criticism about reductionism. On the one hand, if systems biology denies the specificity of organisms, biology would simply be a mere subfield of general systems theories, cybernetics and self-organization theory (Kauffman, 1993). On the other hand, if systems biology maintains and builds on the framework of the Darwinian theory of evolution, it would be no more and no less than another subfield

of biology. As the American philosopher of science Evelyn Fox Keller commented about this crucial debate, self-organizing processes lack the property of function, which is indispensable for any proper understanding of both organisms and machines (Keller, 2007); the difference in function between these is the evolution of complex organisms in contrast to self-steered machines.

The issues of specific function and self-organization go back to the German philosopher Immanuel Kant (1724–1804), who described organisms as self-organizing objects in which every part is a function of the whole and the whole is a function of every part. The strategy of systems biology to explain life therefore seems to follow this definition: the function of a system is a prerequisite to understanding organisms and their subsystems, and it cannot be 'explained away' by reducing it to something more fundamental, such as self-organizing or physicochemical processes.

At the same time, systems biology, in combination with synthetic biology, tries to blur the difference between organisms and other systems, at least for engineering purposes. This move from bio-engineering to creating completely new forms of life has, in principle, far-reaching epistemological consequences. Synthetic biology would ultimately engineer all sorts of things for all sorts of purposes, the biological material being only one possible substrate of the human-created self-organization of matter.

It is always useful to draw analogies from historical experience to make conjectures about current developments. I therefore compare the goals and characteristics of systems and synthetic biology to those of another field of biology: systems ecology. During the mid-twentieth century, ecologists tried to analyse and understand ecosystems as physicochemical systems by following the energy flow and applying rules of energy preservation and optimization (Odum, 1969, 1983). This angle provided new and important insights into ecological systems; however, it did not yield sufficient knowledge to be able to understand, design and manage ecosystems completely. The reduction of organisms to mere processors of energy and matter in ecosystems not only explained away their specific biological functions, but also obviated some of their important features. From an epistemological point of view, one can question whether systems

ecology is completely commensurable with the Darwinian theory of evolution (Potthast, 1999). From the point of view of the data, it seems that even sophisticated tools and sufficient observational information from the 'field' are not enough for a 'complete' physicochemical and/or thermodynamic modelling of ecological systems, owing to the specificity of the biological processes of interacting and evolving organisms.

Obviously, this example supports a more sceptical perspective on systems and synthetic biology and their goal of creating living machines. Even so, these fields will continue to explore what makes organisms, and living systems above the level of the organism, something special in comparison to non-living systems—whether machines or otherwise.

There is more to it. Regardless of whether it is just a buzz or a new emerging paradigm, the mere programmatic attempt to create life has a tremendous impact on funding decisions and ethical debates. There is a normative power of the fictional, the visions and the promises, regardless of their feasibility. Even without any technical and engineering achievements, the idea of organisms as self-organizing machines will shape societal debates and daily lives, as has the information metaphor in genetics. In this sense, systems and synthetic biology might contribute to a perception or understanding of life that is predominantly, if not solely, grounded in biology. The implications of this view have to be discussed within science as well as within society. Ultimately, a 'radical' synthetic and systems view of life is only one perspective out of many, and it cannot and shall not restrict a much broader view of life both within and beyond biology.

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Thomas Potthast, biologist and philosopher, is Managing Director (Wissenschaftlicher Koordinator) of the Interdepartmental Centre for Ethics in the Sciences and Humanities (IZEW) at Tübingen University, Germany. He is also Deputy Spokesperson of the current Postgraduate Research Training Programme “Bioethics: On the Self-Design of Human Beings by Use of Biotechniques” (DFG GRK 889).
E-mail: potthast@uni-tuebingen.de

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