Emergence of design

Kolodkin, A.N.

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In Chapter 1 of this thesis, we discuss a spectrum of philosophical foundations of systems biology as seen through the prism offered by the concept of emergence. Subsequently, we show how emergence can be reconstructed in a computer model and how this model can then be used to understand biological reality, as well as to discover design principles of biological systems. Then we introduce the protocol that we developed for systematic studies of design of biological systems (Chapter 2). In this protocol, one begins by identifying "paradoxical" features in the network and by formulating design questions, e.g. asking what unexpected advantage a specific paradoxical feature may offer. Then, one builds mathematical models of alternative designs, as instantiations of a blueprint scheme that is constructed first as a generalization of the actual design. Only a single questioned feature is altered in any alternative design. Using computation to compare and analyse the performance of alternative designs one then is able to suggest explanations for why the actual design might be advantageous and, consequently, for why evolution has arranged the network in the way it has.

Our protocol for design studies has been applied to several biological examples: a metabolic pathway (Chapter 3), a signaling pathway (Chapter 4), and a "cross-talking" system (Chapter 5). Glycolysis has been chosen as the example of a metabolic pathway: In Chapter 3, we questioned the role of non-phosphorylating glyceraldehyde-3-phosphate dehydrogenase (GAPN) responsible for unidirectional oxidation of GAP to 3-phosphoglycerate and suggested an explanation of why thermopiles such as *S. solfataricus* express this enzyme and why normophiles do not. Nuclear receptor signaling served as the example of a signaling pathway: In Chapter 4, we identified design aspects of the topology of the nuclear receptor signaling network that might appear unnecessarily complex or even functionally paradoxical. We showed how these aspects correspond to potentially important design principles, e.g., (i) 'nuclear' receptors may be partly cytosolic so that they can shuttle signal molecules to the nucleus, (ii) the active export of nuclear receptors (NRs) from the nucleus may ensure that there is sufficient receptor protein to capture ligand at the cytoplasmic membrane, (iii) a three conveyor belts design dissipates GTP-free energy but may serve to enhance the response to nuclear hormones, (iv) the active export of importins may prevent sequestration of NRs in the nucleus, and

(v) the unspecific nature of the nuclear pore may ensure signal-flux robustness. In Chapter 5, we used a similar approach to address paradoxical features in the cross-talk between two types of nuclear receptor, i.e. the glucocorticoid hormone (GR) and the xenobiotic (PXR) nuclear receptors. We showed that (i) the GR negative autoregulation may serve to attenuate the response and (ii) a much higher affinity of ligand to GR than to PXR guarantees a higher sensitivity of GR responsive genes at low ligand concentration and, at the same time, prevents the increase of ligand concentration to potentially toxic levels (O'Brien et al. 2004). Finally, in Chapter 6, we review our main findings in more general contexts, e.g. from the perspective of the future of systems biology and in the anticipation of mechanism-based computer replica of a whole human body – the so-called silicon human.

As a whole, this thesis consists of philosophical, methodological and practical biological parts. Each part contains an innovative aspect and may be valuable by itself. The philosophical part proposes a new look at the concept of emergence. The methodological part proposes a well-defined approach to design studies. The practical part reveals several design principles relevant for biology. However, the essence of this thesis may lie in the interaction between its three parts: The philosophical concepts served as the basis for our methodology, which was then applied successfully to concrete biological systems. The biological questions appeared neither at random nor in isolation. Each question was treated uniformly, in a systematic way and was discussed in the broad context of philosophical and methodological issues. This thesis may hereby illustrate how a new type of systems biology is emerging from the synergy between philosophical, methodological and practical biological aspects of science.