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What is systems biology?

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Systems biology is increasingly popular, but to many biologists it remains unclear what this new discipline actually encompasses. This brief personal perspective starts by outlining the asthetic qualities that motivate systems biologists, discusses which activities do not belong to the core of systems biology, and finally explores the crucial link with synthetic biology. It concludes by attempting to define systems biology as the research endeavor that aims at providing the scientific foundation for successful synthetic biology.

Keywords: systems biology, computational modeling, synthetic biology

INTRODUCTORY APOLOGY

Systems biology is ubiquitous: computational modeling of molecular systems and the integrative interpretation of ever larger postgenomic datasets are accepted as useful, and perhaps even necessary, components of biological research (Serrano, 2007; Westerhoff et al., 2009), being applied in a wide variety of fields (de Lorenzo, 2008; Park et al., 2008; Young et al., 2008; Yuan et al., 2008; Zhu et al., 2008; Feist et al., 2009; Zak and Aderem, 2009).

But despite this broad consensus about the importance of systems biology and its general ingredients, the diversity of definitions of systems biology has become proverbial in recent years: ask two systems biologists for the definition of their discipline, and you will get three answers. This diversity reflects the youth of the field and its highly interdisciplinary nature, with the aims and approaches of the parent disciplines not yet fully integrated as a homogenous new discipline. Despite risks of confusion and ambiguities, the diversity is also highly welcome and encouraged (Bruggeman et al., 2002), for example in the intentionally vague definitions of systems biology handled by many funding agencies, as it is clear that a generous openness towards new ideas is required to provide all the intellectual tools to sustain a research area with as wide a scope as systems biology.

Against this background, any attempt at defining systems biology might seem futile and potentially harmful. However, anyone who is labeling oneself as a systems biologist will have noticed that the question "What is Systems Biology?" comes up in conversation with one's fellow scientists with an astonishing regularity. Usually, the question is followed by a personal definition of the field, along the lines of "to me, all biology is systems biology" or "it's just one of those hypes that you need to follow to get grant money", or, in the most positive cases "this holistic approach is the future of biology, we all will have to do it".

Faced with this challenge, systems biologists have repeatedly tried to come up with more descriptive definitions of what they are doing. These attempts range from brief sound bites, such as "a new kind of biology" or "the successor of molecular biology" to comprehensive, detailed examinations of the historical foundations of the field and its philosophical underpinnings (Westerhoff and Palsson, 2004; Cornish-Bowden, 2006; Powell and Dupre, 2009).

In this inaugural perspective for Frontiers in Systems Biology, I will try to give a brief idiosyncratic answer to the question "What is Systems Biology?", highlighting various aspects that may have been of secondary importance in previous definitions and emphasizing the role of synthetic biology as the most fundamental application domain of the field.

THE ASTHETIC FOUNDATIONS

A first understanding of a scientific field can often be gained by trying to understand the asthetic motivation of its active researchers. What do they consider the beauty of their field? What makes them most excited? Such an analysis will by necessity be rather subjective, but in the case of systems biology it seems to align well with the historic interdisciplinary roots of the field. In my opinion, the three asthetic qualities that seem to be most relevant are the following: diversity, simplicity, and complexity. All three get a new twist in systems biology, and all three are essential for a full systems biological approach.

Diversity has motivated biologists for a long time; the multitude of species, their morphological peculiarities and unique behaviors have driven the natural history approach to biology. Natural history, including the accumulation of large taxonomic collections of plants and animals from exotic locations, was the starting point for the Darwinian revolution in biology. Postgenomic research has opened new realms of biodiversity to be studied and admired: thousands of protein structures and metabolites, tens of thousands of genes

and transcripts, hundreds of thousands of protein variants, all with their unique "morphology and behavior". Systems biologists delight in this diversity and often use quantitative assessments of various "-omes", as the starting point for top-down modeling or to determine general organizing principles.

While it is fashionable to disparage biodiversity research, whether molecular or organismal, as mere "stamp collecting" (Johnson, 2007), it forms the basis of our appreciation of evolutionary processes and of any attempt to delineate the boundaries of the possible in living systems. It is important to realize that in this context, the peculiarities of each of the thousands of measured molecules matter for a systems biologist: they are not just meaningless labels in an unstructured list of observations, but come with their full natural history at the molecular level: interactions with other molecules, specific morphological changes and transitions, a concrete embedding in a larger causal network.

The fascination with diversity is, of course, by no means universal: while biologists take pleasure in the beauty of a collection of butterflies or protein structures, for the physicists the diversity of the elementary particle zoo can be quite abhorrent (even when the number of species is far more limited). Their main drive is towards the establishment of a unified explanation, extracting simplicity from chaos.

Simplicity is almost antipodal to diversity and illustrates the second root of systems biology in the (bio-) physical sciences. The desire for simplicity and unity motivates attempts to identify general laws, usually encapsulated in brief and elegant equations, such as dominate the physical sciences. In biology, this requires the identification of principles that would hold beyond the individual species of interest (molecular or otherwise). In systems biology, the study of universal principles is often associated with bottom-up modeling of small circuits, such as toggle switches, which are expected to follow the same rules independent of their concrete molecular substrate (Tyson et al., 2003). It is also exemplified by the search for general network motifs, which implement recurring functions (such as signal amplifiers or noise filters) at many different places in a biological network (Milo et al., 2002; Shen-Orr et al., 2002; Mangan and Alon, 2003).

It can be questioned whether the identification of general laws is relevant as a research aim for biology, but universal design principles clearly play a central role in engineering approaches that inspire a large part of systems biology. It has turned out that principles like robustness and evolvability often lead to recurrent structural arrangements in the cellular machinery – although we still need to understand to which extent these arrangements can be considered as following general laws, and to which extent they are predictive and useful.

Complexity, finally, is the most specifically systems biology-related asthetic quality of the three. It exemplifies the third root of systems biology in the areas of systems and network theory. Systems biology is only justified as a distinct research area because living systems are complex: the interactions of a large variety of distinct components lead to emergent behavior that cannot be predicted when studying only isolated components or subsystems.

However, complexity is a difficult concept to define in itself: one could, for example, define the complexity of a system as the length of its description after removing all irrelevant random features – for a biological system that would imply abstracting away the accidents of evolution while still retaining the same functionality. For instance, the exact sequence of a protein kinase will be irrelevant for its function in a signal transduction cascade, and it will also be coincidence whether the cascade is initiated by a receptor with seven or five transmembrane helices. And at higher levels, the target of a particular feedback loop may not matter, as long as the resulting gain of the pathway is maintained within the proper limits.

It is obvious that discriminating between random and functional features of a complex system can be an arbitrary procedure: which features are to be considered random and which are part of functionality? Would the relevant description of a fruit fly maintain all mechanisms responsible for the morphological traits of the genus *Drosophila*, or only general characteristics of insects, or perhaps just the general abstract principles that are essential for any living system? The fact that the evolution of complex systems, including the emergence of high-level features like robustness and modularity, is largely driven by non-adaptive processes (Lynch, 2007a,b) makes the decision even more challenging.

But no matter where the boundary is drawn, it is clear that any complete description of a biological system would be very voluminous. Systems biologists deal with this issue continuously, condensing our current knowledge into manageable quantitative or qualitative descriptions (models), navigating the tricky issues of finding the appropriate level of abstraction and handling the perennial incompleteness of the available data. The icon of this aspect of systems biology would be the large network map of metabolic and signaling pathways, and as in the case of molecular diversity, the individuality of the network components matters. A protein–protein interaction map in which proteins are anonymous nodes with arbitrary labels that can be randomly permuted is far less complex than a metabolic pathway map with associated individual kinetic and regulatory information and full consideration of the specific biophysical properties of enzymes and metabolites.

However, the excitement about complexity is also far from universal. For many scientists, the particular details and intricacies of the tangled web of cellular interactions are only boring. The study of complexity seems antithetical to the main movement of biology towards greater reductionism, the progressive dissection of biological mechanisms into ever-smaller components and simpler principles. This apparent conflict will be discussed in more detail below.

ELEMENTS OF A DEFINITION *EX NEGATIVO*

Systems biology is at its most attractive when all three of these asthetic qualities are evident. A prototypical example would be a comprehensive assessment of transcript *diversity* to identify *simple* design principles implementing specific regulatory functions in a *complex* cellular network, such as Kalir et al. performed for the flagellar system of *Escherichia* coli (Kalir et al., 2001; Kalir and Alon, 2004). Thus, good systems biology research should contain a combination of the previous three asthetic qualities. This also means that researchers who are excited only about one (or two) of the three qualities should probably not consider themselves systems biologists.

Examples of such activities at the outskirts of systems biology would be provided by a computational modeler who simulates the control structures of a regulatory pathway, but is intimidated by the molecular diversity of the cellular system, or a mathematician who uses correlation structures in gene expression data to infer causal links in the cellular machinery, but treats the individual genes as uniform black-box entities, or the medical biologist who uses genome-wide molecular profiling to study the intricate network underlying a complex disease phenotype, but ignores the relevance of general engineering principles for the understanding of an evolved biological system. It should also be obvious that method development (whether at the theoretical, computational or experimental level) is not part of the science of systems biology itself but only provides the necessary tools.

Excluding some activities from the core of systems biology naturally leads to an attempt at defining systems biology by clearly and exhaustively stating what does not belong to its realm. This is necessarily controversial, given the financial and institutional consequences such exclusivity may have. Therefore, it is good to remember that the following is just a personal and non-prescriptive attempt at clarifying the unique characteristics of systems biology.

Systems biology is not holistic, at least not in a simple and exclusive sense; it is not some kind of post-modern non-reductionist science that breaks with a perceived physics-centered methodology inappropriate for the biological sciences. This topic has been discussed in detail by (Bruggeman et al., 2002). While systems biology aims at the behavior of biological systems as a whole rather than the behavior of their components in isolation, this activity is perfectly compatible with traditional scientific methodology and reasoning and does not require a weakening of the scientific standards of hypothesis testing and refutation. The conflict between reductionism and the study of complex systems is largely a straw man, set up to re-emphasize the rather obvious fact that molecules are not alive, only organisms are. Ultimately, systems biology must be predictive, thus it must allow the refutation of hypotheses by targeted perturbation of the system – which is most convincingly done by the rewiring of individual components, thus in a reductionist mode. Moreover, most of systems biology is crucially dependent on the availability of reliable data from classical experimentation on individual system components.

Not all biology is systems biology, nor will it ever be so, and not everybody should do it. Large parts of molecular and cell biology are busily expanding our horizon by studying the natural history of cellular components in isolation (or as parts of well-defined substructures and locally linear pathways). This is not only providing essential building blocks for future systems biology, but also continues to be a worthwhile activity in its own right. Not every system is at this point amenable to quantitative modeling, and diverting resources towards "integrative" approaches would be wasteful while the components of the system and their general interactions are uncharacterized.

Finally, not every form of mathematical biology is systems biology, and in particular the study of ecological systems would not be included in the strict definition, even though it has used quantitative modeling and integrated approaches much earlier than the molecular and cell biological domains. Why then should it be excluded now? The reasons initially are historical (modern systems biology grew out of molecular biology and gained momentum in particular after the completion of the human genome project) and pragmatic (molecular systems allow a far more diverse array of experimental intervention). These two reasons, however, would be insufficient, especially when considering that molecular principles manifest themselves at both the cellular and the ecological level and that ecological biology clearly shares the same motivating asthetic qualities as systems biology: biodiversity, simple general laws and complex networks of interaction are at the core of the discipline. The reason for this exclusivity will become clear in the next section, where I will describe what I consider the ultimate aim of systems biology.

A FUTURISTIC PERSPECTIVE

To define a research field, it can be helpful to try to identify its most ambitious ultimate aim, the question that when answered would finish the research program. For biology, this question seems to be "What is Life?" (Schrödinger, 1944). How does this translate into an ultimate aim for Systems biology?

Boogerd et al. have described systems biology as a form of biology that can do without considering evolution (Boogerd et al., 2007a). Given the widespread acceptance of Theodosius Dobzhansky's dictum "Nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973), such a claim makes systems biology look like an almost heretical activity. The focus on the deep historical roots of biological phenomena is deeply embedded in the scientific philosophy of biology. This is what is supposed to set biology apart from the non-historical sciences of physics and chemistry. Boogerd et al. are of course aware of that and qualify their statement by claiming that the absence of evolutionary perspectives in systems biology is just a temporary shortcoming, implying that in the long run systems biology would join the mainstream of biology and its evolutionary interpretations again.

I would argue that the opposite should be the case: a successful systems biology would be judged by its ability to let us move beyond the historical constraints of evolution and to answer the question "What is Life?" in the most general sense, without limitation to one historically contingent subset of possible life forms. Initially, an evolutionary viewpoint can help us understanding the general design principles of living systems: for instance, by revealing the common patterns of cellular and developmental circuitry that achieve the necessary balance between robustness and evolvability that characterizes life. In the long run, however, a true understanding of the organizational principles of life will only be demonstrated if we can show that we are able to design entirely novel (i.e., unevolved and perhaps unevolvable) life forms.

Systems biology is an experimental science, and many definitions of systems biology include repeated iterations between modeling, prediction and experimentation at their core. However, this seems unsatisfactory if the prediction remains restricted to "local" perturbations of existing systems. Predicting successfully how a system will behave in response to a change in a few parameters, while essentially remaining the same, is not enough to prove a true understanding of how the system works. For this, it would be necessary to show that one is able to rebuild the system, using *new* components and *new* blueprints (Kim and Eils, 2008). This will not

lead to a decreasing appreciation of the existing biodiversity, but deepen and enrich biology in general, as the contingently evolved species are put in perspective by the comparison to the much larger realm of potential species.

This is naturally a very ambitious aim, but the recent emergence of synthetic biology as a seriously debated research activity shows that it may not be unrealistic (Endy, 2005; Channon et al., 2008; O'Malley et al., 2008). There are already examples of such an approach: for instance, the artificial circuits of the "repressilator" are convincing proof that we do understand the basic design principles of simple oscillatory systems (Elowitz and Leibler, 2000). For more complex systems, we are still far from such an understanding: for instance, we understand developmental biology well enough to create flies with extra wings (by a simple, local perturbation), but so far we would have no clue how to engineer a pig with wings – which would require a much more far-reaching rewiring of developmental pathways.

Ethical objections might be raised against the creation of novel life as the ultimate aim of Systems biology, but this does not seem to be justified: as in physics, thought experiments could become a standard part of the conceptual tool kit of (systems) biology, and careful proof-of-principle studies might remain focused on ethically uncontroversial partial systems. Thus the ultimate aim of systems biology could be described as "Be able to (re-)design life at the drawing board", with synthetic biology developing the technologies to realize these designs in practice. This ultimate aim will also help to achieve some of the more specific, but no less ambitious, aims of systems biology, such as the provision of personalized medicine (Hood et al., 2004).

Currently, synthetic biology procures its "building blocks" largely by cloning and modification from existing biological systems, but this does not have to remain the case forever (Xie and Schultz, 2006; Lucks et al., 2008; Yeung et al., 2009). For the functional rewiring of the building blocks, already now we are not constrained to follow evolutionary models. The technological limitations of synthetic biology are very obvious (Kwok, 2010), but it is also obvious that many of these coincide with a lack of systems level understanding. The non-linearities and unexpected interactions inherent in complex engineered biosystems are at the same time a main challenge for synthetic biology and the core focus of systems biology. It can therefore be envisaged that these two emerging disciplines will increasingly align their research agenda.

CONCLUDING DEFINITION

So, what is systems biology? Based on the preceding discussions, I suggest the following tentative definition: systems biology is the research endeavor that provides the scientific foundation for successful synthetic biology. It is based on the comprehensive study of the molecular diversity of living systems, both natural and synthetic, the identification of simplifying general principles and patterns that are recurring features in living and engineered systems, and the integration of our biological knowledge in complex models of the regulatory networks that characterize life. In this way, systems biology will not only be a fascinating high-performance version of natural history, but can indeed be considered the "culmination of biology" (Boogerd et al., 2007b).

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