What is systems biology?

Rainer Breitling1,2*

1 Faculty of Biomedical and Life Sciences, University of Glasgow, Scotland, UK
2 Groningen Bioinformatics Centre, University of Groningen, Groningen, Netherlands

INTRODUCTORY APOLOGY

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 aesthetic 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

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 aesthetic 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 aesthetic 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 eukaryotic systems biologists. This apparent conflict will be discussed in more detail below.

Complexity, finally, is the most specifically systems biology-related aesthetic 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, 2007) 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 aesthetic 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 aesthetic 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 aesthetic 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
depth 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
parts of the conceptual tool kit of (systems) biology, and careful proof-
justified: as in physics, thought experiments could become a standard
in practice. This ultimate aim will also help to achieve some of the
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 un-
expected 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 suc-
cessful 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).

ACKNOWLEDGMENTS

I thank Eriko Takano and Marnix Medema for their constructive
criticism of the manuscript. This work was supported by an NWO
Vidi fellowship.

REFERENCES

Boogerd, F. C., Bruggeman, F. J., Hofmeyr, J.-H. S., and Westerhoff, H. V. (2007a).
“Afterthoughts as foundations for systems biology,” in Systems Biology: Philosophical Foundations, eds F. C.
Boogerd, F. J. Bruggeman, J.-H. S. Hofmeyr, and H. V. Westerhoff (Amsterdam: Elsevier), 321–336.
Boogerd, F. C., Bruggeman, F. J., Hofmeyr, J.-H. S., and Westerhoff, H. V. (2007b). “Towards philosophical foundations
of Systems Biology: introduction,” in Systems Biology: Philosophical Foundations, eds F. C. Boogerd, F. J.
Bruggeman, J.-H. S. Hofmeyr, and H. V. Westerhoff (Amsterdam: Elsevier), 3–20.
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. Philos. Psychol. 15, 411–440.
Channon, K., Bromley, E. H., and Woolfson, D. N. (2008). Synthetic biology through biomolecular design and engineering.
Curr. Opin. Struct. Biol. 18, 491–498.
Cornish-Bowden, A. (2006). Putting the systems back into systems biology. Perspect. Biol. Med. 49, 475–489.
de Lorenzo, V. (2008). Systems biology approaches to bioremediation. Curr. Opin. Biotechnol. 19, 579–589.
Dobzhansky, T. (1973). Nothing in biology makes sense except in the light of evolution. Am. Biol. Teach. 35, 125–129.
Elowitz, M. B., and Leibler, S. (2000). A synthetic oscillatory network of tran-
scriptional regulators. Nature 403, 335–338.
Endy, D. (2005). Foundations for engineering biology. Nature 438, 449–453.
Feist, A. M., Herrgard, M. J., Thiele, I., Reed, J. L., and Palsson, B. O. (2009). Reconstruction of biochemical net-
works in microorganisms. Nat. Rev. Microbiol. 7, 129–143.
Hood, L., Heath, J. R., Phelps, M. E., and Lin, B.Y. (2004). Systems biology and new technologies enable predictive
and preventative medicine. Science 306, 640–643.
Johnson, K. (2007). Natural history as stamp collecting: a brief history. Arch. Nat. Hist. 34, 244–258.
Kalir, S., and Alon, U. (2004). Using a quantitative blueprint to reprogram the dynamics of the flagella gene net-
work. Cell 117, 713–720.
Kalir, S., McClure, J., Pabbaraju, K., Southward, C., Romen, M., Leibler, S., Surette, M. G., and Alon, U. (2001).
Ordering genes in a flagella path-
way by analysis of expression kinet-
ics from living bacteria. Science 292, 2080–2083.
Kim, T., and Els, R. (2008). Systems biology and artificial life: towards predic-
tive modeling of biological systems. Artif. Life 14, 1–2.
Kwok, R. (2010). Five hard truths for syn-
thetic biology. Nature 463, 288–290.
Lucks, J. B., Qi, L., Whitaker, W. R., and Arkin, A. P. (2008). Toward scalable parts families for predictable design of
biological circuits. Curr. Opin. Microbiol. 11, 567–573.
Lynch, M. (2007a). The evolution of genetic networks by non-adaptive processes. Nat. Rev. Genet. 8, 803–813.
Lynch, M. (2007b). The frailty of adap-
tive hypotheses for the origins of organismal complexity. Proc. Natl. Acad. Sci. U.S.A. 104(Suppl. 1) 8597–8604.
Mangan, S., and Alon, U. (2003). Structure and function of the feed-forward loop network motif. Proc. Natl. Acad. Sci.
U.S.A. 100, 11980–11985.
Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., and Alon, U. (2002). Network motifs: simple
building blocks of complex networks. Science 298, 824–827.
O’Malley, M. A., Powell, A., Davies, J. F., and Calvert, J. (2008). Knowledge-
making distinctions in synthetic biol-
ogy. Bioessays 30, 57–65.
Park, J. H., Lee, S. Y., Kim, T. Y., and Kim, H. U. (2008). Application of systems biology for bioprocess development.
Trends Biotechnol. 26, 404–412.
Powell, A., and Dupre, J. (2009). From molecules to systems: the importance of looking both ways. Stud. Hist. Philos.
Biol. Biomed. Sci. 40, 54–64.
Schrödinger, E. (1944). What is Life?:
The Physical Aspect of the Living Cell. Cambridge: Cambridge University
Press.
Serrano, L. (2007). Synthetic biology: promises and challenges. Mol. Syst.
Biol. 3, 158.
Shen-Orr, S. S., Milo, R., Mangan, S., and Alon, U. (2002). Network motifs in the transcriptional regulation network of
Escherichia coli. Nat. Genet. 31, 64–68.
Tsoy, J., Chen, K. C., and Novak, B. (2003). Sniffers, buzzers, toggles and
blinker: dynamics of regulatory and
signaling pathways in the cell. Curr. Opin. Cell Biol. 15, 221–231.
Westerhoff, H. V., and Palsson, B. O. (2004). The evolution of molecular biology into systems biology. Nat. Biotechnol. 22, 1249–1252.
Westerhoff, H. V., Winder, C., Mesin, H., Simeonidis, E., Adamczyk, M., Verma, M., Bruggerman, F. J., and Dunn, W. (2009). Systems biology: the elements and principles of life. FEBS Lett. 583, 3882–3890.
Xie, J., and Schultz, P. G. (2006). A chemical toolkit for proteins—an expanded genetic code. Nat. Rev. Mol. Cell Biol. 7, 775–782.
Yeung, N., Lin, Y. W., Gao, Y. G., Zhao, X., Russell, B. S., Lei, L. Y., Miner, K. D., Robinson, H., and Lu, Y. (2009). Rational design of a structural and functional nitric oxide reductase. Nature 462, 1079-U1144.
Young, D., Stark, J., and Kirschner, D. (2008). Systems biology of persistent infection: tuberculosis as a case study. Nat. Rev. Microbiol. 6, 520–528.
Yuan, J. S., Galbraith, D. W., Dai, S. Y., Griffin, P., and Stewart, C. N. Jr. (2008). Plant systems biology comes of age. Trends Plant Sci. 13, 165–171.
Zak, D. E., and Aderem, A. (2009). Systems biology of innate immunity. Immunol. Rev. 227, 264–282.
Zhu, J., Zhang, B., and Schadt, E. E. (2008). A systems biology approach to drug discovery. Adv. Genet. 60, 603–635.

Conflict of Interest Statement: The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 03 March 2010; paper pending published: 22 March 2010; accepted: 13 April 2010; published online: 21 May 2010.

Citation: Breitling R (2010) What is systems biology? Front. Physio. 1:9. doi: 10.3389/fphys.2010.00009

This article was submitted to Frontiers in Systems Biology, a specialty of Frontiers in Physiology.

Copyright © 2010 Breitling. This is an open-access article subject to an exclusive license agreement between the authors and the Frontiers Research Foundation, which permits unrestricted use, distribution, and reproduction in any medium, provided the original authors and source are credited.