Systems Biology: Did we know it all along?

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Abstract

It is often suggested that Systems Biology is nothing new, or that it is irrelevant. Its central paradigm, i.e. that much of biological function arises from the interactions of macromolecules, is not generally appreciated. We here contend that much like molecular biology in its past, Systems Biology is new and old at the same time. It looks in a new way and with new and improved reincarnations of existing and new technologies at scientific issues that the existing disciplines describe but do not resolve. Its main focus is to understand in quantitative, predictable ways the regulation of complex cellular pathways and of intercellular communication so as to shed light on complex biological functions (e.g. metabolism, cell signaling, cell cycle, apoptosis, differentiation, and transformation). It is for the lack of achieving this understanding of living systems that the existing paradigms for biomedical research fail for the majority of diseases on the Northern hemisphere. Systems Biology appears appropriate for these complex and multifactorial diseases.

But of course it is not for us to define what Systems Biology is or should be. Yet, it is important that there be an end to suggestions that Systems Biology is vague or can be anything. As is molecular biology, Systems Biology is rich, wide, and diverse, not vague: most aspects of biology and of mathematical modeling are not part of Systems Biology. This book serves to define this rich and heterogeneous Systems Biology 'bottom up', i.e., by having systems biologists themselves define it.

1 Is Systems Biology something new?

All too often one of our colleagues 'confesses' to not knowing what Systems Biology is, or that Systems Biology is 'nothing but an existing science with a new touch'. Systems Biology 'should be nothing but good old physiology', Systems Biology 'is molecular biology claiming additional money', or 'Systems Biology is the explanation by engineers of how biology works'.

Of course, *this* is nothing new. When *molecular* biology began, it was considered a branch of biochemistry and biophysics. Its first major success was a combination of crystallography, theoretical biology, and chemistry. Later, it was made synonymous with molecular genetics. This view was right and wrong at the same time: on the one hand, molecular biology used concepts that came from the surrounding sciences. Its people were trained biochemists and physicists. On the

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other hand, molecular biology became a discipline of its own, which outgrew its founding sciences. Its success resulted from its focus on a type of molecule that led to a vast number of new and powerful concepts and techniques, each of which consisted of new combinations of existing chemistry and physics. Functional genomics is the contemporary and revolutionary result of its line of work.

How would we define molecular biology? Well, it is the natural science that deals with the individual macromolecules of living organisms, with an emphasis on information-rich molecules. As such it should use chemistry, physics, and mathematics whenever necessary. As molecular biology expanded, it emancipated from the dominance of physical chemists to which it was subject to early on. Biologists with a dislike of physics and mathematics took their place and ultimately molecular biologists even refused to express their concepts with the use of formal mathematical techniques. The cartoon became the highly efficient expression of their models.

Systems Biology is similarly new and not new at the same time. It does use classical physics, chemistry, molecular biology, and mathematics. However, it thrives on the *integration* of these and other sciences, and that *is* relatively new; recent molecular biology made some use of mathematics but only minimally and until recently many molecular biology journals would discriminate against papers with mathematical equations. Systems Biology (or the part thereof that we focus on in this book) has the living cell as object of study, has as its predecessor cell biology. Yet, it is much more than cell biology ever was. Systems Biology is after the mechanisms by which macromolecules through dynamic interactions produce the functional properties of living cells. Systems Biology does not just observe and describe functions in and of living systems, such as physiology does. Systems Biology adds the mechanistic interest of biochemistry and physics to physiology, and of course the analysis tools of mathematics. Indeed, Systems Biology is a science in that it is after principles and generalities rather than special cases. In order to discover those principles, it uses whatever science or technology is available. It is mathematics (in the sense of deducing principles from *a priori*'s) and biology (in the sense of addressing functional issue related to Life) at the same time. And then perhaps most importantly, Systems Biology is also biology in that it is after the principles of Life, the principles that are specific to living systems. These principles are the result of an evolutionary optimization that led to a local maximum in fitness for some habitat. The principles are also confined by the hysteresis of evolution, and by the feature that new life has always been an extension of existing Life. Here Systems Biology combines principles of physics and chemistry with principles of microbiology.

From the above it may be clear that Systems Biology is nothing new, yet highly new at the same time: it is in the *combination* of previous disciplines and in a *new focus* that Systems Biology distinguishes itself from other sciences.

2 Is it important?

In 1995 and 2001 mankind witnessed two of its greatest scientific achievements, i.e. the elucidation of the complete code for a living organism, and for a human being, respectively. Soon, a plethora of new techniques made it possible also to measure the expression of this code, at the level of mRNA, protein and in quite a few cases function (metabolome, fluxome). Thus, in one sense we are now able to determine what Life is, in terms of the concentrations of virtually all its molecular constituents. If we know precisely the contents of living organisms, for sure we must know Life?

As functional genomics data flood the scientific literature, its reader is increasingly confronted with a paradox: one may 'know' everything without understanding it. With every new publication on p53 we seem to understand less, rather than more of how life functions (Lazebnik 2002). What is the problem?

Unlike digital computers, the human mind is indeed much better at understanding a few things than at understanding many. We are confused by larger numbers of data and by many degrees of freedom. Human understanding boils down to the ability to order observations along the lines of relatively few patterns which we then call (empirical) 'laws'. Understanding is even better if we can deduce the one empirical law from the other, or from a small set of underlying principles. Human understanding is fundamentally qualitative. If two factors stimulate process *A* little and another factor inhibits it much more, then we have no way to intuit what the total effect will be. It becomes even more difficult with nonlinear and recursive interactions.

With genomics came the definitive appreciation of the minimum size of Life, i.e. some 300 processes (or at least a number of processes specified by some 300 genes) (Hutchison et al. 1999). The simultaneous action of 300 processes is way above the action of the five that we might be able to understand. Moreover, it is not clear that the principles or laws that govern the behavior of molecules in living cells are as simple as those in physics or chemistry. They may well be based on strongly nonlinear principles that engage tens of degrees of freedom at the same time. Many of the concepts that exist in biology are formulated qualitatively rather than quantitatively and in terms of interactions between already complex objects ('a bird sees a fish and therefore tries to capture it'). Much of Systems Biology may be too complex for the human mind, unless the latter is aided by some kind of information technology. Even in hypothesis driven research, the hypotheses may need to be generated by computers (King et al. 2004). Like in the days of empiricism when physics came about, empirical science, now called data driven hypothesis generation, may become important again. Clearly, with a complexity that is substantial yet bounded by what is needed to sustain Life, Systems Biology is an enormous challenge for science itself, of the same grandeur perhaps as relativistic and quantum mechanics have been before.

Systems Biology is important for science, but beyond that, is it important for society? The point is made often but perhaps not often enough: progress has been appallingly slow in the medical biology that should lead to cures for the diseases

that remain a threat to health in developed societies. Bacterial infectious disease is what we are good at, thanks to antibiotics, but even there the parasite strikes back by being selected for resistance. Viral infections, cancer, heart disease, arthritis, diabetes are all major diseases of this society. Although biology has pinpointed numerous factors that affect the etiology of these diseases, cures are mostly empirical, and often ineffective. Cancer research started off trying to identify the single molecular or other factor responsible for this disease. It was found that in many tumors, glycolysis is increased and biologists went after glycolytic factors as causes of this disease. When this did not work, assays were developed for determining factors that when deleted or expressed ectopically promoted tumorigenesis. Many such oncogenes were scored. Likewise many factors have been found to affect type II diabetes, none of them determining the disease completely. Molecular cell biology research continues to identify single molecules that correlate with these diseases, then studies their direct mechanisms of action, and is funded for it. Functional genomics programs continue to be directed towards determining the patterns of change of all the genes that correlate with the disease phenotype. This effort may work for diagnostics, but will it work for understanding multifactorial disease and for rational development of new drug targets and therapies?

It is time for us to recognize that the biochemistry and molecular biology that we were raised with, is not a good paradigm for the many diseases that have not been eradicated from the wealthy societies of our world. We need something else, yet something that is equally rational and scientific. Many of the diseases have been found to be multifactorial and strongly nonlinear, i.e. the effect of the one factor being determined by the strength of the other (cf. the chapter by Hofmeyr & Westerhoff). Many of these diseases reflect the system's nature of the human being. We propose that the new scientific paradigm that is needed is precisely Systems Biology.

We realize that recognizing the failure of biochemistry and molecular biology and suggesting that systems biology may be required for the battles against cancer, type-II diabetes, arthritis, and heart disease, may be considered iconoclastic. However, society has long been directing its medical biology research towards molecular biology, and there is appreciable conservatism *vis-à-vis* funding the new Systems Biology. The slow change of the funding agenda in some countries and continents is not only costing society money, it also retards the development of cures and drugs, and it slows down the new economic development that should emerge from a better manageable biotechnology.

3 What is it?

Is a definition important? A definition can help to identify a new area of science where there is much potential for progress. It can also help direct research effort to where it should be rather than continuing to be spent on the same topics but under a new name. Scientists wishing to continue doing their own thing under a new funding flag often proclaim that they do not know what Systems Biology is and

that Systems Biology is vague, or that it is just the same emperor in new cloths. For the same reasons it has proven important that molecular biology was defined. It led to scientific organizations that promoted the area almost exclusively (e.g. EMBO) and even to scientific institutes (e.g. EMBL).

Is it important that the definition is precise? Yes, it is, because otherwise old things compete with the new topics for funding and human capital. Is it important that the definition is uniform or homogeneous? Paradoxically perhaps: No. Many excellent scientific disciplines are heterogeneous. Chemistry and molecular biology are just two examples.

How does one then define Systems Biology in such a heterogeneous way? Well, by examples, i.e. by challenging Systems biologists to explain what they find is Systems Biology. This is what this book is about: to define Systems Biology by examples. Reading through the chapters, the reader will find that Systems Biology indeed consists of a number of related, well-defined topics, based in physics, chemistry, biology, *and* mathematics, all focusing on the mechanisms behind the emergence of functionality. Yes, we reckon that the heterogeneous definition given in this book should take precedence over the more homogeneous and limited definition that we use (cf. below). We emphasize that the definition is heterogeneous and dynamic, not vague. By this definition, the majority of present day cell biology, molecular biology, biophysics, and mathematics is excluded: Systems Biology is a new science.

The following is the definition that *we* use for Systems Biology: The science that discovers the principles underlying the emergence of the functional properties of living organisms from interactions between macromolecules. What is it not then? Well, Systems Biology is not the biology of systems, nor is it the chemistry/physics/molecular genetics of molecules *in* biological systems. It is the difference between the two.

This is the definition that we use and actually also the definition we communicated to the authors of the chapters of this book before they started writing. We then asked them to challenge this definition and to add what they found, i.e. the more important aspects of Systems Biology, and then, in order not to get stranded in words, show by example what they mean.

Indeed, most chapters integrate conceptual (theoretical) and experimental (factual, molecular) aspects of cell function. In each case the essence is to demonstrate what Systems Biology is. The examples describe the author's approach and show that the system had properties that were not in the individual molecules, but only arise when the molecules are together and active, and are important for biological function.

At the same time, this book is much more than a book that defines Systems Biology. It contains examples of the most exciting Systems Biology of our times. It is thereby full of suggestions for the new systems biologists. And if the reader understands all the chapters, (s)he is ready to go!