Why Systems Biology Is (Not) Called Systems Biology

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Browsing the shelves of a bookstore during my last visit to London, I noticed a book with the title "Systems Biology", one of about six that have appeared over the last year about this area of research. While at first I felt disappointed that there is yet another book on the market before I have managed writing one myself, these publications are good news, indicating that this new field is blossoming.

Being part of these developments is exciting – I sometimes imagine cell biology going through a period like physics between 1900 and 1950, with experiments and theories being proposed, overthrown, refined and discussed in heated debates about the nature of things. Systems biology's big questions are: How do the components within a cell interact, so as to bring about the cell's structure and realise its functioning? (intra-cellular dynamics); and: How do cells interact, so as to develop and maintain higher levels of structural and functional organisation? (inter-cellular dynamics). A noticeable difference to physics is that, so far, there are no proposals about "theories" that would address these questions – we are pre-occupied with more practical questions related to the identification and characterisation of the relevant components and modules.

Opening then the book, which I discovered in the London bookstore, I read the contents list: "Shotgun Fragment Assembly", "Gene Finding", "Local Sequence Similarities", ... What?? ... "Protein Structure Prediction", "Some Computational Problems Associated with Horizontal Gene Transfer" ... what on earth has this to do with systems biology, I asked myself? At first, I am disappointed but then realise that this is the first volume in a series, the one in my hands dealing with Genomics. O.K. then, the editors consider systems biology as an umbrella under which cell biology, bioinformatics, genomics, proteomics, and all the other Omics come together? I then wonder whether it make sense to re-name cell biology, and what does the word "systems" in systems biology refer to?

The book I am looking at in London argues that the presented "systemic approaches are timely in light of the availability of an increasing number of genomic sequences, and the generation of large volumes of biological data by high-throughput methods." I am not sure what is meant by "systemic approaches" but if we agree that a system, in its most general definition, is a collection of interrelated objects, we may think of macromolecules making up a cell, or cells interacting in the formation of multicellular complexes, as the systems under consideration. Most important to me is however that cells and proteins are interacting in space and time, that is, we are dealing here with (nonlinear) dynamic systems. If you ask me then, systems biology is a merger of systems theory with cell biology.

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I am happy with the definition of systems biology as the field that integrates Omics data but let me explain my personal view on the need for a systems-theoretic perspective. A key concept by which we organise cellular/molecular interactions into biochemical reaction networks is that of a "pathway", understood as a subsystem, contributing towards the cell's functioning. Studying cell function (growth, differentiation, proliferation, apoptosis, ...), the first step is to identify and characterise those components (genes, proteins etc.) that form a functional "module", i.e., an "isolated" subsystem that can be studied in experiments and yet provide information about the cell as a whole. This first step is where high-throughput, whole-genome techniques are important: they help us to identify, select and characterise those components whose spatio-temporal interactions we investigate in systems biology. While during these genomics and bioinformatics tasks we indeed encounter "large volumes of data", in systems biology and particularly cell signalling, it is often the lack of quantitative, sufficiently rich time course datasets that is a, if not the major problem.

Systems biology and bioinformatics are different but complementary.

Cell differentiation is a good example to explain the need for systems theoretical approaches in cell biology. Conducting experiments to explore cell differentiation, we perturb the cell by adding receptor-binding chemical compounds and monitor the response of the cell. One finds that the response depends on various conditions: the level and duration of the stimulus as well initial conditions. Changing any one of these conditions, we may find that the observed response can be completely different. This is due to the nonlinear and dynamic character with feedback mechanisms that generate bistable (or switch-like) systems, which in experiments lead to counter-intuitive response pattern. From this perspective, the emergence of systems biology is motivated by a shift of focus towards an understanding of functional activity of the cell: cell functions are nonlinear spatio-temporal processes.

Studying cell differentiation as a nonlinear dynamic system requires a very different design of experiments than what we are used to. To reveal feedback mechanisms in nonlinear dynamical systems requires sufficiently rich (long) quantitative (accurate) time course data, something most present technologies do not allow, or only with a considerable effort and with higher costs. This will naturally reduce the interest of biologists in systems biology but there is no way around this problem: for nonlinear dynamic processes, only a systems-theoretic approach works!

The role of systems theory in systems biology is to elucidate the functional organisation of cells. This is a complementary but very different effort to genomics, biophysics, and molecular biology, whose primary role it has been to discover and characterise the components of the cell – to describe its structural organisation. A basic philosophical point systems theory makes is that objects and relations between objects have the same ontological status: Life is a relation among molecules/cells and not a property of any molecule/cell; a cell is built up of molecules, as a house is with stones. A soup of molecules is no more a cell than a plane is heap of metal.

The areas of genomics and bioinformatics have justifiably created excitement but also raised expectations for an understanding of diseases and the development of drugs, beyond what can be realised in the near future. I do worry that the increased amount of time and money, required to generate quantitative, accurate time series will deter biologists from systems theoretic approaches. However, even with suitable datasets available, there is a need to further develop theoretical tools as well – a need that is widely ignored and yet another source of concern for systems biology to succeed. Systems biology – understood as a paradigm shift rather than a re-labelling – will require more time than research-political dynamics allow for.

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I am not sure how we can generate excitement and interest without raising unrealistic expectations but I dislike a culture in which scientists feel obliged to claim that things are simpler than they are. Both, nature's complexity but also our bold attempts to study life at all levels – from molecules to cells, to organs, entire organisms and their failure in a disease are something to be amazed about. Nature's complexity is a motivation, not a source of frustration.

Instead of complaining here about things I cannot change, let me tell you about other discoveries I made during my visit to the bookstores in London. I ended up buying Richard Dawkins' latest book „The God Delusion", Marcello Barbieri's „The Organic Codes: An Introduction to Semantic Biology" (2003), and Pier Luigi Luisi's new book „The Emergence of Life: From Chemical Origins to Synthetic Biology". I also noticed in the bookstore a copy of Robert Rosen's 1991 book „Life Itself: A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life", which has been republished. Browsing these books on my way home, it became clear that the authors have a distinct opinion, I may not agree with, but at least theories, concepts and ideas to argue with and hopefully to improve upon. This is what I enjoy so much about reading books from physics – the discussion they have about the nature of things. As Rosen writes in Life Itself:

For nonlinear dynamic processes there is no alternative approach!

"At the moment, biology remains a stubbornly empirical, experimental, observational science. The papers and books that define contemporary biology emanate mainly from laboratories of increasingly exquisite sophistication, authored by virtuosi in the manipulation of laboratory equipment, geared primarily to isolate, manipulate, and characterise minute quantities of matter. Thus contemporary biology simply is what these people do; it is precisely what they say it is."

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