Feedback dynamics and cell function: Why systems biology is called Systems Biology

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A new paradigm, like Systems Biology, should challenge the way research has been conducted previously. This *Opinion* article aims to present Systems Biology, not as the application of engineering principles to biology but as a merger of systems- and control theory with molecular- and cell biology. In our view, the central dogma of Systems Biology is that it is system dynamics that gives rise to the functioning and function of cells. The concepts of feedback regulation and control of pathways and the coordination of cell function are emphasized as an important area of Systems Biology research. The hurdles and risks for this area are discussed from the perspective of dynamic pathway modelling. Most of all, the aim of this article is to promote mathematical modelling and simulation as a part of molecular- and cell biology. Systems Biology is a success if it is widely accepted that there is nothing more practical than a good theory.

Why is Systems Biology called *Systems Biology*?

The scientist's never ceasing creativity to uncover new sources for research funding has led to various interpretations of what Systems Biology is, or ought to be. While Systems Biology appears to be a new discipline, the original conception of Systems Biology as a merger of control theory and molecular- and cell biology is 37 years old.[1] The central dogma of Systems Biology in this setting states that it is system dynamics and organizing principles of complex biological phenomena[2] that give rise to the functioning and function of cells. Cell function, including growth, differentiation, division, and apoptosis, are *temporal processes* and we will only be able to understand them if we treat them as dynamic systems. While the areas of genomics and bioinformatics are identifying, cataloguing and characterising the components that make up a cell, Systems Biology focuses on an understanding of functional activity from a systems-wide perspective. The biological agenda of Systems Biology should subsequently be defined by the following two questions related to intra- and intercellular processes within a cell and in cell populations:

- *How do the components within a cell interact, so as to bring about its structure and realise its functioning?*
- *How do cells interact, so as to develop and maintain higher levels of organization and function?*

A defining feature of Systems Biology is the role mathematical modelling plays. The experiences biologists had with mathematical biology in the past, hindered the acceptance of mathematical modelling in molecular- and cell biology in recent years. To this day the term "mathematical" is frequently hidden behind a "computational approach". The growth of Systems Biology as a research area is therefore welcome and it is with Systems Biology that mathematical modelling is now considered an important part of health research.[3] So why should wet-lab biologists embrace mathematical modelling as a means towards answering the above questions?

The art of mathematical modelling

Our principal aim is to understand causal interactions in cells. Causation is the explanation of change but while changes occur in the realm of matter, the credo of dynamic systems theory is that causation is modelled as a relation between changes of *states*. Thinking of a pathway that is a network of biochemical reactions, the state of the system is defined by the concentration of all proteins considered. The (dynamic) behaviour of a system is thus encoded in the temporal evolution of its state. For anything to change either space or time or both have to be presupposed and thus differential-, difference equations, automata, and other symbolic representations offer themselves as a natural language for encoding observations made in experiments.

Differential equation modelling is often taken to be synonymous with modelling physical systems and it is therefore important to emphasize that dynamic modelling of molecular- or cell biological systems is different from the classical application of differential equations in mechanics. Mathematical models of pathways are *phenomenal* constructions in that interactions among system variables are defined in an *operational* rather than a *mechanistic* manner. Practical, if not principle limitations between organisms and mechanisms, prevent us from physical/mechanistic modelling. Mathematical modelling is therefore an *art*, not unlike writing short stories or aphorisms. A complex story, fact or reality is condensed to few essential aspects. Pablo Picasso argued that art is a lie that makes us realize the truth to which one could add that mathematical modelling is the art of abstraction that makes us realise reality. To illustrate the power of modelling and abstraction—after all we wish to convince biologists of

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the value of "abstract" mathematical concepts—let us consider the following two drawings of a bird (Fig. 1).

The rough sketch on the left is an abstract "model" of a bird and does little more, but also no less, than to distinguish it from other animals. A minor refinement, shown on the right, is sufficient for an amateur naturalist to recognise it as a Western-European lapwing, more precisely a male lapwing. We may improve the model by choosing a finer pen, adding feathers (requiring higher resolution data) or depicting it in flight (a dynamic model rather than a static one). We realise that although our model is not a physical or exact replica model, only a simple abstract representation, yet it allows predictions (that can be *informative* to a curious mind).

While mathematical modelling may be an abstract art, the composition of a picture, the handling of brush and paint is anything but arbitrary. The terms that make up a differential equation model are well defined encodings of molecular interactions contributing towards the synthesis and degradation of a protein. The fact that the left-hand side of a differential equation describes a 'rate of change' or velocity means that such models are close to what is frequently measured in experiments; parameter values can be identified from time series data. The main problem of differential equations is that many biologists associate them with negative experiences in school.

Rather than providing a list of references with successful case studies in Systems Biology, we here argue that abstract mathematical models of inter- or intra-cellular processes, can be both predictive and useful. The most direct influence of mathematical modelling is that it guides the design of new experiments.

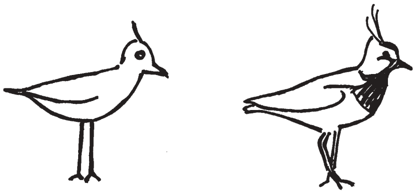

Fig. 1 "These are not birds" (see also Magritte's *Ceci n'est pas un pipe*).

Dynamics and feedback

When we claim that dynamic interactions of system variables give rise to *cell functions*, what does this mean? We first need to realize that in order to *control*, *regulate* or *coordinate* something, we mean to adapt, maintain, optimize. Thereby, implicitly, there must exist a *goal* or *objective*. In order to induce a change towards that goal or objective, information must be *fed back* because only then can the consequences of change can be accounted for. Feedback loops therefore imply a *before* and an *after*, which means that we can only understand cell function as a *dynamic system*. A trend in the analysis of intra- and intercellular dynamics is the study of characteristic behaviour or a *dynamic motif*, including oscillations (damped or sustained), and switching (mono- or bi-stable).[4] The most frequently modeled dynamic motif is that of oscillations (cyclic changes of concentrations). Well known at the level of cell populations, circadian rhythms and the cell cycle, they are now also investigated in the context of signal transduction pathways. The effectiveness of oscillations was already investigated for metabolic pathways in the 1970's and 80's and one would expect a similarly important role of oscillations in cell signalling. The study of the conditions under which cyclic changes arise, although non-trivial, is well established for differential equation modelling, under the names of stability- and bifurcation analysis. Apart from the transfer of information, dynamic motifs and modules serve a cell function. We can distinguish between two key functions. In the first case, where the system is sensitive to inputs from the environment and has the ability to make changes as required, *e.g.*, to track or follow a reference signal it is described as *control*. On the other hand, we refer to *regulation* as the maintenance of a regular or desirable state, making the system robust against perturbations. Regulation that maintains the level of a variable is also referred to as homeostasis. Here we should distinguish two forms of robustness in a control system. The first is robustness against external disturbances (disturbance regulation). In a biochemical pathway, a disturbance might be caused by unwanted cross-talk among pathways or undesirable signals from one or a few, but not sufficiently many, neighbouring cells. The second form of robustness is one which tolerates parameter changes in a system, without significantly changing the system performance. For example if during cell growth or cell differentiation the morphology of the cells changes this would be reflected in changes to model parameters but not necessarily in changes to the model structure. Both forms of robustness are therefore important properties in understanding pathways. Control and regulation appear within or between pathways that are *coordinated* in the context of cell function (growth, differentiation, *etc.*). The identification of dynamic motifs and the development of concepts to investigate the regulation, control and coordination of pathways—in the context of cell function—is a central theme in Systems Biology research. In the next section we are going to discuss the consequences of Systems Biology's central dogma of dynamics as the basis for cell function.

Opportunities and hurdles

If it is the case that feedback dynamics regulate, control and coordinate cell function, then this has consequences on the way we should conduct experiments. To understand interactions in a (non-linear) dynamic system, systems theory tells us that it is necessary to perturb a system systematically with defined stimuli. Towards this end, it will often be necessary to keep some variables constant. Most important, however, is that the experimental data generated are quantitative, accurate and sufficiently rich time series. To achieve conditions that suit current state-of-the-art systems methodologies is an enormous challenge for experimentalists. Such experiments are far more expensive, more laborious and more time consuming than common experiments in functional genomics. The biggest hurdle to the success of Systems Biology is therefore the availability of technologies to conduct quantitative time course experiments. A second important aspect is, however, the will to change the way we think about gene and protein interactions. The need for bioinformatics research is often described in terms of the "vast amounts of data" that are generated. One might argue that in the area of dynamic pathway modelling it is a lack of suitable data that is at present the main problem.

Apart from advances in technologies we need more research into the application of systems methodologies in molecular- and cell biology. From a control engineering and general systems theory perspective, the major challenges in dynamic pathway modelling for the coming years are encapsulated by the following themes:

- Realization Theory: to characterise model structures that could realize given stimulus-response data sets.
- System Identification: to determine values for model parameters; using experimental data or simulation studies.
- Control Analysis: to predict the consequence of changes to a pathway; in particular modifications to parameters, cross-talk and the introduction/removal of feedback loops.

Returning to our question as to why biologists should get enthusiastic about mathematical modelling (as modellers get excited by biology), it is foremost the *complexity* of molecular- and cell-biological systems that makes it necessary to consider dynamic systems theory for modelling and simulation of intra- and inter-cellular processes. To describe a system as 'complex' has become a common way to either motivate new approaches or to describe the difficulties in making progress. It seems therefore a good idea to clarify what complexity means in the context of Systems Biology: With respect to

- The model: the large number of variables that can determine the behaviour.
- The natural system: the connectivity and nonlinearity of relationships.
- The technology: the limited precision and accuracy of measurements.
- The methodology: the uncertainty arising from the conceptual framework chosen (*e.g.* the choice of automata instead of differential equations).

Cellular weather forecasting

Improved technologies for imaging brain activity have tempted neuroscientists into speculations about consciousness and free will. No doubt, we will soon realise that fuzzy images of cellular activities are anything but a step closer to understanding *life itself*. Similarly, our (dramatically) improved ability to identify and characterise cellular components at molecular level should not tempt us in promising too much, too early.

There are major technological and methodological hurdles we have to take before we can fully explain and understand the functioning and function of a cell, organ or organism from the molecular level upwards. Whatever time is required, the complexity of these systems ensures that there is no way around mathematical modelling in this endeavour. A mathematical pathway model does not represent an objective reality outside the modeller's mind. The model is, no more but also no less, a complement to the biologist's reasoning. Mathematics is an extended arm to common sense and mathematics is an essential tool in the handicraft of the natural sciences. As for many things in life, activities that are difficult can also be the most rewarding. Interdisciplinary research in Systems Biology should take functional genomics and bioinformatics towards their natural conclusion—an understanding of functional activity that is fundamental to answer questions in modern bio-medical research.

The risk in this exciting endeavour is that the following thoughts from the beginnings of Systems Biology will remain true in the years to come: "In spite of the considerable interest and efforts, the application of systems theory in biology has not quite lived up to expectations. One of the main reasons for the existing lag is that systems theory has not been directly concerned with some of the problems of vital importance in biology."[1] The challenge is for both the theoreticians and the experimentalists to change their ways: "The real advance in the application of systems theory to biology will come about only when the biologists start asking questions which are based on the system-theoretic concepts rather than using these concepts to represent in still another way the phenomena which are already explained in terms of biophysical or biochemical principles. Then we will not have the 'application of engineering principles to biological problems' but rather a field of Systems Biology with its own identity and in its own right."[1]

Systems Biology has succeeded when it is widely accepted that there is nothing more practical than a good theory.

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