CHAPTER 7

The Predictive Power of Molecular Network Modelling:

Case Studies of Predictions with Subsequent Experimental Verification

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Abstract

Since the 1960s, the mathematical modelling of intracellular systems, such as metabolic pathways, signal transduction cascades and transport processes, is an ever-increasing field of research. The results of most modelling studies in this field are in good qualitative or even quantitative agreement with experimental results. However, a widely held view among many experimentalists is that modelling and simulation only reproduce what has been known before from experiment. A true justification of theoretical biology would arise if theoreticians could predict something unknown, which would later be found experimentally. Theoretical physics has achieved this justification by making many right predictions, for example, on the existence of positrons. Here, we review three cases where experimental groups that were independent of the theoreticians who had made the predictions confirmed theoretical predictions on features of intracellular biological systems later. The three cases concern the optimal time course of gene expression in metabolic pathways, the operation of a metabolic route involving part of the tricarboxylic acid cycle and glyoxylate shunt, and the decoding of calcium oscillations by calcium-dependent protein kinases.

Introduction

The mathematical modelling and simulation of intracellular biological systems, such as metabolic networks, signalling cascades and transport processes, has become a flourishing field of biological research. This field can be traced back to the work by Henri[1] and Michaelis and Menten[2] on enzyme kinetics, yet the proper start of it should probably be dated in the 1960s, with the work by Garfinkel and Hess,[3] Higgins[4] and others.

Modelling and simulation has manifold purposes, the most important being

- Fitting of experimental data by phenomenological equations
- Fitting of experimental data by equations based on mechanistic knowledge and, thus, explanation of these data
- Planning of experiments
- Replacement of expensive or ethically problematic experiments
- Prediction of hitherto unknown phenomena.

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Discovering Biomolecular Mechanisms with Computational Biology,
edited by Frank Eisenhaber.

The latter purpose is obviously the most ambitious goal. However, it is achieved relatively rarely in theoretical biology. Although the acceptance of theoretical (in particular, mathematical) biology appears to increase, as witnessed by the increasing number of such papers in high-ranking journals, experimentalists are often somewhat hesitant with respect to modelling. Many of them believe that it only reproduces what has been known before from experiment. On the other hand, all biochemists make use of the Michaelis-Menten kinetics, which is a form of modelling.

By contrast, theoretical physics is a much more established discipline because it has allowed the prediction of many phenomena that have been found later by experiment. For example, the positron was predicted by P.A.M. Dirac in 1931 and found by C.D. Anderson in 1932 (cf. ref. 5). More recently, powerful methods of theoretical physics, in particular using analogies, enabled a considerable progress in the field of liquid crystals. The analogy between superconductors and the liquid crystal smectic-A phase, found by Nobel Prize winner P.G. de Gennes,[6] turned out to be an extremely powerful tool. By knowing the properties of the normal metal—superconductor phase transition, several properties of the nematic—smectic-A phase transition could be foreseen. The use of the analogy led to the prediction and theoretical description of the twist grain boundary phases[7] (TGB phases). This phase is a liquid crystal analog to the Abrikosov (Nobel Prize winner in 2003) lattice in superconductors.[8] One year after the TGB phase was predicted, an unusual phase was observed in smectic-A liquid crystals.[9] It turned out that the theoretically predicted TGB phase had been discovered experimentally.

In theoretical biology, the successful prediction of phenomena unknown earlier is much less frequent than in physics. What comes to mind is the prediction of three-dimensional structures of proteins, which is often successful, but often it is not.[10] However, this prediction only assigned well-known structure elements such as α-helix and β-sheet to proteins for which the structure had not been known before rather than yielding completely new structures.

Here, we review three cases where theoretical predictions of phenomena or features in intracellular biological systems have indeed been verified later by experimentalists that worked independently of the theoreticians who made the predictions.

The first reported case concerns the prediction of properties of metabolic systems from optimality principles. Biological systems developed through evolution by mutation and selection. Evolution is often considered as an optimisation process that took place over millions of years. However, evolution is almost always coevolution, that is, different species interact so that they cannot optimise their properties in isolation. Therefore, to explain the unlimited possible forms and strategies, approaches more complex than simple optimisation, such as evolutionary game theory, should be used.[11,12] Evolutionary game theory has, for example, been applied to biochemical systems.[13] Fortunately, there are cases where the game-theoretical problem can be transformed into an optimisation problem.[12] Indeed, it seems that many present-day intracellular systems show properties that are optimal with respect to certain selective conditions.[14,15] Hence, system properties may be predicted from mathematical models based on optimality criteria. Several optimality criteria have been proposed. For cellular reaction systems they involve, for example: (i) maximisation of steady-state fluxes,[14,16-18] (ii) minimisation of the concentrations of metabolic intermediates,[14] (iii) minimisation of transition times,[14] (iv) maximisation of sensitivity to an external signal,[19] (v) optimisation of thermodynamic efficiencies,[20] and (vi) minimisation of total enzyme concentration.[21] Here, we discuss the prediction of temporal expression profiles for genes coding for the enzymes of a pathway from the criterion of minimal time required for the conversion of the pathway's substrate into its product. As a side constraint, the limited capacity of the cell to produce and store proteins is taken into account.

The second case is in the field of Metabolic Pathway Analysis. The set of linear pathways in biochemistry textbooks often does not capture the full range of possible behaviours of a metabolic network. A well-known pathway is the tricarboxylic acid (TCA) cycle. It has frequently been realized that in many organisms only part of this cycle is operative, always or under