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Review

How computational models can help unlock biological systems

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ABSTRACT

With computation models playing an ever increasing role in the advancement of science, it is important that researchers understand what it means to model something; recognize the implications of the conceptual, mathematical and algorithmic steps of model construction; and comprehend what models can and cannot do. Here, we use examples to show that models can serve a wide variety of roles, including hypothesis testing, generating new insights, deepening understanding, suggesting and interpreting experiments, tracing chains of causation, doing sensitivity analyses, integrating knowledge, and inspiring new approaches. We show that models can bring together information of different kinds and do so across a range of length scales, as they do in multi-scale, multi-faceted embryogenesis models, some of which connect gene expression, the cytoskeleton, cell properties, tissue mechanics, morphogenetic movements and phenotypes. Models cannot replace experiments nor can they prove that particular mechanisms are at work in a given situation. But they can demonstrate whether or not a proposed mechanism is sufficient to produce an observed phenomenon. Although the examples in this article are taken primarily from the field of embryo mechanics, most of the arguments and discussion are applicable to any form of computational modelling.

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1. Introduction

Few things in the universe are as inspiring to behold as living systems, and one of the recurring mysteries about them is how their remarkable characteristics arise from interactions between relatively simple building blocks. For example, "How can collections of cells each of which is able to take only one of two states, on and off, allow human minds to think complex, meaningful thoughts?" or "How do the various organic and inorganic players in an ecosystem interact so as to produce long-term stability?" or "How do embryos acquire their increasingly complex and elegant forms?" These are profound mysteries.

As medical researchers and biologists strive to address questions of this kind with increasing rigour, they require tools that will allow them to gain insights into the complex interactions that occur in these systems, and one of the best currently-available tools is computational modelling [1–5]. There are many reasons that computational models are so effective in this setting, and a primary goal of this article is to highlight them, while at the same time recognizing their limitations. This article also aims to provide insight into how models work in general and show some of the specific ways that they can be used in the context of biological systems, especially those related to cell and tissue mechanics and embryology.

In general, the goal of a computational model is to replicate the behaviour of the system it parallels and to do so based on actual, known properties of the system components. Achieving this goal may require the model to span a range of length scales and incorporate information from multiple fields of endeavour. As this article argues, models that achieve this challenging goal can serve as an important complement to experimental and theoretical studies, and can provide valuable knowledge.

Before the advent of computers, one could write force balance equations describing equilibrium of forces at a single triple junction and volume constancy equations for single cells. However, studying interactions between meaningful numbers of cells by hand was impractical due to the large number of equations that had to be constructed and solved. To make matters worse, as the cells moved, their geometries changed and the equations had to be re-derived and re-solved for each small increment of motion.

When computers became available to university researchers in the early 1970s, they ushered in a revolution. With the advent of computers, code could be written to automatically construct and solve these equations and to do so repeatedly for multiple times steps. The time course of the cell movements could then be predicted and new things could be learned about how cells in model aggregates behaved [1]. Thus, computers provided a new way for researchers to investigate interactions between different systems elements.

Interest in the mechanics of cell–cell interactions was growing at the time, and there was debate about the nature of cellular forces and how they could drive collective phenomena such as cell sorting and aggregate rounding [6,7]. Some of the earliest computer programs were written to investigate the mechanics of cell–cell interactions and thereby tackle these intriguing questions. Even though many of those early studies were rudimentary by current standards, they were instrumental in defining the field of computational modelling and they unlocked important mysteries about how cells interact with each other [1].

Researchers quickly realized that they could change the properties of the virtual cells in their models and the rules that governed their interactions at will, and that by doing so they could test hypotheses, understand which features gave rise to particular outcomes and carry out almost any kind of virtual experiment that crossed their minds. Over time, the algorithms they used improved and became more reliable, stronger connections were forged between models and real-world experiments, and modelling ultimately entered the mainstream of biology. Indeed, computational models have now become a standard tool for assessing proposed new biological mechanisms, often considered essential even when the associated experimental evidence is strong.

Many of the computational advances needed for these models came out of the fields of engineering and physics. The reason is that during the 1970s, 80s and 90s, computational models came to play an increasingly central role in various branches of engineering, especially its structural, aerospace, mechanical, electromagnetic, fluid dynamics, chemical, control and electrical domains [8]. It was in these contexts that extensive algorithm development took place and that the mathematical theory needed to bring confidence to the calculations was developed. In engineering and physics, a particular technique called the finite element method (FEM) took shape during this period and became the most widely-accepted, general-purpose framework for studying phenomena that involve non-trivial geometries. Many modern cell and tissue models, as well as other kinds of models, draw on conceptual and computational developments associated with this method.

A large variety of computational models arose for studying cells and their interactions during this time, including lattice (Potts), vertex, centric, and finite element models (reviewed by Brodland [1]), and since then, even more models have arisen [2,3,9–13]. Multiple approaches continue to be used because each one has its own inherent strengths and challenges. In addition, several large computational packages have become generally available, including CompuCell, The Virtual Cell and Smoldyn [14–16].

As this article discusses, computational models are based on specific conceptual, mathematical and algorithmic assumptions, and while these presuppositions can bring power and efficiency to the models, they can also introduce differences between the model and the real world that it endeavours to parallel. Determining which model is most appropriate in a particular setting will depend on the focus and goals of the study, with options including deterministic versus stochastic approaches, agent (particle) versus continuum schemes, single- versus multiple-scale approaches and forward versus inverse approaches.

2. The process of modelling

2.1. What does it mean to model something?

In order to better understand what it means to model something, consider Fig. 1, which shows a rectangular box across the top and represents the physical world, where a particular real embryo exists. For purposes of this illustration, we will consider the process of neurulation in amphibian embryos. An axolotl embryo at the start of this process is shown in the upper left corner of the figure. Over time, its neural plate, which consists of most of the visible tissue, rolls up to form a tube – the precursor of the spinal cord and brain – as shown in the other frames in the upper box. The box at the bottom represents the virtual or "*in silico*" world, and there one hopes that a corresponding model embryo is undergoing the same processes. Only when rendered using computer graphics does the

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