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A call for virtual experiments: Accelerating the scientific process

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ABSTRACT

Experimentation is fundamental to the scientific method, whether for exploration, description or explanation. We argue that promoting the reuse of virtual experiments (the *in silico* analogues of wet-lab or field experiments) would vastly improve the usefulness and relevance of computational models, encouraging critical scrutiny of models and serving as a common language between modellers and experimentalists. We review the benefits of reusable virtual experiments: in specifying, assaying, and comparing the behavioural repertoires of models; as prerequisites for reproducible research; to guide model reuse and composition; and for quality assurance in the translational application of models. A key step towards achieving this is that models and experimental protocols should be represented separately, but annotated so as to facilitate the linking of models to experiments and data. Lastly, we outline how the rigorous, streamlined confrontation between experimental datasets and candidate models would enable a "continuous integration" of biological knowledge, transforming our approach to systems biology.

1. Introduction

"Experiment [noun]: An action or operation undertaken in order to discover something unknown, to test a hypothesis, or establish or illustrate some known truth" (Oxford English Dictionary online, 2014).

Experimentation is fundamental to the scientific method, whether for exploration, description or explanation (Hacking, 1983; Radder, 2003). In the exploration of a novel system, children and researchers alike will mess about with things just to see what happens. More formalized experimental protocols ensure reproducible results and form a basis for comparing systems in terms of their response to a specific stimulus. Finally, experiments can be carefully designed to distinguish between competing causal hypotheses based on their different testable predictions about the outcome of the experimental manipulation. One would therefore expect experiments to be central in computational biology too.

Indeed, a mathematical model embodies a thought experiment, a causal hypothesis, and its falsifiable predictions. It is easy to ask *what if* we were to change a parameter, an initial state, or the model structure (Morgan and Winship, 2007). Papers in computational biology focus on describing and analyzing the effects of such changes, and on confronting models with experimental data (Hilborn, 1997). This confrontation often generates new hypotheses, and many if not most new *models* arise by modification of existing ones (Smith et al., 2007; Waltemath et al., 2013). However, most *virtual experiments* are not built to be reproducible (Waltemath et al., 2011b), and thus die with the paper they are published in. This inhibits the critical scrutiny of models, as models are seldom subjected to the same simulation experiments as their predecessors, or revisited later in the light of new data. Perhaps worse, the status quo fails to take full advantage of experiments as a common language between modellers and experimentalists. This limits the relevance of mathematical models for experimental biologists, who often prefer to rely primarily on mental models to develop hypotheses and design tests for them. Despite the growing availability of data and model repositories (Joyce and Palsson, 2006; Le Novere et al., 2006; Li et al., 2010; Lloyd et al., 2008), there has been only a slow uptake of emerging tools and standards for documenting and sharing the protocols for simulation experiments and their results (Cooper et al., 2011b; Waltemath et al., 2011a, 2011b).

We define a *virtual experiment* as the *in silico* analogue of a wet lab or field experiment, performed on a computational model rather than the real system or a physical model (see Box 1 for

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Box 1
Terminology

A *model* is a purposeful simplification of reality, designed to imitate certain phenomena or characteristics of a system while downplaying non-essential aspects (Vik et al., 2014). Its value lies in the ability to generalise insights from the model to a broader class of related systems. Thus, a lab mouse can be a model representing mammals in general; an *in vitro* heart cell can represent the cells in an intact heart; and a set of differential equations can approximate the dynamic behaviour of a biological system.

For mathematical and living biological models alike, an *experiment* is the process of inducing changes or stimuli to elicit some response from the system that can be observed and carries information about the inner workings and/or emergent properties of the system.

An experimental *protocol* is a detailed specification for carrying out an experiment. Whether involving a wet-lab, field or simulated experiment, this will include interventions, recordings, and post-processing. A protocol for a wet-lab experiment will specify environmental conditions, whereas a simulation protocol will translate these into corresponding initial/boundary conditions and parameter values. A simulation protocol may also include details of the numerical algorithm and parameters to use.

A *phenotype* is any observable trait of interest in an organism or a model thereof. The purpose of computational physiology is to mimic measurable phenotypes based on mechanistic descriptions of dynamical systems.

Ontologies are domain-specific lists of concepts and the relations between them. Multiple ontologies can be combined to encode biological knowledge, so that labels can be given a precise technical meaning. For example, consider the phenotype "mass of a heart cell". This is the *quality* "mass", pertaining to a heart cell, which *is a* cell and *is located in* the heart, which *is an* organ. A key feature of formal ontologies is that they are computer-processable, and automated tools can make logical deductions from the relationships stated.

Semantic interoperability (where "semantic" means "relating to meaning") denotes the ability to consistently navigate and query a set of data, model and protocol resources using terms taken from one or more ontologies (de Bono et al., 2011). With *ontological annotation*, new knowledge automatically connects to that which already exists, so that users can discover relevant knowledge without knowing its location in advance, and without having to formulate specific queries to link and select data.

definitions). Here we argue that promoting the reuse of virtual experiments would vastly improve the usefulness and relevance of computational models, including in biomedical endeavours such as the Virtual Physiological Human (Hunter et al., 2013, 2010) and the Human Brain Project (Markram, 2012). We review the benefits of reusable virtual experiments: in specifying, assaying, and comparing the behavioural repertoires of models; as prerequisites for reproducible research; to guide model reuse and composition; and for quality assurance in the application of computational biology models. Next, we discuss potential approaches for implementing virtual experiments, arguing that models and experimental protocols should be represented separately, but annotated so as to facilitate the linking of models to experiments and data (Fig. 1). We follow with some consideration of open questions and challenges that remain before the use of virtual experiments can become widespread. Lastly, we outline a vision for how the rigorous, streamlined confrontation between experimental datasets and candidate models would enable a "continuous integration" of biological knowledge, akin to the strategy used in software development (Duvall et al., 2007).

As a running example we will refer to heart cell modelling, a mature research field (Fink et al., 2011) that relies heavily on experimental manipulation such as electrical pacing and cellular patch clamping (Box 2).

2. The virtues of virtual experiments

2.1. Descriptions of the behavioural repertoire of models

One does not model a *system* so much as a set of *phenomena*. Insofar as a model is a *purposeful* simplification, what should be included or left out depends on what *behaviours* it is supposed to imitate. Furthermore, any useful model must be capable of *not* exhibiting the phenomenon if certain parameter values, initial states, or model structure were different. This is what makes the model causal: it is a statement about sufficient causes to exhibit the phenomenon in question. Such what-if questions are all examples of virtual experiments.

Indeed, many phenomena are *created* by experiments, under conditions so artificial as not to occur in nature, as asserted by Ian Hacking in his classic *Representing and intervening* (Hacking, 1983). Likewise, many phenotypes are defined by a system's response to some stimulus or perturbation. Francis Bacon, four hundred years ago, likened this to "twisting the lion's tail" (Kuhn, 1976); a more modern example is the action potential of isolated, excitable cells, which is evoked by an electric stimulus (Box 2). In either case, experiments bring into play mechanisms whose importance may not be apparent under passive observation.

The behavioural phenotype of a dynamical system is a high-dimensional and complex thing (Gjuvsland et al., 2013). Even a "simple" measure such as the duration of an action potential is a summary of the time-course of transmembrane voltage, which is but one of the myriad variables in a heart cell system. A rich characterization of the phenotype aids in mechanistic interpretation, in constraining parameter estimation, and in exposing models to empirical challenge. For example, the combination of calcium transient and action potential data has been shown to identify more parameter values than action potentials alone (Sarkar and Sobie, 2010; Sobie, 2009).

Virtual experiments serve as assays of a model's behavioural repertoire, both in declaring what a model should do and verifying what it actually does. For example, the Bondarenko heart cell model (Bondarenko et al., 2004) is feature-rich and was designed to accommodate various pacing protocols and a suite of voltage-clamp protocols for different ion currents. On the other hand, the Bernus model (Bernus et al., 2002) was simplified for computational efficiency and stability, while using virtual experiments to ensure that the model still exhibited the various intended behaviours.

Behavioural assays using virtual experiments form a relevant basis for *comparison* within a class of systems. Each species, cell type, or candidate model can be positioned relative to others along phenotypic axes, with the comparison focused on the phenomena of interest. For example, ten Tusscher and co-workers (ten Tusscher et al., 2006) compared heart models based on action potential