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Review

The opportunities and challenges for biophysical modelling of beneficial and adverse drug actions on the heart

Steven A. Niederer[1], Bernardo L. de Oliveira[1,2] and Michael J. Curtis[3]

Abstract

Pharmacology is characterised by linking compound molecular properties to cellular and organ scale therapeutic and toxic outcomes. Biophysical modelling allow data from these disparate sources to be integrated and interpreted based on known physiology and physical constraints of the biological systems of interest. Here we describe the recent use of biophysical models to simulate therapeutic and adverse drug effects on the heart and how this provides a new framework for data integration and identifying drug mechanisms.

Addresses

[1] King's College London Division of Imaging Sciences and Biomedical Engineering, London, UK

[2] Simula Research Laboratory, Lysaker, Norway

[3] Cardiovascular Division, King's College London, The Rayne Institute, London, UK

Corresponding author: Niederer, Steven A (steven.niederer@kcl.ac.uk)

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Introduction

Large genomic [1,2], compound property [3,4] and pathway [5,6] data bases are increasingly utilised to better understand and predict the effectiveness and toxicity of novel compounds [7,8]. Combining information across multiple data sets further enhances the capacity to predict the effect of a drug on patients. Central to this approach is the mapping of information of similarity between records which requires developing novel methods [9–11]. These methods will have the capacity to identify compounds that cause toxic or therapeutic outcomes by integration of their molecular actions.

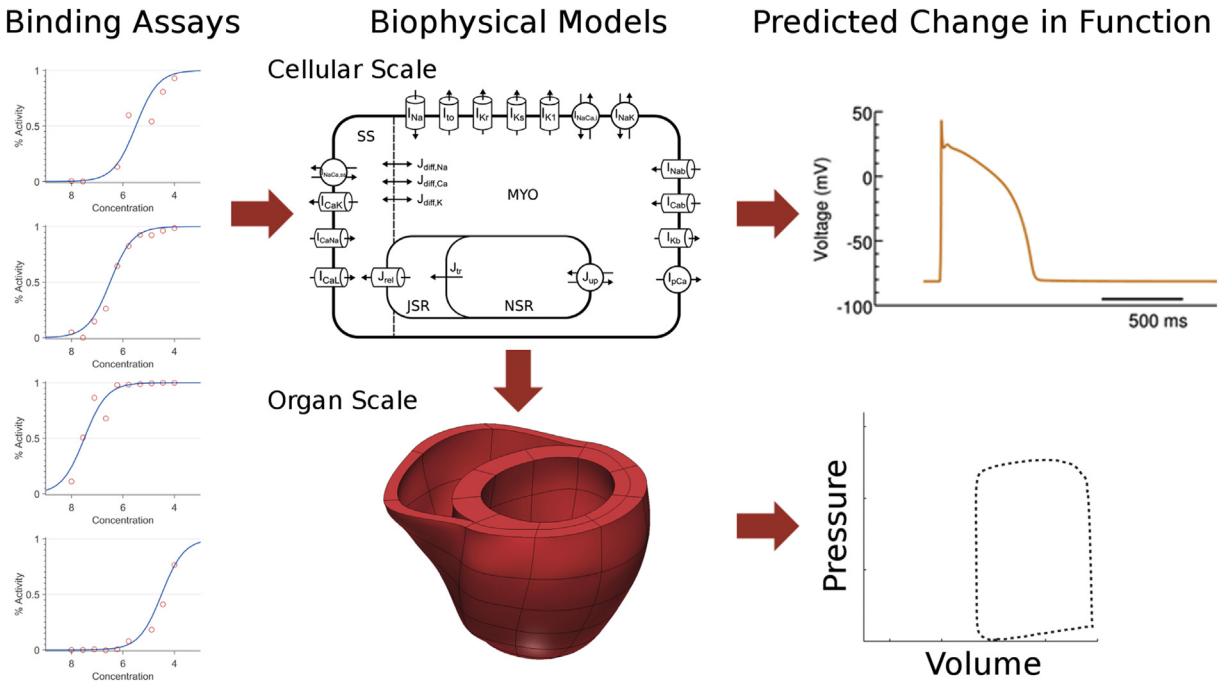
The way such data have been used to date has been to focus on individual measures of molecular effect (e.g., IC50) and extrapolate a whole organ outcome using semi-empirical 'truths', such as a submicromolar affinity for a particular ion current that will, have a certain risk (liability) for causing a certain adverse outcome. This is somewhat limited and, as noted below, can be misleading. While some attempt has been made to combine multiple variables using probabilistic models to predict outcome, this approach makes little or no use of the known physiology and physics of the underlying biological system (integration and interaction). Here we discuss how biophysical models provide a rational framework for data processing and interpretation, as depicted in Figure 1.

Biophysical modelling approaches, including physiome based [12], systems biology [13], quantitative systems pharmacology [14] and physiologically based pharmacokinetic modelling (PKPD) [15,16], provide a framework that encodes quantitative information about physiology and anatomy in accordance with physical principals to generate outcomes that can be judged in terms of how well they mimic the real situation [12,17]. When components of a model are set sufficiently well that they not only allow good recapitulation of the basal state but also recapitulate the effects of well-characterised drugs, this permits inference about the relative role of individual components of the model (i.e., relative contribution of a current and its inhibition to the whole organ effect of a drug). Modeling has therefore increasingly moved from understanding physiology and pathology to interpreting the effects of pharmacological agents [18,19] and medical interventions [17,20]. Here we discuss the recent advances that have led to models being used to interpret drug effects.

Where can computational models add value to conventional pharmacology?

The complexity of drug effects exists at several levels. First, an effect on a single molecular target (e.g., the sodium pump) can have multiple short- and long-term outcomes. Second, most drugs lack molecular target selectivity, meaning that a range of targets require to be

Figure 1



Schematic depiction of the integration of multiple binding assay measurements (left panel) into cellular and organ scale biophysical models (central panel). Where cellular biophysical models represent the molecular regulation of cellular physiology and can be integrated into organ scale models. These models can then predict pharmacologically induced changes in emergent cellular (e.g. action potential) and whole organ (e.g. pressure-volume loop) function.

incorporated into modelling. The latter introduces a need for quite accurate information on relative affinities of the drug for different molecular targets, and efficacy (in the classical pharmacological sense — the ability to achieve a response equal to that of a full agonist). Finally, gaps in knowledge and inconsistencies in reported quantitative vales (for IC50s etc) can render drug characterisation across multiple laboratories a prolonged and lugubrious process, in some cases spanning decades. Underpinning this are mundane issues such as the changes in technology, methodology, preparations and preferred species that occur over time. Consequently interpreting multiple experimental data sets and the disparate hypothesis these generate can be very challenging. Nevertheless, biophysical models provide a framework to formally rationalise how disparate data can be interpreted and combined, accounting for different doses, disparities between species and experimental approaches. The alternative is an informal approach to analysis, whereby assumptions (e.g., about the role of a drug action on IKs, in mediating changes in action potential duration (APD)) are made from isolated data sets (e.g., patch clamp data) and extrapolated to predict what the drug may do in a whole heart. This approach, which is a form of reductionism in reverse ('extrapolationism'?) has often failed and indeed the role of IKs block in mediating reverse rate-dependence, an issue contested 20 years ago by Gintant [21] and Sanguinetti and Jurkiewicz [22] remained contested even quite recently [23]. Integrative modelling using more complex approaches is logically likely to be more yielding simply because it incorporates more than one variable.

Thus, performing a factorial or sensitivity analysis on a computational model [24,25], written with consideration of data on all known variables of potential relevance, can be expected to identify how important each variable is in determining the whole organ drug effect and in turn identify the relative importance of each experimental observation. This approach can then be used to identify which drug target is principally responsible for the therapeutic or toxic effects of the drug and can be used to refine the molecular design, dosage or administration.

Multi-scale biophysical models can also evaluate the relative importance of available data sets [26]. This requires that the model first be validated (in as much as it should consistently predict whole organ effects of drugs of differing molecular specificity and selectivity). A validated model that cannot recapitulate whole organ effects of a novel drug based on a reported data set of values of its IC50s is, in effect, identifying that the data set has dubious provenance. A model that is largely

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