

Review

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

Steven A. Niederer¹, Bernardo L. de Oliveira^{1,2} and Michael J. Curtis³

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)

Current Opinion in Systems Biology 2017, 4:29–34

This review comes from a themed issue on **Pharmacology and drug discovery (2017)**

Edited by **Lars Kuepfer and Tobias Bollenbach**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 1 June 2017

<http://dx.doi.org/10.1016/j.coisb.2017.05.018>

2452-3100/© 2017 Elsevier Ltd. All rights reserved.

Keywords

Safety pharmacology, Proarrhythmia, Torsades de pointes, Simulation.

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.

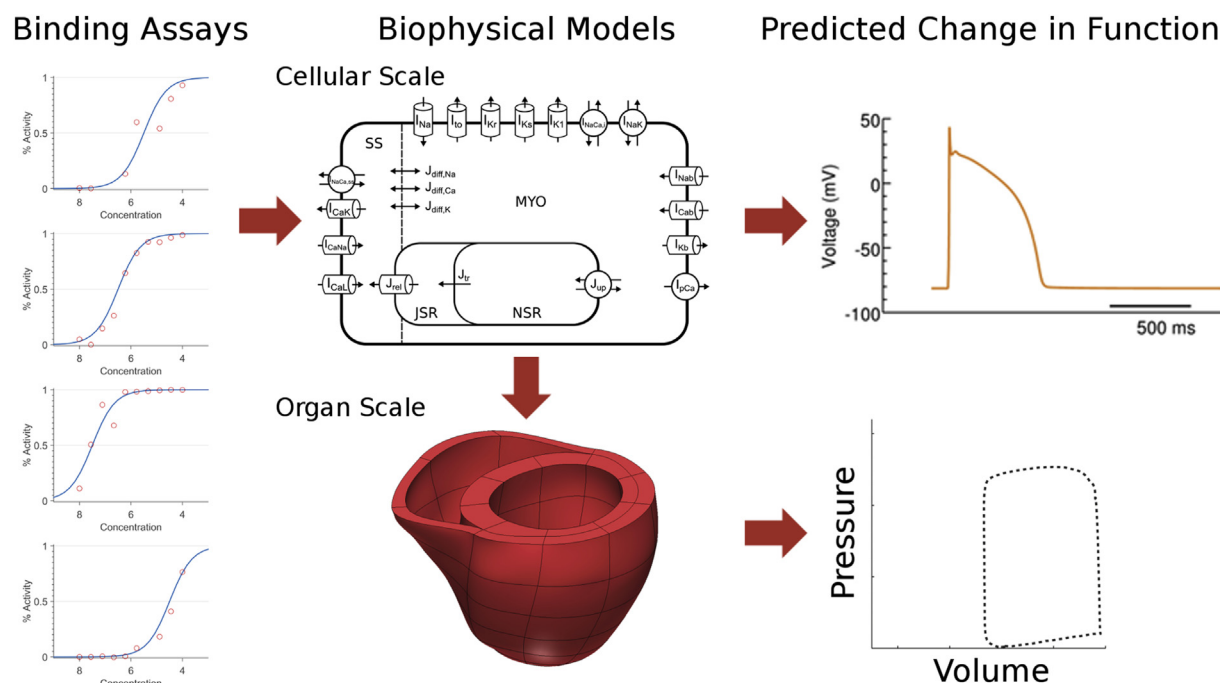
The way such data have been used to date has been to focus on individual measures of molecular effect (e.g., IC₅₀) and extrapolate a whole organ outcome using semi-empirical ‘truths’, such as a submicromolar affinity for a particular ion current that will, have a certain risk (liability) for causing 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 values (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

validated but that has predictive flaws and does not incorporate IC₅₀ values for all known potentially relevant variables (e.g., chloride-bicarbonate exchange, a rather obscure molecular target) is nevertheless of value because it can potentially be used to model whether incorporation of drug effects on the orphan target may change function, informing a decision about whether a search for a drug that has such effects may be justified. This can also be particularly important when seeking to identify unknown off target effects of a drug with a well characterised effect on the whole heart. In other words, modelling can operate in a forward direction (from molecular targets) or a backward direction (from the whole organ) with best fit outcomes used in a reiterative way to obtain the best description of the biological process or the pharmacological specificity and selectivity of a drug.

To illustrate these points, the cardiac myocyte is the standard entry level preparation for elaborating IC₅₀ values for drug effects on ion channels, pumps, antiporters, symporters, and increasingly integrated read-outs such as calcium transients and cell mechanics responses. The inability of an effect on a known molecular target for a drug to recapitulate cellular scale outcomes (as they emerge — data values and their provenance improve with time) implies that actions on at least one other molecular target are necessary to account for the cellular scale outcome, and modelling can be used to identify which pump, channel etc., potentially represent the unknown relevant molecular targets for the drug, using recapitulation of known drug-induced changes in cellular function as the template.

Cardiac models have been created to simulate every scale of function from the whole heart down to protein (drug molecular target) function [27–29]. The heart is intrinsically regulated across scales with tissue scale electrical properties, including anisotropic conductivity and wave curvature altering cellular scale electrophysiology and tissue properties, with shape and boundary conditions of the heart all featuring. This illustrates how reductionist model-free extrapolation of drug molecular effects to the whole organ is generally futile, and akin to an attempt to recapitulate a human foot based only on measurements of the toe. Despite this self-evident truth, there can be concerns about modelling, along the lines that when a model fails to predict exactly the whole organ outcome the model must be flawed and hence of no value, and also along the lines that when a drug's wet biology IC₅₀ data values are inconsistent then any modelling is futile. The latter fails to acknowledge the real world solution; investigators who select to not attempt formal modelling have no option other than to pick and choose what they regard as relevant and important in a model-free fashion that is, almost by definition, context free and valueless. When the research goal is to identify the mechanism of toxicity

of a widely used drug, best in class, for which there is no therapeutic alternative and yet there is toxicity of uncertain cause, it becomes highly inappropriate to not attempt to evolve a model of the toxicity, regardless of the provenance of the wet biology IC₅₀ values used to elaborate the model. Simulating the consequences of drug effects on molecular targets in the context of the whole organ increases our capacity to predict how novel drugs will affect different pathways and whole organ function.

How are biophysical models currently being applied to study toxicity data?

A common adverse drug reaction (ADR) occurs when drugs interact with cardiac ionic channels. Resultant alterations in action potential (AP) propagation, with effects manifested and detected in the electrocardiogram (ECG), may lead to cardiac arrhythmias ('proarrhythmia') with torsades de pointes (TdP) a potentially life-threatening example. Due to a statistical association between risk of TdP and prolongation of the QT interval in the ECG, an effect known to result from prolongation of ventricular APD, several regulatory agencies prohibit the commercialization of drugs that prolong APD and/or prolong the QT interval, with greatest emphasis on the latter (especially the human QT interval). The molecular basis for QT prolongation is, however complex, with a strong statistical link to block of the delayed rectifying potassium current (I_{Kr}) but with enormous nuance (verapamil is a potent I_{Kr} blocker but owing to molecular target promiscuity has no effect on QT interval and no TdP liability). It is crucial to identify TdP liability early in drug discovery so as to exclude the toxic pharmacophore as early as possible to facilitate selection and prioritization of compounds in the process of drug development. However, although there is some insight into the molecular target specificity and selectivity necessary for generating or avoiding a TdP liability (e.g., see above), the nuance remains intractable and this has generated yet another recent multidisciplinary initiative to find a better sequence of investigations at the protein and cell scale to generate an 'integrated' process for ensuring drugs are not discarded needlessly (at patch clamp stage) for a suspected TdP liability that does not exist. This is the Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative [30]. The most important part of CiPA will be the modeling that is intended to be undertaken once a large set of reliable and systematically derived 'wet' lab data (IC₅₀s etc) has been assembled for a broad range of drugs.

In the existing approach to TdP liability testing, there has been a somewhat myopic focus on I_{Kr}. This current plays a major role in cardiac repolarization and is generated by an ion channel, Kir, encoded by the human ether-à-go-go related gene (hERG), resulting in the concept of 'hERG screening', a shorthand for

measurement of block of I_{Kr} , or binding to K_{ir} . The value of I_{Kr} screening is that there are very few (if any) false negatives (drugs that have no effect on I_{Kr} yet cause TdP). However, as noted above, there is an issue with false positives. Thus, this focus on a single ion channel renders 'hERG screening' a low sensitivity approach. The potential value of biophysical models, see Figure 2, is therefore of great interest in the TdP field, as exemplified by the CiPA initiative.

In drug discovery, the expectation is that biophysical models will allow insights and predictions to be made using data acquired at the early high-throughput stages of investigation, with rapid interchange between emerging data and modeling, with the former populating the input for the latter, and the latter informing the direction of the former. Measurements of drug absorption and metabolism can be used to predict drug tissue concentrations [16]. Voltage clamp experiments, performed as part of multiple ion channel screening, using cell lines, generate IC_{50} data that can be readily incorporated into computational models of varying levels of complexity. These models provide a unique method to link drug interactions at the molecular target level to predict altered function at increasingly integrated levels of function, from ionic currents to action potentials [31,32], conduction (reentry) [33–35] and global heart rhythm itself (the ECG) [36–39]. This provides a quantitative link between pre-clinical protein kinetics assays and organ clinical indices.

What are the future opportunities for biophysical models?

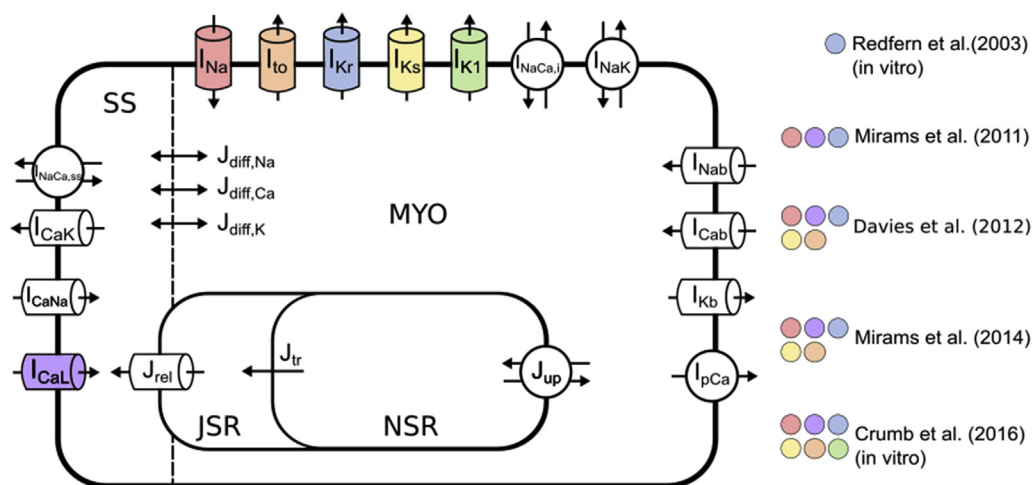
The hope and expectation is that *in silico* testing will play a central role in the regulatory aspect of TdP liability testing (and perhaps other types of testing) in the near

future. The integration of direct drug-molecular target interaction data is a potentially powerful method for modelling acute drug effects; however, it offers only limited potential when it comes to studying chronic cardiotoxicity. Although direct drug-molecular target interaction data can be used to investigate events that serve as triggers of toxicity, it cannot capture the long-term effects that persist after the drugs have been eliminated from the system (adaptive changes and genomic responses).

Chronic cardiotoxicity is often a progressive process that is commonly associated with drug induced damage and alterations in gene expression [40]. A typical example is antineoplastic anthracycline cardiotoxicity that can lead to congestive heart failure years or even decades after the termination of the treatment. Although it is known that anthracycline use can be associated with mitochondrial dysfunction, oxidative stress and alterations in gene expression [41], the precise mechanism(s) resulting in its cardiotoxicity are still not fully elucidated.

Although biophysical models have recently been elaborated to allow study of progressive mitochondrial dysfunction and chronic cardiotoxicity [42], advancements in large-scale quantitative proteomics [43] generate unprecedented additional opportunities for the application of such models in this field. Proteomics databases with consecutive measurements can be used to regulate and fine-tune the abundances of all proteins and enzymes represented in the models at different stages. This may allow the development of novel tools for the systematic identification of pathways and biomarkers for the characterization of progressive pathologically and drug induced heart conditions.

Figure 2



Schematic of cell models showing the development of increasing complex models from single channel ligand based approaches [44] through to integrated 3 [45], 5 [19], [46] and 6 [47] channel approaches for predicting Torsade de Point risk.

Summary

Biophysical cardiac models have provided a framework for furthering our understanding of cardiac physiology and pathology. These models offer the same opportunity for pharmacology to understand the integrative therapeutic and toxic effects of drugs on the heart.

Funding

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 602156 – HeCaToS. The authors acknowledge financial support from the Department of health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Igarashi Y, Nakatsu N, Yamashita T, Ono A, Ohno Y, Urushidani T, Yamada H: **Open TG-GATEs: a large-scale toxicogenomics database.** *Nucleic Acids Res* 2015, **43**: D921–D927. <http://dx.doi.org/10.1093/nar/gku955>.
 2. Ganter B, Snyder RD, Halbert DN, Lee MD: **Toxicogenomics in drug discovery and development: mechanistic analysis of compound/class-dependent effects using the DrugMatrix® database.** 2006.
 3. Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, Hersey A, Light Y, McGlinchey S, Michalovich D, Al-Lazikani B: **ChEMBL: a large-scale bioactivity database for drug discovery.** *Nucleic acids Res* 2012, **40**: D1100–D1107.
 4. Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK: **BindingDB: a web-accessible database of experimentally determined protein–ligand binding affinities.** *Nucleic Acids Res* 2007, **35**: D198–D201.
 5. Kanehisa M, Goto S: **KEGG: Kyoto encyclopedia of genes and genomes.** *Nucleic Acids Res* 2000, **28**: 27–30.
 6. Overbeek R, Larsen N, Pusch GD, D'Souza M, Selkov Jr Evgeni, Kyrpides N, Fonstein M, Maltsev N, Selkov E: **WIT: integrated system for high-throughput genome sequence analysis and metabolic reconstruction.** *Nucleic Acids Res* 2000, **28**: 123–125.
 7. Waters MD, Fostel JM: **Toxicogenomics and systems toxicology: aims and prospects.** *Nat Rev Genet* 2004, **5**: 936–948.
 8. Bai JPF, Abernethy DR: **Systems pharmacology to predict drug toxicity: integration across levels of biological organization.** *Annu Rev Pharmacol Toxicol* 2013, **53**: 451–473.
 9. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, Lerner J, Brunet J-P, Subramanian A, Ross KN, Reich M, Hieronymus H, Wei G, Armstrong SA, Haggarty SJ, Clemons PA, Wei R, Carr SA, Lander ES, Golub TR: **The connectivity map: using gene-expression signatures to connect small molecules, genes, and disease.** *Science* 2006, **313**: 1929–1935.
 10. Shirdel EA, Xie W, Mak TW, Jurisica I: **NAVIGaTing the micro-nome – using multiple MicroRNA prediction databases to identify signalling pathway-associated MicroRNAs.** *PLoS One* 2011, **6**: e17429.
 11. Hattori M, Okuno Y, Goto S, Kanehisa M: **Development of a chemical structure comparison method for integrated analysis of chemical and genomic information in the metabolic pathways.** *J Am Chem Soc* 2003, **125**: 11853–11865.
 12. Hunter PJ, Borg TK: **Integration from proteins to organs: the physiome project.** *Nat Rev Mol Cell Biol* 2003, **4**: 237–243.
 13. Berg EL: **Systems biology in drug discovery and development.** *Drug Discov Today* 2014, **19**: 113–125.
 14. Sorger PK, Allerheiligen SR, Abernethy DR, Altman RB, Brouwer KL, Califano A, D'Argenio DZ, Iyengar R, Jusko WJ, Lalonde R: **Quantitative and systems pharmacology in the post-genomic era: new approaches to discovering drugs and understanding therapeutic mechanisms.** In *An NIH white paper by the QSP workshop group*; 2011:48.
 15. Zhao P, Zhang L, Grillo JA, Liu Q, Bullock JM, Moon YJ, Song P, Brar SS, Madabushi R, Wu TC, Booth BP, Rahman NA, Reynolds KS, Gil Berglund E, Lesko LJ, Huang SM: **Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review.** *Clin Pharmacol Ther* 2011, **89**: 259–267.
 16. Tylutki Z, Polak S: **A four-compartment PBPK heart model accounting for cardiac metabolism - model development and application.** *Sci Rep* 2017, **7**: 39494.
 17. Niederer SA, Smith NP: **Using physiologically based models for clinical translation: predictive modelling, data interpretation or something in-between?** *J Physiol* 2016, **594**: 6849–6863.
 18. Gintant G, Sager PT, Stockbridge N: **Evolution of strategies to improve preclinical cardiac safety testing.** *Nat Rev Drug Discov* 2016, **15**: 457–471.
 19. Davies MR, Wang K, Mirams GR, Caruso A, Noble D, Walz A, Lavé T, Schuler F, Singer T, Polonchuk L: **Recent developments in using mechanistic cardiac modelling for drug safety evaluation.** *Drug Discov Today* 2016, **21**: 924–938.
 20. Trayanova NA: **Mathematical approaches to understanding and imaging atrial fibrillation.** *Significance Mech Manag* 2014, **114**: 1516–1531.
 21. Gintant GA: **Two components of delayed rectifier current in canine atrium and ventricle.** *Circulation Res* 1996, **78**: 26.
 22. Sanguinetti MC, Jurkiewicz NK: **Two components of cardiac delayed rectifier K⁺ current. Differential sensitivity to block by class III antiarrhythmic agents.** *J General Physiol* 1990, **96**: 195.
 23. Tamargo J, Caballero R, Gómez R, Valenzuela C, Delpón E: **Pharmacology of cardiac potassium channels.** *Cardiovasc Res* 2004, **62**: 9–33.
 24. Chang ETY, Strong M, Clayton RH: **Bayesian sensitivity analysis of a cardiac cell model using a gaussian process emulator.** *PLoS One* 2015, **10**: e0130252.
- This paper demonstrates the use of novel methods for perform statistical sensitivity analysis over the high dimensional parameter space of cardiac cell models.
25. Sobie EA: **Parameter sensitivity analysis in electrophysiological models using multivariable regression.** *Biophysical J* 2009, **96**: 1264–1274.
 26. Crozier A, Blazevic B, Lamata P, Plank G, Ginks M, Duckett S, Sohal M, Shetty A, Rinaldi CA, Razavi R, Smith NP, Niederer SA: **The relative role of patient physiology and device optimisation in cardiac resynchronisation therapy: a computational modelling study.** *J Mol Cell Cardiol* 2016, **96**: 93–100.
 27. Quarteroni A, Lassila T, Rossi S, Ruiz-Baier R: **Integrated Heart—coupling multiscale and multiphysics models for the simulation of the cardiac function.** *Comput Methods Appl Mech Eng* 2017, **314**: 345–407.
 28. Crozier A, Augustin CM, Neic A, Prassl AJ, Holler M, Fastl TE, Hennemuth A, Bredies K, Kuehne T, Bishop MJ, Niederer SA, Plank G: **Image-based personalization of cardiac anatomy for coupled electromechanical modeling.** *Ann Biomed Eng* 2016, **44**: 58–70.

29. Krishnamoorthi S, Perotti LE, Borgstrom NP, Ajijola OA, Frid A, Ponnaluri AV, Weiss JN, Qu Z, Klug WS, Ennis DB, Garfinkel A: **Simulation methods and validation criteria for modeling cardiac ventricular electrophysiology.** *PLoS One* 2014, **9**: e114494.
30. Colatsky T, Fermini B, Gintant G, Pierson JB, Sager P, Sekino Y, Strauss DG, Stockbridge N: **The comprehensive in vitro proarrhythmia assay (CiPA) initiative — update on progress.** *J Pharmacol Toxicol Methods* 2016, **81**:15–20.
- This paper highlights the current directions of the CiPa initiative which is informing the use of biophysical models in drug regulation.
31. Le Guennec J-Y, Thireau J, Ouillé A, Roussel J, Roy J, Richard S, Richard S, Martel E, Champéroux P: **Inter-individual variability and modeling of electrical activity: a possible new approach to explore cardiac safety?** *Sci Rep* 2016, **6**:37948.
- Demonstrates how computer simulations can simulate variability to better inform cardiotoxic risk.
32. Obejero-Paz CA, Bruening-Wright A, Kramer J, Hawryluk P, Tatalovic M, Dittrich HC, Brown AM: **Quantitative profiling of the effects of vanoxerine on human cardiac ion channels and its application to cardiac risk.** *Sci Rep* 2015, **5**:17623.
33. Yang P-C, El-Bizri N, Romero L, Giles WR, Rajamani S, Belardinelli L, Clancy CE: **A computational model predicts adjunctive pharmacotherapy for cardiac safety via selective inhibition of the late cardiac Na current.** *J Mol Cell Cardiol* 2016, **99**:151–161.
34. Kirthi Priya P and Reddy MR: **Study of factors affecting the progression and termination of drug induced Torsade de pointes in two dimensional cardiac tissue.** *J Electrocardiol*.
35. Varghese A, Spindler AJ, Paterson D, Noble D: **Rate-dependent activation failure in isolated cardiac cells and tissue due to Na⁺ channel block.** *Am J Physiol* 2015, **309**:H1753–H1763.
36. Richards DF, Glosli JN, Draeger EW, Mirin AA, Chan B, J-I Fattebert, Krauss WD, Oppelstrup T, Butler CJ, Gunnels JA, Gurev V, Kim C, Magerlein J, Reumann M, Wen H-F, Rice JJ: **Towards real-time simulation of cardiac electrophysiology in a human heart at high resolution.** *Comput Methods Biomechanics Biomed Eng* 2013, **16**:802–805.
37. Beattie KA, Luscombe C, Williams G, Munoz-Muriedas J, Gavaghan DJ, Cui Y, Mirams GR: **Evaluation of an in silico cardiac safety assay: using ion channel screening data to predict QT interval changes in the rabbit ventricular wedge.** *J Pharmacol Toxicol Methods* 2013, **68**:88–96.
38. Zemzemi N, Bernabeu MO, Saiz J, Cooper J, Pathmanathan P, Mirams GR, Pitt-Francis J, Rodriguez B: **Computational assessment of drug-induced effects on the electrocardiogram: from ion channel to body surface potentials.** *Br J Pharmacol* 2013, **168**:718–733.
39. Okada J-i, Yoshinaga T, Kurokawa J, Washio T, Furukawa T, Sawada K, Sugiura S, Hisada T: **Screening system for drug-induced arrhythmogenic risk combining a patch clamp and heart simulator.** *Sci Adv* 2015, **1**.
40. Lenčová-Popelová O, Jirkovský E, Mazurová Y, Lenčo J, Adamcová M, Šimůnek T, Geršl V, Štěrba M: **Molecular remodeling of left and right ventricular myocardium in chronic anthracycline cardiotoxicity and post-treatment follow up.** *PLoS One* 2014, **9**:e96055.
41. Carvalho FS, Burgeiro A, Garcia R, Moreno AJ, Carvalho RA, Oliveira PJ: **Doxorubicin-induced cardiotoxicity: from bioenergetic failure and cell death to cardiomyopathy.** *Med Res Rev* 2014, **34**:106–135.
42. de Oliveira BL, Niederer S: **A biophysical systems approach to identifying the pathways of acute and chronic doxorubicin mitochondrial cardiotoxicity.** *PLoS Comput Biol* 2016, **12**: e1005214.
- This paper provides the first use of computational models to study cardiac toxicity in the mitochondria.
43. Aebersold R, Mann M: **Mass-spectrometric exploration of proteome structure and function.** *Nature* 2016, **537**:347–355.
44. Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PKS, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG: **Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development.** *Cardiovasc Res* 2003, **58**:32–45.
45. Mirams GR, Cui Y, Sher A, Fink M, Cooper J, Heath BM, McMahon NC, Gavaghan DJ, Noble D: **Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk.** *Cardiovasc Res* 2011, **91**:53–61.
46. Mirams GR, Davies MR, Brough SJ, Bridgland-Taylor MH, Cui Y, Gavaghan DJ, Abi-Gerges N: **Prediction of thorough QT study results using action potential simulations based on ion channel screens.** *J Pharmacol Toxicol Methods* 2014.
47. Crumb Jr WJ, Vicente J, Johannesen L, Strauss DG: **An evaluation of 30 clinical drugs against the comprehensive in vitro proarrhythmia assay (CiPA) proposed ion channel panel.** *J Pharmacol Toxicol Methods* 2016, **81**:251–262.