Institution: University of Nottingham

Unit of Assessment: 10

Title of case study: Industrial use of mathematical models for drug safety testing

Period when the underpinning research was undertaken: 2005 – present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Helen Byrne	Professor of Mathematical Biology	1998 – 2011
John King	Professor of Theoretical Mechanics	1988 – present
Ingeborg van Leeuwen	Research Fellow	2004 – 2007
Gary Mirams	Principal Research Fellow Professor of Mathematical Physiology	2016 – July 2019 Aug 2019 – present
Maurice Hendrix	Research Software Engineer	2019 – present

Period when the claimed impact occurred: 2014 – present

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Cardiac electrophysiology simulation software developed by Nottingham researchers is used by two of the top 10 largest (by revenue) pharmaceutical companies, GlaxoSmithKline Plc (GSK) and F. Hoffman-LaRoche (Roche), for routine compound profiling and pro-arrhythmic side effect safety testing. The simulator is available via a public portal (https://cardiac.nottingham.ac.uk) where it has been used by over 140 other companies. The simulator applies mathematical models of the electrophysiology of cardiac muscle cells to predict side effects of pharmaceutical compounds and assign them a clinical pro-arrhythmic risk class.

The system allows the global pharmaceutical industry to focus development on compounds with a lower cardiac risk, reducing the likelihood of failing safety tests during later stages of drug discovery. The ability for the industry to select low risk compounds using these computer models has enhanced productivity, generated financial savings and decreased reliance on animal-based testing – at GSK reducing use of a rabbit heart experiment by over 90%.

2. Underpinning research

Professor Gary Mirams has been a core developer of 'Chaste': Cancer, Heart and Soft Tissue Environment, a C++ library for computational physiology throughout its development, since 2005 during his PhD study at Nottingham. At that time Chaste developers within the School of Mathematical Sciences included PhD students Mirams (supported by **[6]** and supervised by Professors Helen Byrne and John King) and Alex Walter together with Dr Ingeborg van Leeuwen and Professor Byrne who, with collaborators, authored the first Chaste research paper published in 2009 **[1]**.

Chaste is the open source electrophysiology solver underpinning all the subsequent cardiac electrophysiology simulations running in industrial settings; it is written to industrial software standards in terms of unit, memory and coverage testing. Chaste is still in active development and the latest 2019.1 version **[5, 9]** features improved CellML conversion by Dr Maurice Hendrix

(Research Software Engineer based at Nottingham) to provide a consistent unit conversion for calcium concentrations in all cardiac models.

Mirams continued Chaste development whilst in Oxford (2008-2016) and used it to show that information on how compounds block multiple ion channels could be used within mathematical cardiac electrophysiology models to predict the overall effect on a cardiac cell and hence clinical risk. These models use complex mechanistic (ordinary-differential-equation) formulations to model the voltage- and concentration-dependent opening and closing of many types of ion channels, pumps and exchangers within a cardiac cell, as well as the subsequent evolution of membrane voltage over time, along with ion concentrations in the cytoplasm and other compartments. Using outputs of these models to predict risk was shown to be more accurate than measuring the degree of drug block of a single potassium-channel encoded by the gene *hERG,* which was the standard approach at the time. Uptake of this simulation approach in industry has been widespread and led to the first versions of the Chaste-based drug effect prediction simulation engine (ApPredict **[2, 7]**) being deployed within GSK by 2014 and subsequently at Roche in 2017.

After returning to Nottingham in 2016, Mirams has developed ApPredict further to provide predictions for new species (including guinea pig myocytes in Aug 2017 alongside rabbit, dog and human models), new risk indicators (the FDA's risk marker based on change in net charge 'qNet' in May 2018), and to handle uncertainty characterisation and propagation. In total, Mirams has made over 230 "repository commits" (code changes) since his return to Nottingham in November 2016 **[2, 8, 9]**. There is a public interface to this simulation engine called ApPortal, with the latest version developed and hosted by Nottingham (https://cardiac.nottingham.ac.uk) which runs simulations and presents qNet predictions.

In a 2017 paper **[3, 8]**, Mirams worked with Bioprojet (Paris, France) to perform and interpret electrophysiology simulations as part of the assessment of their new drug *pitolisant*. The study took information from early screening experiments for particular ion channels, and predicted effects at the whole cell and whole organ levels in rabbit and human, before comparing them with experimental and clinical measurements.

In another 2017 paper **[4, 8]** Mirams worked with Roche to tailor mathematical action potential models to individual batches of stem-cell derived myocytes (which can exhibit high variation) with the aim of making batch-specific predictions. The outcome was a new method for tailoring models to particular cells which was shown to provide increased predictive power of drug activity (based on ion channel screening experiments) relative to an untailored model from the literature.

3. References to the research

NB: University of Nottingham personnel (at the time of publication) are shown in **bold** in the following publication list.

Underpinning references to Nottingham Research Outputs:

1. JM Pitt-Francis, P Pathmanathan, MO Bernabeu, R Bordas, J Cooper, A Fletcher, **GR Mirams**, P Murray, J Osborne, **A Walter**, SJ Chapman, A Garny, **IMM van Leeuwen**, PK Maini, B Rodriguez, JP Whiteley, **HM Byrne**, DJ Gavaghan (2009)
   Chaste: a test-driven approach to software development for biological modelling.
   Computer Physics Communications, 180(12), 2452-2471.
   https://doi.org/10.1016/j.cpc.2009.07.019
2. Software output: the ApPredict open source software (https://github.com/Chaste/ApPredict).
3. X Ligneau, RR Shah, I Berrebi-Bertrand, **GR Mirams**, P Robert, L Landais, P Maison-Blanche, J-F Faivre, J-M Lecomte & J-C Schwartz (2017). *Nonclinical Cardiovascular Safety of Pitolisant: Comparing ICH S7B and CiPA Initiative Studies*. British Journal of Pharmacology 174:4449-4463 https://doi.org/10.1111/bph.14047

4. CL Lei, K Wang, M Clerx, RH Johnstone, MP Hortigon-Vinagre, V Zamora, A Allan, GL Smith, DJ Gavaghan, **GR Mirams**, L Polonchuk (2017). *Tailoring mathematical models to stem-cell derived cardiomyocyte lines can improve predictions of drug-induced changes to their electrophysiology*. Frontiers in Physiology 8:986 https://doi.org/10.3389/fphys.2017.00986
5. FR Cooper, RE Baker, MO Bernabeu, R Bordas, L Bowler, A Bueno-Orovio, HM Byrne, V Carapella, L Cardone-Noott, J Cooper, S Dutta, BD Evans, AG Fletcher, JA Grogan, W Guo, DG Harvey, **M Hendrix**, D Kay, J Kursawe, PK Maini, B McMillan, **GR Mirams**, JM Osborne, P Pathmanathan, JM Pitt-Francis, M Robinson, B Rodriguez, RJ Spiteri, DJ Gavaghan (2020). *Chaste: Cancer, Heart and Soft Tissue Environment*. Journal of Open Source Software 5(47):1848. https://doi.org/10.21105/joss.01848

Grant details and funding awards:

6. EPSRC eScience Pilot Project in Integrative Biology. (GBP2,437,814; 2004-2008; GR/S72023/01, Co-Is Byrne, King)
7. NC3Rs (co-funded by EPSRC), Mathematics in Toxicology Strategic Award, Prediction of human cardiotoxic QT prolongation using in vitro multiple ion channel data and mathematical models of cardiac myocytes (GBP176,136; 2013-2014; NC/K001337/1, PI Mirams)
8. Wellcome Trust, Henry Dale Fellowship, Improving assessment of drug-induced cardiac risk with mathematical electrophysiology models (GBP534,961; 2014-2019; 101222/Z/13/Z, PI Mirams)
9. Wellcome Trust, Senior Research Fellowship in Basic Biomedical Science, Developing cardiac electrophysiology models for drug safety studies (GBP1,918,557, 2019-2024, 212203/Z/18/Z, PI Mirams)

4. Details of the impact

All new pharmaceutical compounds must be carefully screened for unwanted side effects on the heart which can cause fatal arrhythmias. Many drugs have been withdrawn from the market worldwide because of fatalities due to these arrhythmias at a cost of billions of dollars. Even drugs for ailments as mild as hay fever have been withdrawn due to fatalities and an unacceptable increase in arrhythmic risk (e.g. terfenadine), so there is now a huge industrial effort in avoiding this situation occurring for new drug compounds. The root cause has been identified as drug molecules binding to and blocking ion channels in the heart.

Ion channel block can now be screened in immortal cell lines in a dish (*in vitro* testing) at an early stage of drug development without using cardiac muscle tissue from animals. This is the standard screening approach for a number of ion channels in many large pharmaceutical companies. However, clinical risk is a complex function of the degree of block of many cardiac ion channels which is difficult to understand by looking at results of these screens independently.

Innovatively, the mathematical modelling approach developed by Mirams offers a way to integrate information from different ion channel *in vitro* screens, to predict the effect on whole cardiac muscle cells. The resulting simulations can provide a more accurate summary of the risk of a new potential drug compound earlier in drug development and hence more cheaply than the pre-existing approaches. In short, the computational modelling tool, ApPredict, uses the data produced by *in vitro* tests to identify lower-risk compounds to be progressed into translational *in vivo* studies on animals (with a concomitant reduction in the need for animal studies) and ultimately into clinical trials on humans.

Industrial Use of Electrophysiology Simulations

Impact on ApPortal users:
Mirams has been developing the Chaste-based cardiac simulation software known as 'ApPredict' **[1, 2, 6-9]** in partnership with a web developer to embed it in a web interface (ApPortal) since 2011. The ApPredict software takes information on the extent to which drugs

block particular ion channels, then provides a prediction for the integrated effect on the whole cardiac muscle cell.

Improvements by Mirams to ApPredict whilst at Nottingham (2016-onwards) led to the 2019.1 version of ApPortal being made available via a public website where anyone can register for an account and run cardiac safety simulations after manually entering data on the degree to which compounds block specific ion channels. The portal is very widely used and has performed a total of over 7000 simulations for over 350 users. Based on email domain usernames, there are users from 147 companies including Contract Research Organisations, small pharmaceutical companies and 14 of the top 20 largest global pharmaceutical companies (by 2019 revenue); and over 70 educational or research establishments **[A]**.

Impact on the SME Bioprojet-BIOTECH:
In 2017, Mirams worked with Bioprojet-BIOTECH to assess the pro-arrhythmic risk of their new compound 'pitolisant' **[3].** The drug is now marketed as 'Wakix' for treatment of narcolepsy, a condition estimated to affect 1 in 2500 people. Bioprojet states that Mirams' simulation tool led to enhanced confidence in their understanding of the compound action and hence in their assessment of its pro-arrhythmic risk potential **[D]**. They also acknowledge the contribution of the research **[3]** in obtaining FDA approval **[E]** for 'pitolisant' **[D]**.

Impact on GlaxoSmithKline and Roche:
Since Mirams' return to Nottingham in 2016, he has carried out development on the underlying simulation software, funded on a consultancy basis by GlaxoSmithKline **[B]** and Hoffman-LaRoche **[C]**. During the same period, the ApPortal has been extended to provide uncertainty quantification features (uncertainty in model predictions due to the variability associated with the input data), and these are now in use within the companies and public portal **[A, B, C]**. The portal has been deployed inside company firewalls at GSK and Roche where it accesses their safety screening databases directly to acquire input data for the simulations, with the user simply typing in an internal compound ID rather than individual screening results. This system is in regular use by Safety Pharmacology teams at both companies in routine safety testing and compound profiling **[B, C]**.

The Vice President, Non-Clinical Safety at GlaxoSmithKline reports:

> "*ApPredict v2019.1 developed at the University of Nottingham (based on Chaste v2019.1 discussed in Cooper et al.* **[5]***) is now in use at GSK to predict the effects of multiple ion channel block on various cell types: stem-cell derived myocytes, rabbit ventricular myocytes and adult human myocytes.*" **[B]**

Similarly, a Principal Scientist of Pharma Research and Early Development at Roche reports:

> "*The simulator is installed within Roche to predict the effects of multiple ion channel block on stem-cell derived myocytes, guinea pig myocytes and adult human myocytes. We are using the July 2020 version of ApPredict, based on Chaste v2019.1 (Cooper et al.* **[5]***).*" **[C]**

Both pharmaceutical companies use the portal to (i) screen their compounds and prioritise which to take forward (to advance compounds that are less likely to fail later safety tests), leading to enhanced productivity and cost-saving benefits; (ii) to assist in design of later safety tests (to select drug concentrations of most interest and relevance); and (iii) to compare predictions with later safety test results to check whether all findings are consistent and that the drug's action is well understood **[B, C]**. Finally, the worldwide population will be less likely to be given drugs that can cause arrhythmia, and there are significant animal reduction, refinement, replacement (3Rs) benefits **[B, C].**

For example, GSK reports benefits to their business:

> "*Having implemented ApPredict […] allowed GSK to enhance our internal cardiovascular safety strategy and to comply with the shifting landscape in pharmaceutical drug development.*" **[B]**

and also the 3Rs benefits to the approach:

"*Since its implementation in 2017 as part of the established early cardiovascular screening strategy, all small molecules […] progressing to clinical candidates have been evaluated by the ApPredict model, leading to a >90% reduction in animal use*" **[B]**.

Meanwhile, Roche reports:

"*[ApPredict] has been successfully applied in multiple (>10) projects across different therapeutic areas and developmental stages to optimize safety profile of clinical candidates. The main impact included the reduction in the number of animal studies with tens of animals per compound, optimization of the clinical study design by lowering the amount of ECG monitoring and potential waiving of the phase III thorough QT study*" **[C]**.

Provision of Training in Simulation Approaches to Pharma

To encourage knowledge exchange between mathematicians and the pharmaceutical industry Mirams has run workshops for non-mathematician safety pharmacologists to learn how to run cardiac electrophysiology simulations, for example as part of a Continuing Education course for the Safety Pharmacology Society for approximately 30 industrial safety pharmacologists **[F]**. Mirams was an Academic Mentor for Dr Ken Wang based in Roche, Basel, Switzerland on a Roche Postdoctoral Fellowship 2015-2017 (she now has a permanent post there), and has also jointly supervised PhD students (2013-present) with Roche **[C]**. Mirams has a blog featuring accessible articles on Safety Pharmacology topics (Mathematical Matters of the Heart, over 15,000 page views in 2017-2020 as accessed 13 January 2020); the majority of its readers are from the USA (where many large pharma companies are based), followed by UK, Germany, India, France, South Korea, Australia, Canada and the Netherlands **[G]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] ApPortal Usage Statistics, dated 01 December 2020
[B] Letter of support from the Vice President of Non-Clinical Safety, R&D at GlaxoSmithKline, dated 16 December 2020
[C] Letter of support from principal Scientist at Pharma Research and Early Development at Hoffman-LaRoche, dated 01 December 2020
[D] Letter of support from Assistant Research Director of Resp. Pharmacology Department at Bioprojet-BIOTECH, dated 14 September 2019
[E] FDA approval package for Pitolisant, dated 14 August 2019
[F] SPS Continuing Education Course Booklet, pages 39-54, dated 30 September 2018
[G] Blog "Mathematical Matters of the Heart" visitor statistics, dated 13 January 2021