J Physiol 590.11 (2012) pp 2613–2628

The Journal of Physiology

TOPICAL REVIEW

How the Hodgkin–Huxley equations inspired the Cardiac Physiome Project

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Abstract Early modelling of cardiac cells (1960–1980) was based on extensions of the Hodgkin–Huxley nerve axon equations with additional channels incorporated, but after 1980 it became clear that processes other than ion channel gating were also critical in generating electrical activity. This article reviews the development of models representing almost all cell types in the heart, many different species, and the software tools that have been created to facilitate the cardiac Physiome Project.

(Received 8 January 2012; accepted after revision 23 March 2012; first published online 2 April 2012)
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Introduction

The 1952 paper by Hodgkin & Huxley raised quantitative and computational analysis of physiological function to an entirely new level. Precise measurements of sodium and potassium ion channel kinetics were used to formulate differential equations that were then solved to yield accurate predictions of the voltage waveform of the nerve impulse and of its conduction velocity. The kinetic equations took the form of conformational change reactions responsible for opening and closing the channels, with the electrical potential determining the rate coefficients of these reactions. It was this combination of reaction theory with the physics of electric current flow in the nerve axon which was the key to success. Those conformational reactions (m, h and n in the Hodgkin–Huxley (HH) equations) could eventually become identified with molecular configurations of the channel proteins, and so open the way to molecular biological interpretations of the processes involved. This approach differed fundamentally from the purely 'physical' approach adopted, for example, by Cole (Cole & Curtis, 1939; Cole, 1968). Cole had realised that representing the nerve membrane by a capacitor, resistors and batteries was not sufficient. There was inductive

Denis Noble (left) is Emeritus Professor of Cardiovascular Physiology in the Department of Physiology, Anatomy and Genetics at Oxford University. Fifty years ago, he published the first mathematical model of the electrical activity of the heart based on experimental measurements of ion channels. This has since been developed into the virtual heart project within the Human Physiome Project of the International Union of Physiological Sciences (IUPS). **Penelope Noble** (middle) is a research assistant in the same department. During her 15 years working on various projects in the Oxford Cardiac Electrophysiology Group, she has maintained the OXSOFT HEART software, first written by Denis Noble for simulations using cardiac cell models, and then translated for many of the currently available cell models into other computer languages so that they could be run in more recent simulation packages; including COR, CHASTE and OpenCOR. She has been involved in the effort to make all these models publicly available in CellML and in several research studies using the models. Penelope also works as a psychotherapist. **Alan Garny** (right) is a senior research scientist in the same department. Alan studied software engineering before undertaking a DPhil in the group of Denis Noble. Alan has expertise in both cardiac electrophysiological modelling, from single cell to tissue level, as well as in the development of cardiac modelling tools (he is the author of COR, the first public CellML-based environment). He is currently the project manager and lead developer of OpenCOR (a replacement for COR and OpenCell, another CellML tool), as well as still being involved in cardiac electrophysiological modelling.

DOI: 10.1113/jphysiol.2011.224238

behaviour as well to account for. In his analysis, an inductor was added to complete the picture (Cole & Curtis, 1939), but this approach could not connect in the same way to the molecular biology of ion channels. We have also to remember that it was by no means certain at that time that such channels existed. Attempts to attribute the electrical properties of a nerve membrane to natural processes in the lipid structure were still being made. Cole later generously acknowledged the ground-breaking nature of the Hodgkin–Huxley papers: "It is hard to believe that this collection will not remain an obvious turning point in electrophysiology and membrane biophysics" (Cole, 1968, p. 274).

Hodgkin and Huxley's deep insights, fusing conformational reaction kinetics and electrical processes, were therefore critical to their success. They were also fortunate in the choice of preparation. The squid giant nerve axon was not only large enough to permit the insertion of the relatively large voltage clamp electrodes; it was also one of the simplest excitable cells, with just two identifiable ion channels. Other excitable cells, such as the heart, have proved far more complex. One of us (D.N.) received a letter from Cole with a gift of his book (Cole, 1968) in which he confessed "Nerve has been so tedious. How can the heart be much more difficult?"

Initially, it was thought that the heart could be analysed with relatively modest extensions of the Hodgkin–Huxley equations. Noble added the inward potassium rectifier, I_{K1} (Hutter & Noble, 1960; Noble, 1965), and greatly slowed the kinetics of the delayed rectifier, I_K, both of which were identified in the experimental work on which the 1962 model was based (Hall *et al.* 1963*a*; Hall & Noble, 1963*b*; Noble, 1965). This was sufficient to generate voltage waveforms very similar to those recorded experimentally in the conducting tissue of the ventricle (the Purkinje fibres) and to reconstruct important experiments on the conductance changes and dependence on ion concentrations (Noble, 1962, 1966). But it was not long before the extension of the voltage clamp technique to the heart (Deck & Trautwein, 1964) revealed a much richer array of ion channels, including multiple delayed rectification channels (Noble & Tsien, 1968, 1969*a*,*b*), calcium channels (Reuter, 1967) and the involvement of the sodium–potassium (Gadsby, 1980) and sodium–calcium (Reuter & Seitz, 1968) exchangers.

The early canonical models

Other recent review articles (Noble, 2007, 2011) have analysed the detailed interaction between experiment and theory that led to the early canonical models. Here, we will focus on the modelling implications as an introduction to the central part of this article, which will be to review the current state of cardiac cell modelling and the tools that have been developed. These early models include the McAllister–Noble–Tsien (MNT) (McAllister *et al.* 1975), Beeler–Reuter (BR) (Beeler & Reuter, 1977), Noble–Noble (NN) (Noble & Noble, 1984), Noma–Irisawa (NI), DiFrancesco–Noble (DN) (DiFrancesco & Noble, 1985), Hilgemann–Noble (HN) (Hilgemann & Noble, 1987) and Earm–Noble (EM) (Earm & Noble, 1990) models.

The MNT model added the multiple slow potassium ion channels and the calcium ion channels. These were significant extensions in themselves, but the importance of the MNT model is that it was the first to use detailed experimental measurements for deriving the voltage dependence of the rate equations in the HH formulation. This model set the quantitative standard, and as a consequence it had considerable success in explaining experimental results, such as the counter-intuitive effects of small current perturbations on cardiac rhythm (McAllister *et al.* 1975, see Fig. 14; Weidmann, 1951). It was also the basis for the extension to the ventricular muscle cells developed in the BR model, which was the first model of cells from the ventricular muscle mass rather than from the Purkinje conducting tissue.

The DN model incorporated the hyperpolarizing-activated mixed cation (Na^+–K^+) channel I_f (DiFrancesco, 1981) to replace the role of I_{K2} in the MNT model. This also was a significant extension in terms of types of ion channels and it opened the way to more accurate models of pacemaker activity. There was, however, an additional aspect which was ground-breaking. This was the incorporation for the first time of changes in intracellular and extracellular ionic concentrations and of the intracellular calcium signalling system. This was the most significant departure from the HH formulation. Cardiac models continued to be inspired by the Hodgkin–Huxley work, but they also started to include many processes that were not in the HH nerve equations.

It was the modelling of calcium movements that led to the HN and EM models. These were based on Hilgemann's (1986*a*,*b*) demonstration that calcium efflux begins *during* the repolarization process rather than when this process is complete. This work matched the prediction of the DN model that there should be a contribution of sodium–calcium exchange current to the action potential itself. The EM model extended this approach and was the first model to be based on work on single cardiac cells rather than multicellular cardiac tissue.

A review of current heart cell models

There are now so many cardiac cell models that it is impossible to adequately review each one separately. We have chosen rather to categorize the models using some fairly subjective criteria that will also convey the extent to

which this field of research has matured. We have reached the stage at which many of the more recent developments are better characterised as extensions or refinements of previous models. It is becoming more difficult for such developments to be truly ground-breaking in the sense in which the earlier canonical models were. That does not mean that further ground-breaking models are not required. On the contrary, the challenge has become greater, and we will discuss that challenge later in this article. There is rather a focus on 'fixing' problems with previous models as experimentalists obtain new and better data and computational modellers discover applications for which the models are not well-suited. Extensions and refinements (fixing) are important. It matters, for example, in simulating whole-organ re-entry arrhythmias to have accurate descriptions of the recovery processes after each excitation, while pharmaceutical researchers will require good simulations of repolarization and the T wave of the ECG. Different applications will lay stress on the accuracy of different aspects of the cell models. That is one of the reasons why there are now so many models. Each has its own strengths and weaknesses.

Our categorisations must therefore be seen in this light.

In the ground-breaking category (Table 1), we have placed those models that established the field, introduced important new mechanisms or involved major reformulations. For the reasons already explained, the earliest models (prior to 1990) are naturally in this category since they broke the ground at an early stage, but the list also includes a considerable number of more recent models. In the part-ground-breaking category, we have listed models that have established new aspects of the modelling, and this list includes many of the recent formulations.

The next category is 'ground-breaking extensions' (Table 2), which includes models that significantly extended existing models and were in part ground-breaking themselves. This includes some widely used models. For example, the Luo & Rudy, 1994 model has been widely used because the authors made important advances in the modelling itself, in addition to making the code readily available. All the models we have placed in this category have incorporated significant advances.

The third category is 'fixers' (Table 3), i.e. models whose primary purpose was to fix problems encountered in previous models. This is important. As models become more complex and include many new components and observations, it becomes increasingly difficult to ensure that all the previous advantages of a model are retained intact. In a highly interactive system like the cardiac electrophysiological system, altering one component inevitably affects many others involved in those interactions.

The fourth category, 'extensions' (Table 4), includes models whose primary purpose was to extend previous models in the light of new experimental results or of new demands by those using the models for particular applications.

The fifth category, 'rearrangements' (Table 5), refers to models that re-categorised the elements of the model or used new nomenclature. This also is an important activity since ontology and nomenclature raise large problems. This is well-illustrated by cardiac electrophysiology since ion channels were originally given names by those focused on the function in terms of ion current carried and their roles in the electrical changes. As the proteins responsible became identified, and as the genes responsible were found, nomenclature naturally shifted towards this molecular biological viewpoint.

Our final category, 'problems' (Table 6), is naturally highly subjective. In this category, we have included models which have various problems that we think require high-lighting for those considering using them. For example, those models which are unable to simulate delayed after depolarizations (Fink *et al.* 2011). In a strong sense, all models have problems. All models are partial representations of reality and, when used in contexts for which they were not intended or which the authors could not have anticipated, the deficiencies became readily apparent.

Some of the models fit into more than one category and have been included in all applicable. The fifth and final category includes examples only and is not an exhaustive list. Note that the number of citations for each model is determined from Scopus and since 1996. The number of ordinary differential equations (ODEs) for each model is also included where known/available. In addition, it is important to note that we are only including whole cardiac cell models in this review.

Researchers in this field face such a bewildering array of models (over 100 in our tables) that a classification of this kind is required. We are aware, however, that others may classify the models differently, and that the utility of a model, which is after all just a mathematical representation of a particular process, depends strongly on the use to which it is put. All the models we have listed have their advantages as well as their limitations.

A review of tools in cardiac cell modelling: CellML and OpenCOR

Software tools have, in their own way, also witnessed great advances over the past 60 years. Hodgkin & Huxley (1952) had to compute their model 'by hand', a process which took Andrew Huxley 8 h to compute only 8 ms worth of electrical activity.

Less than 10 years later, one of us (D.N.) decided to rely on University College London's Ferranti Mercury

Table 1. Ground-breaking

No.	Model	Type	Species	ODEs	Citations	Comments
1	Noble, 1962	Purkinje	Mammalian	4	175	First cardiac cell model.
2	Krause *et al.* 1966	Ventricle	Mammalian			First ventricular cardiac cell model.
3	McAllister *et al.* 1975	Purkinje	Mammalian	10	88	Introduction of repolarising potassium currents (I_{x1} and I_{x2}) and second-inward calcium current (I_{si}). First use of experimental data to derive rate equations.
4	Hunter *et al.* 1975	Purkinje	Mammalian	1	38	Polynomial model with a single variable.
5	Beeler & Reuter, 1977	Ventricle	Mammalian	8	411	First well-used mammalian ventricular model.
6	Yanagihara *et al.* 1980	SAN	Mammalian	7	64	First sino-atrial node (SAN) model.
7	DiFrancesco & Noble, 1985	Purkinje	Mammalian	16	298	Introduction of the sodium–calcium exchanger, ionic concentrations, etc.
8	Hilgemann & Noble, 1987	Atrium	Rabbit	15	90	First atrial model and revolutionized calcium dynamics.
9	Rasmusson *et al.* 1990*a*	Atrium	Frog	16	29	First, and only, frog atrial model.
10	Rasmusson *et al.* 1990*b*	SAN	Frog	14	25	First, and only, frog SAN model.
11	Luo & Rudy, 1991	Ventricle	Guinea pig	8	619	First guinea-pig ventricular model (with Noble *et al.* 1991).
12	Noble *et al.* 1991	Ventricle	Guinea pig	17	85	First guinea-pig ventricular model (with Luo & Rudy, 1991).
13	Winslow *et al.* 1993				51	First network models.
14	Endresen, 1997	SAN	Mammalian	3	12	Simplification.
15	Fenton & Karma, 1998	Ventricle	Mammalian	3		Simplification with just three membrane currents.
16	Jafri *et al.* 1998	Ventricle	Guinea pig	31	179	Introduction of mechanistic calcium dynamics into the Luo & Rudy models.
17	Noble *et al.* 1998	Ventricle	Guinea pig	22	205	Introduction of the dyadic space for calcium (Cads), repolarising potassium currents ($I_{Kr/s}$), persistent sodium current (I_{pNa}), stretch and drug effects.
18	Priebe & Beuckelmann, 1998	Ventricle	Human	22	190	First human ventricular model. Introduced formulations for the normal and failing hearts.
19	Winslow *et al.* 1999	Ventricle	Canine	33	230	First canine ventricular model.
20	Ramirez *et al.* 2000	Atrium	Canine	25	88	First canine atrial model.
21	Bondarenko *et al.* 2004	Ventricle	Mouse	41	75	First mouse ventricular model.
22	Iyer *et al.* 2004	Ventricle	Human	67	76	Joint first human ventricular model (see ten Tusscher *et al.* 2004) but with Markov formulations for the fast sodium current (I_{Na}), transient outward current (I_{to}), rapid delayed rectifier current (I_{Kr}) and L-type calcium current (I_{CaL}).
23	ten Tusscher *et al.* 2004	Ventricle	Human	17	289	Joint first human ventricular model from human data.
24	Cortassa *et al.* 2006	Ventricle	Mammalian	50	45	Introduction of electrophysiology, contraction and mitochondrial bioenergetics together.
25	Aslanidi *et al.* 2009*b*	Purkinje	Canine	30	17	First canine Purkinje model from canine Purkinje data.
26	Inada *et al.* 2009	AVN	Mammalian	29	1	First, and only, atrio-ventricular node (AVN) model.
27	Li *et al.* 2010	Ventricle	Mouse	36	3	Complete refit of mouse model from mouse data.

Table 1. Continued

No.	Model	Type	Species	ODEs	Citations	Comments
28	Sampson *et al.* 2010	Purkinje	Human	82	7	Human Purkinje model from more detailed human data.
29	Corrias *et al.* 2011	Purkinje	Rabbit			Refit of most ionic currents from rabbit Purkinje data.
30	Li & Rudy, 2011	Purkinje	Canine			Complete refit of canine Purkinje model from canine Purkinje data.
31	O'Hara & Rudy, 2011	Ventricle	Human	41		Substantially increased human-specific model accuracy from human data.

Table 2. Ground-breaking extensions

No.	Model	Type	Species	ODEs	Citations	Comments
1	Wilders *et al.* 1991	SAN	Mammalian		83	Introduction/refinement of the T-type calcium current (I_{CaT}) into/for SAN.
2	Luo & Rudy, 1994	Ventricle	Guinea pig	19	818	Introduction of after-depolarizations through calcium dynamics.
3	Dokos *et al.* 1996	SAN	Rabbit	18	63	New formulation for the sodium–calcium exchanger (NCX) and the background sodium current (I_{bNa}).
4	Lindblad *et al.* 1996	Atrium	Rabbit	28	84	First rabbit atrial model.
5	Courtemanche *et al.* 1998	Atrium	Human	21	286	First human atrial model (with Nygren *et al.* 1998).
6	Nygren *et al.* 1998	Atrium	Human	29	189	First human atrial model (with Courtemanche *et al.* 1998).
7	Rice *et al.* 1999	Ventricle	Guinea pig		67	Inclusion of a contraction component.
8	Clancy & Rudy, 1999	Ventricle	Guinea pig		195	Inclusion of genetic mutations.
9	Dumaine *et al.* 1999	Ventricle	Guinea pig		265	Study of mutations in I_{Na} SCN5A and Brugada syndrome.
10	Greenstein *et al.* 2000	Ventricle	Canine	51	118	Markov formulation for the calcium-sensitive transient outward current (I_{toCa}), Kv4.3 and 1.4 channels.
11	Zhang *et al.* 2000	SAN	Rabbit	15	164	Regional differences in the rabbit SAN.
12	Clancy & Rudy, 2001	Ventricle	Guinea pig		76	Inclusion of genetic mutations.
13	Mazhari *et al.* 2001	Ventricle	Canine		55	Markov formulation for HERG model and LQT mutations.
14	Clancy & Rudy, 2002	Ventricle	Guinea pig		130	Inclusion of genetic mutations.
15	Fox *et al.* 2002	Ventricle	Canine	13	149	Showing of calcium alternans.
16	Kurata *et al.* 2002	SAN	Rabbit	27	72	Introduction of sustained inward current (I_{st}).
17	Matsuoka *et al.* 2003	Ventricle	Mammalian	37	81	Combined with Negroni & Lascano, 1996 contraction model.
18	Sarai *et al.* 2003	SAN	Mammalian	41	35	Combined with Negroni & Lascano, 1996, contraction model.
19	Saucerman *et al.* 2003	Ventricle	Rat		84	First β-adrenergic signalling formulation.
20	Hund & Rudy, 2004	Ventricle	Canine	29	104	Canine version of Luo & Rudy, 1994 from canine data, and inclusion of Cads and calcium/calmodulin-dependent protein kinase (CAMK).
21	Lovell *et al.* 2004	SAN	Rabbit	36	14	Regional differences in the rabbit SAN and Markov formulation.
22	Shannon *et al.* 2004	Ventricle	Rabbit	46	142	New calcium dynamics formulation.

Table 2. Continued

No.	Model	Type	Species	ODEs	Citations	Comments
23	Michailova *et al.* 2005	Ventricle	Canine	34	12	Formulation for metabolism, i.e. Ca/Mg buffering, ATP, ADP, MgATP regulationn of the sodium potassium pump (NaK) and calcium pump (CaP).
24	Iribe *et al.* 2006	Ventricle	Guinea pig	23	12	Interval–force relations.
25	Mangoni *et al.* 2006	SAN	Mouse	22	24	First mouse SAN model.
26	Pasek *et al.* 2006	Ventricle	Rat	41	12	Inclusion of T-tubules.
27	Livshitz & Rudy, 2007	Ventricle	Canine	18	31	New mechanistic sarcoplasmic reticular calcium-release current (I_{rel}).
28	Niederer & Smith, 2007	Ventricle	Rat		24	Stretch in rat ventricular cells (from the Pandit *et al.* 2001 model) including sodium–hydrogen exchanger (NHE), chloride–bicarbonate exchanger (AE) and stretch-activated channels (SAC).
29	Bueno-Orovio *et al.* 2008	Ventricle	Human	4	26	Simplified human model. Fast inward current (I_{fi}), slow inward current (I_{si}) and slow outward current (I_{so}). No calcium dynamics.
30	Mahajan *et al.* 2008	Ventricle	Rabbit	26	64	Markov formulation for I_{CaL}, and calcium cycling model for the study of APD and calcium alternans at rapid heart rates.
31	Stewart *et al.* 2009	Purkinje	Human	20	10	First human Purkinje model.
32	Aslanidi *et al.* 2009*a*	Atrium	Rabbit	29	7	Regional differences in rabbit atrial model.

Table 3. Fixers

No.	Model	Type	Species	ODEs	Citations	Comments
1	Jafri *et al.* 1998	Ventricle	Guinea pig	31	179	Of Luo & Rudy, 1994.
2	Noble & Noble, 2001	Ventricle	Guinea pig	20		Of Noble *et al.* 1998.
3	Garny *et al.* 2003*a*	SAN	Rabbit	15	30	Of Zhang *et al.* 2000.

computer (Fig. 1) for his cardiac modelling work (Noble, 1960, 1962). This type of computer was first delivered in August 1957. At the time, Tom Kilburn (Manchester University) was reported saying that "programming for the machine is very simple, using the Autocode technique. The Mercury Autocode system can be learned by a programmer in a few days and has made it possible for anyone to write his own programs." By today's standards, describing the programming as 'simple' is far from correct.

As might be expected, there was fierce competition (between numerical analysts, crystallographers and particle physicists) to gain access to the computer since it was the only machine in the whole of London University. So, as a 'simple' biologist, D.N. was initially refused access to the machine: 'you don't know enough mathematics and you don't even know how to program!' (Noble *et al.* 2012).

His only other option was to use a Brunsviga Model 20 mechanical calculator (*ca.* 1910; Fig. 2) which he did to compute the upstroke phase of his model, i.e. ∼2 ms worth of cardiac electrical activity (Noble, 1962, Fig. 7). However, with a full action potential being ∼500 ms long, it became clear that using the Brunsviga was not going to be a long-term solution. Some mathematics and programming had to be learned, and it paid off since upon reapplication, D.N. was granted time on the Mercury computer (. . . between 2 am and 4 am).

To put the performance into perspective, the Ferranti Mercury computer operated at 10 kiloFLOPS (i.e. 10,000 floating point operations per second) while the current fastest supercomputer (the Fujitsu K computer) has a peak performance of 10.51 petaFLOPS (i.e. ∼1 trillion, or $\sim 10^{12}$, times faster). Even the iPhone 4S, Apple's most recent iPhone, has a peak performance of ∼141 megaFLOPS (i.e. ∼14,100 times faster).

In terms of computation time, it used to take ∼2 h on the Mercury computer to compute 1 s worth of cardiac electrical activity using the Noble 1962 model (Noble, 1962). Nowadays, it takes less than 1 ms to compute the same model using COR (Garny *et al.* 2003*b*, 2009) (http://cor.physiol.ox.ac.uk/), i.e. ∼10 million, or 10^7,

Table 4. Extensions

No.	Model	Type	Species	ODEs	Citations	Comments
1	McAllister *et al.* 1975	Purkinje	Mammalian	10	88	From Noble, 1962.
2	Bristow & Clark, 1982	Purkinje	Mammalian		15	From McAllister *et al.* 1975.
3	Irisawa & Noma, 1982	SAN	Mammalian			From Yanagihara *et al.* 1980.
4	Noble & Noble, 1984	SAN	Mammalian	15	65	From DiFrancesco & Noble, 1985.
5	DiFrancesco & Noble, 1985	Purkinje	Mammalian	16	298	From McAllister *et al.* 1975.
6	Reiner & Antzelevitch, 1985	SAN	Mammalian		9	From Bristow & Clark, 1982.
7	Hilgemann & Noble, 1987	Atrium	Rabbit	15	90	From DiFrancesco & Noble, 1985.
8	Noble *et al.* 1989	SAN	Mammalian	14		From Noble & Noble, 1984.
9	Earm & Noble, 1990	Atrium	Rabbit	16	57	From Hilgemann & Noble, 1987.
10	Noble *et al.* 1991	Ventricle	Guinea pig	17	85	From Hilgemann & Noble, 1987.
11	Karma, 1993	Ventricle	Mammalian	2	150	From FitzHugh & Nagumo, 1961 nerve model.
12	Nordin, 1993	Ventricle	Guinea pig	14	42	From DiFrancesco & Noble, 1985 with 3 regions bulk calcium.
13	Demir *et al.* 1994	SAN	Rabbit	27	108	From Rasmusson *et al.* 1990*b*.
14	Luo & Rudy, 1994	Ventricle	Guinea pig	19	818	From Luo & Rudy, 1991.
15	Zeng *et al.* 1995	Ventricle	Guinea pig		263	From Luo & Rudy, 1994 with I_K components.
16	Lindblad *et al.* 1996	Atrium	Rabbit	28	84	From Demir *et al.* 1994.
17	Courtemanche *et al.* 1998	Atrium	Human	21	286	From Luo & Rudy, 1994.
18	Espinosa, 1998	Ventricle	Rat	21		From Noble *et al.* 1998.
19	Jafri *et al.* 1998	Ventricle	Guinea pig	31	179	From Luo & Rudy, 1994 and calcium dynamics from Rice *et al.* 1999.
20	Noble *et al.* 1998	Ventricle	Guinea pig	22	205	From Noble *et al.* 1991.
21	Nygren *et al.* 1998	Atrium	Human	29	189	From Lindblad *et al.* 1996.
22	Priebe & Beuckelmann, 1998	Ventricle	Human	22	190	From Luo & Rudy, 1994.
23	Riemer *et al.* 1998	Ventricle	Guinea pig		50	From Luo & Rudy, 1994 with stretch.
24	Clancy & Rudy, 1999	Ventricle	Guinea pig		195	From Luo & Rudy, 1994.
25	Demir *et al.* 1999	SAN	Rabbit	29	47	From Demir *et al.* 1994.
26	Dumaine *et al.* 1999	Ventricle	Guinea pig		265	From Luo & Rudy, 1994 with I_{to}.
27	Rice *et al.* 1999	Ventricle	Guinea pig		67	From Jafri *et al.* 1998.
28	Viswanathan *et al.* 1999	Ventricle	Guinea pig	25	101	From Luo & Rudy, 1994 with regional differences in I_{Kr}.
29	Winslow *et al.* 1999	Ventricle	Canine	33	230	From Jafri *et al.* 1998.
30	Faber & Rudy, 2000	Ventricle	Guinea pig	25	217	From Luo & Rudy, 1994.
31	Greenstein *et al.* 2000	Ventricle	Canine	51	118	From Winslow *et al.* 1999.
32	Sakmann *et al.* 2000	Ventricle	Guinea pig	21	67	From Noble *et al.* 1998.
33	Clancy & Rudy, 2001	Ventricle	Guinea pig		76	From Luo & Rudy, 1994.
34	Mazhari *et al.* 2001	Ventricle	Canine	*x*	55	From Winslow *et al.* 1999.
35	Pandit *et al.* 2001	Ventricle	Rat	26	122	From Demir *et al.* 1994.
36	Puglisi & Bers 2001	Ventricle	Guinea pig		96	From Luo & Rudy, 1994 with I_{to} and calcium-induced calcium current.
37	Bernus *et al.* 2002	Ventricle	Human		63	From FitzHugh & Nagumo, 1961 and Priebe & Beuckelmann, 1998.
38	Clancy & Rudy, 2002	Ventricle	Guinea pig		130	From Luo & Rudy, 1994.

Table 4. Continued

No.	Model	Type	Species	ODEs	Citations	Comments
39	Fenton *et al.* 2002	Ventricle	Mammalian		188	From Fenton & Karma, 1998.
40	Fox *et al.* 2002	Ventricle	Canine	13	149	From Jafri *et al.* 1998 and Winslow *et al.* 1999.
41	Greenstein & Winslow, 2002	Ventricle	Canine		91	From Greenstein *et al.* 2000.
42	Kneller *et al.* 2002	Atrium	Canine		28	From Ramirez *et al.* 2000.
43	Cabo & Boyden, 2003	Ventricle	Canine	16	45	From Luo & Rudy, 1994 with normal and infarcted hearts.
44	Mitchell & Schaeffer, 2003	Ventricle	Mammalian	2	34	From Karma, 1993.
45	Pandit *et al.*2003	Ventricle	Rat	26	32	From Pandit, 2001, with diabetes.
46	Seemann *et al.* 2003	Ventricle	Human		6	From Priebe & Beuckelmann, 1998 and contraction from Sachse, 2003.
47	Hund & Rudy, 2004	Ventricle	Canine	29	104	From Luo & Rudy, 1994.
48	Shannon *et al.* 2004	Ventricle	Rabbit	46	142	From Puglisi & Bers, 2001.
49	Coutu & Metzger, 2005	Ventricle	Rat		12	From Winslow *et al.* 1999, Rice *et al.* 1999 and Negroni-Lascano, 1996.
50	Michailova *et al.* 2005	Ventricle	Canine	34	12	From Winslow *et al.* 1999.
51	Fink *et al.* 2006	Ventricle	Human		21	From ten Tusscher *et al.* 2004.
52	Flaim *et al.* 2006	Ventricle	Canine		18	From Greenstein *et al.* 2000 with late sodium current (I_{NaL}).
53	Greenstein *et al.* 2006	Ventricle	Canine		50	From Greenstein *et al.* 2000 with calcium-induced calcium release from Hinch *et al.* 2004.
54	Iribe *et al.* 2006	Ventricle	Guinea pig	23	12	From Noble *et al.* 1991 and Noble *et al.* 1998.
55	Mangoni *et al.* 2006	SAN	Mouse	22	24	From Zhang *et al.* 2000.
56	Pasek *et al.* 2006	Ventricle	Rat	41	12	From Pandit *et al.* 2001.
57	Sato *et al.* 2006	Ventricle	Canine		38	From Mahajan *et al.* 2008 and Fox *et al.* 2002.
58	Simitev & Biktashev, 2006	Atrium	Human	3	9	From Courtemanche *et al.* 1998.
59	ten Tusscher & Panfilov, 2006*a*	Ventricle	Human	19	104	From ten Tusscher *et al.* 2004.
60	ten Tusscher & Panfilov, 2006*b*	Ventricle	Human		37	From ten Tusscher & Panfilov, 2006*a*: a reduced version of the model along the principles of FitzHugh & Nagumo, 1961.
61	Cherry *et al.* 2007	Left atrium Pulmonary vein	Canine	4	12	From Fenton & Karma, 1998.
62	Livshitz & Rudy, 2007	Ventricle	Canine	18	31	From Luo & Rudy, 1994.
63	Benson *et al.* 2008	Ventricle	Canine		21	From Hund & Rudy, 2004 with regional differences.
64	Fink *et al.* 2008	Ventricle	Human	27	20	From ten Tusscher *et al.* 2006*a*.
65	Mahajan *et al.* 2008	Ventricle	Rabbit	26	64	From Puglisi & Bers, 2001.
66	Pasek *et al.* 2008	Ventricle	Guinea pig	55	11	From Pasek *et al.* 2006.
67	Saucerman & Bers, 2008	Ventricle	Rat		28	From Shannon *et al.* 2004 and CAMK from Saucerman *et al.* 2003.
68	Stewart *et al.* 2009	Purkinje	Human	20	10	From DiFrancesco & Noble, 1985 and ten Tusscher *et al.* 2004/2006, and data for human Purkinje potassium currents from Han, 2002.
69	Wang & Sobie, 2008	Ventricle	Rat	35	17	From Bondarenko *et al.* 2004.

Table 4. Continued

No.	Model	Type	Species	ODEs	Citations	Comments
70	Aslanidi *et al.* 2009*b*	Purkinje	Canine	30	17	From Benson *et al.* 2008.
71	Aslanidi *et al.* 2009*a*	Atrium	Rabbit	29	7	From Lindblad *et al.* 1996.
72	Decker *et al.* 2009	Ventricle	Canine		22	From Hund & Rudy, 2004.
73	Koivumäki *et al.* 2009	Ventricle	Mouse		5	From Bondarenko *et al.* 2004, contraction from Cortassa *et al.* 2006 and CAMK from Bhalla & Iyengar, 1999.
74	Maleckar *et al.* 2009	Atrium	Human	30	9	From Nygren *et al.* 1998.
75	Grandi *et al.* 2010	Ventricle	Human	39	16	From Shannon *et al.* 2004.
76	Li *et al.* 2010	Ventricle	Mouse	36	3	From Bondarenko *et al.* 2004.
77	Aslanidi *et al.* 2011	Atrium	Human			From Shannon *et al.* 2004 for different cell types.
78	Carro *et al.* 2011	Ventricle	Human			From Grandi *et al.* 2010 to study arrhythmias.
79	Grandi *et al.* 2011	Atrium	Human			From Grandi *et al.* 2010.
80	Heijman *et al.* 2011	Ventricle	Canine			From Luo & Rudy, 1994 with new β-adrenergic signalling.

Table 5. Rearrangements (examples only)

No.	Model	Type	Species	ODEs	Citations	Comments
1	McAllister *et al.* 1975	Purkinje	Mammalian	10	88	I_{Kr} and I_{Ks}, recorded by Sanguinetti & Jurkiewicz, 1990, and used in the Noble *et al.* 1998 model, are the same currents as Ix1 and Ix2 in the McAllister *et al.* 1975 model.
	Noble *et al.* 1998	Ventricle	Guinea pig	22	205	
2	Dokos *et al.* 1996	SAN	Rabbit	18	63	Part of a trend in SAN models.
	Kurata *et al.* 2002	SAN	Rabbit	27	72	
	Lovell *et al.* 2004 and a few others	SAN	Rabbit	36	14	
3	Luo & Rudy, 1994	Ventricle	Guinea pig	19	818	Several attempts to 'perfect' the guinea pig ventricular cell model.
	Jafri *et al.* 1998 and several others	Ventricle	Guinea pig	31	179	
4	Shannon *et al.* 2004	Ventricle	Rabbit	46	142	There was only a minimal amount of difference in the formulations to justify a new model. For example, Grandi et al 2010 is a human model with Shannon *et al.* 2004 (rabbit model) calcium dynamics formulations. There are several examples of this same issue, where a model is labelled as one species but due to lack of data, or other issues, reuses modelling of components from data for another species. The two rabbit models do have substantial differences in their calcium dynamics models.
	Mahajan *et al.* 2008	Ventricle	Rabbit	26	64	
	Grandi *et al.* 2010	Ventricle	Human	39	16	

times faster. (Note that COR has a time discretisation of 1 ms, so the effective speed-up may be even greater than the reported value.)

To program the Mercury computer was similarly time consuming (and error prone): people had to punch holes in a paper tape which was fed into the computer for execution. D.N. would later code his models in the ALGOL programming language before switching to Turbo Pascal (TP) on an IBM PC running MS-DOS. This latter move resulted, in 1984, in the very first public cardiac modelling software: OXSOFT HEART (OH). At that time, computing was very expensive, so to support its further development, OH was sold to academic institutions and industries around the world.

OH went through several releases and became a *de facto* reference in the field. However, some 20 years later, an issue

Table 6. Problems (examples only)

No.	Model	Type	Species	ODEs	Citations	Comments
1	Many models					Do not show the correct response, with regards to action potential duration (APD), to hyper/hypokalaemia while experimental data report a reduction/increase in APD.
2	Luo & Rudy, 1991	Ventricle	Guinea pig	8	619	Not suitable for delayed after-depolarization-related studies (Fink *et al.* 2011).
	Courtemanche *et al.* 1998	Atrium	Human	21	286	
	Bondarenko *et al.* 2004	Ventricle	Mouse	41	75	
3	Espinosa, 1998	Ventricle	Rat	21		Not suitable for early after-depolarization related studies (unpublished data from our group).
	Matsuoka *et al.* 2003	Ventricle	Mammalian	37	81	
	Corrias *et al.* 2011	Purkinje	Rabbit			
4	Luo & Rudy, 1991	Ventricle	Guinea pig	8	619	Calcium dynamics described as code not mechanism.
	Luo & Rudy, 1994	Ventricle	Guinea pig	19	818	
5	Clancy & Rudy, 1999	Ventricle	Guinea pig		195	Some issues with the model code which is not available.
	Zhang *et al.* 2000	SAN	Rabbit	15	164	
	Clancy & Rudy, 2001	Ventricle	Guinea pig		76	
	Clancy & Rudy, 2002	Ventricle	Guinea pig		130	
6	Priebe & Beuckelmann, 1998	Ventricle	Human	22	190	Stiffness in equations leading to lengthy running times.
	Faber & Rudy, 2000	Ventricle	Guinea pig	25	217	
7	Many models					'Drift' in intracellular potassium and sodium concentrations over time. This issue has since been addressed – see Livshitz & Rudy, 2009.
8	Human ventricular models					Fail to show APD shortening with increased extracellular calcium, as investigated by Grandi *et al.* 2009.
9	Decker *et al.* 2009	Ventricle	Canine		22	Cannot be used to model some of the effects of drugs.

with the TP language meant that OH could not be run reliably, if at all, on modern computers (they had become 'too fast'). Another issue was that OH was an MS-DOS application while most people had, by then, switched to Microsoft Windows. Also, OH was written in a procedural language which made it difficult to maintain and update.

To address these issues, work on Heart 5.0, a Microsoft Windows replacement for OH, was started in the late 1990s, using an object-oriented approach. Around the same time, other efforts also came to life or became more prominent, e.g. Cell Editor, CM16, CMISS (http://www.cmiss.org/), Continuity (http://www.continuity.ucsd.edu/), iCell (http://ssd1.bme.memphis.edu/icell/), LabHEART (http://www.labheart.org/) and Virtual Cell (http://www.nrcam.uchc.edu/).

The main issue with the above software was that cardiac cell models were still hard-coded. Therefore, though maintenance was made easier by using an object-oriented approach, fixes and/or updates to a model, as well as the addition of new models, involved editing the software code and recompiling it.

Model development has always consisted of several stages, all of which are subject to human error (Garny *et al.* 2009). For example, someone interested in a published model would get the equations, initial conditions, etc. from the corresponding article. However, published information would rarely be error-free, making it difficult for that person to reproduce the results of the model's authors. The model user might also make mistakes of their own.

For this reason, and others, the group of Peter Hunter (Auckland, New Zealand) specified CellML (http://www.cellml.org/), an XML-based language for supporting the definition and sharing of models. The mathematics is encoded using MathML (another XML-based language; http://www.w3.org/Math/), providing the model with a consistent mathematical representation. This, in turn, allows for model equations to be generated and published directly from the CellML code, independently of the operating system and programming language used, thus encouraging model evolution and re-use.

CellML specifications were released in August 2001 (CellML 1.0) and refined in February 2006 (CellML 1.1). CellML 1.1 introduced a concept by which it is now possible to re-use parts or all of a model description. Work on CellML 1.2 is currently under way and some of the topics currently being discussed include support for variable typing, delayed variables, stochastic variables and probability density functions.

Since the release of CellML, several tools have become available for editing, validating, sharing,

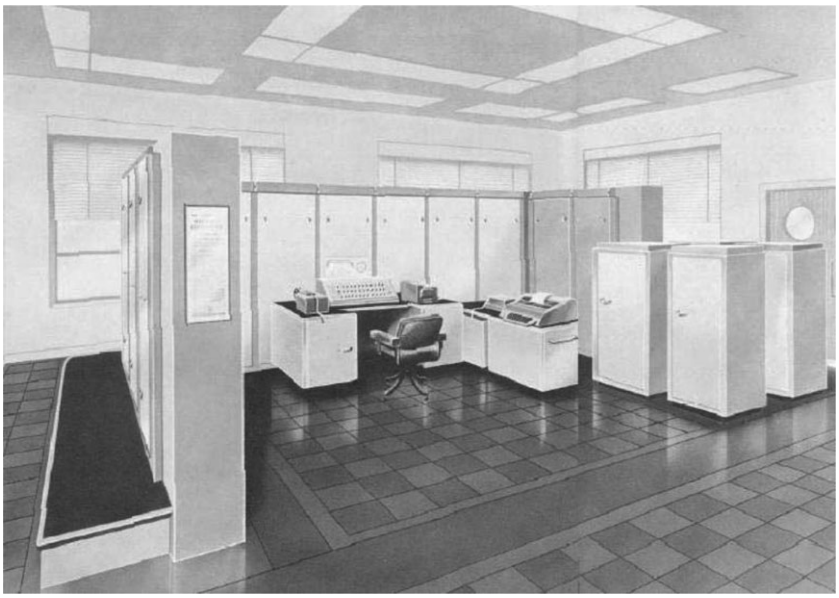

Figure 1. Schematic representation of the Ferranti Mercury computer, a valve-based machine
It had no screen and no graphics. Communication was via punched-hole paper tape.

curating and simulating CellML files, as well as for generating code from CellML. COR was the first such tool to be made publically available (Garny *et al.* 2008 (http://cor.physiol.ox.ac.uk/); Garny *et al.* 2003*b*, 2009) and though its development has now ceased, it is still being used extensively around the world. Other tools include AGOS (http://www.fisiocomp.ufjf.br/), CellML Model Repository (http://models.cellml.org/), CESE (http://cese.sourceforge.net/), JSim (http://www.physiome.org/jsim/), OpenCell (formerly known as PCEnv; http://www.opencell.org/), PyCml (https://chaste.cs.ox.ac.uk/cellml/) and Virtual Cell (http://www.nrcam.uchc.edu/).

Both COR and OpenCell share similar goals, so their authors decided to join forces and work on a combined product named OpenCOR (http://www.opencor.ws/). OpenCOR is a cross-platform environment (Microsoft Windows, Linux and Mac OS X) which relies on the Auckland CellML API (http://www.cellml.org/tools/api/) for its CellML support. It can be used both as a command line tool and through a graphical user interface, and uses a plugin approach, making it easy for anyone to extend (OpenCOR is an open source project: https://github.com/opencor/opencor/).

Figure 2. The Brunsviga Model 20 mechanical calculator (*ca*. 1910)

OpenCOR is still being actively developed, but it will be possible to use it to organise, edit, simulate and analyse CellML files. Organisation will be done through the CellML Model Repository (http://models.cellml.org/), a file browser (to access local files) and a file organiser (to virtually organise files). Editing will be based on a view that renders a CellML file in a particular way. For example, there will be a raw XML view, a COR-like view (as in COR), and a tree-like view (as in OpenCell). There will also be support for metadata editing using domain-specific ontologies. This will allow for CellML files to be comprehensively annotated which, in turn, will help the re-use of model components. In addition to the simulation capabilities of COR and OpenCell, OpenCOR will support SED-ML, an XML-based format for the description of simulation experiments (http://www.sed-ml.org/). Analysis features will mainly be provided by the community (through the plugin approach used by OpenCOR). For example, there could be a plugin for the analysis of cardiac action potentials to extract key parameters from them (e.g. upstroke velocity, action potential amplitude, action potential duration at 90% repolarisation).

Discussion

This article has been written to serve several purposes. The first was to acknowledge the ground-breaking work of Hodgkin and Huxley, 60 years on from their seminal paper, and to show how their work inspired the development of computational modelling of the heart. Initially, that work was seen as an extension of the HH approach with

new cardiac-specific data. During the 1980s, the approach shifted towards incorporation of components that have no equivalent in the HH nerve modelling. Later developments used the models in applications that were not anticipated in the early stages, such as incorporation of cell models in tissue and organ models, and extensions to drug action and device applications. The result has been the creation of a bewildering array of cell models.

A thorough investigation on the novelty and significance of *each* of these models would have provided researchers with a great resource, but this would have gone far beyond the scope of this article. The second purpose of this article has therefore been to document and comment on these models, hoping that it will still help researchers to identify what models and tools to use in their own work.

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Acknowledgements

We would like to thank the CellML community at large for their efforts and model curation work. Also, thanks to Drs Elizabeth Cherry, Flavio Fenton, Martin Fink, Gary Mirams, Steven Niederer and Blanca Rodriguez for their help in ensuring the model list is complete to the best of all of our knowledge, as well as for their additional thoughts, insights and comments on the models and their uses.