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Review

# The Noble cardiac ventricular electrophysiology models in CellML

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## Abstract

We present a review of the cardiac ventricular cell electrophysiology models developed by Prof. Denis Noble and colleagues as an example of how models may be published using a web-based CellML publication framework. The models reviewed have been marked-up in CellML and then used to compute all results presented here. The models are freely available from a website<sup>2</sup> as are the specific numerical experiments discussed in this review and the tools used to perform the simulations.

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*Keywords:* Cardiac cellular electrophysiology; Cell model; CellML; Numerical simulation

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<sup>2</sup><http://www.physiome.org.nz/publications/PBMB-2005-89/Nickerson>

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## 0. Introduction

Mathematical modelling of cardiac cellular electrophysiology has undergone significant development over the last five decades driven by major technological developments that provide improved experimental techniques and ever-increasing computational power. Improving experimental techniques allow scientists to examine cellular structure and function from the whole cell down to individual molecules and atoms while increasing computational power provides modellers with a critical tool required for analysis of the immense amount of experimental data available. Such analysis leads to structural and functional predictions at all spatial and temporal scales to feed back into and help guide experiment design.

The spectrum of electrophysiological models now available encompasses simple polynomial-based models of electrical activation through to complex three-dimensional models of the stochastic calcium dynamics within the diadic subspace associated with the calcium-induced calcium release underlying cardiac cellular contraction. In addition to what has traditionally been known as cellular electrophysiology, whole cell models are now beginning to include signal transduction and metabolic pathways and the spatial distribution of proteins within cellular and subcellular structures.

A significant and ongoing drawback to the widespread use of any given cell model is the inability of scientists to easily share their model with collaborators and colleagues around the world. The current gold-standard source for a model is the peer reviewed publication of the model and the results it produces. From this published set of equations other scientists attempt to incorporate the model into their favourite simulation package (Matlab, Mathematica, LabView, etc.) or to write stand-alone code in their preferred language. This is not always an easy task as the publication may be missing the full set of boundary or initial conditions for a given simulation, or perhaps there were typographical errors in the original publication. To aid the use of a model some authors are now making their computational code freely available, with Yoram Rudy's group being a prime example of this by providing the source code for the Luo–Rudy based models available on their website (Luo and Rudy, 1991, 1994; Zeng et al., 1995; Viswanathan et al., 1999; Faber and Rudy, 2000; Clancy and Rudy, 2002, <http://rudylab.wustl.edu>). Even with source code available, however, there is still room for errors to creep into a new implementation of the model when translating the model into a new programming language or using a different numerical solution technique or incorporating stand-alone code into a more general simulation package. Thus each new implementation of a model must be rigorously validated to be deemed a correct implementation of a given cellular model. This of course begs the question of what criteria to test the model against. The graphs provided in the original publication? Simulation results obtained from the author's own code? In the first case, comparing a numerical solution to printed graphs is probably not accurate enough and the publication is generally unlikely to cover the full range of applicability of the model; this makes the second a more favourable validity test—but only if the author's code is available and is itself a valid implementation of the published model.

With the development of CellML comes a new paradigm for the specification of these models in a solution method and implementation-independent manner (Hedley et al., 2001a,b; Cuellar et al., 2003). CellML is an XML language designed for the exchange and storage of cellular models, although it is applicable to a much wider range of mathematical models. Similar to the HTML standard underpinning the success of the World Wide Web and the Internet, XML-based CellML is both human and machine readable and provides a fairly basic set of tags which can be used to mark-up complex interactions between a set of mathematical equations represented in the MathML language (<http://www.w3c.org/math>) (see Fig. 1 for an example of CellML code). While the use of CellML can never replace the need for a peer reviewed publication of a model, it can enhance the availability of the model and ease the burden of implementation validity checking by the model users.

Through the use of CellML and the open-source tools which are becoming available (<http://cellml.sourceforge.net>), a model author is able to describe their model in a way that others are able to easily access and incorporate into their own computational codes or simulation package of choice. The model equations can be specified once and used in all implementations and publications of the model. Similarly all boundary and initial conditions required for a particular computational experiment can be specified just once and used by the community. With the establishment of a publicly accessible repository of models and simulation tools, authors are able to submit validated models and simulation results to ensure that others are able to accurately reproduce their simulations. In this paradigm the onus of model validity no longer rests with the model user but with the model author and the software engineers writing the CellML application libraries and tools. The advantage now being that the repository of models and simulation results

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```

<component name="IbCa">
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  <variable name="g_bCa" units="nS_per_pF"
    public_interface="in"/>
  <variable name="Vm" units="mV" public_interface="in"/>
  <variable name="E_Ca" units="mV" public_interface="in"/>
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      <apply><times/>
        <ci>g_bCa</ci>
        <apply><minus/>
          <ci>V</ci>
          <ci>E_Ca</ci>
        </apply>
      </apply>
    </apply>
  </math>
</component>

```

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Fig. 1. An sample piece of CellML code representing the common background  $\text{Ca}^{2+}$  current,  $I_{bCa} = g_{bCa}(V_m - E_{Ca})$ . In this component we define the current variable (*IbCa*) as an output and the parameters of the equation (conductance ( $g_{bCa}$ ), membrane potential ( $V_m$ ), and reversal potential ( $E_{Ca}$ )) as inputs.

consists of data the author has declared accurately represents their model and provides a much larger basis for testing the code and ensuring robustness and compatibility.

As described in the on-line supplement, the model simulations presented in the following sections were performed using the *mozCellML* application — a Mozilla-based model simulation environment. Other simulation applications available include the *Virtual Cell* (<http://www.nrca-m.uchc.edu>), *Cellular Open Resource* (<http://cor.physiol.ox.ac.uk>), the *Cell Electrophysiology Simulation Environment* (<http://cese.sourceforge.net>), and *CMISS* (<http://www.cmiss.org>). In order to be able to perform simulations using a model encoded in CellML an application must first translate the model into a form suitable for its use. The application of such a translation involves interpreting the mathematics of the model (MathML) in the context of the associated data from the CellML. Each of the applications above perform the translation differently: *mozCellML* and *CMISS* translate the CellML model into C or Fortran code, respectively, which is then compiled into a dynamic shared object which is loaded into the application's memory for direct use; *Virtual Cell* uses XML-based style-sheets to transform the CellML into its native format; *CESE* translates the model into Java source code conforming to the JavaBeans specification allowing the direct use of the code; and *COR* translates directly into machine code for internal use of the model.

Fig. 2 presents a brief timeline of the development of cardiac ventricular cellular electrophysiology models, all of which have been successfully described in CellML. As an example of how models might be published using the CellML paradigm, we here provide a review of the ventricular cell models developed by Prof. Denis Noble and his colleagues. In a career spanning the first physiologically realistic cardiac cell electrophysiology model in 1962 (Noble,

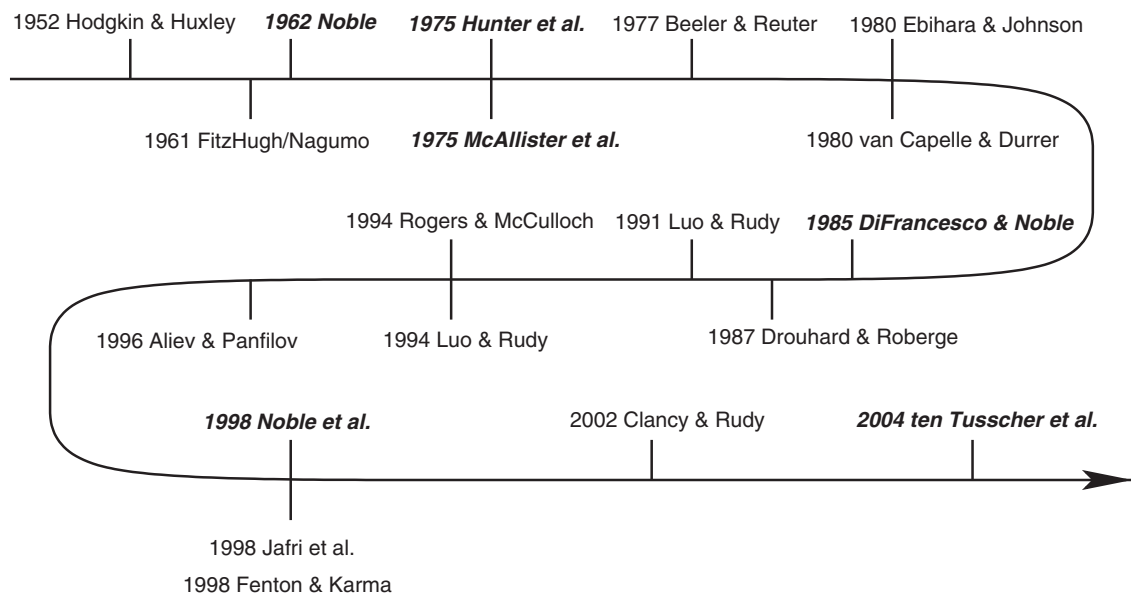
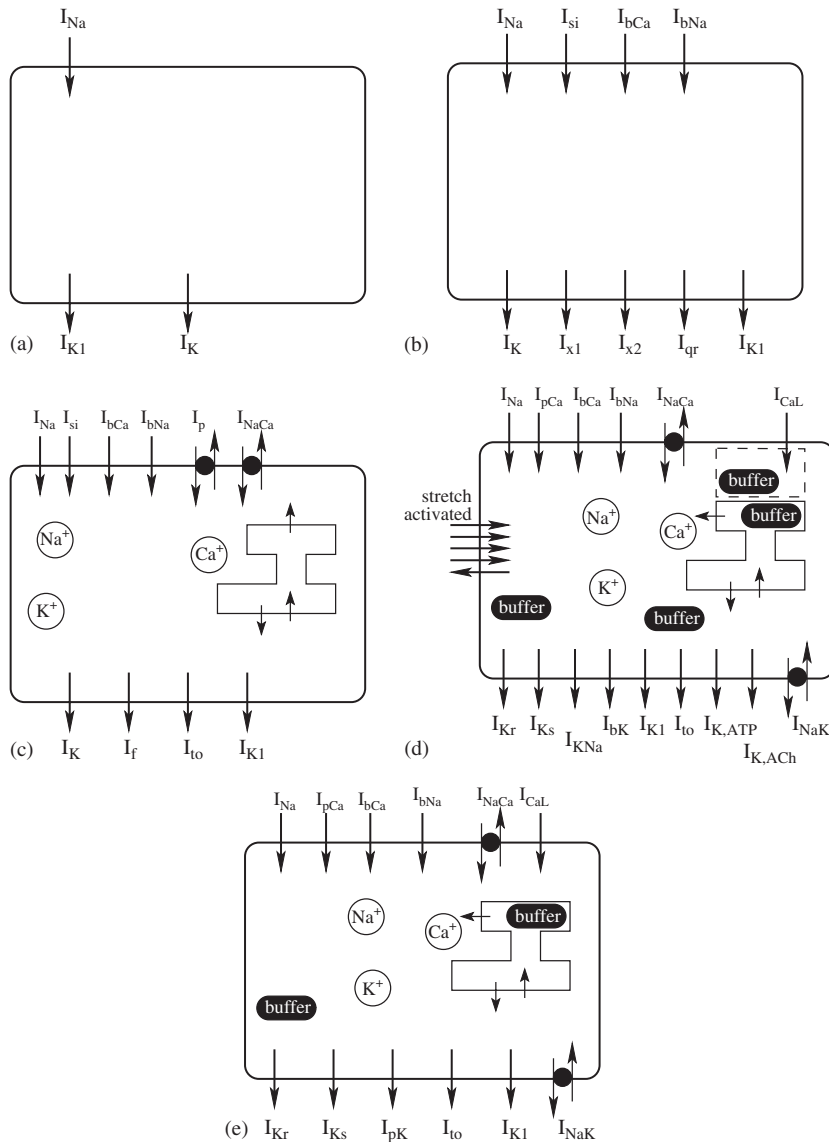


Fig. 2. A brief timeline of the development of cardiac ventricular cellular electrophysiology models. All these models have been described using CellML, with the models discussed in this review shown in italicised bold type. (Aliev and Panfilov (1996); Beeler and Reuter (1977); Drouhard and Roberge (1987); Ebihara and Johnson (1980); Fenton and Karma (1998); FitzHugh (1961); Nagumo et al. (1962); Rogers and McCulloch (1994); van Capelle and Durrer (1980)).

1962) through to the recent development of a detailed, but computationally efficient, human ventricular action potential model [ten Tusscher et al. \(2004\)](#), Prof. Noble founded the discipline of cardiac electrophysiology modelling and has continued to be one of the main driving forces behind the continual development of cellular electrophysiology models.

A schematic summary of the models reviewed in the following sections is presented in [Fig. 3](#). Note the increasing complexity of the models as they attain greater biophysical detail, until the ten



**Fig. 3.** Stylised schematic diagrams of each of the biophysically based cellular models reviewed. The ion carried by each current is not shown and the generic “buffer” is used to indicate the number of types of buffering in the model and its location. (a) Noble (1962), (b) [McAllister et al. \(1975\)](#), (c) [DiFrancesco and Noble \(1985\)](#), (d) [Noble et al. \(1998\)](#) and (e) [ten Tusscher et al. \(2004\)](#).

Tusscher et al. (2004) model where increased detail is traded-off against keeping the computational cost of the numerical solution of the model feasible for a incorporation of the cell model into larger scale tissue and organ simulations. All models and simulations presented here are available from <http://www.physiome.org.nz/publications/PBMB-2005-89/Nickerson>, and following the instructions found there it is possible to run the simulations presented below directly from this website.

## 1. 1962 Noble

Following the discovery that there were at least two  $K^+$  conductances in the heart,  $I_{K1}$  and  $I_{K2}$  (initially known as  $I_{K2}$ ), Noble (1962) developed a model to test whether this combination of  $K^+$  currents plus a Hodgkin and Huxley (1952) type  $Na^+$  channel could be used to describe the long-lasting action and pacemaker potentials of the Purkinje fibres of the heart.

The  $Na^+$  current equations in this model are very similar to the Hodgkin and Huxley (1952) description, with the curves now fitted to voltage-clamp data from Purkinje fibre experiments. The  $I_{K1}$  current is assumed to be an instantaneous function of the membrane potential and falls when the membrane is depolarised (a time-independent rectification current). The  $I_{K2}$  current slowly rises when the membrane is depolarised, described using Hodgkin and Huxley (1952)  $K^+$  current equations, with two main modifications: the maximum value,  $\bar{g}_{K2}$ , was made much smaller than in nerve in order that the increase in  $g_{K2}$  produced by depolarisation should not offset the decrease in  $g_{K1}$ ; and the rate constants were divided by 100 in order to take account of the very much slower onset of this effect in Purkinje fibres.

Fig. 4 shows the action potentials generated for the free running (pacemaker) version of the model and those for the stimulated quiescent version. Noble (1962) obtain a quiescent version of their model by adding  $0.001 \text{ mS mm}^{-2}$  to the  $K^+$  conductance — represented by the  $g\_K\_add$  parameter in the CellML model.

## 2. 1975 Hunter et al.

In a different approach to modelling cellular electrophysiology, Hunter et al. (1975) look at the mathematics of electrical impulse propagation in excitable cells, namely conduction in fibres of uniform geometry. One motivation for this work was establishing a quantitative technique for calculation of conduction velocities in nerve fibres.

The model built on earlier work which assumed that at a given threshold potential an instantaneous change in membrane electromotive force occurs — which is incorrect, as the ionic current was known to be a smooth (even if sometimes steep) function of potential. Thus, Hunter et al. (1975) propose various continuous polynomial functions for the ionic current. Polynomial functions were used as they could be chosen to give very good fits to current–voltage relations found in excitable cells without having to include more than a few powers in the polynomial equation.

Like the earlier discontinuous models, however, the polynomial models still model the ionic current as purely voltage–dependent, whereas in real cells the ionic current is also an independent

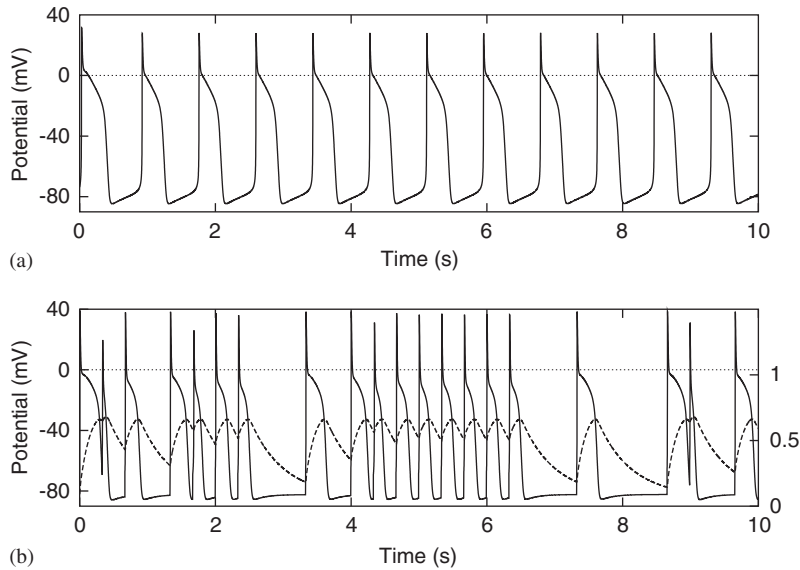


Fig. 4. Results from simulating the Noble (1962) model. (a) the action potentials generated by the free running (pacemaker) version of the model (c.f. Noble (1962), Fig. 6) and (b) the quiescent version of the model with a periodic stimulus of  $400 \mu\text{A mm}^{-3}$  with a duration of 1 ms applied with a frequency of 3 Hz (c.f. Noble (1962)), Fig. 12). Shown in (b) with the broken line is the gating variable for the potassium  $I_K$  current ( $n$ ).

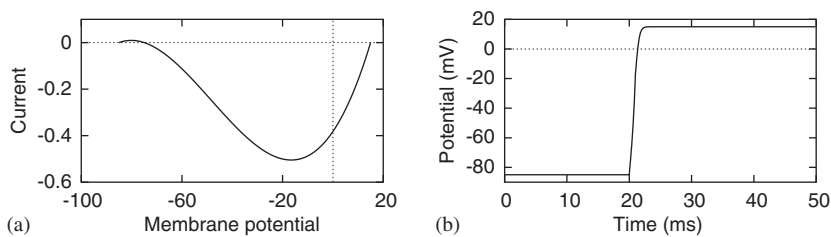


Fig. 5. Results from simulation of the Hunter et al. (1975) cubic polynomial model of activation. The activation is initiated with an applied 1 ms duration stimulus of  $100 \mu\text{A mm}^{-3}$  at time 20 ms: (a) current–voltage relationship and (b) membrane potential.

function of time. Hunter et al. (1975) mention some contemporary models which include time dependence through the addition of a recovery variable. However, for the purposes of reproducing the conduction process they state that this is an unnecessary modification since at normal temperatures it is the activation properties that limit conduction.

Results from the third-order polynomial model are presented in Fig. 5 — this version of the model has become known as the cubic model of electrical activation and used in various studies of electrical propagation in continuum tissue models. Plotting the current–voltage relationship for this model illustrates its cubic nature, as shown in Fig. 5(a), and the continuous activation of the membrane potential can be seen in Fig. 5(b).

### 3. 1975 McAllister et al.

With the development of more extensive experiments on cardiac membranes, McAllister et al. (1975) found that previous cardiac models based on modifications to the Hodgkin and Huxley (1952) nerve model were inadequate in important ways. Using the wealth of data then available, McAllister et al. (1975) developed a new model of cardiac Purkinje fibres containing many significant advances from the Noble (1962) model.

The model contains two time-dependent inward currents: a fast  $\text{Na}^+$  current ( $I_{\text{Na}}$ , similar to that of Hodgkin and Huxley (1952)); and a secondary inward current ( $I_{\text{si}}$ ) with slower kinetics and partly carried by  $\text{Ca}^{2+}$ . There is a transient outward  $\text{Cl}^-$  current ( $I_{\text{qr}}$ ) activated during strong depolarisations. Finally, instead of the single  $\text{K}^+$  current of Hodgkin and Huxley (1952) and Noble (1962), McAllister et al. (1975) found three distinguishable time-dependent  $\text{K}^+$  currents ( $I_{\text{K2}}$ ,  $I_{x_1}$ , and  $I_{x_2}$ ). None of these  $\text{K}^+$  currents quantitatively resembled the squid  $\text{K}^+$  current.

In addition to these currents, McAllister et al. (1975) expand the time-independent leakage current from the Hodgkin and Huxley (1952) nerve model into three distinct components, based on the possible ionic composition of the currents. The outward background current is carried mainly by  $\text{K}^+$  ( $I_{\text{K1}}$ ) and corresponds to the outward membrane current that may be recorded below the  $I_{x_1}$  and  $I_{x_2}$  threshold in  $\text{Na}^+$ -free solutions. They also define an inward background current carried by  $\text{Na}^+$  which gives the measured resting potential deviation from that of the  $\text{K}^+$  equilibrium potential (the primary cause of the resting potential value). The third component came from experimental evidence that  $\text{Cl}^-$  contributes to the current flow during the pacemaker and plateau phases of the action potential. While McAllister et al. (1975) formulated the three background time-independent currents in terms of specific ions, they note that there was at that time no reliable means to experimentally dissect the total background current so their formulation was rather tentative and does not imply that there necessarily exists such distinct membrane channels.

Fig. 6(a) presents a comparison between the action potentials from the McAllister et al. (1975) and DiFrancesco and Noble (1985) models.

### 4. 1985 DiFrancesco & Noble

Making use of the extensive developments in experimental work since the development of the McAllister et al. (1975) cardiac Purkinje model (e.g., Fabiato and Fabiato, 1975; Colatsky, 1980; Gadsby, 1980, DiFrancesco and Noble (1985) published a new model of cardiac Purkinje fibre electrophysiology — a model which remains the most comprehensive of all Purkinje fibre ionic current models. Some results from model simulations are shown in Fig. 6, including a comparison to the action potential from the McAllister et al. (1975) model.

This model provided the first description of ion exchangers in a cellular model — the sodium pump ( $\text{Na}^+$ – $\text{K}^+$  exchange),  $\text{Na}^+$ – $\text{Ca}^{2+}$  exchanger and the SR  $\text{Ca}^{2+}$  pump. The development of this model involved a modelling avalanche (Noble and Rudy, 2001), in which the addition of  $\text{Na}^+$ – $\text{K}^+$  exchange to match experimental data for  $\text{K}^+$  concentrations in the extracellular spaces led to the inclusion of other mechanisms to maintain the intracellular cation balances ( $\text{Na}^+$  and  $\text{Ca}^{2+}$ ) since they are all linked via the sodium pump and  $\text{Na}^+$ – $\text{Ca}^{2+}$  exchanger. The model also, in

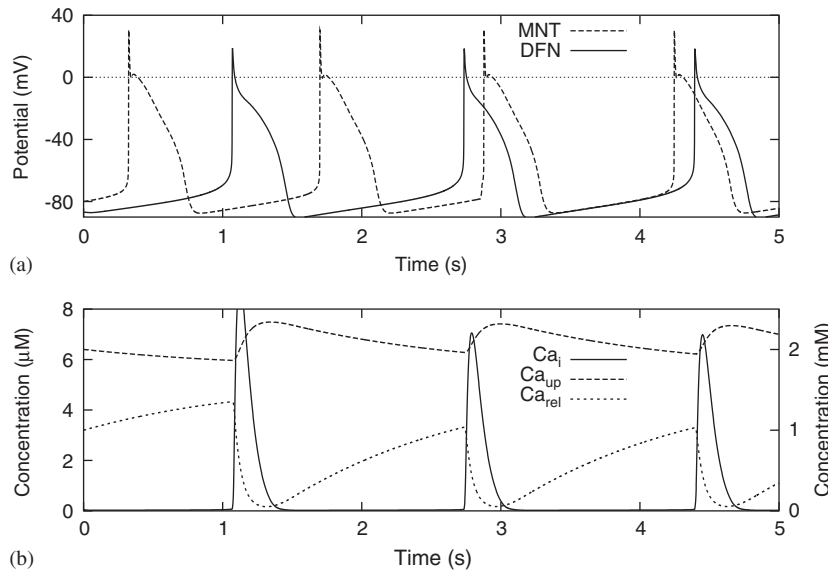


Fig. 6. (a) illustrates the pacemaker action potentials generated by the DiFrancesco and Noble (1985) (DFN) and McAllister et al. (1975) (MNT) Purkinje models. (b) shows the intracellular calcium transients for the DFN model, with the left axis in giving the scale for the intracellular calcium transient ( $Ca_i$ ) and the scale for the SR uptake and release calcium stores ( $Ca_{up}$  and  $Ca_{rel}$ , respectively) shown on the right axis. These results are for the pacemaker version of the DFN model, obtained by shifting the  $y$  gating variable 10 mV DiFrancesco and Noble (1985).

another first, included intracellular events through the incorporation of a model of  $Ca^{2+}$  release from the SR.

In a good example of the model's predictive power, the DiFrancesco and Noble (1985) model showed that in order to maintain a resting intracellular  $Ca^{2+}$  concentration below  $1 \mu\text{M}$  the  $Na^+-Ca^{2+}$  exchanger must operate with a 3:1 ( $Na^+:Ca^{2+}$ ) stoichiometry rather than the widely accepted (at that time) 2:1. This stoichiometry predicts that there must be a current carried by the  $Na^+-Ca^{2+}$  exchanger and that, if dependent on intracellular  $Ca^{2+}$ , it must be strongly time dependent. Shortly after the publication of this model experimental data showing the validity of these predictions was published Kimura et al., 1986.

However, while the model keeps the resting  $Ca^{2+}$  concentration within physiologically acceptable limits ( $\sim 0.01\text{--}1.0 \mu\text{M}$ ), the peak value reached ( $7 \mu\text{M}$ ) is outside those limits (Fig. 6(b)). This inaccuracy in the model was corrected in the development of the Hilgemann and Noble (1987) atrial cell model (and later versions of the Noble model, i.e., Noble et al. (1998), Section 5) through the inclusion of intracellular  $Ca^{2+}$  buffers.

## 5. 1998 Noble et al.

The Noble et al. (1998) guinea-pig ventricular cell electrophysiology model is an extension and update of the earlier Noble et al. (1991) ventricular model built from the initial Purkinje fibre.

(e.g., Noble, 1962; McAllister et al., 1975; DiFrancesco and Noble, 1985) and atrial (e.g., Hilgemann and Noble, 1987; Earm and Noble, 1990) cellular models.

This version of the Noble model includes a diadic space between the sarcolemma and junctional SR — equivalent to the restricted subspace of the Jafri et al. (1998) model. In the Noble et al. (1998) model, the L-type  $\text{Ca}^{2+}$  channels (or at least a large fraction of them) empty into the diadic space and the concentration of  $\text{Ca}^{2+}$  in the diadic space is used to both initiate calcium-induced calcium release from the SR and to terminate the L-type  $\text{Ca}^{2+}$  current ( $I_{\text{Ca(L)}}$ ). The fraction of L-type  $\text{Ca}^{2+}$  channels emptying into the diadic space is an extra parameter in the model which is usually set to 100%. Unlike the Jafri et al. (1998) model, however, the Noble et al. (1998) model assumes that activation of SR calcium release sites by the diadic space  $\text{Ca}^{2+}$  triggers release directly from the SR into the bulk myoplasm.

In addition to the diadic space, the Noble et al. (1998) model follows Zeng et al. (1995) and splits the delayed  $\text{K}^+$  current ( $I_{\text{K}}$ ) into a rapidly activating component ( $I_{\text{Kr}}$ ) and a slowly activating component ( $I_{\text{Ks}}$ ). The rapidly activating component is divided into two further components:  $I_{\text{Kr1}}$  for the fast deactivation component; and  $I_{\text{Kr2}}$  for the slow component. The slow component of the deactivation,  $I_{\text{Kr2}}$ , is slower than the deactivation rate of  $I_{\text{Ks}}$ .

The Noble et al. (1998) model also includes mechanisms for cellular contraction and tension generation, stretch- and tension-dependent processes, and drug-receptor interactions. For the case of normal, healthy myocytes these processes have little or no effect on the bulk cellular electrophysiology.

Results from the Noble et al. (1998) model are given in Fig. 7 which demonstrate the effect of the removal of the persistent sodium current on the membrane potential and intracellular  $\text{Ca}^{2+}$  transients (c.f. Noble et al., 1998, Fig. 5).

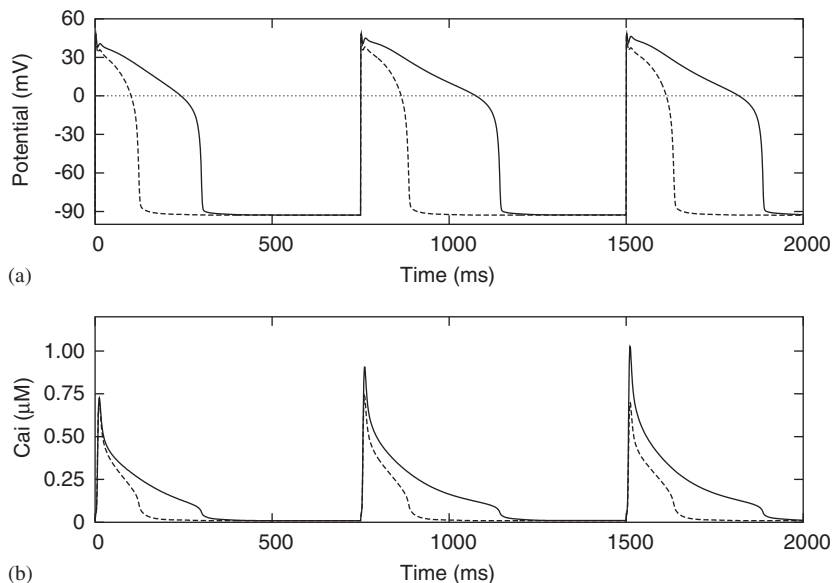


Fig. 7. The transmembrane action potential (a) and intracellular calcium transient (b) from the Noble et al. (1998) model. The broken line was produced by turning off the persistent  $\text{Na}^+$  current (c.f. Noble et al. (1998), Fig. 5). The model is paced with a 1 ms duration current injection of  $250 \mu\text{A} \cdot \text{mm}^{-3}$  with a period of 750 ms.

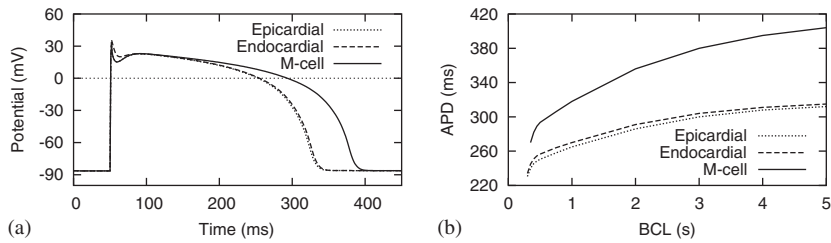


Fig. 8. Transmembrane action potentials (a) and restitution properties (b) for the three cell type variants of the [ten Tusscher et al. \(2004\)](#) human ventricular model. The restitution curves in (b) were obtained following the dynamic restitution protocol of [ten Tusscher et al. \(2004\)](#).

## 6. 2004 ten Tusscher et al.

[ten Tusscher et al. \(2004\)](#) proposed a cellular model suitable for use in simulations of electrical activation and propagation in human tissue. Being designed for tissue and organ simulations requires that the model is computationally efficient while still being able to represent the underlying electrophysiology.

Most of the major ionic currents in the model (fast  $\text{Na}^+$ , L-type  $\text{Ca}^{2+}$ , transient outward, rapid delayed rectifier, slow delayed rectifier, and inward rectifier) are based on recent experimental data. The model includes a simple representation of intracellular  $\text{Ca}^{2+}$  dynamics with the removal of a separate diadic subspace and using a simplified buffering approximation in the cytosol and sarcoplasmic reticulum. This added a low computational cost to the model while allowing the realistic modelling of key experimental observations.

In their study, [ten Tusscher et al. \(2004\)](#) compared their model to those of [Priebe and Beuckelmann \(1998\)](#) and [Courtemanche et al. \(1998\)](#). The [Priebe and Beuckelmann \(1998\)](#) model was the only existing human ventricular model at that time and consists of a modified [Luo and Rudy \(1994\)](#) model based partly on human data, and the [Courtemanche et al. \(1998\)](#) model is an atrial model. Through the inclusion of much more recent and detailed experimental data from human studies [ten Tusscher et al. \(2004\)](#) demonstrated the enhanced applicability of their model.

The [ten Tusscher et al. \(2004\)](#) model provides slight parameter and equation variations to model differences in epicardial, endocardial, and M cell types. [Fig. 8](#) presents results obtained from the model highlighting the differences between the three cell types described in the model.

## 7. Discussion

We have discussed above the problems currently associated with the distribution and implementation of published cellular electrophysiology models. In Sections 1–6 we have demonstrated the application of a new publication and distribution paradigm whereby models are described using the CellML language. From a single CellML source a model can be used for simulation and publication without the need to separately write code for model simulations and to type the equations and parameters into a word processor. We have omitted publishing the model equations above due to space constraints but all the models are available on-line and the

simulations can easily be performed using open-source software (see <http://www.physiome.org.nz/publications/PBMB-2005-89/4/Nickerson>).

One issue still to be addressed in this model publication framework is that of model curation. This important issue is currently being considered as part of the IUPS Physiome Project (<http://www.physiome.org.nz>), which has given rise to several points that will guide the evolution and curation of the CellML model repository.

Any model published in a refereed journal may contain typographical or other errors. These will sometimes be corrected in subsequent errata, published either in the same journal or on a website. These modifications should be regarded as part of the original published model and not as new versions of the model. That is, the changes should be noted on the CellML metadata for that model but the CellML model should include the corrections and not treat them as new versions of the model. An update of a previously published model, published as a new refereed paper, should be encoded as a new CellML model. When using CellML 1.1 it is possible to include components from existing models and reuse them in the development of a new model.

It is also difficult to guarantee that a CellML model is free of encoding errors, although a number of tests are run to check, for example, consistency of dimensionality. Simulation code itself may also have subtle errors making it prudent to test the CellML model with at least two independently written simulation programs (and certainly at least one simulation program that has been developed independently of the code used in the development of the model).

The author of the original model is the best person or group to check the validity of the CellML encoding for that model. Each model in the CellML model repository should therefore have a “level-of-confidence” index indicating whether the model is validated by an independent researcher and/or validated by the author. The repository should have facilities for recording comments from the user community on the particular model. These features are being added to the CellML website.

The question of whether a model is physiologically valid is of course a separate issue that has hopefully been addressed in the reviewing process for the original publication. It would, however, be useful to reference review publications on the CellML website that provide a commentary on a range of models and, in particular, give some guidance to newcomers to a particular field.

In summary, we have demonstrated how CellML can be used to reduce errors and discrepancies between model publication and implementation. With the tools now becoming available the ease with which a new cellular model published using CellML can be accessed by the wider scientific community is rapidly increasing. We have demonstrated the CellML framework in the context of the historical development of models associated with Prof. Denis Noble because we believe that this framework is a logical continuation of his pioneering efforts and will help to promote the use of models in all areas of biology.

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