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A two-variable model robust to pacemaker behaviour for the dynamics of the cardiac action potential

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ABSTRACT

Ionic models with two state variables are routinely used in patient specific electro-physiology simulations due to the small number of parameters to be constrained and their computational tractability. Among these models, the Mitchell and Schaeffer (MS) action potential model is often used in ventricle electro-physiology due to its ability to reproduce the shape of the action potential and its restitution properties. However, for some choices of parameters characterising this ionic model, unwanted pacemaker behaviour is present. The absence of any a priori criterion to exclude unstable parameter combinations affects parameter fitting algorithms, as unphysiological solutions can only be discarded a posteriori. In this paper we propose an adaptation of the MS model that does not exhibit pacemaker behaviour for any combination of the parameters. The robustness to pacemaker behaviour makes this model suitable for inverse problem applications.

1. Introduction

Cardiac ionic models are mathematical models describing the electrical response of a cardiac myocyte following an applied electrical stimulus.

When an electrical stimulus is applied to a cardiac myocyte, an action potential is generated by the flux of ionic species across the cell membrane. Complex mathematical models [2,15,24] describe the ionic current generated by each ionic species. Though physiologically accurate, these models are expensive to solve numerically due to their large number of state variables and their non-linear formulation; moreover, when personalising such models, an additional challenge arises from the large number of parameters to constrain.

In contrast, phenomenological ionic models aim to describe the collective effects of the ionic currents by a smaller number of state variables (usually 2–3) and parameters, and are obtained either by simplifying a complex ionic model [7,16], or by trying to reproduce the shape of the action potential [1,8]. In the field of personalised models, particular emphasis has been given to the models with two state variables, due to their numerical tractability and the reduced number of parameters to be constrained [4,10,20,23,27].

Among the available two state-variable ionic models, the one introduced by Mitchell and Schaeffer (MS) [16] is often employed in ventricular electro-physiology inverse problems [4,21,23]. This model is capable of reproducing the shape of the action potential and the restitution properties of the action potential duration (APD), [12,14]. The MS model is characterised by 5 parameters. It is obtained by simplifying the model proposed by Fenton and Karma, [7] (3 state variables, 13 parameters), which in turn is obtained by simplifying the more complex Luo Rudy I [15] biophysical ionic model (8 state variables, 63 parameters).

For some choices of the parameters, the MS model suffers from the so called "pacemaker cell behaviour". That is, the trans-membrane potential cyclically depolarises and repolarises in the absence of any applied external stimulus, as depicted in Fig. 1A. In Fig. 1B (blue line) the solution of the MS model under pacemaker behaviour is depicted in the phase space. From an analysis of the MS model equations, it is possible to analytically define the relation between the gate variable and the trans-membrane potential delimiting the values of the state variables producing a depolarisation. This curve is called a nullcline, and it is split into a left branch, (v_m^-) and a right branch, (v_m^+) depicted in Fig. 1B. Once activated when the system moves towards the initial (at rest) condition, if the phase portrait crosses the nullcline branch v_m^-, the system "falls" into a condition where a depolarisation occurs, and a new action potential will be produced even though no external stimuli were applied. The sets of parameters that yield

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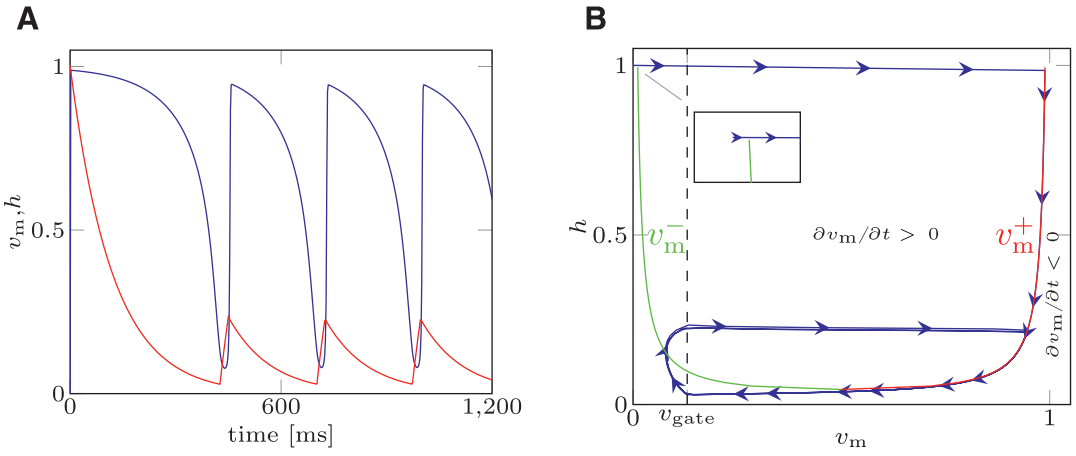

Fig. 1. (A) State variable for MS model affected by pacemaker behaviour. (B) Nullclines (green: left branch, v_m^-; red: right branch, v_m^+) and phase portrait for MS model affected by pacemaker behaviour. Parameter values are reported in the Table 2 of example 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pacemaker cell behaviour do not delimit a closed region of the parameter space. This phenomenon has been observed and reported both in 0D and tissue models, [5,22]. However, to the best of our knowledge there are no criteria for determining a priori which combination of parameters will produce pacemaker activity.

For patient specific modelling, this unwanted behaviour represents a problem for parameter estimation, since it necessitates a stability test for each estimated parameter set, [5].

Particularly affected by this phenomenon are the sequential data assimilation techniques [3,9,11]: since the values of the parameters are sequentially updated to minimise the discrepancy between the output of the model and the measurements of the system under study, if a combination of parameters yielding pacemaker behaviour is produced, the algorithm adopted could become unstable and diverge.

To overcome these limitations, in this paper we derive and introduce a two state-variable ionic model that describes the action potential phases by 5 parameters, has the same benefits as the MS model, and is robust to pacemaker behaviour. These characteristics make it suitable for generating personalised electrophysiology models for clinical applications, in particular when a sequential data assimilation technique is employed. This paper is organised as follows: in Section 2 we introduce the mathematical formulation of the new ionic model; in Section 3 we prove the absence of pacemaker behaviour in the phase plane; in Section 4 we derive an asymptotic derivation of the restitution curves and compare it to the one described in [16] for the standard MS model; and in Section 5 we compare the solutions and the restitution properties of the new model with the MS model for some numerical examples.

2. The modified Mitchell–Schaeffer ionic model

The standard MS ionic model [16] describes the ionic currents that flow across the cell membrane with a gated-inward ionic current, representing the current produced by the flux of the sodium ions, and an ungated outward ionic current, representing the current produced by the flux of the potassium ions. The two state variables characterising the MS model represent the electric potential of the cell membrane and the gate dynamics of the sodium ion channels. The model can be written in the generalised form proposed by [6]:

$$\frac{\partial v_m}{\partial t} = h\frac{(v_m + a)(v_m + a - \lambda)(1 - v_m)}{\tau_{in}} - \frac{v_m}{\tau_{out}} + J_{stim} \tag{1}$$

$$\frac{\partial h}{\partial t} = \begin{cases} \frac{1-h}{\tau_{open}} & v_m \le v_{gate} \\ -\frac{h}{\tau_{close}} & v_m > v_{gate} \end{cases} \tag{2}$$

where J_{stim} is an externally applied electrical stimulus, v_m is the trans-membrane potential, h is the gate variable of the inward current, v_{gate} is the activation threshold potential and $\tau_{in}, \tau_{out}, \tau_{open}, \tau_{close}$ are the 4 time constants affecting the 4 characteristic phases of the trans-membrane potential. The standard MS model described in [16] is obtained by imposing $a = \lambda = 0$; the parameters a and λ were introduced by [6] and used to control the excitability of the system.

The modified Mitchell–Schaeffer (mMS) ionic model presented in this paper is obtained by first replacing $a = 0$ and $\lambda = v_{gate}$ in (1): consequently, if $v_m < v_{gate}$, then $\partial v_m/\partial t < 0$ and the system naturally evolves towards the rest condition instead of producing an action potential, in contrast to the original MS model where there is a range of values $v_m^-(h) \le v_m < v_{gate}$ yielding $\partial v_m/\partial t > 0$.

The effect of the potassium ion current is negligible when $v_m \le v_{gate}$ and the cell is returning to a quiescent state. It is possible to introduce gating effects to the outward ionic current with the complement of the gate variable, $(1-h)$, adopting an expression similar to the one introduced in [25]. This leads to the following system of ODEs:

$$\frac{\partial v_m}{\partial t} = h\frac{v_m(v_m - v_{gate})(1 - v_m)}{\tau_{in}} - (1 - h)\frac{v_m}{\tau_{out}} + J_{stim} \tag{3}$$

$$\frac{\partial h}{\partial t} = \begin{cases} \frac{1-h}{\tau_{open}} & v_m \le v_{gate} \\ -\frac{h}{\tau_{close}} & v_m > v_{gate} \end{cases} \tag{4}$$

Remark. The robustness to pacemaker behaviour is obtained by modifying the cubic polynomial on the right hand side of Eq. (1). The addition of gating on the outward current has three advantages: first, when $h = 1$ the threshold value of the transmembrane voltage above which an action potential is triggered is equal to v_{gate}; second, for $h = 1$ the transmembrane potential at the end of the upstroke will be $v_m = 1$; third, as will be discussed in Section 4, the analytical solution of the mMS model coincides to the analytical solution of the MS model for the same set of ionic parameters for a particular choice of v_{gate}.

3. Robustness to pacemaker behaviour

The study of the robustness of the mMS model to pacemaker behaviour consists in determining if the condition $\partial v_m/\partial t > 0$