1 Introduction
A NUMBER of membrane models for the cardiac action potential have been published for Purkinje fibres (NOBLE, 1962; McALLISTER et al., 1975; DiFRANCESCO and NOBLE, 1985) and ventricular muscle (BEELER and REUTER, 1977). The equations for the ionic currents in these models were derived by fitting mathematical expressions to voltage clamp experimental results, based on the method set up by Hodgkin and Huxley (1952) in their study of the membrane ionic currents in the nerve membrane. Owing to the empirical nature of the equations for the ionic currents, membrane models evolve as new experimental facts become available. For example, the DiFrancesco-Noble (DN) model (DiFRANCESCO and NOBLE, 1985) is built up on the McAllister-Noble-Tsien (MNT) model (McALLISTER et al., 1975) which is based on the Noble (N) model (NOBLE, 1962). Models of the fast sodium current have been markedly improved through measurements by investigators such as EIBHARA and JOHNSON (1980) for ventricular strands and COLATSKY (1980) for Purkinje fibres. The DN model incorporates new currents and reinterprets old ones; it represents the state-of-the-art of the membrane models for cardiac Purkinje fibres.

Membrane models have been used extensively for the study of propagation since the work of Hodgkin and Huxley (1952). Recent examples, by no means comprehensive, include the work by BERKINBLIT et al. (1970) with inhomogeneous fibres, SPACI et al. (1982) with discontinuous conduction, JOYNER et al. (1984) with coupled cells, ROBERGE et al. (1986) in two-dimensional preparations, RUDY and QUAN (1987) on discrete structure and HENRIQUEZ and PLONSEY (1990) on changes with depth. As the DN model represents membrane behaviour more realistically than previous models, its incorporation into propagation for Purkinje fibres is a natural goal.

The equations in the DN model are based on experimental results obtained from different fibres in different laboratories (DiFRANCESCO and NOBLE, 1985). Therefore, the model simulates the behaviour of a composite 'Purkinje fibre'. The membrane action potential DN model (no propagation) has been shown to reproduce experimental results regarding steady-state current-voltage relationships, voltage clamp currents and effect of changes in ionic concentrations in the action potential (DiFRANCESCO and NOBLE, 1985). The purpose of the present study is to evaluate the DN model with respect to electrical excitability. Studies on electrical excitability often involve decisions on whether a stimulus causes a propagated action potential or not. Therefore, to compare the behaviour of the DN simulated Purkinje fibre to electrical stimulation with real fibres, we have implemented a propagation model using the DN model for the membrane.

Abstract—Propagation, re-entry and the effects of stimuli within the conduction system can be studied effectively with computer models when the pertinent membrane properties can be represented accurately in mathematical form. To date, no membrane models have been shown to be accurate representations during repolarisation and recovery of excitability, although for the Purkinje membrane the DiFrancesco-Noble (DN) model has become a possibility. The paper examines the DN model, restates its equations and compares simulated waveforms in a number of propagation contexts to experimental measurements reported in the literature. The objective is to determine whether or not the DN model reproduced phenomena such as supernormality, shortening in action potential duration during pacing rate increases, alternation of duration with changes in rhythm, graded responses and 'all-or-none' repolarisation in a quantitatively realistic way, as each of these come from time and space dependencies not directly a part of the ionic current measurements on which the DN model is based. The results show that the DN equations correctly simulate these situations and support the goal of having a model that is broadly applicable to Purkinje tissue, including refractory period properties and response to electrical stimulation.

Keywords—Cardiac conduction system, DiFrancesco-Noble model, Propagation

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In addressing that question, we have simulated a variety of well-established properties of cardiac tissue (strength/interval curves, supernormality, changes in action potential duration with pacing rate, alternation of duration with changes in rhythm, graded responses and ‘all-or-none’ repolarisation) and compared them with the corresponding measurements in real tissue. The close agreement between the simulated and real fibre establishes the DN model as a useful tool in the study of phenomena involving propagation like cardiac arrhythmias (e.g. re-entry) and electrical excitability, where the correct behaviour of the refractory period and response to stimulation is crucial.

The importance of establishing a close link between these experimentally measured propagation results and the DN model is twofold. First, of theoretical interest is the fact that no prior model has been shown to reproduce accurately measured results during repolarisation and recovery, and a variety of failures of various models in particular cases have been mentioned anecdotally. Thereby, there has been a substantial question as to whether or not the DN model would effectively reproduce such events, particularly the more subtle changes. Secondly, and of immediate practical interest, membrane models have become indispensable tools for understanding the basis of propagation and for its control through well designed pacemakers. In this regard, having a model that accurately reproduces the measured events of repolarisation and recovery allows the use of computer simulation as a tool in such a design, which is of great practical importance because of the prevalence of disorders of cardiac rate and rhythm, often involving questions of electrical recovery and re-entry, in the human heart.

2 Methods

2.1 Propagation model

The fibre model used is a continuous cable in which the junctional and the myoplastic resistances are distributed uniformly in an effective intracellular resistance. For simplicity, we consider the membrane impedance as a single capacitance, as opposed to two capacitances (FOZZARD, 1966), in parallel with the ionic currents described by the DN model. For a fibre in a volume conductor the cable equation can be expressed as

\[
I_m = \frac{a}{2R_i} \frac{\partial^2 V_m(x, t)}{\partial x^2} = I_{ion} + C_m \frac{\partial V_m(x, t)}{\partial t}
\]  

(1)

where \( I_m \) is the transmembrane current at a certain patch of the membrane (in \( \mu A/cm^2 \)), \( a \) is the fibre radius (0-001 cm), \( R_i \) is the intracellular resistance (0-250 k\Omega cm), \( V_m \) is the transmembrane potential (in mV), \( I_{ion} \) is the ionic current (in \( \mu A/cm^2 \)) and \( C_m \) is the specific membrane capacitance (1-2 \( \mu F/cm^2 \)).

The following finite difference equation approximates the partial differential equation for the \( j \)th node of the fibre at time \( t \):

\[
\frac{a}{2R_i} \frac{(V_m(j+1) - 2V_m(j) + V_m(j-1))}{\Delta x^2} = (I_{ion}) + C_m \frac{(V_m(j+1) - V_m(j))}{\Delta t}
\]

(2)

The subscripts represent the discretised values of the spatial variable, the superscripts represent the discretised values of the time variable, \( \Delta x \) is the space discretisation step (100 \( \mu m \)) and \( \Delta t \) is the integration time step (10 \( \mu s \)).

The finite difference equation (eqn. 2) in the form for explicit extrapolation for \( V_m \) is

\[
(V_m(j+1) = (V_m(j) + \frac{a\Delta t}{2C_m R_i} \times \frac{(V_m(j+1) - 2V_m(j) + V_m(j-1))}{\Delta x^2})
\]

(3)

We solved the finite difference equation (eqn. 2) for 100 nodes (1 cm fibre). \( V_m(j) \) advanced in time with the forward time-centred space scheme (eqn. 3). Both ends of the fibre were considered sealed (i.e. no intracellular current) so at both ends (nodes 1 and 100) the boundary condition was \( \partial V_m/\partial x = 0 \).

2.2 Membrane model

The membrane ionic current at each node \( I_{ion} \) was calculated using the equations listed in the Appendix. Those equations were taken from the default mode of operation of the program ‘Heart’ (OXSOFT, 1990), which implements the DN model equations for a patch of membrane. The equations are similar to those in DIFRANCESCO and NOBLE (1985) but not the same in detail.

3 Results and discussion

3.1 Strength/interval curve

First, the strength/interval curve of the simulated Purkinje fibre was compared to the measurements of SPEAR and MOORE (1974a). The procedure followed was: first, stimulate the fibre at one end (node 2) with a cathodal (depolarising) suprathreshold stimulus \( S_1 \) (to elicit an action potential); secondly, stimulate the fibre at the same node with a cathodal stimulus \( S_2 \) with a certain coupling interval (the difference between the times at which \( S_1 \) and \( S_2 \) are applied) and a certain strength. For each coupling interval, the strength of the \( S_2 \) stimulus was increased from zero to a strength that caused a propagated action potential; this strength is the threshold of the \( S_2 \) stimulus at that coupling interval. The threshold of the stimulus \( S_2 \) with a coupling interval of 500 ms is defined here to be the diastolic threshold (after 500 ms the threshold of the stimulus \( S_2 \) is constant). The coupling interval was varied from 500 ms, in decrements of 5 ms, until no propagated response could be elicited for current strengths up to the maximum strength. The maximum strength used for the \( S_2 \) stimulus was five times the diastolic threshold. The maximum coupling interval at which no propagated response could be elicited is called the effective refractory period. The duration of all the stimuli was 1 ms.

Fig. 1 shows the strength/interval curve for a simulated (Fig. 1a) and a real (Fig. 1b) Purkinje fibre (SPEAR and MOORE, 1974a). In both the fibre simulation and the real fibre, the strength of the current required to elicit a propagated action potential increases as the coupling interval between stimuli \( S_1 \) and \( S_2 \) decreases, except during the period of supernormality.

The period of supernormality is characterised by a decrease in the current required to excite the membrane (the dip in the strength/interval curves, between 300 and 400 ms, in Fig. 1), compared with periods where the tissue is more recovered. Supernormality results from the fact that excitability is restored before the fibre is fully repolarised (HOFFMAN and CRANEFIELD, 1960). Even though supernormality is usually associated with anodal stimulation (HOFFMAN and CRANEFIELD, 1960; ORIAS et al., 1950; HOFFMAN et al., 1951; CRANEFIELD et al., 1957), supernormal excitability has been demonstrated with