APPROXIMATIONS OF THE SODIUM CURRENT GATING VARIABLES (m&h): A STUDY ON A SINGLE AND MULTI-CELLS PURKINJE FIBER

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ABSTRACT

The sodium current gating variables (m & h) as described by (H-H) model are time and voltage dependent functions. Using there functions limits the number of cells to be considered in multi-dimensional representation of the myocardium. In this work we offer simplified equations for (m & h) keeping minimal deviation of membrane potential and sodium current compared with the exact solution. Results obtained show that the proposed approximations decrease the processing time in a 60 cell one dimensional fiber to one tenth the time for the exact solution. No significant effect is noticed regarding the shape and velocity of the membrane action potential wave and sodium current.

Keywords: Ionic current , depolarization , gating variables , transmembrane potential , purkinje fiber .

INTRODUCTION

One of the accepted models describing the gating mechanism of ionic permeation in neuromuscular cells is the Hodgkin and Huxley (H-H) model [1]. Following such model, there were two models describing the individual components of the ionic current in a single purkinje cell and myocardial cell, namely; the Mcallister, Nobel and Tsien (M.N.T) model [2], and the Beeler-Reuter model [3] respectively. Each model has more than 100 parameters in order to give accepted results regarding the shape of the membrane potential and current components in normal operations as well as under voltage clamp conditions. This large number of parameters used limits the number of cells required in any multi-cell representation of the myocardium during normal conditions. The target of the present work is to approximate the (M.N.T.) model of a single Purkinje cell during early depolarization so as to enable the use of large number of cells. Our technique is to simplify the two gating variables of sodium current (m & h).

METHODS AND RESULTS

To model the behaviour of the ionic current component in early depolarization, they may be represented by a sum of two components; the sodium current and the sum of all other currents representing the early depolarization response of all other ions [4]. Therefore, the ionic current density (J_{ion}) could be written as,

$$J_{ion} = J_{Na} + J_R \tag{1}$$

where

J_{Na} = Sodium current density
J_R = Sum of all other currents densities representing the early depolarization response of all other ions, J_R could be written as [4],

$$J_R = g_R * (V_m - V_R) \tag{2}$$

where

g_R = early depolarization conductance = 0.05 ms/cm^2
V_m = membrane potential (m volts)
V_R = resting potential P = -80 mvolts

Also, J_{Na} could be written as [2],

$$J_{na} = \bar{g}_{Na} m^3 h (V_m - N_{Na}) \tag{3}$$

where

$\bar{g}_{Na}$ = Peak sodium conductance = 35 ms/cm2
V_{Na} = Sodium equilibrium voltage = 33.4 mvolts
m&h = activation and inactivation gating respectively

(m) & (h) are given by (H-H) equations [1], and their parameters as given by the (M.N.T.) model [2] such that:

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \quad (4)$$

where

$$\alpha_m = (V_m + 47)/(1 - e^{-0.1(V_m + 47)}) \quad (5)$$

$$\beta_m = 40\, e^{-0.056(V_m + 72)} \quad (6)$$

Also,

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h \quad (7)$$

where

$$\alpha_h = 0.0085\, e^{-0.184(V_m + 71)} \quad (8)$$

$$\beta_m = 40\, e^{-0.1.82(V_m + 10)} \quad (9)$$

At steady state, we can write:

$$m_\infty = (V_m) = \frac{\alpha_m}{\alpha_m + \beta_m} \quad (10)$$

$$\tau_m = (V_m) = \frac{1}{\alpha_m + \beta_m} \quad (11)$$

Similarly,

$$h_\infty = (V_m) = \frac{\alpha_h}{\alpha_h + \beta_h} \quad (12)$$

$$\tau_h = (V_m) = \frac{1}{\alpha_h + \beta_h} \quad (13)$$

where m_∞ and h_∞ are the steady state values of m and h, τ_m and τ_h are the time constants of both m and h variations respectively.

h- approximation :

Using equations (1) to (9), the exact shape of transmembrane potential shows an early depolarization phase occurring in (0.2 - 0.3) msec for a cell stimulated by 100 μA/cm^2 for 0.1 msec.

From Figure (1), τ_h ranges from 5 to 40 msec during the rapid phase of depolarization, this is a very long time constant range compared to the period of depolarization. Also, from Figure (2), it is evident that during this significant period of depolarization, the value of the h-variable decrease from 1 down to 0.9. Therefore, we could expect a good approximation of h by assigning a constant value for it ranging from 1 to 0.9. That is;

$$h = k \quad (14)$$

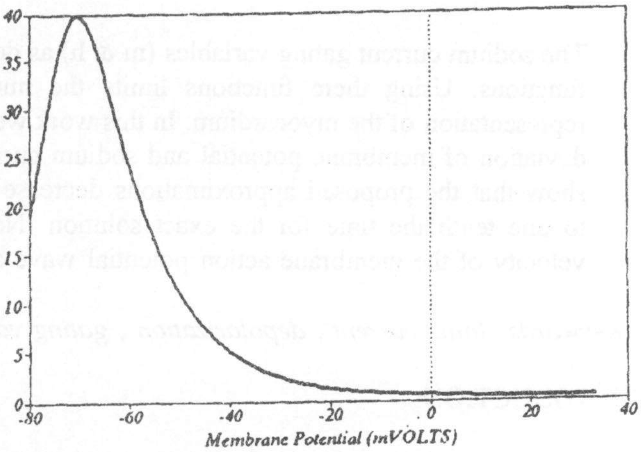
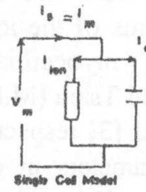


Figure 1. τ_h (mesc) versus membrane potential.



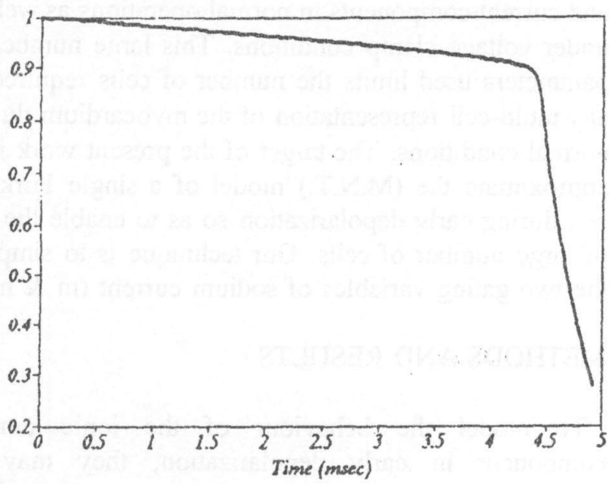


Figure 2. h-kinetics in a single cell stimulated by 100 μ/A/xm^2 for 0.1 msec.

Several values were tested to get the optimum value of k. The best values of k obtained was 0.975. The solution of the transmembrane potential equation with h-approximation compared to the exact solution is shown in Figures (3) and (4). It is evident that approximation of h has a minimal effect on the membrane potential and sodium current pattern.

m- approximation:

Unlike the inactivation time constant (τ_h), Figure (5) shows that τ_m is a small time constant. If we consider a zero time constant, the value of m equals its steady state value m_∞ Figure (16). Therefore considering the small time constant τ_m we may expect m to be near m_∞ (V_∞) but with a small lag. This means that m is a function of m_∞ (V_m-ΔV_m) where ΔV_m is a shift in membrane potential. Thus we can write the following empirical formula

$$m = k_1\, m_\infty\, (V_m - \Delta V_m) \qquad (15)$$

Several values for k_1 and ΔV_m were tested to give the optimum fit with the exact solution of the transmembrane potential (V_m) and sodium current (i_{Na}). Best results were obtained for k_1 = 0.835 and ΔV_m = 4.5 mv.

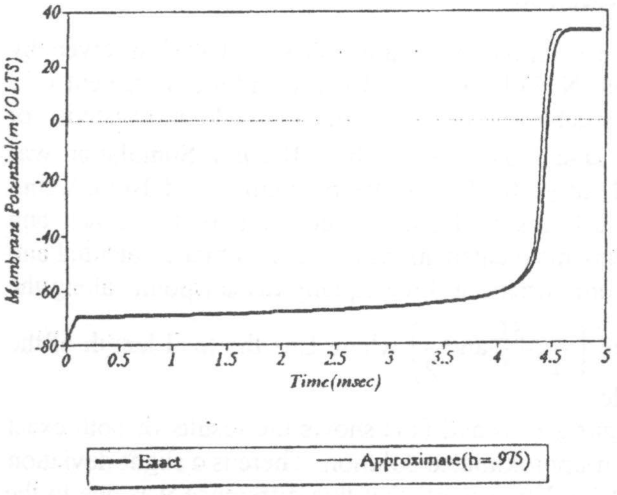


Figure 3. Member potential variation with time in a single cell for exact and h-approximate calculations.

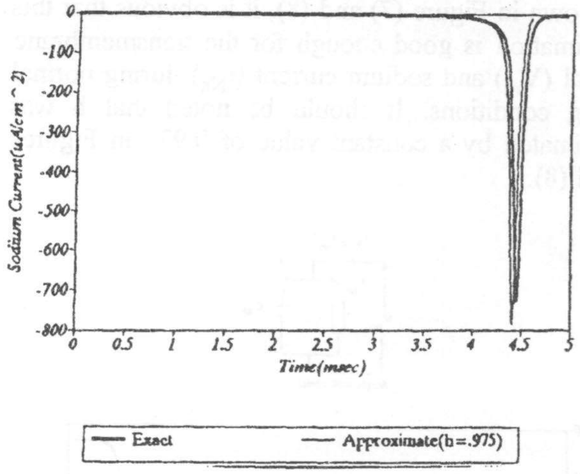


Figure 4. Sodium current variation with time in a single cell for exact and h-approximate calculations

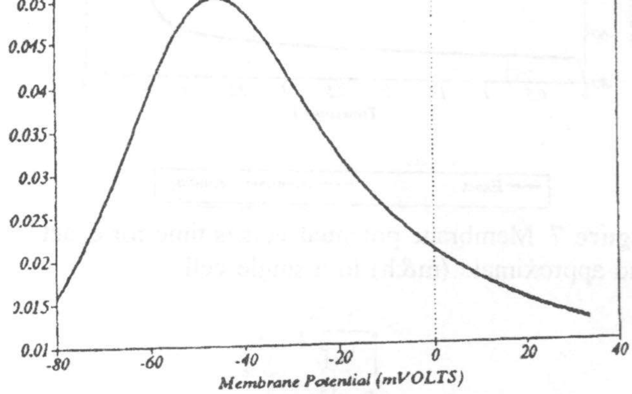


Figure 5. τ_m (msec) versus membrane potential.

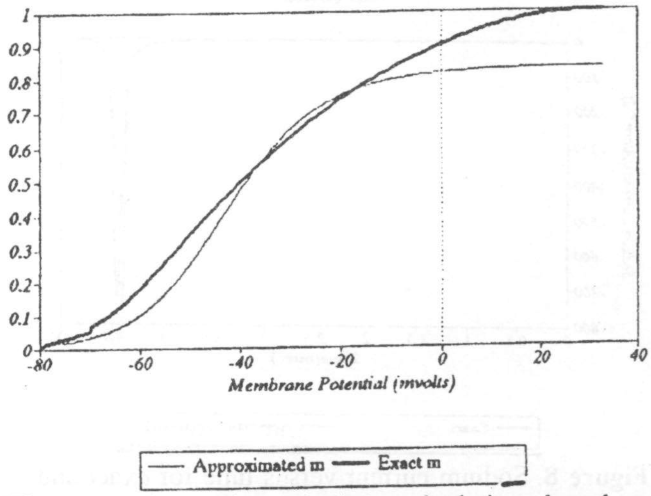


Figure 6. Approximated (m) calculation based on equation (15) compared to an exact (m) calculations.

As shown in Figure (7) and (8), it is obvious that this approximation is good enough for the transmembrane potential (V_m) and sodium current (i_{Na}) during normal working conditions. It should be noted that h was approximated by a constant value of 0.975 in Figures (7) and (8).

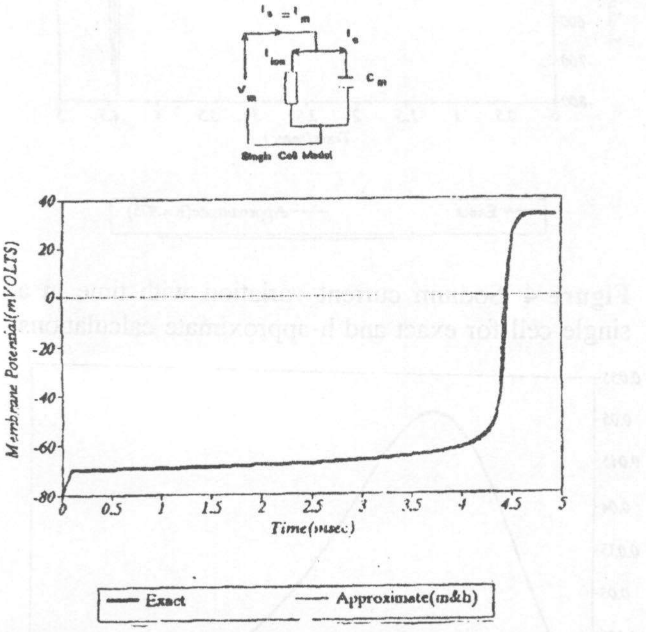


Figure 7. Membrane potential versus time for exact and approximate (m&h) in a single cell.

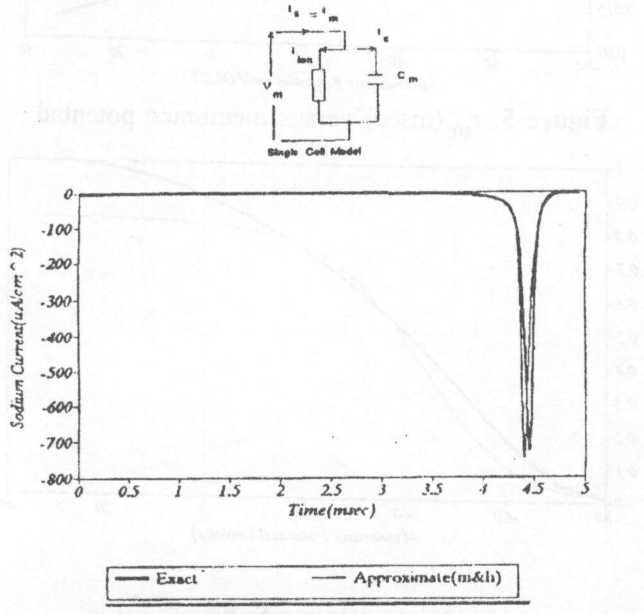


Figure 8. Sodium current versus time for exact and approximate (m&h) in a single cell.

(m & h) approximations in a multi-cell cable fiber:

(m) and (h) approximation, equations (14) and (15), were applied on a one dimensional multi-cell cable purkinje fiber to test the effect of these approximations on the computational time saving. We have compared the solution in both case for (m) & (h) calculated exactly following equation (4) to (9) and those approximated by equations (14) and (15).

In the one-dimensional case a second order differential equation is considered along x-direction, Figure (9), such that:

$$\frac{a}{2f_i}\frac{\partial^2 V_m}{\partial x^2} = i_m \tag{16}$$

and

$$i_m = C_m\frac{\partial V}{\partial t} + J_{ion} \tag{17}$$

where

a is the cable radius (μm)
f_i is the intracellular resistivity (Ω-cm)

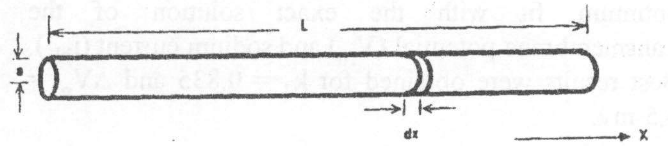
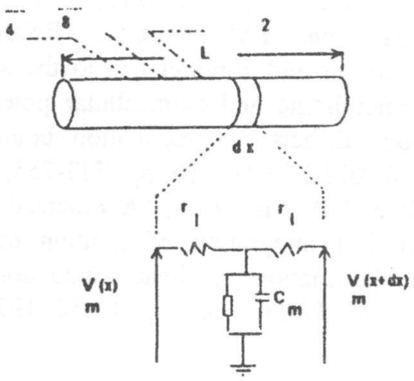


Figure 9. Multi-cell on dimensional cable fiber representation.

The solution of equation (16) and (17) is given by Crank-Nicholson method [5] for a time increment of 2 μsec, cable radius of 25 μm intracellular resistivity of 450 Ω-cm and cell length of 183 μm. Stimulation was made at (x=0), Figure (9), by a current of 100 μA/cm2 for 0.1 msec. Results were drawn for exact and approximate calculations of the membrane potential and sodium current at three equally distant points along the cable $\left(\frac{L}{4}, \frac{3L}{8} \text{and} \frac{L}{2}\right)$ where L is the total length of the cable.

Figures (10) and (11) shows the results of both exact and h-approximated solution. There is a slight deviation at (L/4). We suggest that this difference was due to the effect of the stimulating current. However at (3L/8) and (L/2), the exact and approximate methods almost coincide and the approximation gives satisfactory results. Performing the second step of approximation (including both m & h), a slight difference appears in the longitudinal wave velocity. Yet approximately no effect on the shape of the membrane potentials and sodium currents at the three defined locations, Figures (12) and (13). The difference in longitudinal velocity was less than 0.6% which is insignificant. For 60 cells, the computational time of the approximated solution was reduced by almost 1 : 10 compared with that of the exact solution.



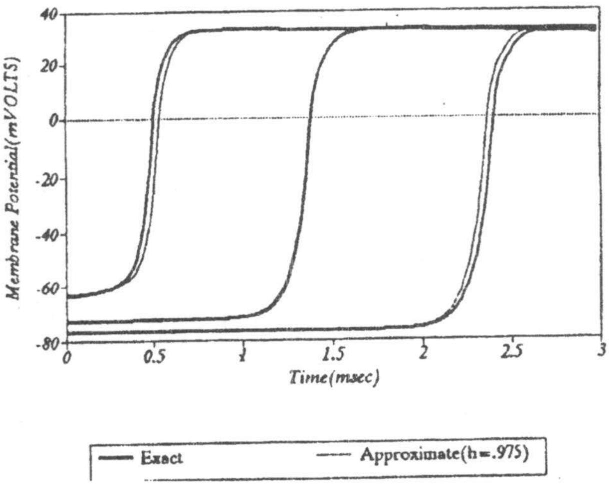


Figure 10. Membrane potential at L/4,3L/8 and L/2 points along the cable calculated exactly compared to those with approximated (h).

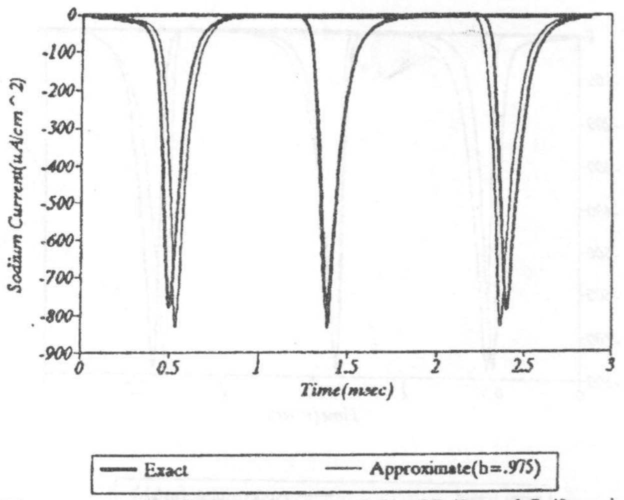


Figure 11. Sodium current at L/4, 3L/8 and L/2 points along the cable calculated exactly compared to those with approximated (h).

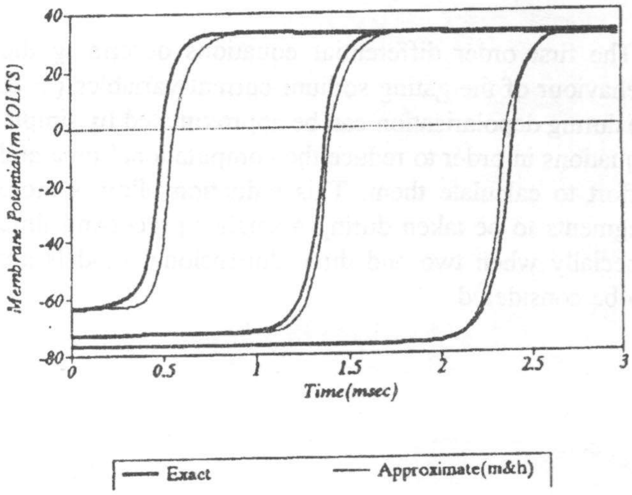


Figure 12. Membrane potential at L/4, 3L/8 and L/2 points along the cable calculated exactly compared to those with approximated (m&h).

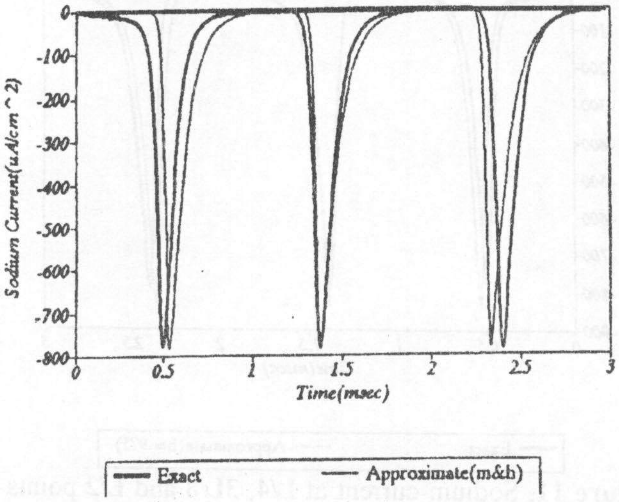


Figure 13. Sodium current at L/4, 3L/8 and L/2 points along the cable calculated exactly compared those with approximated (m&h).

CONCLUSIONS

The first order differential equations describing the behaviour of the gating sodium current variables (m & h) during depolarization can be approximated by simple equations in order to reduce the computational time and effort to calculate them. This reduction allowas more segments to be taken during a smaller processing time specially when two and three dimensional models are to be considered.

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