Computers in Biology and Medicine 77 (2016) 261–273

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Quadratic adaptive algorithm for solving cardiac action potential models

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ARTICLE INFO

Article history:
Received 30 November 2015
Received in revised form
2 September 2016
Accepted 3 September 2016

Keywords:
Computer simulation
Action potential
Numerical method
Cardiac action potential model
Adaptive method

ABSTRACT

An adaptive integration method is proposed for computing cardiac action potential models accurately and efficiently. Time steps are adaptively chosen by solving a quadratic formula involving the first and second derivatives of the membrane action potential. To improve the numerical accuracy, we devise an extremum-locator (el) function to predict the local extremum when approaching the peak amplitude of the action potential. In addition, the time step restriction (tsr) technique is designed to limit the increase in time steps, and thus prevent the membrane potential from changing abruptly. The performance of the proposed method is tested using the Luo-Rudy phase 1 (LR1), dynamic (LR2), and human O'Hara-Rudy dynamic (ORd) ventricular action potential models, and the Courtemanche atrial model incorporating a Markov sodium channel model. Numerical experiments demonstrate that the action potential generated using the proposed method is more accurate than that using the traditional Hybrid method, especially near the peak region. The traditional Hybrid method may choose large time steps near to the peak region, and sometimes causes the action potential to become distorted. In contrast, the proposed new method chooses very fine time steps in the peak region, but large time steps in the smooth region, and the profiles are smoother and closer to the reference solution. In the test on the stiff Markov ionic channel model, the Hybrid blows up if the allowable time step is set to be greater than 0.1 ms. In contrast, our method can adjust the time step size automatically, and is stable. Overall, the proposed method is more accurate than and as efficient as the traditional Hybrid method, especially for the human ORd model. The proposed method shows improvement for action potentials with a non-smooth morphology, and it needs further investigation to determine whether the method is helpful during propagation of the action potential.

1. Introduction

The electrical phenomena in membrane-excitable cells can be numerically simulated using membrane models. Such membrane models consist of equations for many of the individual ionic currents that are known or hypothesized to exist. These equations are often derived from Hodgkin-Huxley-type (HH-type) equations, which employ the concept of gating variables [1,2]. The behavior of time-dependent gating variables is governed by a particular type of ordinary differential equation (ODE).

Runge-Kutta (RK) numerical methods have been widely employed for the integration of ODEs to solve linear or nonlinear gating variables, and as such are often used in computer simulations of membrane models, including the Luo-Rudy phase 1 (LR1), Luo-Rudy dynamic (LR2) [16,18], and the human O'Hara-Rudy dynamic (ORd) [17] ventricular cell models. Rush and Larsen (RL) developed an integration method that employs an analytical solution for ODEs, based on the assumption that the coefficients of the equations are constant when the membrane action potential (AP) changes slowly [3,4]. The RL method allows a much larger time step size than that of RK methods when integrated into the McAllister-Noble-Tsien (MNT) cardiac Purkinje fiber model [5]. Victorri et al. [6] proposed a variant of the RL integration method, the so-called Hybrid, to select the time steps adaptively and monitor the change in the membrane potential to reduce the required amount of computation. Recently, some studies have proposed various improved RL- or RK-type methods to integrate the ODEs for linear or non-linear gating variables, in relation to computing the Jacobian matrix or other numerical techniques [7–14]. However, these highly accurate numerical methods require

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http://dx.doi.org/10.1016/j.compbiomed.2016.09.001
0010-4825/

significantly increased computation times. Originally, the Hybrid integration method selects a time step size that is governed by a couplet membrane potential offset, the minimal (ΔV_{min}), and the maximal (ΔV_{max}) [4,6]. A large time step is chosen when the membrane potential changes slowly, while a small time step is chosen when the membrane potential changes rapidly. Therefore, the Hybrid numerical method is able to increase the computational efficiency. However, the Hybrid method may choose a large time step near to local extrema and transition zones, because dV/dt is small, thus making the simulation inaccurate.

The goal of this study is a to develop a second-order accuracy for the adaptive method, which can properly select time steps to reduce computation times and improve the computational performance when the membrane potential encounters dramatic variations.

To correct the problem near to local extrema and transition zones, where dV/dt is small but d^2V/dt^2 is large, we take d^2V/dt^2 into consideration in choosing the time step. Moreover, we devise a function, the extremum-locator (*el*), to locate the local extrema of the AP to improve the accuracy. For convenience, we call the method CCL, an abbreviation of Chen-Chen-Luo, using the initials of the authors of this manuscript.

To study the performance, we test the algorithms using LR1 and LR2 [16,18] with the right ventricular (RV) models [21,22], the human ORd model [17] incorporating the human Markov I_{Ks} model [24], and the Courtemanche atrial model [25] incorporating a Markov I_{Na} model [26]. The results show that the traditional Hybrid method may choose a large time step (1 ms) near the peak and fail to capture the profile of the peak region. This flaw distorts the action potential and shortens or enlarges the action potential duration (APD). In contrast, our new method chooses a sufficiently small time step according to the change of the AP, and the resulting AP is stable. For stiff ionic models with Markov chains, the Δt_{max} of Hybrid methods have to be set to 0.1 ms or less manually to stabilize the simulation. In contrast, CCL methods can adjust time step size automatically and generate a stable AP.

Overall, our method is efficient, and more accurate than the traditional Hybrid method using the ORd model.

2. Models and numerical methods

2.1. Cardiac cell models

2.1.1. The Luo-Rudy guinea pig ventricular model

The phase 1 Luo-Rudy (LR1) ventricular model [16] is a mathematical reconstruction of the ventricular action potential (AP) and is based on Hodgkin-Huxley-type formulas [15]. The rate of change of the membrane potential (V) is defined as $dV/dt = -1/C\cdot(I_i+I_{st})$, where C ($1\mu F/cm^2$) is the membrane capacitance, I_{st} is a stimulus current, and I_i is the sum of the six ionic currents, defined as $I_i=I_{Na}+I_{Si}+I_K+I_{K1}+I_{Kp}+I_b$, where I_{Na} is the time-dependent sodium current, I_{Si} is the slow inward current, I_K is the time-dependent potassium current, I_{K1} is the time-independent potassium current, I_{Kp} is the plateau potassium current, and I_b is the time-independent background current. The ionic currents are governed by the time- and voltage-dependent opening and closure of ionic gates, whose gating variables are calculated using eight Ordinary Differential Equations (ODEs).

2.1.2. The Luo-Rudy dynamic model of the ventricular myocyte

We opted to use a modified dynamic LR2 model of the ventricular model (VM) action potential with the right ventricular (RV) cell model [18–20]. The action potential of the RV model consists of a significant “notch-and -dome” format in phase 2, where the membrane potential is nearly flat [21]. We expect that would cause an unpredictable change in the transmembrane potential and result in a distorted AP [22], and the LR2-RV model could be a perfect problem to test the adaptive methods.

In this model, the VM action potential was mathematically constructed including: ionic currents, pumps and exchangers and processes regulating intracellular concentration changes of Na^+, K^+ and Ca^{2+}. There was also a linkage between the sarcolemmal Ca^{2+} entry during the action potential upstroke and the Ca^{2+} release process of the junctional sarcoplasmic reticulum (JSR) that enabled relationships between the action potential time course and Ca^{2+} homeostasis to be theoretically considered. The electrical heterogeneity of ion channels [18] was expressed in the epicardial VM cell of the ventricle. Specifically, the density ratio of slow (I_{Ks}) to rapid (I_{Kr}) delayed rectifiers, G_{Ks}/G_{Kr}, for the epicardial cell was set at 23 in the right ventricle [19,20]. Additionally, the transient outward potassium current (I_{to}) was incorporated into the model by using the formulation of Dumaine et al. [21]. The maximum conductance G_{to} of I_{to} for the epicardial cell was adjusted to be 1.1 mS/μF in the right ventricle (RV) [21]. Detailed formulations and program source code of the LR2 model can be found in References [23].

2.1.3. The human O'Hara-Rudy dynamic (ORd) model of the ventricular myocyte

O'Hara et al. constructed their model based on undiseased human heart data [17]. They replaced the L-type Ca^{2+} current, K^+ currents, and Na^+/Ca^{2+} exchange in existing models. The ORd model enables us to simulate the three type epicardium cardiomyocyte (the epicardium, mid-myocardium and endocardium) electrophysiology by modify various ion channels parameters according to their electrophysiological characteristics. In this study, we select the epicardial cell, owing to its significant “notch-and-

Table 1
Performance of four methods applied to the LR1 ventricular AP model.

Method	V_{max} (mV) (%)	$(dV/dt)_{max}$ (mV/ms) (%)	APD_{90} (ms) (%)	TNP (ms) (%)	CPU_{time} (s) (fold)
RK4					
0.0001 ms	45.44 (100)	380.92 (100)	382.52 (100)	1.5046 (100)	1610 (1)
RL[a]					
0.001 ms	45.59 (100.33)	380.79 (99.97)	382.34 (99.95)	1.53 (101.69)	123.71 (7.68E−02)
0.0001 ms	45.46 (100.04)	380.91 (100)	382.35 (99.96)	1.51 (100.36)	1251.51 (7.77E−01)
Hybrid 0.05–0.2 mV[b]					
0.001–1 ms	45.57 (100.29)	380.92 (100)	382.5 (99.99)	1.56 (103.68)	0.34 (2.11E−04)
0.001–0.5 ms	45.57 (100.29)	380.92 (100.00)	382.47 (99.99)	1.56 (103.68)	0.4 (2.48E−04)
0.001–0.1 ms	45.57 (100.29)	380.92 (100)	382.44 (99.98)	1.56 (103.68)	0.8 (4.97E−04)
CCL 0.1 mV[c]					
0.001–1 ms	45.47 (100.07)	380.45 (99.88)	382.56 (100.01)	1.51 (100.36)	0.18 (1.12E−04)
0.001–0.5 ms	45.47 (100.07)	380.45 (99.88)	382.64 (100.03)	1.51 (100.36)	0.23 (1.43E−04)
0.001–0.1 ms	45.47 (100.07)	380.45 (99.88)	382.48 (99.99)	1.51 (100.36)	0.71 (4.41E−04)

Note: (a) RL, the Rush-Larsen method with fixed integration time step of 0.001 and 0.0001 ms; (b) Hybrid, the Hybrid method with a couplet of (0.05–0.2-mV) with a minimum time increment of 0.001 ms during stimuli (protective zone) with the various global time steps of Δt_{max}(1, 0.5 and 0.1 ms); (c) CCL, the Chen-Chen-Luo method with given membrane potential offset $\Delta V=0.1$–mV with a minimum time, Δt_{min}, step of 0.001 ms and various maximum time steps, Δt_{max}, (1, 0.5 and 0.1 ms); V_{max}, peak amplitude of the membrane potential from phase 0 to phase 1 of the AP; $(dV/dt)_{max}$, maximum rate of the rise of V; APD_{90}, action potential duration from the onset of stimulation to 90% repolarization; TNP, timespan near peak: membrane potential 38.96 mV - V_{max} −38.96 mV; CPU_{time}, computation time.