Spatial Heart Simulation and Adaptive Wave Propagation

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INTRODUCTION

Sudden cardiac death, caused mostly by ventricular fibrillation, is responsible for at least five million deaths in the world each year. Despite decades of research, the mechanisms responsible for ventricular fibrillation are not well understood. As most computational studies are limited primarily to planar simulations, experiments so far have not elucidated the mechanisms responsible for spatial phenomenon (Janse, Wilms-Schopman, & Coronel, 1995) of ventricular fibrillation.

It would be important to understand how the onset of arrhythmias that cause fibrillation depends on details such as heart size (Winfree, 1994), geometry (Vetter & McCulloch, 1998; Panfilov, 1999), mechanical and electrical state, anisotropic fiber structure (Fenton & Karma, 1998), and inhomogeneities (Antzelevitch et al., 1999; Wolk, Cobbe, Hicks, & Kane, 1999). The main difficulty in development of a quantitatively accurate simulation of an entire three-dimensional human heart is that human heart muscle is a strongly excitable medium whose electrical dynamics involve rapidly varying, highly localized fronts (Cherry, Greenside, & Henriquez, 2000).

In ventricular tissue (which is the most important to study) the width of a depolarization front is usually less than half mm and a simulation that approximates the dynamics of such a front requires a spatial resolution of $\Delta x \leq 0.1$ mm. Forasmuch the muscle in an adult heart has a volume of 250 cm^3, and so a uniform spatial representation requires at least $2.5 \cdot 10^8$ nodes. Taking into account that each node's state is described with at least 50 floating number (with at least 4 byte resolution) the necessary storage space rises higher than 50GB (personal computers have no opportunity to handle such a huge amount of data in memory). It is known that the rapid depolarization of the cell membrane (this is the fastest event in heart functioning) blow over in few hundred microseconds. A reasonable resolution of this event requires a time step $\Delta t \leq 25$ microseconds. Since dangerous arrhythmias such as ventricular fibrillation may require several seconds to become established, the 10^{10} floating point numbers associated with the spatial representation would have to be evolved over 10^5 - 10^6 time steps. Such a huge uniform mesh calculation currently exceeds all existing computational resources (Cherry, Greenside, & Henriquez, 2003).

Previous efforts to improve the efficiency of simulations have followed several approaches. The most common way of simplification is based on a reduced mathematical model that can reproduce some of the behavior observed in more complex models but with only a few coupled fields. One widely used example is the two-variable FitzHugh–Nagumo model (FitzHugh, 1961), which describes behavior of a general excitable medium. This model can be modified to approximate various types of cardiac dynamics (Berenfeld & Pertsov, 1999). Another example is a three-variable model developed by Fenton and Karma (Fenton & Karma, 1998) that is designed to reproduce the restitution curves of more complex cardiac models. Albeit these and other simplified models can reproduce many known features of cardiac electrical propagation, some electronic (Fenton, 2000) and drug effects cannot be handled properly. Accordingly, efficient algorithms for more quantitatively-based models are still desirable.

The spatiotemporal structure of wave dynamics in excitable media suggests an automatically adjustable resolution in time and space. The basic idea of this improvement (Cherry et al., 2000, 2003) is deducted

from experiments (Winfree et al., 1996; Witkowski et al., 1998) and simulation (Courtemanche, 1996), which recommends that the function of electrical membrane potential of a ventricular cell $f_V(t,x,y,z)$ in the fibrillating state consists of many spirals (for approximately two-dimensional tissue such as the right ventricle and atrium) or of many scroll waves (for thicker cardiac tissue such as the left ventricle). An interesting property of these spatiotemporal disordered states is that the dynamics is *sparse*: at any given moment, only a small volume fraction of the excitable medium is depolarized by the fronts, and away from them the dynamics are slowly varying in space and time. This idea permits the decrement of necessary computational effort and storage space (only the time dependent depolarization fronts have to be represented with high resolution instead of the whole tissue volume) for regular beats but the total front volume can greatly increase with a fibrillating state. By varying the spatiotemporal resolution to concentrate computational effort primarily along the areas with large spatial and temporal gradients, it is possible to reduce greatly the computational effort and memory required.

Most of previous studies (Rousseau & Kapral, 2000; Vigmond & Leon, 1999) implemented the adaptivity, locally and dynamically, by varying either the spatial or temporal resolution, but not both. However, these methods decreased the global processing volume significantly and they generally could not yield computational savings as significant as the time- and space-adaptive strategies. All of these adaptive approaches have the advantages that they are largely model- and method-independent.

The heart modeling method presented in this article is based on an algorithm developed by Berger and coworkers (Bell, Berger, Saltzman, & Welcome, 1998) and used successfully for three-dimensional simulations. Although the earlier presented methods involved dynamic time and space analysis, the a priori heart irregularities were neglected. The Purkinje fiber net has an unknown shape and highly varies from patient to patient. To handle this problem, we involved in our method the average heart tissue-topology that admits the appliance of probabilistic descriptions.

The rest of the article describes the applied human cell and tissue model, the time and spatial position dependent heart and torso model, the adaptively variable resolution wave-propagation method, and the parallel processing of these algorithms aided by graphic cards.

MATERIALS AND METHODS

Applied Human Cell and Tissue Model

We used the ten Tusscher heart cell model (ten Tusscher, Noble, Noble, & Panfilov, 2004) for ventricular and Nygren's model (Nygren, Fiset, Firek, Clark et al., 1998) for atrial cells, to investigate the accuracy and efficiency of the simulation algorithm. These models are based on recent experimental data on most of the major ionic currents, such as the fast sodium, L-type calcium, transient outward, rapid and slow delayed rectifier, and inward rectifier currents. With the inclusion of basic calcium dynamics, the contraction and restitution mechanism of the muscle cells can be investigated.

The model is able to reproduce human epicardial, endocardial, and M cell action potentials, to modify the internal state of the cells and to show that differences can be explained by differences in the transient outward and slow delayed rectifier currents. These properties allow the study of evolvement of reentrant arrhythmias. The conduction velocity restitution of this model is broader than in other models and agrees better with available data. We conclude that the applied model can reproduce a variety of electrophysiological behaviors and provides a basis for studies of reentrant arrhythmias in human heart tissue.

As presented in ten Tusscher et al. (2004), the cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries representing the different ionic currents and pumps. The electrophysiological behavior of a single cell can be described by equation (1):

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_{memb}} \tag{1}$$

where V is the voltage, t is time, I_{ion} is the sum of all trans-membrane ionic currents, I_{stim} is the externally applied stimulus current, and C_{memb} is the cell capacitance per unit surface area.

The ionic current's sum is given by the equation (2):