Why do we need supercomputers to understand the electrocardiographic T wave?

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Abstract

**introduction** Propagation of depolarisation and repolarisation in myocardium result from an interplay of membrane potential, transmembrane current, and intercellular current. This process can be represented mathematically with a reaction-diffusion (RD) equation. Solving RD equations for a whole heart requires a supercomputer. Therefore, earlier models used predefined action potential (AP) shapes and fixed propagation velocities. We discuss why RD models are important when T waves are studied.

**methods** We simulated propagating AP with an RD model of the human heart, which included heterogeneity of membrane properties. Computed activation times served as input to a model that used predefined AP, and to a “hybrid model” that computed AP only during repolarisation. The hybrid model was tested with different spatial resolutions. ECGs were computed with all three models.

**results** Computed QRS complexes were practically identical in all models. T waves in the fixed-AP model had 20 to 40\% larger amplitudes in leads V1–V3. The hybrid model produced the same T waves as the RD model at 0.25-mm resolution, but underestimated T-wave amplitude at lower resolutions.

**conclusion** Fixed AP waveforms in a forward ECG model lead to exaggerated T waves. Hybrid models require the same high spatial resolution as RD models.
List of abbreviations

**AP** action potential, 2, 4, 5, 6, 7

**ECG** electrocardiogram, 2, 4, 5, 7

**RD** reaction-diffusion, 2, 4, 5, 7

**TNNP** Ten Tusscher–Noble–Noble–Panfilov [membrane model], 5
1 Introduction

Mathematical models have played a prominent role in the study of ion channels in the cardiac cell membrane, where a succession of models, experiments, and refutations has led to the theories that are currently successful in explaining the action potential (AP) [1]. Accurate models for human ventricular myocytes are now available [2, 3]. By connecting such models together one can create a model that simulates propagating action potentials in the heart. Such models are called reaction-diffusion (RD) models, where “reaction” represents the ionic current sources and “diffusion” is the mathematical description of the current spread through the tissue.

Because of the steepness of the myocardial action potential upstroke, and the consequent steepness of the spatial distribution of transmembrane potential, reaction-diffusion models must have a high spatial resolution of 0.1 to 0.25 mm. Thus, modeling an entire (human) heart with such models requires evaluation of potentials at 12 million points or more [4]. Such models require at least 8 GB memory – twice as much as a personal computer can possibly have – and take several days of processor time to compute a single heartbeat. Supercomputers with tens or hundreds of processors and very large memory are typically used to run such models [5].

A more economical way to model the entire heart is to assume a fixed AP shape and fixed propagation velocities [6]. This removes the need to evaluate ionic currents and diffusion currents at millions of sites, and allows the use of a much lower spatial resolution (in the order of 1 mm). The disadvantage of this approach is that AP changes due to electrical current flow between cells with different characteristics or different activation times are not taken into account.

One of the compromises that can be made between reaction-diffusion and fixed-AP models is a reaction-diffusion model at low spatial resolution. Because such a model would not be able to simulate propagated depolarisation, its elements must be stimulated at fixed activation times. The advantage over a fixed-AP model is that the effect of cellular coupling is taken into account during the plateau and repolarisation phase of the AP.

We compared the accuracy of such models for the purpose of ECG simulation.
2 Methods

We simulated propagating AP with an RD model of the human heart at 0.25-mm resolution. Details of this model have been described previously [4, 5]. Ionic currents were computed with the 2004 version of the TNNP model of the human ventricular myocyte [3]. The model included transmural and left to right-ventricular heterogeneity of membrane properties. Computed activation times served as input for two simplified models:

- a “fixed-AP” model, which used predefined AP, and
- a “hybrid model,” an RD model in which all cells were stimulated at fixed times, but AP shapes were computed.

Fixed AP were obtained from simulations of isolated cells, and represented the same heterogeneity of cell types as the heart model. The hybrid model was tested with spatial resolutions of 0.25, 0.5, and 1.0 mm. ECGs were computed with all three models.
3 Results

As expected, computed QRS complexes were practically identical in all models. Figure 1 shows that T waves in the fixed-AP model had 20 to 40% larger amplitudes in the precordial leads V1–V3, became biphasic in lead III, and notched in leads II and aVF. In contrast, the hybrid model produced the same T waves as the RD model at 0.25-mm resolution, but underestimated T-wave amplitude in V1–V3 at lower resolutions. The case of 1-mm resolution is shown in figure 2.

[Figure 1 about here.]

[Figure 2 about here.]
4 Discussion

Fixed AP waveforms in a forward ECG model can lead to exaggerated T waves. Hybrid models only equal RD models when used with the same spatial resolution. This presents only a very small efficiency improvement over a full RD model. Thus, accurate simulation of electrocardiographic T waves does require an RD model. In contrast, the QRS complex is not very sensitive to the shape of the AP, and can be simulated with any model that correctly represents activation times [6, 7]. Only in case of severe propagation problems does this imply the use of an RD model.

The differences in T-wave shape that we observed are probably specific for strong transmural heterogeneity of repolarisation times. If such large gradients are not present in a model, the use of high spatial resolution is likely to be less important.

Our hybrid model used activation times determined by our RD model. Using exactly the same activation times allowed us to determine T-wave changes independent of activation order. In practice, of course, activation times for a hybrid model must be computed somehow. Typically, fixed propagation velocities are used for such purposes [6]. Another interesting method is to use a modification of the membrane model that slows down the depolarizing sodium current to make the depolarisation wavefront thicker and less steep [8]. This allows the use of a lower spatial resolution. However, the side effects of such modifications are hard to predict, so this method too should be used with caution.
References


Figure 1: ECG simulated by the full RD model (black) and by the fixed-AP model (red online/grey). Tick marks at the horizontal axis are placed at 100-ms intervals. The vertical scale is in milliVolts.
Figure 2: ECG simulated by the full RD model at 0.25-mm resolution (black) and by the hybrid model at 1-mm resolution (red online/grey). Tick marks at the horizontal axis are placed at 100-ms intervals. The vertical scale is in milliVolts.