Diffusion Reaction Eikonal Alternant Model: Towards Fast Simulations of Complex Cardiac Arrhythmias

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Abstract

Reaction-diffusion (RD) computer models are suitable to investigate the mechanisms of cardiac arrthymias but not directly applicable in clinical settings due to their computational cost. On the other hand, alternative faster eikonal models are incapable of reproducing reentrant activation when solved by iterative methods. The diffusion reaction eikonal alternant model (DREAM) is a new method in which eikonal and RD models are alternated to allow for reactivation. To solve the eikonal equation, the fast iterative method was modified and embedded into DREAM. Obtained activation times control transmembrane voltage courses in the RD model computing, while repolarization times are provided back to the eikonal model. For a planar wave-front in the center of a 2D patch, DREAM action potentials (APs) have a small overshoot in the upstroke compared to pure RD simulations (monodomain) but similar AP duration. DREAM conduction velocity does not increase near boundaries or stimulated areas as it occurs in RD. Anatomical reentry was reproduced with the S1-S2 protocol. This is the first time that an iterative method is used to solve the eikonal model in a version that admits reactivation. This method can facilitate uptake of computer models in clinical settings. Further improvements will allow to accurately represent even more complex patterns of arrhythmia.

1. Introduction

Reaction-diffusion (RD) computer models are suitable to investigate the mechanisms of cardiac arrhythmias but not directly applicable in clinical settings due to their computational cost. For instance, The monodomain equation correspond to one of the RD models in which equal extra and intracellular anisotropy ratios are assumed:

$$\beta C_{\mathrm{m}} \frac{\partial V_{\mathrm{m}}}{\partial t} = \nabla \cdot \sigma_{\mathrm{m}} \nabla V_{\mathrm{m}} - \beta(I_{\mathrm{ion}}(V_{\mathrm{m}}, \eta)) \qquad (1)$$

where β is the surface-to-volume ratio, C_{m} is the capacitance per unit area, V_{m} is the transmembrane voltage, σ_{m} is twice the harmonic mean of the extra and intracellular conductivities and, I_{ion} is the current density passing through the ionic channels that depends on state variables η.

Alternatively, numerical solutions of the eikonal equation are significantly faster than RD equations due to the simplicity of the eikonal equation and the relaxed mesh resolution requirements:

$$\sqrt{\nabla T^{\top} M \nabla T} = 1 \,, \qquad (2)$$

where M is the squared conduction velocity (CV) tensor and T is the mapping function between nodes' coordinates and their activation times (AT). The eikonal model provides a close approximation of electrical wave propagation under healthy conditions if only one activation cycle is represented. However, standard eikonal methods do not account for repolarization or reactivation of the cardiomyocytes. This limitation prevents the simulation of reentry, which is a major limitation in the context of complex arrhythmia. To overcome this problem, Pernod et al. and Gassa et al. introduced new methods based on a modified version the Fast Marching Method (FMM) to allow reactivation of the nodes while solving the eikonal equation [1, 2]. Nonetheless, numerical errors can appear when using single pass methods because the characteristics of the anisotropic Eikonal equation do not align with the gradient vector of its viscosity solution [3]. These numerical errors are more relevant in areas where the gradient of the wave-front does not match the characteristic of T. These errors do not decrease numerical stability and then can be unnoticed. Alternative methods have been proposed to solve the anisotropic eikonal equation such as the Fast Iterative Method (FIM) [4] and the Buffered Fast Marching Method [5].

There are two factors that hinder reproducing reentry with iterative solution methods. First, ATs can change several times while solving the eikonal equation iteratively unlike in single pass methods. Second, ATs and repolarization times (RTs) have a mutual dependency. The RT of every node in a given cycle depends on the effective refrac-

tory period and AT in the same cycle. Similarly, the AT depends on whether repolarization from the activation in previous cycle happens before or after an activation attempt. These two conditions are challenging for the calculation of the AT in the next cycle given that the AT from the first cycle is constantly being updated. Normally, the final converged ATs are only known at the end of the simulation. However, ATs are required earlier in the algorithm when simulating reentry. In this work, DREAM is introduced as a novel method to overcome this major limitation.

2. Methods

DREAM is a mixed model in which the RD model and the eikonal model are combined and alternated in time. The goal of this model is to accurately simulate reactivation patterns in low-resolution meshes where the RD model would fail (i.e. element size of $800\,\mu\mathrm{m}$). DREAM is inspired by the reaction eikonal model [6] and the multi-frontal Fast Marching Method [1]. The FIM is used to solve the anisotropic eikonal equation.

Figure 1 shows the steps involved in DREAM. First, the FIM is iterated until the minimum AT of the nodes in the active list is greater than a given period of time τ_e (Figure 1, Step 1). Then, the calculated ATs are used to compute I_diff that approximates the diffusion current of a planar wavefront on a high resolution patch (element size of $200\,\mu\mathrm{m}$) solved with the pure monodomain model [2]. I_diff is defined as a triple Gaussian function with parameters optimized to decrease the error between I_diff and the diffusion current in a high resolution mesh (Figure 2). Then, the RD model is computed by adding I_diff to the right hand side of the parabolic equation of the system (Figure 1, Step 2):

$$\beta C_\mathrm{m} \frac{\partial V_\mathrm{m}}{\partial t} = I_\mathrm{diff} - \beta(I_\mathrm{ion}(V_\mathrm{m}, \eta)) \qquad (3)$$

similar to the RE$^-$ version of the reaction eikonal model [6].

To avoid conflict due to the constant updates of the ATs, the RD model is only computed until $t = \tau_\mathrm{e} - \tau_\mathrm{s}$, where τ_s is a "safety margin" in time to assure that the nodes with ATs that belong to the interval $[0, \tau_\mathrm{e} - \tau_\mathrm{s}]$ are not affected by following iterations (Figure 1, Step 3). While the RD model is running, RTs are defined as the time points when the transmembrane voltage of an activated node X crosses the threshold $\nu_{th} = -70\,\mathrm{mV}$) to more negative values (Figure 1, Step 4).

It is possible that some activated nodes do not cross that threshold in the interval $[0, \tau_\mathrm{e} - \tau_\mathrm{s}]$. Nonetheless, their RTs are required to know whether they can be reactivated in the next FIM iteration. To solve this issue, the ionic model is used to approximate the V_m to obtain approximated RT ($\tilde{RT}$). The ionic model is run for

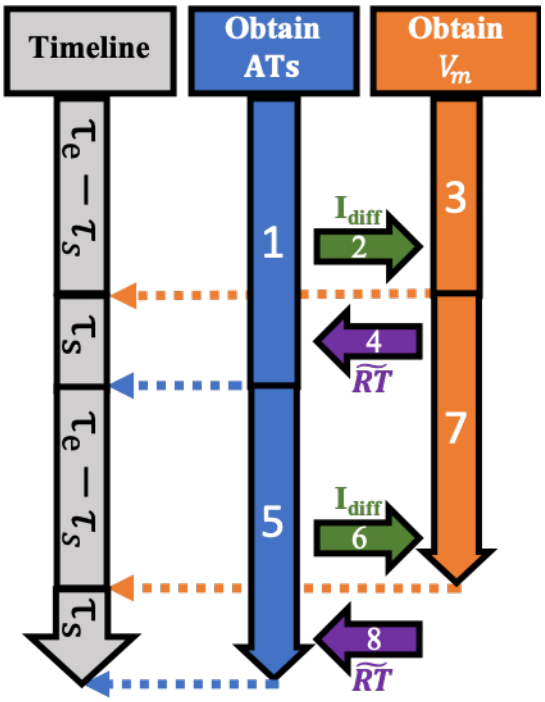

Figure 1. Steps of DREAM algorithm: Eikonal and RD models alternate to calculate ATs and V_m, respectively. ATs calculated with FIM are used to compute I_diff needed in the RD model. V_m calculated with the RD model is used to get real or approximated RTs needed in the FIM to solve eikonal equation. Numbers indicate the order in which DREAM runs every step, τ_e is the time period calculated by FIM every iteration, and τ_s is the safe margin of time to avoid conflicts between cycles

$t \in [\tau_\mathrm{e} - \tau_\mathrm{s}, \min(\tilde{\mathrm{RT}}, 2\tau_\mathrm{e})]$. Once all the nodes are assigned with real or approximated RTs, the eikonal model runs again until the minimum AT of the nodes in the active list is greater than $2\tau_\mathrm{e}$. This process is repeated by alternating models until t reaches the end of the simulation time (Figure 1, Steps 5, 6, 7 and 8).

To test the model, two experiments were performed the first in a 2D patch and the second in a 3D ring. The 2D patch consisted of a triangular mesh of $5 \times 5\,\mathrm{cm}$ and resolutions of $200\,\mu\mathrm{m}$ and $800\,\mu\mathrm{m}$ for the RD model and DREAM, respectively. The planar waves were produced by stimulating one edge of the patch. The second stimulus was applied $400\,\mathrm{ms}$ after the first stimulus at the same location. The monodomain model was selected as the RD model. CV for DREAM was $1000\,\mathrm{mm\,s^{-1}}$ and the conductivities were tuned accordingly for the RD model. We chose the human atrial cell model suggested by Courtemanche et al. [7]. For the anatomical reentry in a 3D mesh, a ring-shaped mesh of tetrahedral elements was used. The average resolution in the ring was $576\,\mu\mathrm{m}$) for both mod-

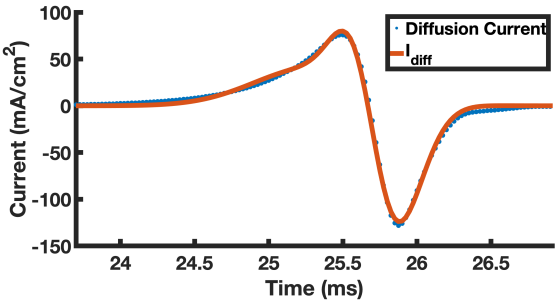

Figure 2. I_{diff} fitted to the diffusion current obtained from pure monodomain simulation of a planar wave on a high-resolution mesh. A triple Gaussian is used to approximate the diffusion current. AT $\approx$ 24 ms.(Sample Frequency: 1 kHz)

els. The inner and outer diameters were 20 and 24 mm respectively. The CV in the longitudinal direction was 200 mm s^{-1} with an anisotropy ratio of 3. Monodomain conductivities were tuned to match these velocities. An S1-S2 protocol was used to induce unidirectional block followed by reentry. The first stimulus was applied at approximately 60° from the first stimulus and 328 ms) later. The sample frequency was 1 kHz unless stated otherwise. All tissue simulations were performed using openCARP [8].

3. Results

In the RD model, wave propagation in the 2D high-resolution patch was accelerated close to the stimulated edge and the opposing mesh boundary. DREAM in the 2D low-resolution patch kept a constant CV everywhere. Figure 3 compares action potentials (APs) in both models. Action potential durations (APDs) difference between models was smaller than 1 ms (Figure 3A) and the upstroke was closely matching with a small overshoot in DREAM (Figure 3B). The CV after the second stimulus in DREAM model did not change while the APD shortened. In the RD model both APD and CV decreased as expected. If the time period between stimulus was prolonged to 1000 ms, CV and APD did not change in both models (data not shown).

The experiment in the ring produced an anatomical reentry in both models. Figure 4 shows the maps of the last AT for each node at 850 ms in both models and the difference map between the two models. The reentry cycle length was ≈320 ms at that moment. The cycle length in DREAM simulation remained constant over time while the cycle length in the RD model prolonged over time due to CV restitution. In the RD model (Figure 4A), these differences were smaller and the wave-front was almost perpendicular to the boundaries. In DREAM (Figure 4B), nodes located at the inner boundary had earlier ATs than the nodes located at the outer boundary at the same angle due to the

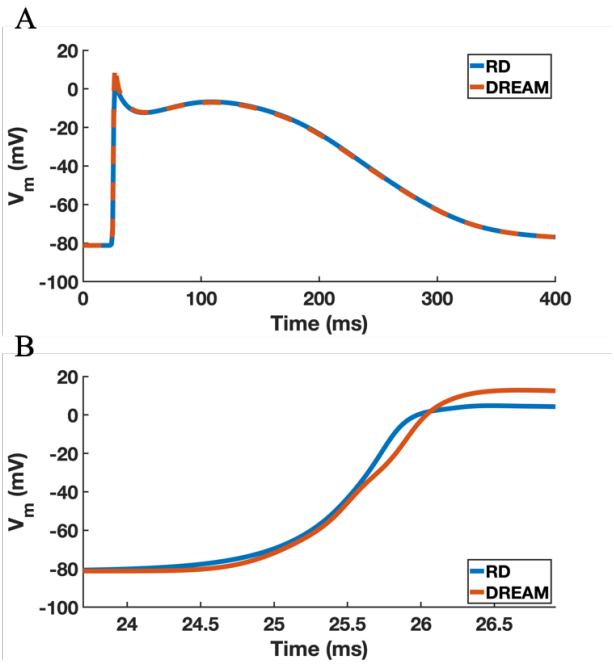

Figure 3. A) Complete APs of RD and DREAM for a node in the center of the mesh. B) AP upstroke (Sample Frequency: 4 kHz).

shorter geodesic distance to the stimulus location. The difference map (Figure 4C) shows that propagation in the RD model accelerated at the outer boundary and slowed down at the inner boundary.

4. Discussion

DREAM features several characteristics from previously implemented eikonal models [1, 2, 6]. The novelty of this model lies in incorporating node reactivation while solving the eikonal equation with an iterative method. The FIM has the advantage of being more suitable for propagation in anisotropic media than single pass methods as FMM [4]. Additionally, the FIM can parallelize which would further increase computational speed in the future. The DREAM requires slightly longer computational times than the RD model when compared on the same mesh. However, computational speed is gained from the possibility to use the DREAM in coarse meshes in which the RD models diverge.

Our results show that reactivation patterns such as prepacing a 2D patch and anatomical reentries are possible. To reproduce physiological reentries, it is necessary to incorporate at least the influence of the diastolic interval on the CV [2, 9]. Nonetheless, additional factors (i.e. wall thickness, wave-front curvature, source-sink mismatch effects) that markedly affect CV should also be incorporated to accurately reproduce diseased conditions.

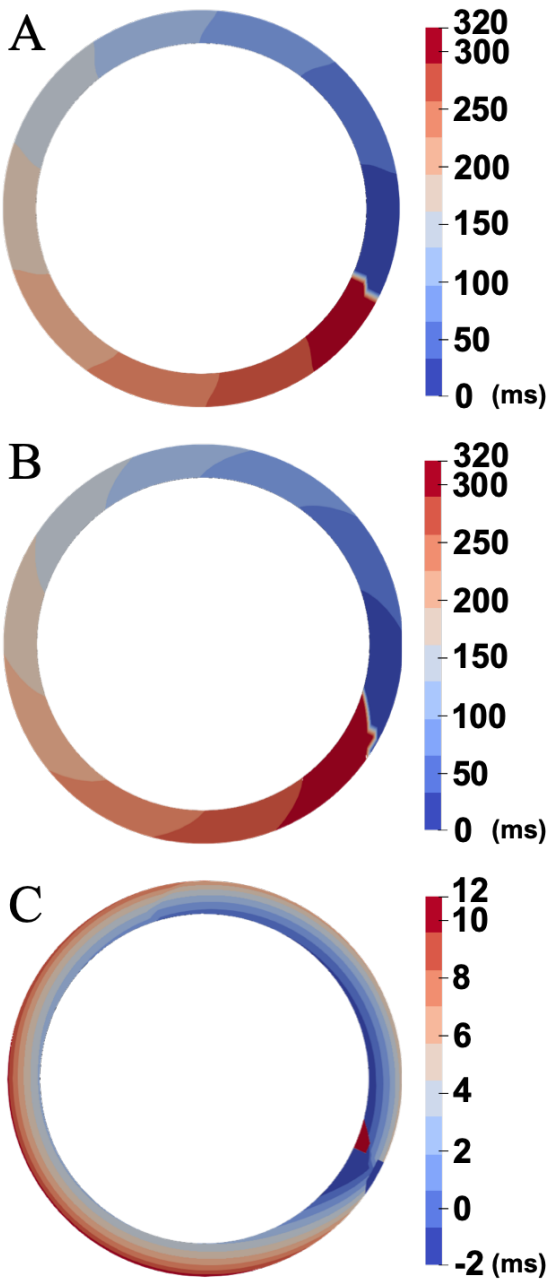

Figure 4. Anatomical reentry: A) ATs in the RD model (AT_{RD}). B) ATs in DREAM (AT_{DREAM}). C) Error map AT_{DREAM} - AT_{RD}.

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References

[1] Pernod E, Sermesant M, Konukoglu E, Relan J, Delingette H, Ayache N. A multi-front eikonal model of cardiac electrophysiology for interactive simulation of radio-frequency ablation. Computers Graphics 2011;35(2):431–440.

[2] Gassa N, Zemzemi N, Corrado C, Coudière Y. Spiral waves generation using an eikonal-reaction cardiac electrophysiology model. In International Conference on Functional Imaging and Modeling of the Heart. Springer, 2021; 523–530.

[3] Sethian JA, Vladimirsky A. Ordered upwind methods for static hamilton–jacobi equations: Theory and algorithms. SIAM Journal on Numerical Analysis 2003;41(1):325–363.

[4] Fu Z, Kirby RM, Whitaker RT. A fast iterative method for solving the eikonal equation on tetrahedral domains. SIAM Journal on Scientific Computing 2013;35(5):C473–C494.

[5] Cristiani E. A fast marching method for hamilton-jacobi equations modeling monotone front propagations. Journal of Scientific Computing 2009;39(2):189–205.

[6] Neic A, Campos FO, Prassl AJ, Niederer SA, Bishop MJ, Vigmond EJ, Plank G. Efficient computation of electrograms and ecgs in human whole heart simulations using a reaction-eikonal model. Journal of Computational Physics 2017;346:191–211.

[7] Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. American Journal of Physiology Heart and Circulatory Physiology 1998;275(1):H301–H321.

[8] Plank G, Loewe A, Neic A, Augustin C, Huang YL, Gsell MA, Karabelas E, Nothstein M, Prassl AJ, Sánchez J, et al. The opencarp simulation environment for cardiac electrophysiology. Computer Methods and Programs in Biomedicine 2021;208:106223.

[9] Loewe A, Poremba E, Oesterlein T, Luik A, Schmitt C, Seemann G, Dössel O. Patient-Specific Identification of Atrial Flutter Vulnerability–A Computational Approach to Reveal Latent Reentry Pathways. Frontiers in Physiology 2019; 9:1910.

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