# The Inverse Problem of Phase Singularity Distribution: An Eikonal Approach

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## Abstract

*The aim of this paper is to develop a tool to construct initial conditions for a cardiac propagation model, in which phase singularities are positioned at predefined locations. Our approach relies on the eikonal-diffusion equation (extended to handle reentrant activations) to generate phase maps describing reentries around phase singularities. Through a mapping between phase and cell state, these phase maps are used to create initial conditions from which evolution is simulated in the monodomain framework.*

*This method was applied to initiate functional reentries in an atrial model. Reentrant circuits were placed at 24 different anatomical locations. Phase singularities tracked during the simulations meandered in the vicinity of the desired locations specified in the eikonal problem. The results suggest that this tool could help in the creation of a library of different forms of simulated arrhythmias.*

## 1. Introduction

Phase singularity analysis provides a tool to quantify the complex spatio-temporal behavior observed in computer models or animal models of cardiac arrhythmia [1]. During a reentrant activation, a phase singularity is located at the center of the rotating wave or at the pivot point of a U-turn. Tracking phase singularities in simulated or experimental data is a well established process [2]. It enables to count the number of simultaneous wavelets and identify the location of arrhythmogenic regions associated with reentries or wavebreaks.

The associated inverse problem consists in constructing an initial condition for a reaction-diffusion system (describing electrical propagation in the heart) with a given spatial distribution of anatomical/functional reentries. This problem is inspired by the desire to reproduce the wavelet dynamics measured in experiments or in patients when only limited information is available (typically pathways of reentry) [3]. Another application is to facilitate the initiation of a large number of episodes of the same arrhythmia. This would help investigate the effect of intra- or interpatient variability in simulation studies.

We aim to tackle this problem by solving an eikonal-diffusion equation that generates phase maps. This equation predicts activation times based on tissue conduction properties (only depolarization is considered). In a previous work, the eikonal-diffusion equation was extended to handle anatomical/functional reentries and wavefront collisions [4]. A dedicated finite-element-based method was developed to solve this equation on a triangular mesh. Boundary conditions on activation times were used to specify pathways of reentry.

In this paper, this eikonal approach is applied to initiate functional reentries in a simplified atrial model. The ability to initiate spirals waves at predefined locations is evaluated. Monodomain simulations are run to track the evolution and assess the stability of phase singularities.

## 2. Methods

### 2.1. Models of cardiac propagation

The propagation of the cardiac impulse in the myocardium can be described by the evolution of the membrane potential field $V_m(\mathbf{x}, t)$. According to the monodomain theory, this evolution is governed by a reaction-diffusion equation [5]:

$$C_m \frac{\partial V_m}{\partial t} = \beta^{-1} \nabla \cdot \boldsymbol{\sigma} \nabla V_m - I_{\text{ion}} \qquad (1)$$

where $C_m$ is the membrane capacitance per unit area of membrane, $\beta$ is the area of membrane per unit volume, $\boldsymbol{\sigma}$ is the (effective) conductivity tensor, and $I_{\text{ion}}$ is the membrane ionic current. No-flux boundary condition is assumed.

Activation time $\tau$ can be defined as the time at which $V_m$ crosses the threshold $-60$ mV when the time derivative of $V_m$ is positive. The resulting field $\tau(\mathbf{x})$ forms an activation map. An equation for this field can be derived from the monodomain equation using singular perturbation theory, leading to the so-called eikonal-diffusion equation [4, 6]:

$$\|\mathbf{c}\nabla\tau\| = \mathbf{1} + \nabla \cdot (\mathbf{D}\nabla\tau) \ . \qquad (2)$$

The link with the monodomain equation is obtained through the relations:

$$\mathbf{c} = \left(\frac{k_m \boldsymbol{\sigma}}{\beta C_m}\right)^{1/2} \quad \text{and} \quad \mathbf{D} = \frac{\boldsymbol{\sigma}}{\beta C_m} \,. \tag{3}$$

The membrane model-dependent parameter $k_m$ is such that the conduction velocity ($CV$) of a plane wave is $CV = \sqrt{k_m \sigma / \beta C_m}$. No-flux boundary condition on $\tau$ is assumed [6].

The eikonal-diffusion equation is still valid for reentrant activations. To account for the periodic nature of wavefront propagation, the phase transformation $\phi = \exp(2\pi i \tau / T)$ is applied, where $T$ is the period of reentry [4]. In this complex formulation, the transformed eikonal-diffusion equation can handle anatomical/functional reentries as well as wavefront collisions. A dedicated iterative finite-element-based method has been developed to solve this equation on a triangular mesh [4]. The algorithm starts with an initial estimate of a reentrant activation map reproducing the desired qualitative or topological features (such as reentrant pathways). The activation map is then corrected by successive Newton iterations applied to the transformed (non-linear) eikonal-diffusion equation [4]. The period $T$ for which a reentrant solution exists (for given conduction and membrane properties) is automatically determined as part of the process [7] (only the phase $2\pi\tau/T$, which is defined modulo $2\pi$, is used until then).

## 2.2. Simulation of reentries

The procedure for initiating a spiral wave at a predefined location on a triangulated surface representing the cardiac tissue is as follows:

1. Draw a closed curve representing the presumed trajectory of the phase singularity on the surface (Fig. 1A). The interior region of the curve is typically composed of a strip of triangles. The length of the curve is intended to be roughly the wavelength of the depolarization wave.

2. Set $\tau$ to values from 0 to $T$ along the closed curve (according to the curvilinear coordinate).

3. Interpolate $\tau$ in the entire surface by solving the Laplace problem $\Delta\tau = 0$ with the boundary condition defined at step 2. Discontinuities are handled by phase transformation, like for the eikonal-diffusion problem [7].

4. Solve iteratively the eikonal-diffusion equation, starting with the interpolated activation map computed at step 3 as initial condition (Fig. 1B). During this step, the triangles in the interior region of the curve ("spiral core") are discarded.

5. Create a mapping between activation time and cell state using a single-cell simulation of a cardiac cell paced at cycle length of $T$ [7].

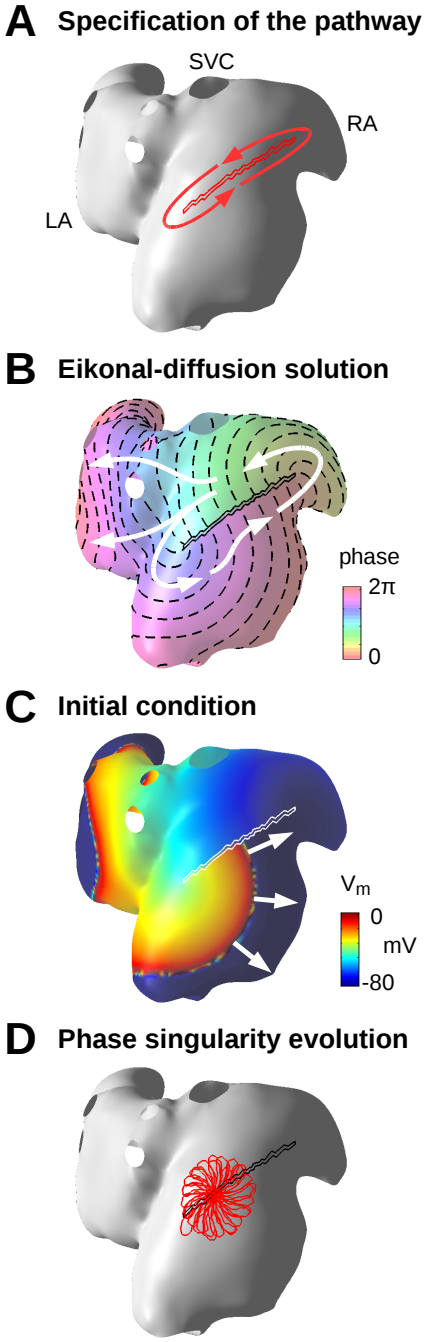


Figure 1. Illustration of the method in a model of human atria (right-anterior view): (A) Reentrant pathway, in red. (B) Activation map obtained by solving the eikonal-diffusion equation; 20 isochrones are shown as dashed lines. (C) Initial condition constructed from the activation map. (D) Trajectory of the phase singularity (in red) resulting from the monodomain simulation. LA: left atrium; RA: right atrium; SVC: superior vena cava.

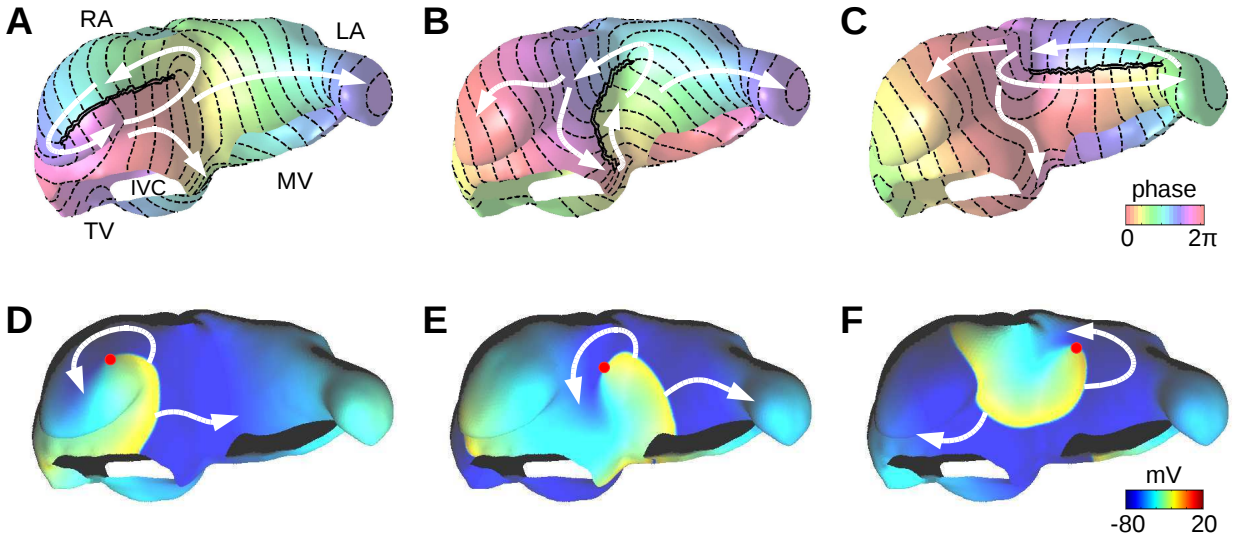


Figure 2. Initiation of functional reentry at three different locations in an atrial model (top view). (A)–(C) Activation maps obtained by solving the eikonal-diffusion equation; 20 isochrones are shown as dashed lines. (D)–(F) Membrane potential maps after about one period simulated from the initial condition constructed from the activation map just above. The red dot indicates the location of the phase singularity. LA: left atrium; RA: right atrium; MV: mitral valve; TV: tricuspid valve; IVC: inferior vena cava.

6. Create an initial condition (tissue state) for the monodomain equation by applying the mapping (step 5) to the activation map (step 4), see Fig. 1C.

7. Run a monodomain simulation from the initial condition (step 6).

8. Track the evolution of phase singularities (Fig. 1D) using a method adapted from Iyer et al. [2].

This approach was applied to a simplified model of the human atria (Fig. 1A). The atrial epicardium was represented by a triangular surface mesh (13,798 nodes). Monodomain simulations were run in 3D cubic mesh (748,741 nodes) representing the atrial myocardium. The coarse atrial surface model lied within the bulk of the 3D model to enable extrapolation of tissue state from 3D-surface to full 3D.

Parameters for monodomain propagation were $C_m = 1$ $\mu$F/cm$^2$, $\beta = 2000$ cm$^{-1}$ and $\sigma = 4.2$ mS/cm (uniform isotropic). Membrane kinetics was described by the Courtemanche et al. model [8]. The L-type calcium current reduced by 75% to reduce action potential duration and stabilize functional reentries. Relation (3) was used to compute the parameters of the corresponding eikonal-diffusion equation.

## 3. Results

Twenty-four reentrant pathways were drawn manually on the atrial surface using an interactive tool developed in Matlab (Fig. 1A). Pathway length was 10.2±0.5 cm, slightly longer than the wavelength of depolarization waves (conduction velocity × effective refractory period), which was about 8.8 cm. The eikonal-diffusion problem was solved in each case. The resulting activation maps are shown in Figs. 2A–C for three different examples of reentrant pathways. These maps constitute a plausible extrapolation of the activation times specified along the reentrant pathway.

Simulations were run from the initial condition constructed from the computed activations maps. Reentrant activity was simulated for 3 s. Membrane potential maps illustrating the dynamics of spiral waves are represented in Figs. 2D–F. The phase singularity meandered in the vicinity of the desired location specified in the eikonal problem (Fig. 1D). The other end of the depolarization wave was anchored around an anatomical obstacle, typically a valve. The distance between the midpoint of the initial path of reentry and the center of gravity of the phase singularity trajectory was 1.3±0.9 cm. There were two exceptions in which the reentry self-terminated within 1 s.

## 4. Discussion and conclusions

The eikonal-diffusion equation has been used in previous works to simulate paced or normal macroscopic propagation in the heart [6]. We extended this approach to handle reentrant activity [4]. In this paper, its application to the initiation of spiral waves at predefined locations is investi-

gated. The results demonstrate the ability to flexibly design simulations reproducing global, macroscopic information about wavelet dynamics (location of a spiral wave, possibly a mother rotor). This information could be obtained from endocardial recordings in patients. Future works are needed to test the approach when a larger number of phase singularities are present.

Spirals can be initiated by cross-shock stimulation. However, this requires adjustment of the time interval between the first and the second stimulation, as well as the simulation of a complete paced beat. Vulnerability windows are often short. Another advantage of the eikonal approach is the ability to control the location of both ends of the depolarization wave (for example, one phase singularity and an end anchored around one of the anatomical obstacles).

The method is currently limited to 3D models with small thickness (such as the atria) since the eikonal solver was implemented for 3D surface only. While anisotropy was not introduced for the sake of simplicity, previous works suggest that the eikonal approach sill applies in the general inhomogeneous anisotropic case [4]. Note that an initial condition computed assuming uniform conduction properties could also be used to run a simulation in an anisotropic model.

The eikonal-diffusion model does not need to include microscale anatomical details; a coarse mesh can be used. The simulation is eventually performed in a reaction-diffusion model incorporating a full description of the conduction properties. Inaccuracies in propagation patterns are corrected in the course of the first period of reentry.

This tool could help in the development of dedicated models aimed at better understanding clinical case reports, as well as in the creation of a library of different forms of simulated arrhythmias.

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