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MODELLING CARDIAC STRUCTURAL HETEROGENEITY VIA SPACE-FRACTIONAL DIFFERENTIAL EQUATIONS

Nicole Cusimano[1], Félix Del Teso[2], and Luca Gerardo-Giorda[1]
[1]BCAM - Basque Center for Applied Mathematics, Alameda Mazarredo 14, 48009 Bilbao, Spain,
{ncusimano,lgerardo}@bcamath.org
[2]NTNU - Norwegian University for Science and Technology, Alfred Getz' vei 1, 7034 Trondheim, Norway,
felix.delteso@ntnu.no

SUMMARY

We discuss here the use of non-local models in space and fractional order operators in the characterisation of structural complexity and the modeling of propagation in heterogeneous biological tissues. In the specific, we consider the application of space-fractional operators in the context of cardiac electrophysiology, where the lack of clear separation of scales of the highly heterogeneous myocardium triggers peculiar features such as the dispersion of action potential duration, that have been observed experimentally, but cannot be described by the standard monodomain or bidomain models. We describe the methodology and compare the results of a standard monodomain model with results of a model with a non-local component in space.

Key words: *Cardiac electrophysiology, Monodomain model, fractional Laplacian*

1 INTRODUCTION

The mechanical activity of cardiac chambers is governed by the excitation patterns produced by the electrophysiology of the heart itself. Accuracy in the description of such an activity is thus of paramount importance when attempting to capture the overall cardiac dynamics.

Mathematical models of electrical propagation in excitable media are typically developed via the homogenisation principle, namely, under the assumption that microscopic inhomogeneities in the medium have a negligible effect on the transport phenomena observed at the macroscopic scale. In highly heterogeneous structures, such as cardiac or neural tissue, where there is no clear separation of scales, this hypothesis is questionable. In fact, experimental data point at peculiar features of the electrophysiological dynamics, such as wide action potential foot [1] and a marked dispersion of action potential duration (APD) [2], that cannot be captured by standard models. Alternative modeling strategies are thus needed to provide additional insight into the effect produced by structural heterogeneity on electrical pulse propagation.

In the last few decades, mathematical models involving differential operators of non-integer order have been considered in a variety of disciplines (such as physics, engineering, chemistry, rheology, economics) with the aim of reproducing transport phenomena whose characteristics significantly deviate from the classical Markovian and Gaussian features, typical of standard diffusion models. Although the interest in fractional operators linked to practical applications is increasingly growing, the successful implementations of fractional models to model real life phenomena are still scarce.

To the best of our knowledge, the work by Bueno-Orovio et al. [3] is the first example of using a space-fractional mathematical model in cardiac electrophysiology. The biophysical justification behind the use of such a fractional operator for this particular application is based on potential electric field theory. The inhomogeneities present on a variety of length scales in biological tissue give rise to secondary sources that add up to the primary source field corresponding to the assumption of a uniform and infinite volume conductor. These secondary sources can be seen as a dipole modulation of the electrical potential associated with a point source in a homogeneous tissue (monopole). By

using Riesz potential theory, the authors in [3] showed that a fractional model can be interpreted as a smooth transition between monopole and dipole behaviour, with increasing degree of heterogeneity as the order of the fractional operator decreases. Although capturing peculiar features of action potential propagation in heterogeneous media, and showing good agreement with experimental data, their numerical simulations are restricted to one dimensional intervals.

The numerical methodology introduced in [3] is based on the approximation of eigenpairs of the nonlocal operator. If its extension to two and three dimensional cartesian domains is pretty straightforward, its application to real geometries is not practical, as eigenvalues and eigenfunctions are not known analytically in these cases.

Motivated by the promising results provided by the use of space-fractional differential operators, and by the lack of treatment of non cartesian geometries, we developed in [5] a method to approximate fractional operators on general bounded domains with a variety of boundary conditions. This method allows us to devise a nonlocal model of electrical wave propagation that is consistent with the physical intuition and interpretation of the problem, and is flexible enough to be considered on realistic cardiac geometries.

2 METHODOLOGY

Mathematical models of electrical signal propagation in cardiac electrophysiology consist of suitable spatially distributed formulations of specified cell models reproducing the response of a single excitable cell to an applied electrical stimulus. Cell models describe the temporal evolution of the transmembrane potential u and the changes in u caused by the opening and closing of the various ion channels present in the cell membrane, driving the movement of ions into and out of the cell. A classical approach adopted in order to account for pulse propagation is to introduce spatial dependence in the model via the monodomain formulation. The latter consists of a coupled ODE-PDE system whose PDE component is a nonlinear parabolic equation (see, e.g. [4]).

The space-fractional formulation of the monodomain model can obtained by replacing the diffusion term in the parabolic part with a nonlocal operator. Here we consider the fractional Laplacian of order $s \in (0,1)$, $(-\Delta)^s$, and the resulting system reads:

$$\begin{aligned} \chi\left(C_m \frac{\partial u}{\partial t} + I_{\text{ion}}(u, \mathbf{z})\right) &= -D(-\Delta)^s u + I_{\text{stim}} \\ \frac{d\mathbf{z}}{dt} &= \mathbf{f}(u, \mathbf{z}), \end{aligned} \tag{1}$$

where χ is the cell surface-to-volume ratio, C_m is the membrane capacitance per unit area, $\mathbf{z}$ is a suitable vector of secondary variables used in the description of the dynamics of the ion channels in the cell membrane, I_{ion} is the sum of all transmembrane ionic currents, D is a constant conductivity, I_{stim} is the electrical stimulus, and $\mathbf{f}$ is a vector-valued function describing the temporal evolution of $\mathbf{z}$. System (1) is completed by suitable initial conditions and homogeneous Neumann boundary conditions to model an insulated domain.

The crucial issue with fractional order differential operators is that they are naturally defined on the entire space $\mathbb{R}^n$, $n \geq 1$. However, in the majority of practical cases one needs to mathematically model quantities that are defined on a bounded domain $\Omega \subset \mathbb{R}^n$ only. The main challenge is how to suitably restrict, adapt, or interpret the definition of a fractional operator so that it preserves its nonlocal character, all while providing a well-posed problem on Ω.

Based on the spectral definition of the fractional Laplacian and via the heat semi-group formalism, we propose in [5] a novel numerical approach for the discretisation of fractional powers of the Laplacian on bounded and possibly irregular domains, coupled with homogeneous Dirichlet, Neumann, or Robin boundary conditions. Combining finite elements and a suitable quadrature rule, the method is well suited for treating complex domains like the cardiac chambers. The main focus in [5] is the discretisation of $(-\Delta)^s u$ for a given function $u : \Omega \to \mathbb{R}$, but our approach provides a natural framework for the numerical treatment of fractional parabolic problems on bounded domains such as (1).

3 PRELIMINARY RESULTS

Promising results have been obtained in one spatial dimension in [6], where the authors investigate the effect of changing the order of the fractional Laplacian on action potential shape and spatial propagation. We present here some preliminary results on a two dimensional slice of cardiac tissue reconstructed from CT scan. The ionic model we implemented is the Rogers-McCulloch variant of the FitzHugh-Nagumo one [7], featuring a resting potential of 0 mV, a peak potential of 100 mV, and an APD of around 100 msec. In this first set of tests we consider a constant conductivity in the whole domain. In Figure 1, we plot the spatial domain Ω (left), and the time course of the action potential computed with the fractional monodomain (with $s = 0.75$) at five different points labeled from A to E (right): APD dispersal and wide foot of the depolarization phase are visible.

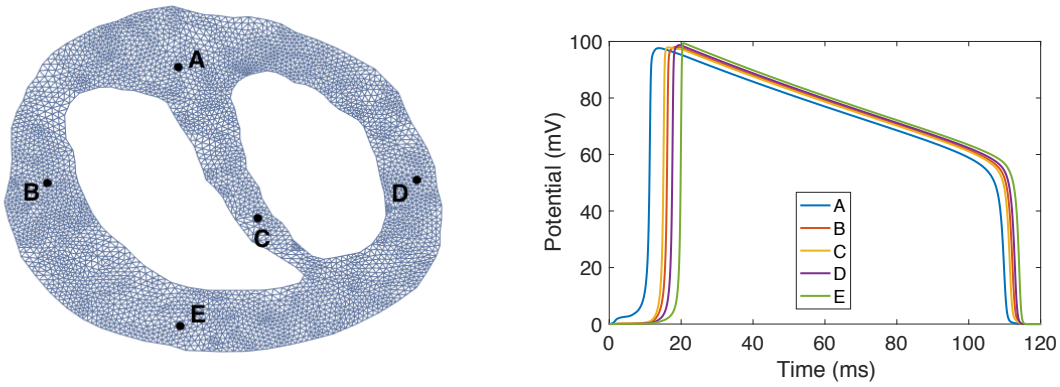

Figure 1: Left: computational domain. Right: action potential course in points A, B, C, D, and E

In Figure 2, we compare, in terms of APD, the results of a standard monodomain and a spatial fractional monodomain. In particular, we compute APD_{90}, namely the APD computed at 90% repolarization. The use of fractional monodomain allows us to capture a pronounced dispersion of APD_{90}, a feature expected in highly heterogeneous structures [1] that the standard formulation of the monodomain fails to exhibit.

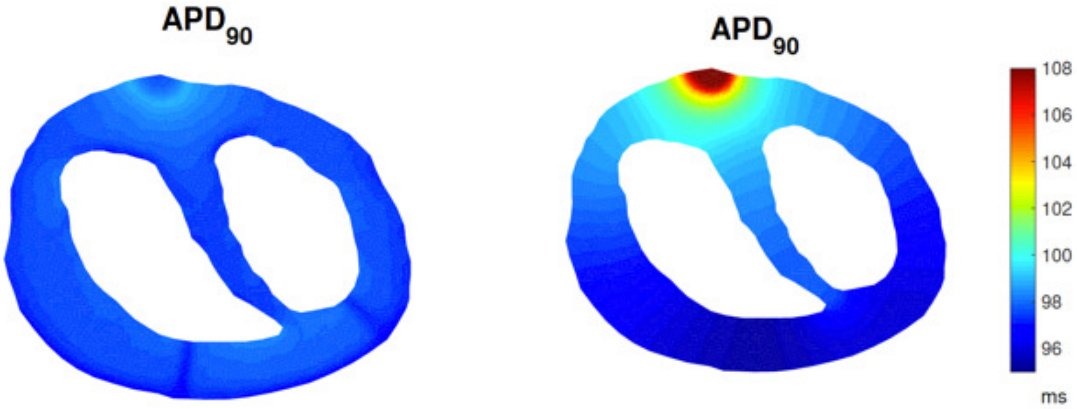

Figure 2: APD: comparison between standard (left) and fractional (right) monodomain.

4 CONCLUSIONS

The fractional monodomain, being nonlocal, shows great potential in modeling the effect of cardiac microstructure on the electrical propagation in the myocardium. The theoretical approach followed in [5] and the numerical method developed therein, allow us to set up the problem on general bounded

domains and to treat numerically system (1) in this general setting. We show how this strategy can be implemented on bounded geometries of practical interest, coupled with physically meaningful boundary conditions.

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