A Novel Paradigm for In Silico Simulation of Cardiac Electrophysiology Through the Mixed Collocation Meshless Petrov-Galerkin Method

Konstantinos A Mountris[1], Carlos Sanchez[1,3], Esther Pueyo[1,2]
[1] Aragon Institute of Engineering Research, University of Zaragoza, IIS Aragon, Zaragoza, Spain
[2] CIBER in Bioengineering, Biomaterials & Nanomedicine (CIBER-BBN), Spain
[3] Defense University Centre (CUD), General Military Academy of Zaragoza (AGM), Zaragoza, Spain

Abstract

Multi-scale cardiac electrophysiological modeling involves high computational load due to the inherent complexity as well as to limitations of the employed numerical methods (e.g., Finite Element Method - FEM). This study investigates the use of the Meshless Local Petrov-Galerkin Mixed Collocation (MLPG-MC) method to simulate cardiac electrophysiology. MLPG-MC is a truly meshless method where both the unknown function and its gradient are interpolated using nodal collocation. A $3\ cm \times 3\ cm$ *human ventricular tissue was simulated based on the monodomain reaction-diffusion model using the operator splitting technique. MLPG-MC or FEM were used to solve the diffusion term and the O'Hara-Virág-Varró-Rudy AP model to represent cellular electrophysiology at baseline and under 30%* I_{Kr} *inhibition (IKr30). Mean differences between MLPG-MC and FEM in AP duration at 90% (*APD_{90}*), 50% (*APD_{50}*) and 20% (*APD_{20}*) repolarization levels were 4.47%, 4.16% and 3.29% for baseline conditions and 3.66%, 2.10% and 1.62% for IKr30 conditions. The computational time associated with each of the two methods was comparable. In conclusion, considering that MLPG-MC does not involve any mesh requirements and is well suited for massive parallelization, this study shows that it represents a promising alternative to FEM for cardiac electrophysiology simulations.*

1. Introduction

In silico modeling and simulation represents a powerful tool in cardiac electrophysiology research [1]. Mathematical models built upon available human and animal data can be an adjunct tool to experimental and clinical investigations at cell, tissue and whole-heart levels, contributing to shed light on the mechanisms underlying physiological and pathological processes in heart function and to guide the development of novel treatments for cardiac diseases [2–4].

To simulate the propagation of the electrical impulse in the heart, the well-known bidomain [5] and monodomain models [6] are commonly used. The monodomain model, which is a simplification of the bidomain model, is frequently considered for its simplicity. Electrical propagation is simulated by solving the following reaction-diffusion equation:

$$\partial V/\partial t = -I_{ion}/C + \nabla \cdot (\boldsymbol{D}\nabla V) \quad (1)$$

where V is the transmembrane potential, C is cell capacitance per unit surface area, $\boldsymbol{D}$ is the diffusion tensor and I_{ion} is the total ionic current, whose computation involves solving a system of ordinary differential equations of voltage-dependent variables representing channel states and ionic concentrations.

The Finite Element Method (FEM) is usually employed to numerically solve equation (1). Despite the robustness and maturity of FEM, its accuracy strongly depends on the quality of the mesh discretization for the geometry of the problem at hand. Due to the rapidly varying reaction term, a very fine spatio-temporal discretization is required to ensure accuracy and avoid spurious oscillations in the wavefront calculated by using FEM. A family of macro finite elements has been proposed to allow solving the reaction-diffusion equations in coarse meshes with high accuracy [6]. Nevertheless, in cases where complex geometric features need to be considered, as when modeling fibrosis or infarction scars, the generation of a high-quality mesh can become a cumbersome process. The use of lower quality meshes can lead to deterioration in the accuracy of FEM.

Meshless Methods (MMs) have been proposed as an alternative to FEM where the mesh generation requirement is alleviated, since the solution is computed by considering a cloud of points in the problem domain and the boundaries of such domain [7]. Several MMs, such as the Smooth Particle Hydrodynamics (SPH) [8] and the Local Radial Basis Function Collocation (LRBFC) [9] methods have been successfully applied to simulate cardiac electrophysiology. Another meshless method of great interest due to its high efficiency is the Meshless Local Petrov-Galerkin Mixed Collocation (MLPG-MC) method [10, 11]. In MLPG-MC,

 ISSN: 2325-887X DOI: 10.22489/CinC.2019.382

the solution to the weak form of equation (1) is obtained by using collocation on a cloud of field nodes to achieve similar accuracy and efficiency as FEM but without any requirement on connectivity information.

The aim of this work is to evaluate the applicability of the MLPG-MC method for simulation of electrical propagation in cardiac tissue as an alternative to FEM.

2. Materials and methods

2.1. Meshless Local Petrov-Galerkin Mixed Collocation method

In meshless methods the approximation of an unknown field function is performed by a trial function, defined on a set of arbitrarily distributed nodes, which is required to be continuous to the whole domain of interest. However, in the local Petrov-Galerkin framework, the weak-form of equation (1) can be constructed by selecting trial and test functions from different spaces with the continuity requirement applying locally [12]. In this way, the spatial integration is performed in small locally defined integration areas. Choosing the Moving Least Squares (MLS) approximation [13] as the trial function and the Dirac function as the test function, the local integration is replaced by collocation and the MLPG-MC method is derived. In this method, the MLS approximation is used to interpolate both the unknown membrane potential V and its gradient. In contrast to standard collocation techniques, second order derivatives are not required to approximate the solution.

By using the operator splitting technique [14], the reactive and diffusive terms in equation (1) can be solved separately, where the diffusive term in the MLPG-MC formulation is given by the following equation:

$$CV^I_{,0}\sum_{J=1}^{m}\Phi^J(\boldsymbol{x}^I)-\sum_{J=1}^{m}\Phi^J_{,i}(\boldsymbol{x}^I)\boldsymbol{D}\Phi^J_{,i}(\boldsymbol{x}^I)V^J=0 \quad (2)$$

where I is the index of the collocation node, J is the index of a neighbor node and m is the number of neighbor nodes in the support domain and $V_{,0}$ represents $\partial V/\partial t$, i.e. the derivative of transmembrane potential and $\Phi(\boldsymbol{x})$ is the MLS basis function evaluated at point $\boldsymbol{x}$ in the tissue. The notation $_{,i}$ indicates the derivative over the i^{th} coordinate.

2.2. Tissue model

A bidimensional square tissue with side length $l = 3\,cm$ was considered to simulate electrical propagation in human ventricular myocardium at baseline conditions as well as under $30\%I_{Kr}$ inhibition (IKr30). The tissue was partitioned into three layers representing endocardium, mid-myocardium and epicardium, as shown in Figure 1. Fiber direction was chosen parallel to the x-axis. The longitudinal conductivity was set to $k_x = 0.0013\ mS/cm^2$ and the transversal to longitudinal ratio to $\tau = 0.25$.

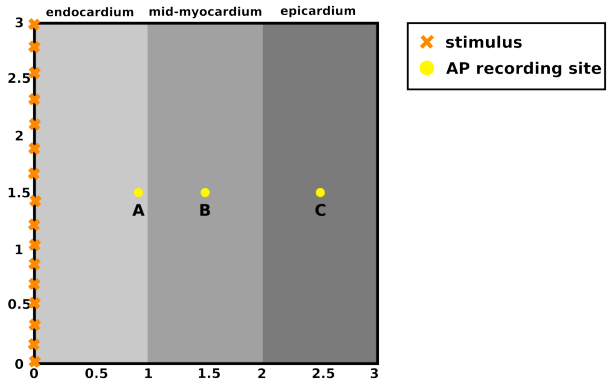

Figure 1. Simulated ventricular tissue. Gray-level zones denote the endocardial (left), mid-myocardial (center) and epicardial (right) layers of the tissue.

2.3. Simulations

Stimuli of twice diastolic threshold amplitude, 2-ms duration were applied at a cycle length of $CL = 1000\ ms$ at the edge $x = 0$ starting at time $t = 50\ ms$. Steady-state action potentials (APs) were evaluated at steady-state at points A (0.9 cm, 1.5 cm), B (1.5 cm, 1.5 cm) and C (2.5 cm, 1.5 cm). The location of point A was selected to avoid recording artifacts occurring near the stimulation area.

Simulations were performed by considering an in-house C++ implementation of the monodomain model where the operator splitting technique was used. The reactive term considered the O'Hara-Virág-Varró-Rudy ventricular cell model to represent human ventricular cell electrophsyiology. The MLPG-MC method was employed for calculation of the diffusive term. The simulation was performed on a cloud of equidistant nodes with a spacing of $d = 0.015cm$. Time integration was performed explicitly using adaptive time-stepping for the reactive term as in [14] with a time step for the diffusive term of $dt_D = 0.08\ ms$ and a time step for the reactive term of $dt_R = dt_D/k$. The coefficient k is given by

$$k = k_0 + \text{int}(|dV/dt|),$$

where dV/dt is the membrane potential derivative, int() denotes the integer part function and $k_0 = 5$ if $dV/dt > 0$ and $k_0 = 1$, otherwise. The results obtained with the MLPG-MC method were compared with those from a FEM simulation performed on a quadrilateral mesh composed of the equidistant nodes of the MLPG-MC point cloud by using isoparametric elements.

3. Results

Simulated AP signals obtained using MLPG-MC and FEM methods were very similar, as illustrated in Figure 2, which presents AP recordings measured at point B (central node of the tissue) at baseline (top panel) and under IKr30 conditions (bottom panel). The maximum relative difference in transmembrane potential was found for the AP signal measured at point A. Such maximum difference was of 8.70% at baseline and 5.42% under IKr30 conditions.

Conduction velocity (CV) at baseline was the same for both methods: $CV_{FEM} = CV_{MLPG-MC} = 66.7cm/s$. No difference was found in the resting membrane potential either.

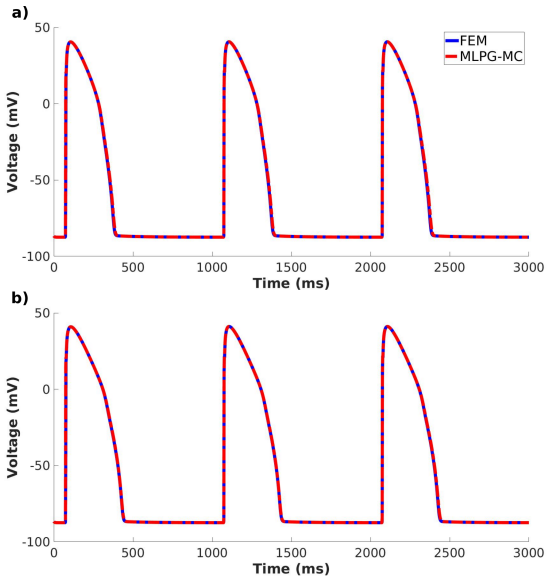

Figure 2. Action potential for central node (point B) under (a) baseline and (b) 30% I_{Kr} inhibition conditions.

The markers APD_{90}, APD_{50}, APD_{20}, which describe the AP duration at 90%, 50%, 20% repolarization levels, respectively, as well as peak membrane potential V_{max} and maximum upstroke velocity dV/dt_{max} were evaluated for simulations using MLPG-MC and FEM methods. Relative differences between the two methods regarding each of those five markers are presented in Figure 3 for baseline (top panel) and IKr30 conditions (bottom panel). Different colors in the figure correspond to each of the points A, B and C in the endo-, mid- and epicardial layers of the simulated tissue.

The computational time was very similar for both methods: $t_{MLPG-MC} = 24$ min and $t_{FEM} = 23$ min for each simulated cardiac cycle at $CL = 1000\ ms$.

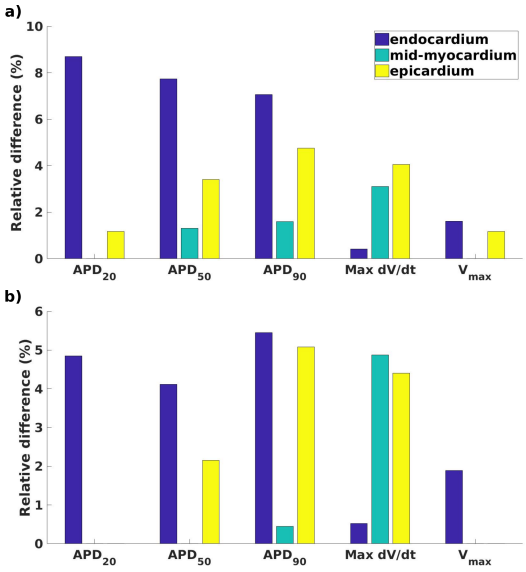

Figure 3. Relative percentage difference between FEM and MLPG-MC for endocardium (point A), mid-myocardium (point B), and epicardium (point C) under (a) baseline and (b) 30% I_{Kr} inhibition conditions.

4. Discussion

This work has demonstrated the feasibility of a meshless method, the MLPG-MC method, for simulation of cardiac electrical propagation in a human ventricular tissue. The MLPG-MC method provided numerical solutions that were in close agreement with those obtained with the FEM method, which is the method most commonly used for *in silico* simulation of cardiac electrophysiology.

Relative differences between MLPG-MC and FEM methods evaluated at baseline for AP duration, peak membrane potential and maximum upstroke velocity were always below 8.70 %, which is in accordance with findings from previous studies where meshless methods were tested. Specifically, Lluch et al. [8] found a maximum difference of 10.90% in depolarization time between meshless SPH and FEM methods. It is possible that the recorded difference between meshless and FEM methods is due to the non-interpolating nature of the majority of meshless methods. The non-interpolating attribute could pose difficulties capturing the very rapidly varying reaction term describing the cardiac cell dynamics. This hypothesis was supported by the findings of the present study. The relative percentage difference was found lower under IKr30 conditions (up to 5.42%), where the reaction term variation is slower (APD prolongation due to I_{Kr} inhibition).

An investigation on the performance of meshless methods using different meshless basis functions could provide further insight and allow establishing the meshless meth-

ods in cardiac electrophysiological simulations. Meshless methods are very flexible and allow to eliminate the mesh requirement. This attribute is of great interest especially in medical applications where good quality meshes may be cumbersome to generate automatically. Moreover, meshless methods are suitable for massive parallelization which allows the relatively easy implementation of large-scale models. Establishing the meshless methods in the cardiac modeling may contribute to a more extensive application of *in silico* cardiac electrophysiology in the clinical practice.

5. Conclusions

The feasibility of a meshless method, the MLPG-MC method, for *in silico* simulations of cardiac electrophysiology has been demonstrated. A comparison with the finite element method at baseline and under reduced repolarization reserve conditions has revealed that both methods render very similar results at a comparable computational cost. The MLPG-MC method presents the additional advantages of not requiring a mesh discretization and being more suited for massive parallelization.

Acknowledgments

This work was supported by the European Research Council under the grant agreement ERC-2014-StG638284, by MINECO (Spain) through project DPI2016-75458-R and by European Social Fund (EU) and Aragn Government through BSICoSgroup (T39_17R). Computations were performed by the ICTS NANBIOSIS (HPC Unit at University of Zaragoza).

References

[1] Mayourian J, Sobie EA, Costa KD. An introduction to computational modeling of cardiac electrophysiology and arrhythmogenicity. In Experimental Models of Cardiovascular Diseases. Springer, 2018; 17–35.

[2] Pueyo E, Corrias A, Virág L, Jost N, Szél T, Varró A, Szentandrássy N, Nánási PP, Burrage K, Rodríguez B. A multiscale investigation of repolarization variability and its role in cardiac arrhythmogenesis. Biophysical Journal 2011; 101(12):2892–2902.

[3] Carro J, Pueyo E, Matas JFR. A response surface optimization approach to adjust ionic current conductances of cardiac electrophysiological models. Application to the study of potassium level changes. PloS one 2018; 13(10):e0204411.

[4] Grandi E, Morotti S, Pueyo E, Rodriguez B. Getting to the heart of safety pharmacology. Frontiers in Physiology 2018;9:678.

[5] Henriquez CS. Simulating the electrical behavior of cardiac tissue using the bidomain model. Critical Reviews in Biomedical Engineering 1993;21(1):1–77.

[6] Heidenreich EA, Ferrero JM, Doblaré M, Rodríguez JF. Adaptive macro finite elements for the numerical solution of monodomain equations in cardiac electrophysiology. Annals of Biomedical Engineering 2010;38(7):2331–2345.

[7] Garg S, Pant M. Meshfree methods: A comprehensive review of applications. International Journal of Computational Methods 2018;15(04):1830001.

[8] Lluch E, Doste R, Giffard-Roisin S, This A, Sermesant M, Camara O, De Craene M, Morales HG. Smoothed particle hydrodynamics for electrophysiological modeling: An alternative to finite element methods. In International Conference on Functional Imaging and Modeling of the Heart. Springer, 2017; 333–343.

[9] Yao G, Yu Z. A localized meshless approach for modeling spatial–temporal calcium dynamics in ventricular myocytes. International Journal for Numerical Methods in Biomedical Engineering 2012;28(2):187–204.

[10] Atluri S, Liu H, Han Z. Meshless local Petrov-Galerkin (MLPG) mixed collocation method for elasticity problems. CMES Computer Modeling in Engineering Sciences 2006; 4(3):141.

[11] Zhang T, He Y, Dong L, Li S, Alotaibi A, Atluri SN. Meshless local Petrov-Galerkin mixed collocation method for solving cauchy inverse problems of steady-state heat transfer. CMES Computer Modeling in Engineering Sciences 2014;97(6):509–553.

[12] Atluri SN, Zhu T. A new meshless local Petrov-Galerkin (MLPG) approach in computational mechanics. Computational mechanics 1998;22(2):117–127.

[13] Lancaster P, Salkauskas K. Surfaces generated by moving least squares methods. Mathematics of computation 1981; 37(155):141–158.

[14] Qu Z, Garfinkel A. An advanced algorithm for solving partial differential equation in cardiac conduction. IEEE Transactions on Biomedical Engineering 1999;46(9):1166–1168.

Address for correspondence:

Konstantinos A Mountris

BSICoS GROUP, University of Zaragoza, Campus Río Ebro, I+D Building, D-5.01.1B, Mariano Esquillor, s/n street, 50018, Zaragoza, Spain

kmountris@unizar.es