Improved Machine Learning Strategies and Algorithms for Transmembrane Potential Estimation in Homogeneous Medium

Enrique Feito-Casares[1], Francisco M. Melgarejo-Meseguer[1],
Arcadi García-Alberola[2], José Luis Rojo-Álvarez[1]

[1] Departamento de Teoría de la Señal y Comunicaciones y Sistemas Telemáticos y de Computación. Universidad Rey Juan Carlos, Spain
[2] Hospital Clínico Universitario Virgen de la Arrixaca. Unidad de Arritmias, Murcia, Spain

Abstract

Introduction. *Research on improved methods for the inverse problem in cardiology and electrophysiology is active today. Recently, the use of machine learning methods has been proposed, allowing us to consider the biophysical equations of the problem. In this work, we propose to explore improvements in using kernel methods for estimating the inverse problem, with kernel given by the Green's function for the infinite homogeneous potential and with recently proposed cross-validation strategies for least squares estimation.* ***Materials and Methods.*** *Three solvers were implemented: least squares with Zero-Order Tikhonov (ZOT) regularization, Support Vector Regression (SVR), and constrained L2 (CL2) optimization. The study evaluates transmembrane action potential estimation in 1D (fiber) and 2D (tissue) simulations using the Luo-Rudy model.* ***Experiments and results.*** *The ZOT method was the most unstable. The SVR method provided biased results, although intermediate and acceptable accuracy, except at the edges of spatial action potentials. The CL2 method provided better performance under certain conditions of the implemented cross-validation procedure.* ***Conclusions.*** *Kernel methods, with refined algorithmic formulations and cross-validation criteria, offer an alternative for cardiac inverse problem estimation.*

1. Introduction

Diagnosing Cardiovascular Diseases of electrophysiological origin rely on invasive approaches that pose a significant drawback to the patient. For instance, electrophysiological studies (EPS) reach the inner heart using a catheter, measuring the heart proximal extracellular potential. Nevertheless, EPS does not provide measures regarding the transmembrane potential of heart cells.

Accurately estimating the transmembrane potential from proximity extracellular potential is important for revealing the underlying mechanisms of cardiovascular diseases such as arrhythmias. Current research on these methods incorporates regularized estimation algorithms [1] and even deep learning approaches [2]. Nevertheless, cross-validation techniques have not been combined with estimators using kernel methods. The objective is to improve current cross-validation techniques and apply them to kernel-based estimation methods, where the kernel is given as Green's function accounting for the underlying biophysical information of the problem being considered [3].

2. Materials and Methods

We present next the mathematical formulation of the electrocardiographic forward and inverse problems. Additionally, models for inverse estimation based on the Laplacian kernel are introduced, along with the free parameter search method based on cross-validation.

Electrophysiological simulation models often provide mathematical representations of the electrical activity in cardiac cells. In this study, the transmembrane potential is simulated using the Luo-Rudy model, which forms the basis for resolving the forward problem and evaluating the presented inverse estimating techniques [4].

2.1. Bioelectric Equations and Notation

The forward problem represents how the extracellular potential is generated due to the mixed contribution of the transmembrane potential of each cardiomyocyte. The conduction volume can be considered to have a 3D geometry with several conductivities. We consider the 1D and 2D tissue equations and assume a homogenous conductivity medium. The spatial equation for a homogeneous volume conductor with conductivity σ_0 is

$$v_e(\boldsymbol{r}) = \frac{1}{4\pi\sigma_0}\int_{S'}\frac{\nabla^2 v_m(\boldsymbol{r}')}{|\boldsymbol{r}-\boldsymbol{r}'|}dS', \qquad (1)$$

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where v_m is the source potential at the surface S' and v_e is the potential field, considered at the immediate epicardial surface (tissue plane), and $\boldsymbol{r}$ ($\boldsymbol{r}'$) is the position vector of a field point [5].

Discretization of the involved surfaces is often performed using the Finite Element Methods (FEM) techniques, which yield an implicit equation to calculate the extracellular potential. The bioelectrical problem can be subsequently summarized on transfer matrix $\boldsymbol{T}$, combining the spacial Laplacian matrix $\boldsymbol{L}$ and the inverse distances matrix $\boldsymbol{H}$ discretized from equation (1), and this allows the forward problem reformulation in vector-matrix form,

$$\boldsymbol{T} = \boldsymbol{L}\boldsymbol{H} \Longrightarrow \boldsymbol{v}_e = \boldsymbol{T}\boldsymbol{v}_m, \tag{2}$$

where $\boldsymbol{v}_e$ and $\boldsymbol{v}_m$ denote the vector form for the extracellular and transmembrane potentials, respectively. The size of the $\boldsymbol{T}$ matrix depends on the number of sensor elements and source elements on the considered surface. In this setting, the transmembrane potential estimation problem can be defined as the prediction of the transmembrane potential given a known forward operator $\boldsymbol{T}$ and measurement of extracellular potential $\boldsymbol{v}_e$ [6].

2.2. Laplacian Kernels and Generalization

We selected three algorithms that rely on the Laplacian kernel, and they are presented in the following section. Note that the model contains the underlying biophysical problem rather than being a blind learning model.

The Zero-order Tikhonov (ZOT) method has been widely employed for solving the inverse problem, and it involves using the least squares (LS) model along with regularization techniques to stabilize ill-conditioned problems. The optimization problem can be stated as

$$\hat{\boldsymbol{v}}_m(\gamma) = \arg\min_{\boldsymbol{v}_m} \left\{ \|\boldsymbol{v}_e - \boldsymbol{T}\boldsymbol{v}_m\|^2 + \gamma \|\boldsymbol{v}_m\|^2 \right\}, \tag{3}$$

where regularization parameter γ provides smoothness to the solution. The solution has a closed-form equation given by

$$\hat{\boldsymbol{v}}_m(\gamma) = \left(\boldsymbol{T}^\top \boldsymbol{T} + \gamma^2 \boldsymbol{R}^\top \boldsymbol{R} \right)^\dagger \boldsymbol{T}^\top \boldsymbol{v}_e. \tag{4}$$

The ZOT model is used here as a baseline to compare the rest of the proposed models.

On the other hand, the use of kernel methods to address non-linear regression problems constitutes a promising approach as it provides sparse and implicit regularized solutions even on different noisy conditions [7]. In some symmetric conditions, the $\boldsymbol{T}$ matrix can be symmetric and positive-definite to be used as the Gram matrix associated with a kernel function and mapping function ϕ, satisfying Mercers Kernel conditions. This kernel can also be seen as Green's function for the infinite homogeneous conductor problem [3], and this approach enables the use of Support Vector Regression (SVR) as a machine-learning-based estimation technique with matrix $\boldsymbol{T}$ as a precomputed kernel. The ε-SVR represents a regression of the transmembrane potential in an unknown space where the relation with the extracellular potential is linear, given by

$$\boldsymbol{v}_e\left(x_i, y_i, z_0\right) = \left\langle \boldsymbol{w}, \phi\left[\boldsymbol{v}_m\left(x_i, y_i, 0\right)\right] \right\rangle, \tag{5}$$

where $\boldsymbol{w}$ is a nonlinear regressor in a Reproducing Kernel Hilbert Space, and ϕ is a nonlinear mapping from the transmembrane potential to that space. The ε-SVR is suitable to address this estimation problem, as it can be set as an ε parameter that depends on the magnitude of the residuals, as well as other free parameters in the SVR methodology.

Finally, we stated a constrained L2 (CL2) formulation of the problem by stating the inverse estimation problem as an optimization problem with a convex objective function and a set of constraints, as minimizing

$$\|\boldsymbol{v}_e - \boldsymbol{T}\boldsymbol{v}_m\|^2 + \gamma \|\boldsymbol{v}_m\|^2 \tag{6}$$

subject to $\boldsymbol{v}_m \geq \boldsymbol{v}_r$, where $\boldsymbol{v}_r$ denotes the resting membrane potential. The introduction of constraints to the model serves to minimize the bias while simultaneously restricting the optimization problem to positive values.

Estimation methods in this context frequently have to deal with several signals in the presence of various noise sources, needing stabilization of their solution through the use of so-called regularization techniques. There are numerous approaches to regularizing the inverse problem in the literature. However, few sample studies implement cross-validation strategies to search the free parameters [8]. An out-of-sample cross-validation strategy adapted from the one proposed in the previously cited work was used to search the free parameters ε-SVR, as well as the γ parameter in ZOT and CL2 algorithms.

3. Experiments and Results

This section presents the performance of the proposed methods on simulated data under various noise and sampling conditions.

In space, the experimental data presented a uniform or non-uniform sampling. The uniformity occurs when the nodes, either in 1D or 2D, are equidistant. For the non-uniform case, a uniform random variable $U(0, \Delta_s n)$ was added to the position of the nodes from the uniform case. Where Δ_s is the uniform internodal sampling distance, and n is a parameter controlling stochastic behavior. Furthermore, we evaluated the estimators under various noise circumstances to identify the most robust one. The introduced noise is measured with the signal-to-noise ratio (SNR) in decibels (dB).

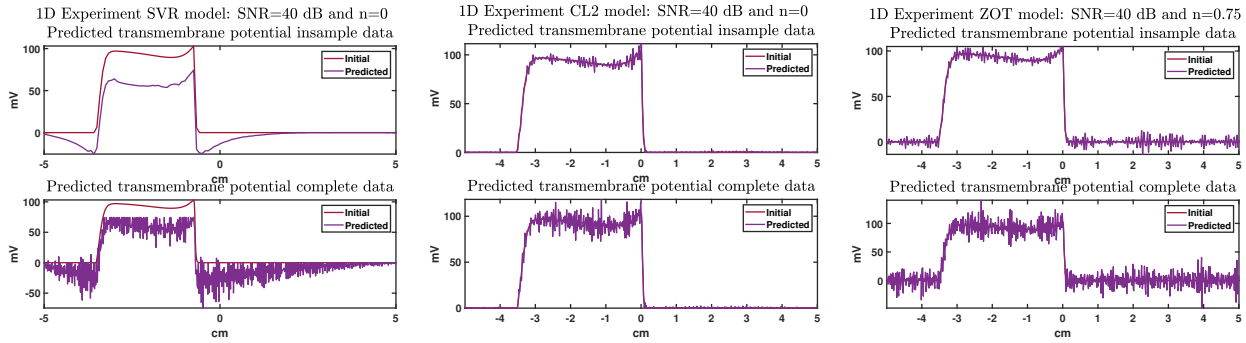
MAE		Uniform sampling $(n = 0)$			Non-uniform sampling $(n = 0.75)$		
		10 dB	25 dB	40 dB	10 dB	25 dB	40 dB
SVR model	Training Data	49.20	38.29	38.33	151.75	44.66	8.13
	Complete Data	73.48	44.11	37.17	607.75	137.02	47.21
CL2 model	Training Data	22.86	6.14	1.13	15.86	5.11	1.32
	Complete data	14.42	5.92	2.09	16.88	5.19	3.13
ZOT model	Training data	44.82	11.68	1.95	25.12	5.90	3.44
	Complete Data	45.37	64576.64	47.50	67.87	12.06	15.00

(a)

MAE		Uniform sampling $(n = 0)$			Non-uniform sampling $(n = 0.75)$		
		10 dB	25 dB	40 dB	10 dB	25 dB	40 dB
SVR model	Training data	31.00	22.28	22.49	16.89	23.77	40.51
	Complete data	54.33	43.33	35.00	53.18	72.05	86.94
CL2 model	Training data	5.70	0.89	0.21	6.19	0.82	0.16
	Complete data	16.11	4.97	1.81	20.10	10.65	5.55
ZOT model	Training data	6.26	1.90	0.21	3.93	0.95	0.36
	Complete data	146.72	28.37	17415.96	170.25	448.51	39.60

(b)

Table 1: MAE evaluated for each model across a range of SNR scenarios, spanning from 15 dB to 45 dB, under both uniform and non-uniform conditions on 1D with different data split, (a) 50% data in training and (b) 20% data in training.



(a) (b) (c)

Figure 1: Predictions on the best performing conditions according to Table (1), for SVR (a), CL2 (b), and ZOT (c) models.

MAE		Uniform sampling $(n = 0)$		
		20 dB	30 dB	45 dB
CL2 model	Training data	19.02	7.81	2.37
	Complete data	90.21	32.50	18.22
ZOT model	Training data	25.74	12.32	5.78
	Complete data	55.55	33.35	26.60

Table 2: MAE evaluated for each model across a range of SNR scenarios, spanning from 15 dB to 45 dB, under uniform conditions on a plane.

The 1D experiments were performed on a fiber with 601 cells with a length of 10 cm. Two data distributions were tested, one with 50% of data in the training set and the other with 20% of data in the training set. The results are depicted in Table (1), showing that the CL2 model was the best performing overall, followed by the ZOT model and finally by the SVR model. The SVR model provided acceptable accuracy but biased predictions, especially at the border of the spatial action potential. Qualitative results of the best performing conditions are shown in Figure (1).

The 2D experiments were performed on a plane with 10 000 cells with a 3x3 cm surface, and the dataset is divided into 50% train and 50% test. The findings are presented in Table (2), which exhibits that the CL2 model outperformed the other models in all the measures. Moreover, the qualitative outcomes of the predictions on the optimal conditions are depicted in Figure (2). The SVR model was not used because the even more severe ill-conditioning of the problem in 2D did not allow a search for free parameters, so it represents ongoing work.

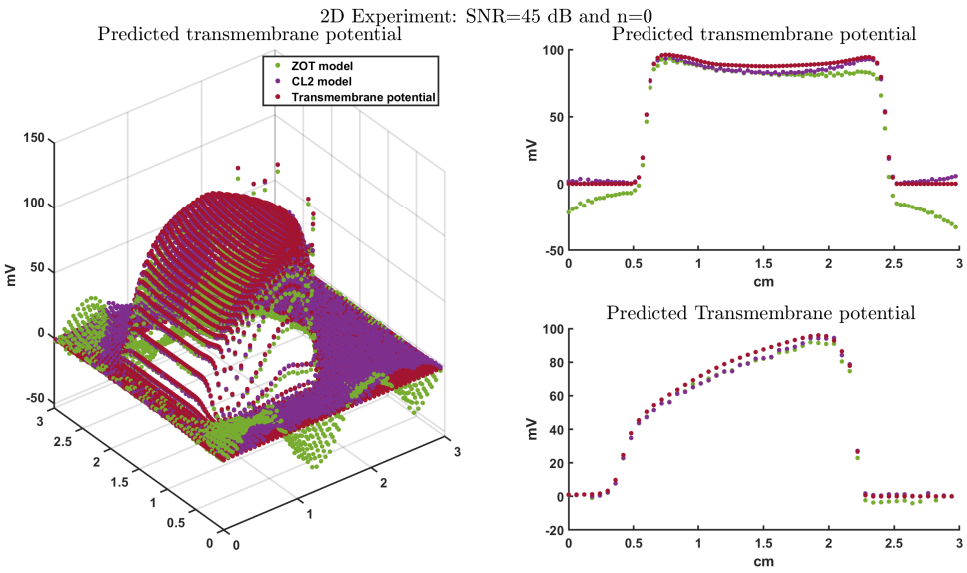


Figure 2: Predictions from models for training data on the best working conditions according to Table (2), with a low level of noise, and the cells on the plane are equidistant.

4. Conclusions

The presented study provides evidence that kernel methods offer an alternative approach to estimating the cardiac inverse problem within a homogeneous and infinite conductor when utilized with cross-validation techniques with the inclusion of biophysical equations. The ill-conditioning of the inverse problem deteriorates the performance of the proposed algorithmic solvers under certain circumstances, including scenarios involving significant noise, non-uniform sampling, or high-dimensional geometries. Further studies will address the problem in scenarios of realistic complexity and geometries.

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Address for correspondence:
José Luis Rojo–Álvarez Dep. of Signal Theory and Communications University Rey Juan Carlos, Fuenlabrada (Madrid), Spain Phone: +34 91 488 8464. Mail to: joseluis.rojo@urjc.es