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Evaluation of fifteen algorithms for the resolution of the electrocardiography imaging inverse problem using ex-vivo and in-silico data

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2 ABSTRACT

3 The electrocardiographic imaging inverse problem is ill-posed. Regularization has to be applied
4 to stabilize the problem and solve for a realistic solution. Here, we assess different regularization
5 methods for solving the inverse problem. In this study, we assess i) zero order Tikhonov
6 regularization (ZOT) in conjunction with the Method of Fundamental Solutions (MFS), ii) ZOT
7 regularization using the Finite Element Method (FEM) and iii) the L1-Norm regularization of
8 the current density on the heart surface combined with FEM. Moreover, we apply different
9 approaches for computing the optimal regularization parameter, all based on the Generalized
10 Singular Value Decomposition (GSVD). These methods include Generalized Cross Validation
11 (GCV), Robust Generalized Cross Validation (RGCV), ADPC, U-Curve and Composite RESidual
12 and Smoothing Operator (CRESO) methods. Both simulated and experimental data are used for
13 this evaluation. Results show that the RGCV approach provides the best results to determine the
14 optimal regularization parameter using both the FEM-ZOT and the FEM-L1-Norm. However for the
15 MFS-ZOT, the GCV outperformed all the other regularization parameter choice methods in terms
16 of relative error and correlation coefficient. Regarding the epicardial potential reconstruction,
17 FEM-L1-Norm clearly outperforms the other methods using the simulated data but, using the
18 experimental data, FEM based methods perform as well as MFS. Finally, the use of FEM-L1-Norm
19 combined with RGCV provides robust results in the pacing site localization.

20 **Keywords:** Inverse Problem, Tikhonov Regularization, L1-Norm Regularization, Regularization Parameter Choice, Fundamental
21 Solutions Method, Finite Element Method, Robust Generalized Cross Validation, Generalized Singular Value Decomposition, Pacing
22 Site Localization, Electrocardiography

1 INTRODUCTION

23 The non-invasive electrocardiographic imaging (ECGI) is an imaging technique that allows one to non-
24 invasively reconstruct the electrical activity of the heart using electrocardiograms and a patient specific
25 heart-torso geometry. This clinical tool is used by electrophysiologists to understand the mechanisms
26 underlying arrhythmias and to localize targets for ablation therapy, such as for atrial fibrillation [1, 2].

27 This technology is based on a mathematical relationship defining the propagation of the electrical activity
 28 between the heart and the torso surface Γ_{ext} . Given the extracellular electrical potential u_H on the epicardial
 29 heart boundary Γ_H , the distribution of the electrical potential u_T in the torso domain Ω_T and specifically
 30 at electrodes distributed on the body surface Γ_{ext} , could be obtained by solving the following Laplace
 31 equation.

$$\begin{cases} \nabla \cdot (\sigma_T \nabla u_T) = 0, & \text{in } \Omega_T, \\ \sigma_T \nabla u_T \cdot n_T = 0, & \text{on } \Gamma_{ext}, \\ u_T = u_H, & \text{on } \Gamma_H. \end{cases} \quad (1)$$

32 where σ_T stands for the torso conductivity tensor and n_T is the outward unit normal to the torso external
 33 boundary Γ_{ext} . This is what we call a forward problem. Now, given a body surface potential distribution
 34 and knowing that the flux of potential over the body surface is zero, could we obtain the right distribution of
 35 the electrical potential on the heart surface ? This is what we call an inverse problem in electrocardiography.
 36 In almost all of the works reported in the literature, the mathematical approach used for solving the inverse
 37 problem is based on a transfer matrix which has been first formulated by Barr and Spach [3]. The transfer
 38 matrix can be computed using different approaches such as the finite element method (FEM) [4, 5] or the
 39 boundary elements method like in [6, 7, 8, 9, 10, 3] method of Fundamental Solutions (MFS) [11] or mixed
 40 methods like the factorization of boundary value method [12] or finite element with mixed element types
 41 [4]. In this study, we are only interested in FEM and MFS. Using any of these numerical approaches, the
 42 governing equation (1) can be reduced to a matrix-vector system:

$$Ax = b, \quad (2)$$

43 where \mathbf{A} is the transfer matrix, its form depends on the numerical method used. The vector \mathbf{x} is either the
 44 unknown epicardial potentials on the surface of the heart in the case of the FEM or a vector of weighting
 45 coefficients from which it's possible to reconstruct the epicardial potential in the case of MFS. Finally, \mathbf{b}
 46 represents either the body surface potentials (BSPs) for the first case or a concatenation of the BSPs and a
 47 null vector representing the non flux boundary condition for the second case.

48 Generally, the inverse problem of electrocardiography is known to be ill-posed in the sense of Hadamard
 49 [13] which means that a small perturbation of the Cauchy data may lead to a high variation in the inverse
 50 solution. This could be explained at the discrete level by the ill-conditioning of the transfer matrix \mathbf{A} and the
 51 measurement noise that we have in the vector \mathbf{b} . To overcome this, a regularization approach is often used
 52 to solve Eq. (2). However, this has led to a large variety of different inverse algorithms being developed. To
 53 date, few studies have attempted to compare the different methods available. Cheng et al.[14] looked at
 54 different regularization methods and methods to compute the regularization parameter. Since this work,
 55 many new methods have been developed.

56 A recent work by Barnes and Johnston [15] compares several regularization techniques but without
 57 changing either the regularization operator or the numerical method defining the transfer matrix. Finally,
 58 both of these studies were based purely on simulated data, and their applicability to experimental or clinical
 59 work is unknown.

60 In this work we compare not only different methods for computing the transfer matrix, but also different
 61 regularization operators and different methods for optimizing the regularization parameter to assess how
 62 they perform on two sets of data: simulated and experimental.

2 METHODS

63 To date, the regularization approach most commonly used to solve the electrocardiographic imaging inverse
64 problem is the Tikhonov regularization defined by the following objective function:

$$\min_x \{ \|Ax - b\|^2 + \lambda^2 \|Lx\|^2 \}, \quad (3)$$

65 where \mathbf{L} is the regularization operator, λ is the regularization parameter and $\|\cdot\|$ is the L2-norm. Here, \mathbf{L}
66 can be the identity matrix (zero-order) or an approximation operator of a potential's derivative form (first
67 or second order). Independent of the numerical method used to compute the transfer matrix, the best way
68 to analyze the different methods to computing the optimal regularization parameter is to use the GSVD of
69 the couple $\{\mathbf{A}, \mathbf{L}\}$ for first or second order Tikhonov regularization and the singular value decomposition
70 of \mathbf{A} for zero-order.

71 2.1 Generalized Singular Value Decomposition

72 In the case where $\mathbf{L} = \mathbf{I}$, we use the Singular Value Decomposition of the $m \times n$ transfer matrix \mathbf{A} ,
73 where $m \geq n$, m is the number of torso nodes and n is the number of heart nodes.

74 Following [16], we decompose \mathbf{A} as follows

$$\mathbf{A} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^T = \sum_{i=1}^n \mathbf{u}_i \sigma_i \mathbf{v}_i^T, \quad (4)$$

75 where \mathbf{U} is a $m \times n$ orthonormal matrix containing the left singular vectors of \mathbf{A} , \mathbf{V} is a $n \times n$ orthonormal
76 matrix containing the right singular vectors of \mathbf{A} and $\mathbf{\Sigma}$ is a $n \times n$ diagonal matrix with the singular
77 values of \mathbf{A} on its diagonal. Note that \mathbf{u}_i , \mathbf{v}_i and σ_i are respectively, the columns of \mathbf{U} , \mathbf{V} and the singular
78 values of \mathbf{A} arranged in a decreasing order. In terms of the singular value decomposition, the solution of
79 the regularized problem expressed by:

$$\min_x \{ \|Ax - b\|^2 + \lambda^2 \|x\|^2 \}, \quad (5)$$

80 can be written as [16]:

$$\mathbf{x} = \mathbf{A}^\dagger \mathbf{b} = (\mathbf{A}^T \mathbf{A} + \lambda^2 \mathbf{I})^{-1} \mathbf{A}^T \mathbf{b} = \sum_{i=1}^n \frac{\sigma_i^2}{\sigma_i^2 + \lambda^2} \frac{\mathbf{u}_i^T \mathbf{b}}{\sigma_i} \mathbf{v}_i. \quad (6)$$

81 It can be shown that the two terms of (5) can be written as [17]:

$$\rho_1(\lambda) = \|Ax - b\|^2 = \sum_{i=1}^n \frac{\lambda^4 \mu_i^2}{(\lambda^2 + \sigma_i^2)^2} + \|r_\perp\|^2 \quad (7)$$

82 and

$$\eta_1(\lambda) = \|x\|^2 = \sum_{i=1}^n \frac{\sigma_i^2 \mu_i^2}{(\lambda^2 + \sigma_i^2)^2}, \quad (8)$$

83 where $\|r_\perp\|^2 = \|Ax_{LSS} - b\|^2$ is the residual of the least squares solution x_{LSS} and $\mu_i = \mathbf{u}_i^T \mathbf{b}$.

84 In the case where $\mathbf{L} \neq \mathbf{I}$, the Generalized Singular Value Decomposition of the pair $\{\mathbf{A}, \mathbf{L}\}$ is defined by

85 [18]:

$$A = PCZ^{-1}, \quad L = QSZ^{-1}, \quad (9)$$

86 where \mathbf{P} and \mathbf{Q} are respectively $m \times n$ and $n \times n$ orthogonal matrices. \mathbf{C} and \mathbf{S} are $m \times n$ and
 87 $n \times n$ diagonal matrices satisfying $C^T C + S^T S = I$ where $\text{diag}(\mathbf{C}) = \{\sigma_1 \dots \sigma_n\}$ and $\text{diag}(\mathbf{S}) =$
 88 $\{\nu_1 \dots \nu_n\}$. Diagonal elements of \mathbf{C} and \mathbf{S} satisfy $0 \leq \sigma_1 \leq \dots \leq \sigma_n \leq 1$ and $1 \geq \nu_1 \geq \dots \geq \nu_n \geq$
 89 0 . The matrix \mathbf{Z} is non singular. We define $\bar{\lambda}_i = \frac{\sigma_i}{\nu_i}$ as the generalized singular values of the pair $\{\mathbf{A}, \mathbf{L}\}$.
 90 Using the generalized singular value decomposition, the solution of the problem expressed by Eq. (3) can
 91 be written as [19]:

$$x^* = A\#b = (A^T A + \lambda^2 L^T L)^{-1} A^T b = \sum_{i=1}^n \phi_i \frac{p_i^T b}{\sigma_i} z_i, \quad (10)$$

92 where Φ is a $n \times n$ diagonal matrix containing the **filter factors** defined by:

$$\phi_i = \frac{\bar{\lambda}_i^2}{\bar{\lambda}_i^2 + \lambda^2}, \quad \text{for } i = 1 \dots n. \quad (11)$$

93 It can be shown that the two terms of (3) can be written in terms of generalized singular values as [19]:

$$\rho_2(\lambda) = \|Ax^* - b\|^2 = \sum_{i=1}^n \left(\frac{\lambda^2}{\bar{\lambda}_i^2 + \lambda^2} \right)^2 (p_i^T b)^2 + \sum_{i=n+1}^m (p_i^T b)^2, \quad (12)$$

94 and [20]

$$\eta_2(\lambda) = \|Lx^*\|^2 = \sum_{i=1}^n \left(\frac{\bar{\lambda}_i}{\bar{\lambda}_i^2 + \lambda^2} \right)^2 (p_i^T b)^2. \quad (13)$$

95 2.2 Regularization Techniques

96 Several regularization techniques can be applied to the ill-posed inverse problem of electrocardiography.
 97 In this study, we focus on two methods.

98 2.2.1 Zero Order Tikhonov Regularization

99 Using the zero order Tikhonov regularization, the objective function can be expressed by (5). This type
 100 of regularization places a constraint on the magnitude of the reconstructed epicardial potentials which is
 101 known to provide a smooth solution but may lead to the loss of meaningful information.

102 2.2.2 L1-Norm Regularization of the current density over the heart surface

103 Previous studies have shown that using the L1-Norm can provide a better reconstruction when applied
 104 in different fields [21, 22, 23]. In this paper, we choose to apply the regularization scheme used in [9].
 105 Here, we penalized the L1-Norm of the normal derivative of the solution. The potential normal derivative
 106 represents the distribution of electrical flux over the epicardial surface.

107 This will yield less smoothed potentials than zero-order Tikhonov. The use of current density in the
 108 regularization of the inverse problem in electrocardiography was first introduced by S.Khoury [24] and
 109 proved to provide significant improvement in the inverse problem.

110 The objective function using L1-Norm based regularization is given by:

$$\min_x \|Ax - b\| + \lambda^2 \|\nabla x \cdot \mathbf{n}_H\|_1, \tag{14}$$

111 where \mathbf{n}_H is the outward unit normal to the epicardium surface.

112 Using the Finite Element Method, and thanks to the linearity of the solution of problem (1) to its boundary
 113 conditions, we can define the Dirichlet-To-Neumann operator D satisfying:

$$\begin{pmatrix} \frac{\partial u_T}{\partial n}(p_1) \\ \vdots \\ \frac{\partial u_T}{\partial n}(p_n) \end{pmatrix} = D \begin{pmatrix} x_1 \\ \vdots \\ x_n \end{pmatrix}, \tag{15}$$

114 where D is an n-by-n matrix and the points (p_1, p_2, \dots, p_n) are the coordinate tuples of the heart mesh
 115 vertices. Note that the operator D is different from the gradient over the surface used for the total variation
 116 regularization. In fact the gradient of x over the heart surface $(\nabla_{\Gamma_H} x)$ is the tangential component of
 117 electrical potential gradient (∇u_T) , whereas Dx is its normal component. Thus one could write the 3D
 118 gradient of the potential on the epicardial boundary as the sum of both components $(\nabla u_T = (\nabla_{\Gamma_H} x + Dx$
 119 $))$. The operator ∇_{Γ_H} depends only on the epicardial surface Γ_H , whereas, D depends on the whole torso
 120 domain Ω . The objective function (14) can be expressed as follows:

$$\min_x \|Ax - b\| + \lambda^2 \|Dx\|_1. \tag{16}$$

121 The L1-Norm regularization of the current density leads to a non-linear problem. Following [25], we can
 122 smoothly approximate the L1-Norm of the derivative by:

$$\|Dx\|_1 = \sum_{i=1}^n |[Dx]_i| \approx \sum_{i=1}^n \sqrt{|[Dx]_i|^2 + \beta}, \tag{17}$$

123 with β a small constant satisfying $\beta > 0$ and $[Dx]_i$ the i^{th} component of the vector Dx .

124 This approximation leads to an interesting formulation of the L1-Norm regularization problem in the form
 125 of a set of equations whose resolution as $\beta \rightarrow 0$ gives an estimate of the solution of (16). The linear
 126 problem to be solved is then,

$$\left[A^T A + \lambda^2 D^T W_\beta(x) D \right] x = A^T b, \tag{18}$$

127 where $W_\beta(x)$ is a diagonal matrix called **weight matrix**, expressed by:

$$W_\beta(x) = \frac{1}{2} \text{diag} \left[\frac{1}{\sqrt{|[Dx]_i|^2 + \beta}} \right]. \tag{19}$$

128 We notice that (19) has an effect on the variation of the normal derivative penalty. In fact, when the local
 129 normal derivative is too small, the weight goes to larger values imposing greater smoothness on the solution.
 130 When the local normal derivative is large, the weight goes to small values allowing larger gradients in the
 131 solution in these regions.

132 The above formulation can be further simplified in a way that it can be seen as a first-order Tikhonov
 133 regularization. In fact, thanks to the diagonality of $\mathbf{W}_\beta(\mathbf{x})$, (18) can be written such that:

$$\left[\mathbf{A}^T \mathbf{A} + \lambda^2 \mathbf{D}^T \left(\sqrt{\mathbf{W}_\beta(\mathbf{x})} \right)^T \left(\sqrt{\mathbf{W}_\beta(\mathbf{x})} \right) \mathbf{D} \right] \mathbf{x} = \mathbf{A}^T \mathbf{b} \quad (20)$$

134 which leads to:

$$\left[\mathbf{A}^T \mathbf{A} + \lambda^2 \tilde{\mathbf{D}}^T(\mathbf{x}) \tilde{\mathbf{D}}(\mathbf{x}) \right] \mathbf{x} = \mathbf{A}^T \mathbf{b} \quad (21)$$

135 where $\tilde{\mathbf{D}}(\mathbf{x}) = \sqrt{\mathbf{W}_\beta(\mathbf{x})} \mathbf{D}$.

136 Computationally, the equation (21) is still non-linear since the weighting matrix $\mathbf{W}_\beta(\mathbf{x})$ depends on the
 137 solution \mathbf{x} . To overcome this constraint, we suggest to use the zero-order Tikhonov solution instead of the
 138 solution itself. Thus, the problem that we solve is

$$\left[\mathbf{A}^T \mathbf{A} + \lambda^2 \tilde{\mathbf{D}}^T(\mathbf{x}_0) \tilde{\mathbf{D}}(\mathbf{x}_0) \right] \mathbf{x} = \mathbf{A}^T \mathbf{b}, \quad (22)$$

139 where \mathbf{x}_0 is the zero-order Tikhonov solution determined by the Finite Element Method.

140 2.3 Methods for choosing regularization parameter

141 In this section, we detail the formulation of several methods used for choosing the optimal regularization
 142 parameter in terms of, both, the singular value decomposition in the case of the zero-order Tikhonov
 143 regularization and the generalized singular value decomposition in the case of L1-Norm regularization of the
 144 current density treated as a first-order Tikhonov regularization. It's fundamental for a good regularization
 145 parameter λ to satisfy the **Discrete Picard Condition** (DPC) [26]. In other words, this means that the
 146 singular values σ_i and the generalized singular values $\bar{\lambda}$ that are greater than λ must decay to zero slower
 147 than the corresponding $|\mathbf{u}_i^T \mathbf{b}|$ and $|\mathbf{p}_i^T \mathbf{b}|$, respectively.

148 2.3.1 U-Curve

149 The U-Curve is a plot of the sum of the inverse of $\eta_1(\lambda)$ (respectively, $\eta_2(\lambda)$) and the inverse of the
 150 corresponding residual $\rho_1(\lambda)$ (respectively, $\rho_2(\lambda)$) in the case where $L = I$ (respectively, $L \neq I$), in
 151 terms of λ on a log-log scale:

$$\begin{cases} Ucurve(\lambda) = \frac{1}{\rho_1(\lambda)} + \frac{1}{\eta_1(\lambda)}, & \text{if } L = I, \\ Ucurve(\lambda) = \frac{1}{\rho_2(\lambda)} + \frac{1}{\eta_2(\lambda)}, & \text{if } L \neq I. \end{cases} \quad (23)$$

152 The U-Curve method was proposed by [27, 28] and tested by [27, 28, 29] for the selection of the
 153 regularization parameter in the inverse problem. These works presented the method as a tool to determine
 154 the interval to which the regularization parameter belongs, providing a better computing efficiency.

155 According to [27] results, $Ucurve(\lambda)$ is strictly decreasing on the interval $[0, \delta_n^{2/3}]$ and strictly
 156 increasing on the interval $[\delta_1^{2/3}, \infty]$ where δ_1 and δ_n are respectively the biggest and the smallest
 157 singular values (generalized singular value in the case where $L \neq I$). Thus, $Ucurve(\lambda)$ reaches a local

158 minimum in the interval $[\delta_n^{2/3}, \delta_1^{2/3}]$. If we have at least one non-zero singular value, we can ensure the
 159 uniqueness of the $Ucurve(\lambda)$ minimizer, λ_u , the optimum value of λ .

160 2.3.2 ADPC

161 As mentioned above, the optimal regularization parameter should satisfy the DPC. Therefore, ADPC
 162 is a regularization parameter choice method based on this condition. The idea is to look for the last
 163 index i before the DPC is no longer satisfied [10]. This means before σ_i becomes smaller than $|u_i^T b_t|$
 164 in a log-log scale where t is time. For the sake of simplification, $\log(|u_i^T b_t|)$ is fitted by a polynomial
 165 $p_t(i, \log(|u_i^T b_t|))$ of degree 5 to 7. Then, for each p_t , we seek for $\alpha_t = \sigma_{maxi}$ such that $\log(\sigma_i) \geq p_t$.
 166 The ADPC regularization parameter is then $\lambda = median(\alpha_t)$.

167 2.3.3 CRESO

168 The Composite REsidual and Smoothing Operator (CRESO) method was introduced by Colli Franzone
 169 [30]. It chooses the parameter that corresponds to the first local maximum of the derivative of the difference
 170 between the constraint term and the residual term with respect to λ^2 .

$$\begin{cases} C(\lambda) = \frac{d}{d(\lambda^2)}(\lambda^2\eta_1(\lambda) - \rho_1(\lambda)), & \text{if } L = I, \\ C(\lambda) = \frac{d}{d(\lambda^2)}(\lambda^2\eta_2(\lambda) - \rho_2(\lambda)), & \text{if } L \neq I. \end{cases} \tag{24}$$

171 In terms of the singular value decomposition, this can be written as [17, 20]:

$$\begin{cases} C(\lambda) = \sum_{i=1}^n \frac{\sigma_i^2 \mu_i^2 (\sigma_i^2 - 3\lambda^2)}{(\sigma_i^2 + \lambda^2)^3}, & \text{if } L = I, \\ C(\lambda) = \sum_{i=1}^n \frac{\bar{\lambda}_i^2 \alpha_i^2 (\bar{\lambda}_i^2 - 3\lambda^2)}{(\bar{\lambda}_i^2 + \lambda^2)^3}, & \text{if } L \neq I. \end{cases} \tag{25}$$

172 where $\alpha_i = p_i^T b$, $i = 1 \dots n$.

173 2.3.4 GCV

174 The Generalized-Cross Validation (GCV) [31] is also a well-known method to choose the regularization
 175 parameter. It provides the optimal value of λ by minimizing the function

$$\begin{cases} G(\lambda) = \frac{\rho_1(\lambda)}{[Trace(I - AA^\dagger)]^2}, & \text{if } L = I, \\ G(\lambda) = \frac{\rho_2(\lambda)}{[Trace(I - AA^\#)]^2}, & \text{if } L \neq I. \end{cases} \tag{26}$$

176 The function $G(\lambda)$ is, according to **Wahba** [31], equal to the weighted linear combination of the m
 177 prediction errors by leaving out, in each time, the k^{th} data point, $k = 1 \dots m$ and resolving the inverse
 178 problem by the use of the $m - 1$ remaining data points. The idea is that the optimum of the regularization
 179 parameter provides the best prediction of a measurement as a function of the others. In terms of singular

180 value decomposition, $G(\lambda)$ is expressed by [31, 19]:

$$\left\{ \begin{array}{l} G(\lambda) = \frac{\sum_{i=1}^n \frac{\lambda^4 \mu_i^2}{(\sigma_i^2 + \lambda^2)^2} + \|r_{\perp}\|^2}{\left(m - \sum_{i=1}^n \frac{\sigma_i^2}{\sigma_i^2 + \lambda^2}\right)^2}, \quad \text{if } L = I, \\ G(\lambda) = \frac{\sum_{i=1}^n \frac{\lambda^4 \alpha_i^2}{(\bar{\lambda}_i^2 + \lambda^2)^2} + \sum_{i=n+1}^m \alpha_i^2}{\left(m - \sum_{i=1}^n \frac{\bar{\lambda}_i^2}{\bar{\lambda}_i^2 + \lambda^2}\right)^2}, \quad \text{if } L \neq I. \end{array} \right. \quad (27)$$

181 It's known that the GCV method has good asymptotic properties as $n \rightarrow \infty$ [32, 33, 34]. However, it
 182 may not be reliable for small or medium values of n and can give values of λ that are too small resulting
 183 in a very noisy regularized solution.

184 2.3.5 RGCV

185 In [35], a new method called Robust GCV (RGCV) is proposed and proved to be more reliable than GCV
 186 for small values of n and generally more accurate. The RGCV estimate is defined by the minimizer of the
 187 following function:

$$R(\lambda) = [\gamma + (1 - \gamma)\xi(\lambda)] G(\lambda), \quad (28)$$

188 where $G(\lambda)$ is given by (26) and $\xi(\lambda)$ is defined as:

$$\left\{ \begin{array}{l} \xi(\lambda) = \text{Trace} [(AA^\dagger)^2] = \sum_{i=1}^n \frac{\sigma_i^4}{(\lambda^2 + \sigma_i^2)^2}, \quad \text{if } L = I, \\ \xi(\lambda) = \text{Trace} [(AA^\#)^2] = \sum_{i=1}^n \frac{\bar{\lambda}_i^4}{(\lambda^2 + \bar{\lambda}_i^2)^2}, \quad \text{if } L \neq I. \end{array} \right. \quad (29)$$

189 Here, γ is called a robustness parameter, $\gamma \in [0, 1]$.

190 The RGCV method is based on the average influence $\frac{1}{m} \sum_{i=1}^m \|Ax_\lambda - Ax_\lambda^{[i]}\|^2$, where $\|Ax_\lambda - Ax_\lambda^{[i]}\|^2$
 191 is a measure of the influence of the i^{th} data point on the regularized solution. It's trivial that, when $\gamma = 1$,
 192 $R(\lambda)$ is reduced to $G(\lambda)$. It can be shown that the term $(1 - \gamma)\xi(\lambda)$ penalizes the too small values of
 193 λ . In fact, when $\lambda \rightarrow \infty$, $\xi(\lambda) \rightarrow 0$, so $\frac{1}{\gamma}R(\lambda)$ becomes equivalent to $G(\lambda)$. Otherwise, if $\lambda \rightarrow 0$,
 194 $\xi(0) = n$, so $\frac{1}{\gamma}R(\lambda) \gg G(\lambda)$ for small values of γ which means that the smaller γ , the more robust is
 195 the RGCV method [35].

3 EXPERIMENTAL METHODS AND SIMULATION PROTOCOLS

196 3.1 Data sets

197 ECGI reconstructions were performed on two different sets of data:

198 I. Simulated data obtained by considering a realistic 3D heart-torso geometry segmented from CT-Scan
 199 images as illustrated in **Figure 1** (see [36] for more details). The propagation of the electrical wave
 200 was computed using the monodomain reaction-diffusion model. The transmembrane currents used to
 201 compute the extracellular potential distribution throughout the torso were computed by solving a static
 202 bidomain problem in an homogeneous, isotropic torso model [37]. Synchronized electrical potential on
 203 the epicardium and on the body surface were extracted in order to test the inverse methods. The torso
 204 mesh contained 2873 nodes and the heart mesh 519 nodes.

205 II. Experimental data were obtained using an ex-vivo pig heart perfused in Langendorff mode suspended
 206 into a human-shaped torso tank. The heart was paced by 2 ms pulses at 2 Hz, with constant current
 207 amplitudes 2x the diastolic threshold, on the left and right ventricular epicardial surface, mimicking
 208 ectopic activity. Epicardial ventricular electrograms were recorded using a 108-electrode sock (of which
 209 93 were used) simultaneously with torso potentials from 128 electrodes embedded in the tank surface as
 210 it appears in **Figure 2**.

211 Tank and sock unipolar electrograms were recorded at 2 kHz (BioSemi, the Netherlands) and referenced
 212 to a Wilson's central terminal defined using tank electrodes. A multi-lead signal averaging algorithm
 213 was used to remove noise and non-synchronized p-waves on recordings. In most cases, retrograde VA
 214 conduction was present with P-waves only present during the non-analyzed ST-segment. The tank mesh
 215 contains 1234 nodes and the epicardium 649 nodes. For the application of described inverse methods,
 216 potential recordings need to be available for all the mesh nodes. To do so, a linear interpolation was
 217 applied to the ex-vivo recordings. More details about the ex-vivo experimental protocol can be found in
 218 Bear et al. [38].

219 For all the carried out tests using the L1-Norm regularization, β is kept fixed and equal to 10^{-5} .

220 3.2 Choice of the robustness parameter

221 The choice of γ for the RGCV tests is based on the study made by Barnes and Johnston [15]. In fact,
 222 they proved that applying RGCV with $\gamma = 0$ gives a good approximation of the optimal regularization
 223 parameter, especially when using realistic geometries and potential measures. To justify this choice, **Figure**
 224 **3** represents a plot of the RGCV criterion in terms of the parameters λ and γ where the color map defines
 225 the value of the RGCV function and the red marks correspond to the local minima. We observe that the
 226 local minima are almost reached at the same λ value except the case where $\gamma = 1$ corresponding to the
 227 GCV. For organization reasons, we present here only a graph realized using experimental data at a specific
 228 time step, but we observe the same behavior for all the other cases. This confirms the fact that for the
 229 inverse problem of electrocardiography, RGCV is not sensitive to γ when $\gamma \in [0, 0.5]$.

230 3.3 Evaluation criteria

231 To assess the accuracy of the results obtained by the different approaches, we define the relative error
 232 (**RE**) and the correlation coefficient (**CC**):

$$RE = \sqrt{\frac{\sum_{i=1}^n (x_i^c - x_i^e)^2}{\sum_{i=1}^n (x_i^e)^2}} \quad (30)$$

233

$$CC = \frac{\sum_{i=1}^n [x_i^c - \bar{x}^c] [x_i^e - \bar{x}^e]}{\sqrt{\sum_{i=1}^n (x_i^c - \bar{x}^c)^2 \sum_{i=1}^n (x_i^e - \bar{x}^e)^2}} \quad (31)$$

234 where x^c and x^e denote respectively the computed epicardial potential and the known one. n is either the
 235 number of epicardial nodes or the total number of time steps. In the first case, \bar{x}^c and \bar{x}^e are the spatial
 236 mean values of x^c and x^e over the n epicardial nodes. Otherwise, \bar{x}^c and \bar{x}^e are the temporal mean
 237 values of x^c and x^e over the n time steps. The means and the standard deviations of RE and CC are then
 238 computed and represented as bar graphs. The accuracy of pacing sites localization is measured by the
 239 geodesic distance between real and estimated pacing sites.

4 RESULTS

240 4.1 Epicardial potential reconstruction

241 4.1.1 Simulated Data

242 First, we assessed regularization techniques and numerical methods using simulated data. The five
 243 regularization parameter choice criteria described above were assessed using all the suggested numerical
 244 methods: MFS, FEM-ZOT and FEM-L1 which make 15 different algorithms.

245 **Figure 4** presents the mean and the standard deviation of the spatial REs and CCs of the reconstructed
 246 potentials by the different numerical tests. For MFS, GCV gives the best estimation of the optimal
 247 regularization parameter in terms of relative error (0.24 ± 0.15) and correlation coefficient (0.98 ± 0.04).
 248 we notice an improvement by 10% comparing to RGCV and CRESO methods. These 3 techniques
 249 outperform with different grades ADPC and U-Curve which seem to be unsuitable for MFS resolution.

250 For all the runned simulations using FEM, GCV and ADPC fail to compute the optimal regularization
 251 parameter. In fact, GCV tends to be flat for small values of λ which make it difficult to pick a minimum.
 252 RGCV is suggested to help with this difficulty. We observe here that it outperforms U-Curve by nearly 30%
 253 using the zero order Tikhonov and 20% using the L1-norm regularization of the current density while it
 254 gives similar results to CRESO in terms of both spatial RE and CC.

255 **Figure 4** shows also the accuracy of L1-norm regularization in the reconstruction of epicardial potential
 256 maps. We observe that it provides the minimum of mean relative error (0.21 ± 0.2) and the maximum of
 257 spatial correlation coefficient (0.99 ± 0.04).

258 **Figure 5** and **Figure 6** show simulated epicardial potential maps (A) and reconstructed ones using FEM-
 259 ZOT (B) and FEM-L1-Norm (C) at the stimulation sample time and at 212ms, after the electrical pacing
 260 leading to a reentry arrhythmia, respectively. It can be seen that L1-Norm regularization provides a better
 261 reconstruction compared to the zero-order Tikhonov regularization especially on the regions where we
 262 have a potential leap. This fits exactly with the role of the L1-Norm regularization which is a better way to
 263 detect the gradient changes compared to Zero order Tikhonov.

264 4.1.2 Experimental Data

265 Preprocessing of the experimental data revealed the existence of a few localized sites of ischemia
 266 produced due to electrode pressure on the epicardium. This produced monophasic action potential-like
 267 signals. These electrodes were identified when the potential was greater than a fixed threshold equal to
 268 50% of the maximum signal magnitude in the plateau phase, 250ms after pacing. This choice is based on
 269 observations of the QT interval in order to eliminate the ischemic signals. This leads us to run two sets
 270 of comparisons, with all the working electrodes and after removing the above threshold electrodes. We
 271 observe that results after thresholding are better than those obtained with ischemic signals. For the sake of
 272 clarity, we present here only results after thresholding. **Figure 7** shows the mean and standard deviation
 273 of spatial RE and CC. We observe a degradation of the metrics for the three models of experimental data
 274 (RV, LV and BiV). This can be explained by different factors, the subject of section 4.4. In **Figure 7**, we

275 observe that using MFS, all the methods demonstrated similar trends in RE mean values. It shows also
276 that GCV outperforms the other methods in terms of spatial correlation coefficient. For FEM, GCV and
277 ADPC have always difficulties in computing the optimal value of the regularization parameter while RGCV,
278 CRESO and U-C urve perform the same with a mean relative error near to 0.95 for all the three paced
279 rhythms. Regarding the performance, there is not a clear difference among all the methods.
280 For the sake of completeness, statistical detailed results of RE and CC in time and space on the reconstructed
281 potential for all cases are reported in the supplementary material.

282 4.2 Localization of pacing sites

283 For the localization of pacing sites, we used three different experiments, two of them provide LV, RV
284 and BiV pacing data sets and the other one has only RV and LV models. In summary, we have 3 cases of
285 LV pacing, 3 cases of RV pacing and 2 cases of BiV pacing. In **Figure 8** (respectively, **Figure 9**) (top),
286 we show measured and reconstructed potential maps right at the pacing sample time in an LV-pacing
287 (respectively, RV-pacing) case. The detected pacing sites are marked by bigger red crosses than the actual
288 pacing site and the length of the green segment between them represents the geodesic distance. For the
289 sake of comparison, only the simulation using the regularization parameter technique providing the better
290 localization is selected for the figures. The case where the reconstructed epicardial potential do not allow
291 us to extract the pacing sites are reported in **Table 1** as non applicable (N.A) cases.

292 For the LV-pacing (respectively, RV-pacing) case , we observe that L1-norm regularization of the current
293 density combined with RGCV provides the best localization with an error of 0.45cm (respectively,
294 2.15cm). It outperforms FEM-ZOT 2.55cm (respectively, 2.16cm) and MFS 0.83cm (respectively,
295 3.15cm) that give similar approximations. We also plot in the bottom of the figure the time course of the
296 electrical potential at the actual pacing site position detected from the measured data. For LV-pacing case,
297 MFS, (respectively FEM-ZOT and FEM-L1) present temporal relative error and correlation coefficient equal
298 to $(0.83, 0.72)$ (respectively $(0.86, 0.75)$, $(0.8, 0.72)$). For the RV-pacing case, MFS, (respectively
299 FEM-ZOT and FEM-L1) present temporal relative error and correlation coefficient equal to $(1.05, 0.3)$
300 (respectively $(1.12, 0.40)$, $(1.01, 0.33)$).

301 For both LV and RV-pacing we observe that none of the methods is clear-cut.

302 In the case of a bi-ventricular pacing (BiV), not all the methods were able to locate both pacing sites.
303 Only MFS-ZOT combined with GCV, FEM-ZOT and FEM-L1 with RGCV succeed to detect the two
304 pacing sites with more-less good accuracy. **Figure 10** presents the real and estimated pacing sites and their
305 electrograms for a BiV pacing rhythm for which all the methods work. The **Figures 10B, C** and **D** show
306 the results for the BiV pacing sites. Errors of localization of the LV pacing site are 1.3cm for FEM-L1,
307 1.8cm for FEM-ZOT and 2.3cm for MFS. The bottom row of each panel represents the reconstructed
308 electrograms in the real pacing sites using the specified method. The temporal relative errors and correlation
309 coefficients for LV are $(0.80, 0.71)$ using FEM-L1, $(0.86, 0.75)$ with FEM-ZOT and $(0.83, 0.72)$ using
310 MFS. As shown in **Figure 10B**, MFS nearly fails to detect the left ventricular pacing site. The epicardial
311 potential in the whole left ventricle is almost in the same range. For the RV pacing site, results are nearly
312 the same as for the LV pacing site.

313 The performance in terms of pacing site localization of the 15 algorithms on the set of the experimental
314 data are reported in **Table 1** where we provide the mean values and standard deviations of pacing sites
315 localization errors for the three cases, LV, RV and BiV. We remark that, L1-norm regularization of the
316 current density combined with RGCV parameter choice method outperforms all the other methods with
317 minimum errors and more stable standard deviations.

318 4.3 Limitations

319 4.3.1 The imperfect knowledge of the transfer matrix

320 It's important to mention that in this work, the use of simulated data provides an optimal knowledge of
 321 the transfer matrix A , which is not the case of experimental data. It explains somehow the degradation of
 322 the results using the experimental data. To assess the impact of the transfer matrix, we computed a relative
 323 error defined by:

$$RE_d = \frac{\|Ax_{ex} - b\|}{\|b\|} \quad (32)$$

324 where x_{ex} is the exact solution whether it's the simulated epicardial potential or the measured one.
 325 The RE_d is almost equal to zero using the simulated transfer matrix. However, it increases for the
 326 experimental data to reach, for some time steps, $RE_d \approx 0.9$. Although this issue is out of the scope of
 327 this paper, the degradation can be due to different factors like the measurement errors and geometrie's
 328 inaccuracy due to the fact that the heart is moving during the experiment, but also to the mathematical
 329 modeling of the physical phenomenon which is reduced to the Laplace equation. These hypotheses make
 330 the issue subject to further analyzes.

331 4.3.2 Experimental protocols

332 Obviously, the experimental conditions have a very important impact on the quality of the data that
 333 we obtain from experiments. One of the limitations of this study is the dataset of epicardial signals. In
 334 fact, the experimental protocol described in [38] indicates that the epicardial surface is not totally covered
 335 with electrodes which provides less information and biased results. Further studies should be done in
 336 this context. The protocols we have set until now do not include endocardial stimulation, this is one of
 337 the limitation of our work. Of course, if we have to evaluate the methods against endocardial and septal
 338 stimulations we have to make use of a W-shape geometry of the ventricles including endocardial, epicardial
 339 and septal surfaces instead of a nut-shape geometry that only represents the epicardial surface.

5 DISCUSSION AND CONCLUSION

340 In this paper, we numerically assessed 15 different algorithms for the resolution of the inverse problem of
 341 electrocardiography based on the Generalized Singular Value Decomposition of the pair {Transfer matrix,
 342 Regularization matrix} combined with different regularization parameter choice methods. Although the
 343 L1-Norm of the normal derivative regularization method has been presented before [24, 9] to solve the
 344 ECGI inverse problem, there are two novelties in this paper: First, the non quadratic scheme was solved
 345 using the generalized singular values decomposition, Whereas, in [9] authors use an iterative method.
 346 Second, the regularization method was combined with five regularization parameter choice methods to
 347 assess its performance on simulated and experimental data. In [15], authors used only ZOT regularization
 348 and compared results only on simulated data. In this paper and in the majority of the studies looking
 349 for the ECGI inverse solution, the problem is formulated in terms of electrical potential. There are other
 350 approaches, where the problem is formulated in terms of propagating wave front [39, 40]. In [41], the
 351 activation and recovery times and the transmembrane potentials are constructed. Other approaches are
 352 interested in constructing directly dominant frequencies on the heart surface and torso surfaces [42, 43].

353 The evaluation of the different approaches studied in this paper is based on the reconstruction of the
 354 epicardial potential maps and the localization of pacing sites. For that, we used 3 different cardiac paced
 355 rhythms: left-ventricular, right-ventricular and bi-ventricular pacing.

356 Unlike the work presented by Barnes and Johnston in [15], this study considered two types of transfer
357 matrices: MFS and FEM and two different approaches of regularization: zero-order Tikhonov and L1-Norm.
358 This study demonstrated that, when using the MFS discretization approach, the GCV method is more
359 appropriate and optimal than RGCV and the other parameter choice methods. Otherwise, for the FEM
360 approach, the RGCV gives the best results using simulated data. But also, GCV and ADPC provide very
361 weak results with FEM, this is mainly due to the fact that the minimization criteria in both cases chooses
362 the regularization parameter λ at the lower bound of the provided interval.

363 However, for the experimental data, all the methods perform nearly the same with a slight difference in
364 terms of both spatial and temporal relative error and correlation coefficient when comparing the epicardial
365 potential distribution. We think that this is mainly due to the magnitude of the recorded potentials but
366 also to the noise and other experimental uncertainties. Results show, also, that L1-Norm regularization of
367 the potential normal derivative yields generally the best solution. For the purpose of benchmarking, the
368 represented algorithms were evaluated against the data set used in the paper [44]. Results are reported
369 in the supplementary material. They show similar performance for the sinus rhythm model using the
370 L1-norm regularization of the current density. This last regularization has a better performance for the
371 atrial fibrillation models compared to all the ZOT based methods but weaker results than the Bayesian
372 approach [44, 45]. This should be subject of several further studies.

373 Regarding the pacing site localization, **Table 1** show clearly that the estimation of pacing sites is more
374 accurate using L1-norm regularization than other methods with minimum errors and less variance despite
375 the fact that it depends of the epicardial potential reconstruction. This is due to the use of L1-Norm
376 regularization that preserves the spatial gradient changes in the solution which is not the case for the L2-
377 Norm regularization that tends to give smoother solutions. Despite the good performance of the methods in
378 the case of LV and RV, they have faced difficulties in localizing two pacing sites for the BiV pacing and
379 localize in some cases only one pacing site nearly equidistant to the two real ones. Some limitations of
380 this study have been explored such as the imperfect knowledge of the transfer matrix and the noise in the
381 ground truth data that could lead to biased results. This explains the degradation of the RE and CC metrics
382 in terms of electrical potential for the experimental data compared to the simulated model.

383

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FIGURES AND TABLES

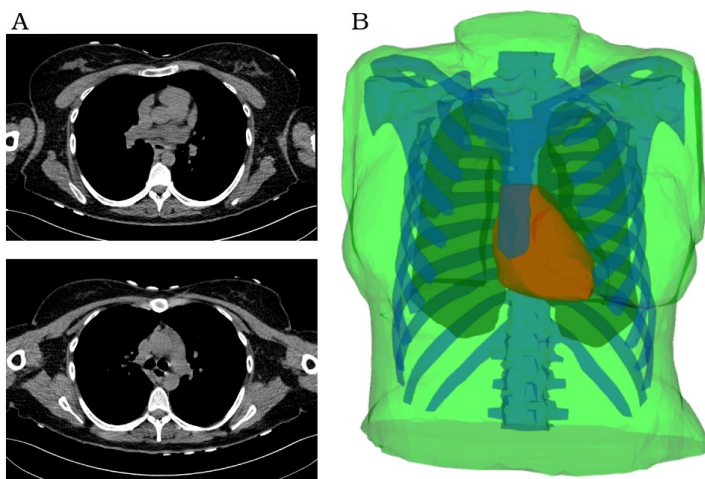


Figure 1. A : Two slices of the CT-scan images. B : Torso geometry showing the epicardium (heart-torso interface Σ) (red), lungs (yellow), bones (blue) and torso external boundary Γ_{ext} (green).

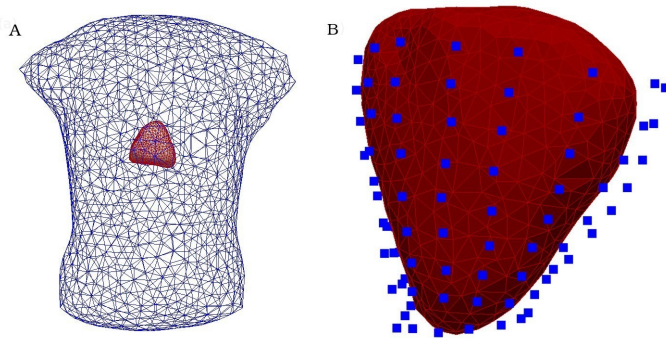


Figure 2. A : The heart-human-shaped torso tank model used for the experimental data simulations. The heart consists of 761 nodes and 1518 elements and the tank contains 1177 nodes and 2350 elements. B : the heart geometry covered by the sock consisting of 108 electrodes (blue points).

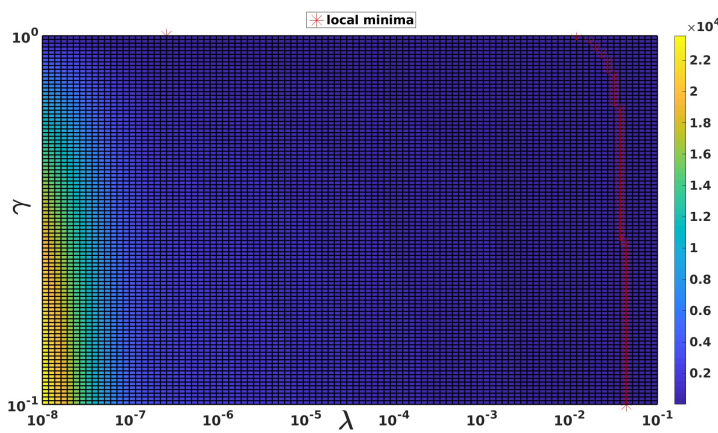


Figure 3. The RGCV criterion plotted in terms of λ and γ . The red markers are the grid points where $RGCV(\lambda, \gamma)$ is minimum when γ is fixed

		CRESO	GCV	RGCV	UCurve	ADPC
RV	MFS-ZOT	2.8 ± 1.2	2.4 ± 1.1	1.9 ± 0.9	2.4 ± 0.8	2.5 ± 0.8
	FEM-ZOT	2.7 ± 0.8	N.A	2.7 ± 0.9	2.0 ± 0.1	N.A
	FEM-L1	1.9 ± 0.5	N.A	1.8 ± 0.3	1.8 ± 0.4	N.A
LV	MFS-ZOT	1.7 ± 0.7	2.1 ± 0.3	2.0 ± 1.1	1.3 ± 0.6	2.1 ± 0.2
	FEM-ZOT	2.1 ± 0.4	N.A	2.8 ± 1.0	3.0 ± 0.2	N.A
	FEM-L1	1.3 ± 0.5	N.A	1.2 ± 0.6	1.3 ± 0.6	N.A
BiV	MFS-ZOT	$2.5/N.A$	$2.3/1.5$	$0/N.A$	$2.3/N.A$	$2.7/2.0$
	FEM-ZOT	$1.8/N.A$	N.A	$1.8/2.1$	$2.5/N.A$	N.A
	FEM-L1	$2.5/N.A$	N.A	$1.3/1.4$	$1.4/N.A$	N.A

Table 1. mean errors and standard deviations of localization of pacing sites for the 2 paced rhythms RV,LV using the 3 numerical methods MFS-ZOT, FEM-ZOT and FEM-L1 combined with the regularization parameter choice methods. For BiV, values are the geodesic distances (LV/RV).N.A means that one could not extract the pacing site from the reconstructed signals.

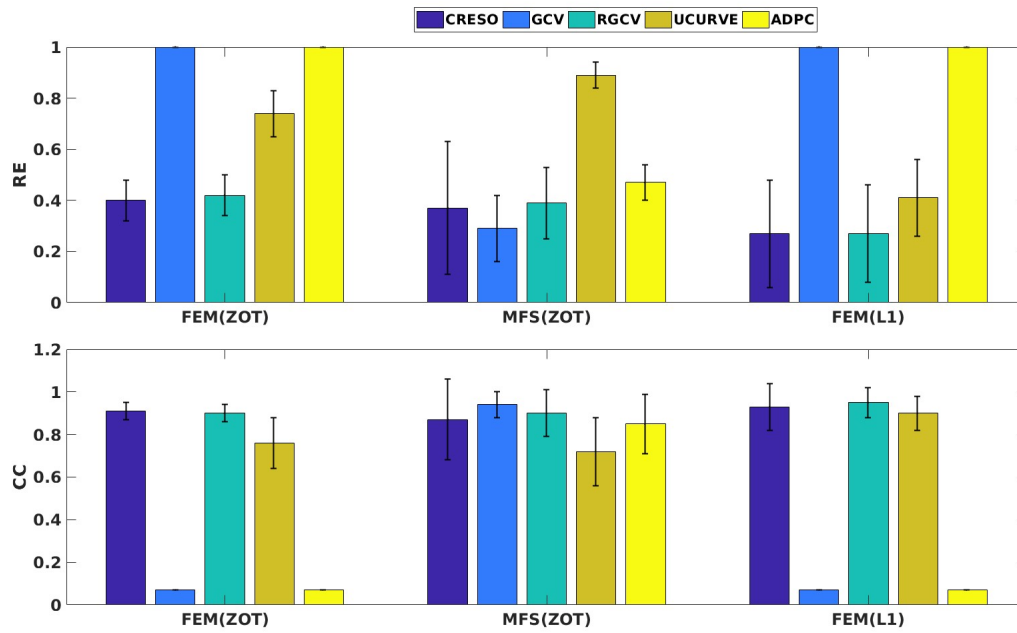


Figure 4. Bar graphs of means of relative errors and correlation coefficients with the standard deviations for simulated data.

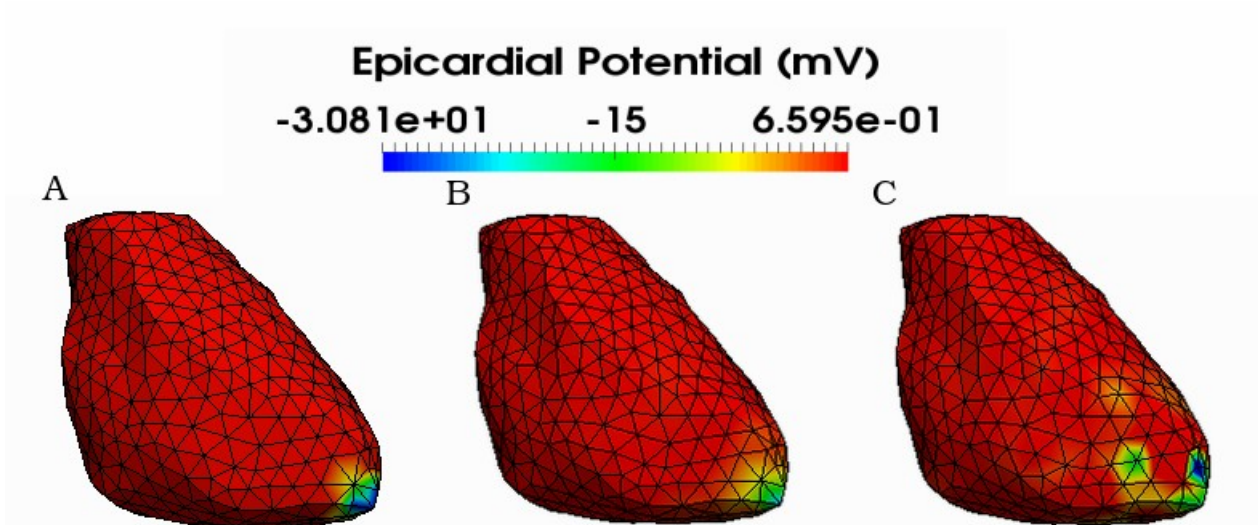


Figure 5. Simulated (A) and reconstructed epicardial potential distributions on the epicardium at the stimulation sample time using FEM-ZOT (B) with the optimal regularization parameter (RGCV), L1-Norm (C) with the optimal regularization parameter (RGCV).

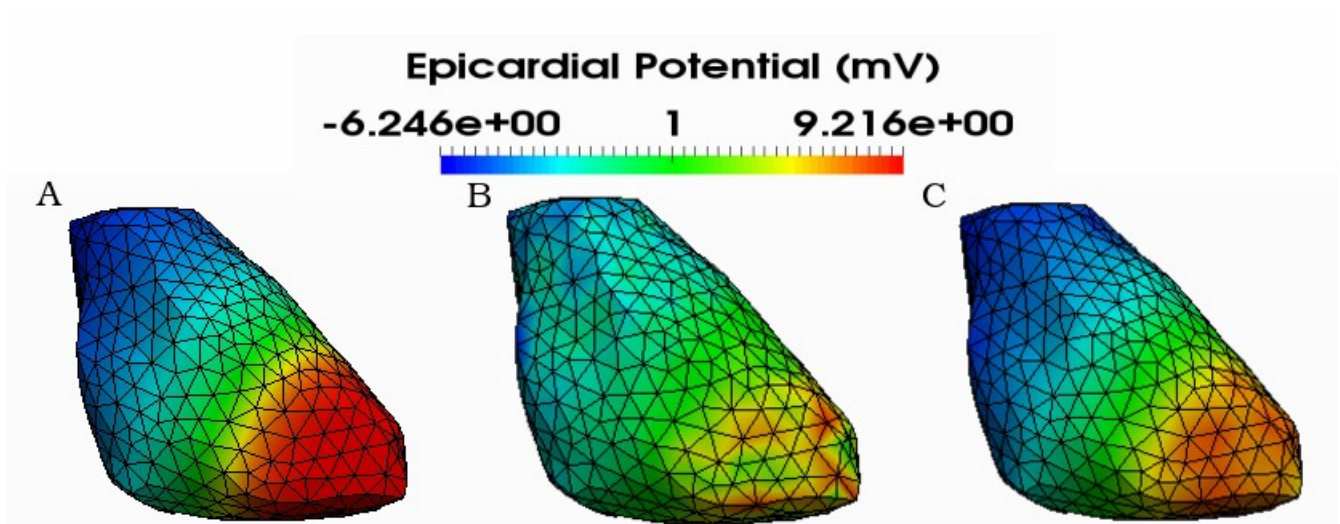


Figure 6. Simulated (A) and reconstructed epicardial potential distributions on the epicardium at 212ms after stimulation using FEM-ZOT (B) with the optimal regularization parameter (RGCV) and L1-Norm (C) with the optimal regularization parameter (RGCV).

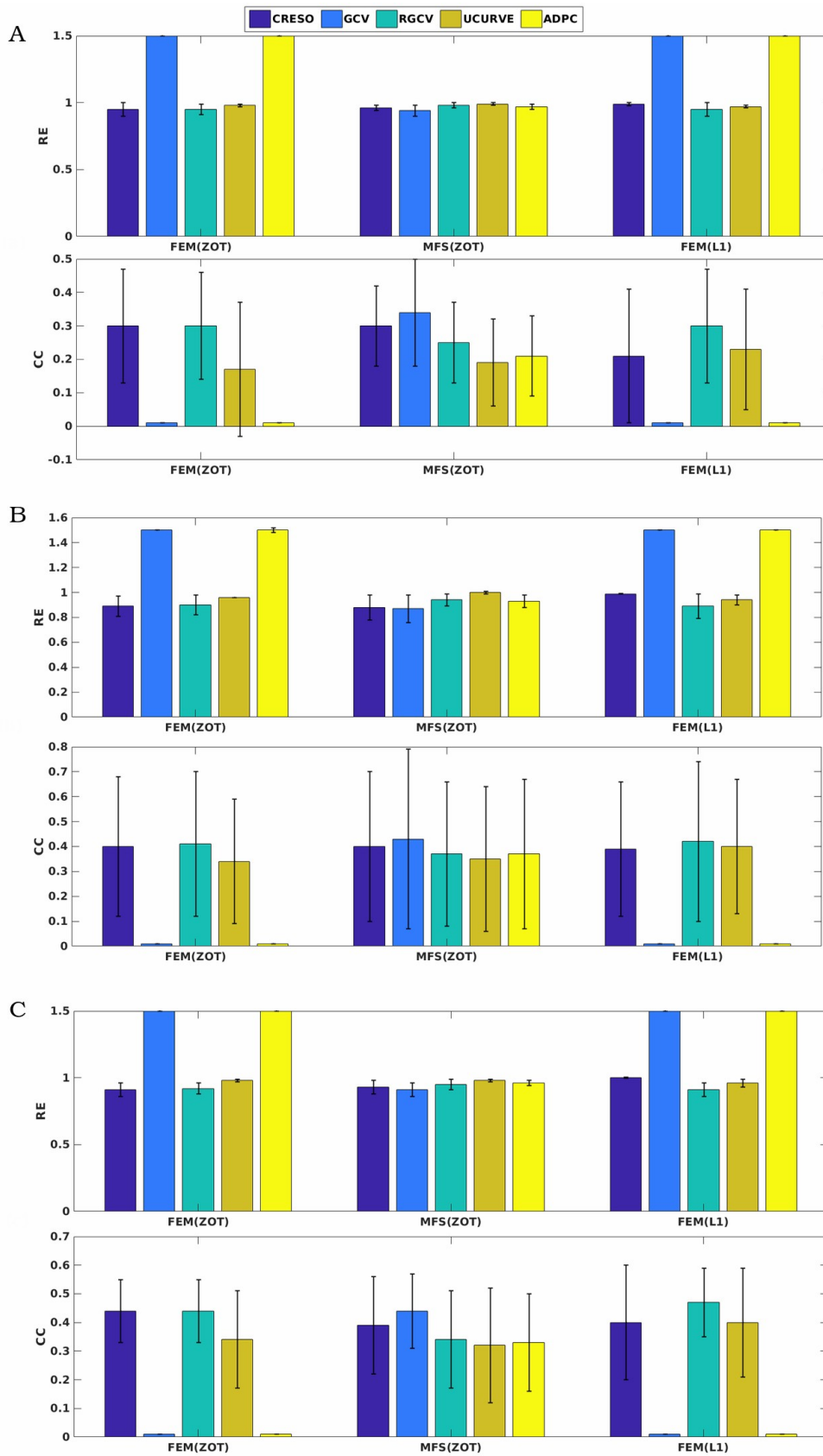


Figure 7. Spatial mean relative errors and correlation coefficients and their standard deviations for reconstructed epicardial potentials with all the algorithms for three paced rhythms: A : Biv, B : RV and C : LV

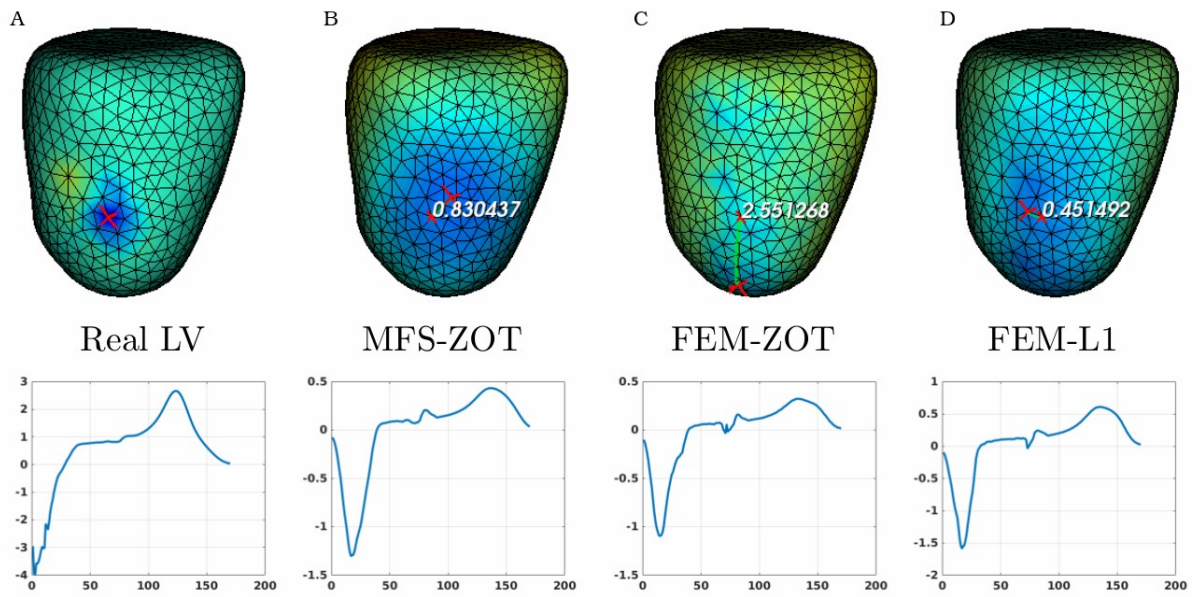


Figure 8. Real (A) and the estimated LV pacing sites (top) and its electrograms (bottom) using MFS-ZOT (B), FEM-ZOT (C) and FEM-L1 (D), respectively.

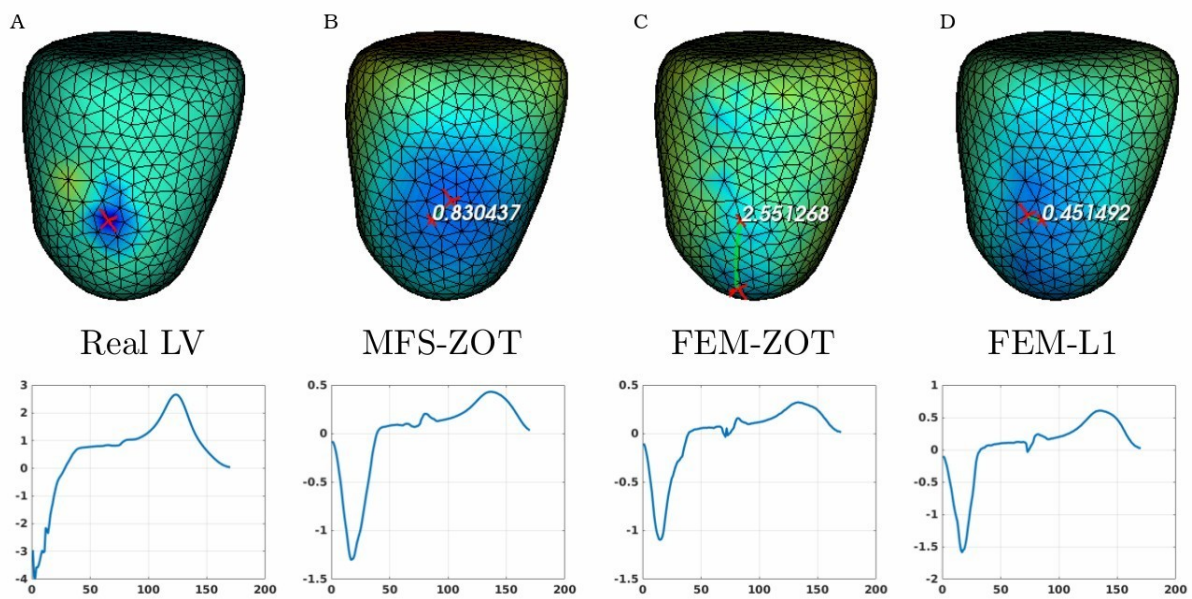


Figure 9. Real (A) and the estimated RV pacing sites (top) and its electrograms (bottom) using MFS-ZOT (B), FEM-ZOT (C) and FEM-L1 (D), respectively.

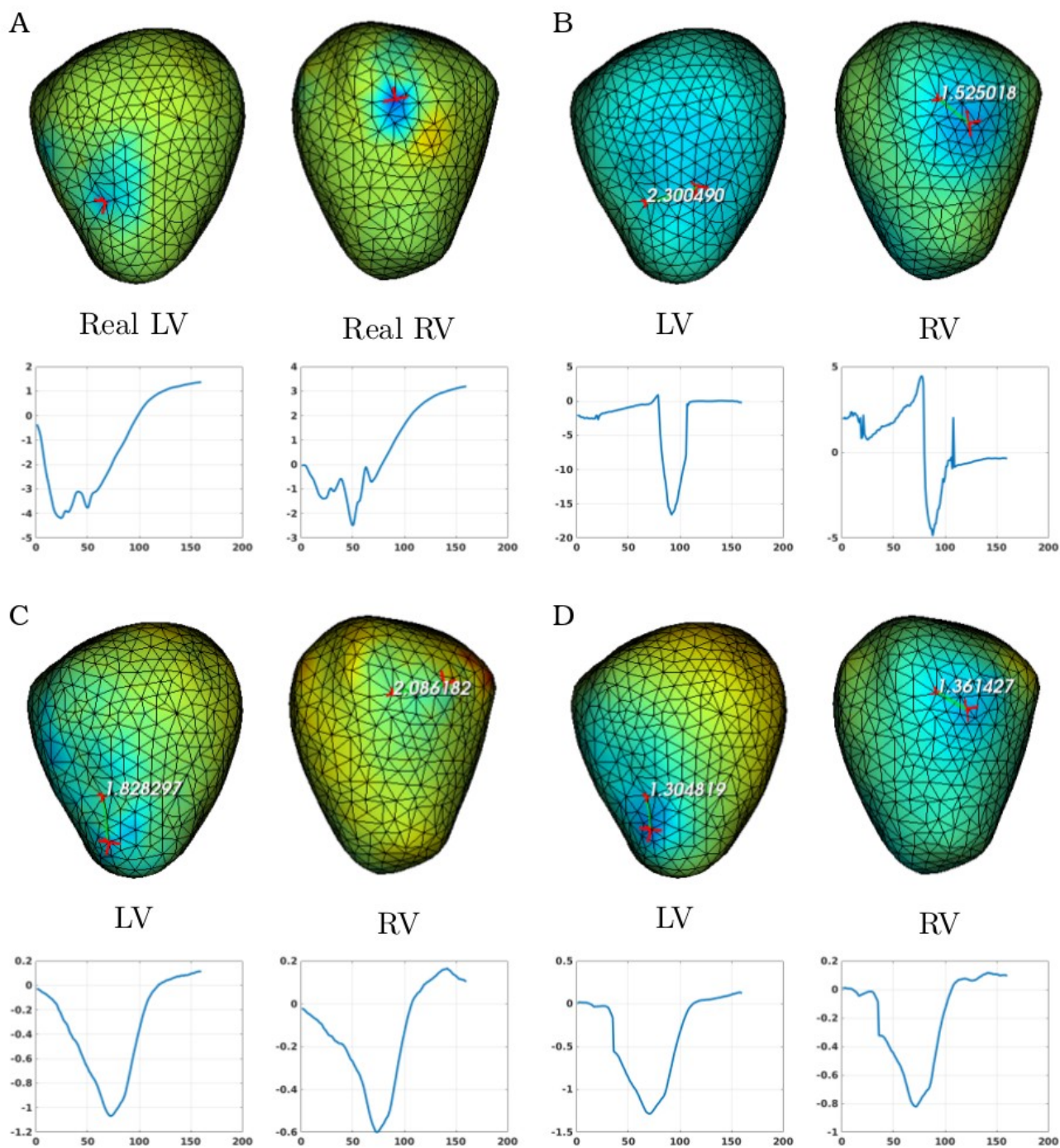


Figure 10. Real (A) and the estimated BiV pacing sites with its electrograms using the numerical methods (B) MFS-ZOT, (C) FEM-ZOT and (D) FEM-L1. In each panel, LV and RV pacing sites (top) with their electrograms (bottom) are represented using the mentioned numerical method.