



Accurate and efficient cardiac digital twin from surface ECGs: Insights into identifiability of ventricular conduction system

Thomas Grandits ^{a,b}, Karli Gillette ^{c,d}, Gernot Plank ^{c,d}, Simone Pezzuto ^{b,e}

^a Department of Mathematics and Scientific Computing, University of Graz, Heinrichstraße 36, 8010 Graz, Austria

^b Euler Institute, Università della Svizzera italiana, Via Buffi 13, 6900 Lugano, Switzerland

^c Gottfried Schatz Research Center: Medical Physics and Biophysics, Medical University of Graz, Neue Stiftingtalstraße 6, 8010 Graz, Austria

^d BioTechMed-Graz, Mozartgasse 12/II, 8010 Graz, Austria

^e Department of Mathematics, University of Trento, Via Sommarive 14, 38123 Trento, Italy

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ABSTRACT

Digital twins for cardiac electrophysiology are an enabling technology for precision cardiology. Current forward models are advanced enough to simulate the cardiac electric activity under different pathophysiological conditions and accurately replicate clinical signals like torso electrocardiograms (ECGs). In this work, we address the challenge of matching subject-specific QRS complexes using anatomically accurate, physiologically grounded cardiac digital twins. By fitting the initial conditions of a cardiac propagation model, our non-invasive method predicts activation patterns during sinus rhythm. For the first time, we demonstrate that distinct activation maps can generate identical surface ECGs. To address this non-uniqueness, we introduce a physiological prior based on the distribution of Purkinje-muscle junctions. Additionally, we develop a digital twin ensemble for probabilistic inference of cardiac activation. Our approach marks a significant advancement in the calibration of cardiac digital twins and enhances their credibility for clinical application.

1. Introduction

CDT technology aims to build a 1:1 *in silico* replica of a subject's heart (Niederer et al., 2021). Built upon advanced biophysical simulations, CDTs are informed with constant or periodic real-time updates from observations (Laubenbacher et al., 2024), to accurately track the physiological state of a patient's heart. Based on the mechanistic nature of the used modeling technologies, a critical element in the CDT paradigm is the inherent assumption that virtual and physical hearts are closely intertwined such that any stimulus or perturbation leads to the same emergent response, whether this occurs in the real or virtual space. CDTs fulfilling this assumption offer immense transformative potential for personalizing medical care, as they provide safe and effective means of assessing a patient's cardiac function to support diagnosis, stratification and optimal planning of therapies (Corral-Acero et al., 2020; Cluitmans et al., 2024).

Realizing this promising vision of building high fidelity CDTs at scale poses a number of technological challenges. Complex modeling workflows must be implemented comprising two distinct stages – referred to as *anatomical* and *functional twinning* – dedicated to building

anatomically accurate models of the heart from medical images, and, subsequently, calibrating a vast number of parameters of the model to assimilate electrophysiological function between model and patient heart, respectively. Significant progress has been made in terms of automating anatomical twinning to build patient heart anatomies at scale (Crozier et al., 2016). Less developed and markedly more challenging are functional twinning methodologies. The vast majority of simulation studies using models labeled as CDTs refrain from functional twinning. Rather, the same average parameters are used across the board for all patients, and like-for-like comparisons with clinically observable signals such as electrograms (EGMs) or the ECG are avoided as these would reveal substantial discrepancies between virtual model and physical reality (Sung et al., 2022; Bishop and Plank, 2025). Recent efforts to develop enhanced functional twinning technologies show promise to lift current restrictions in the calibration of models. A key advance was the introduction of more efficient methods for evaluating the biophysical model that now facilitate cardiac electrophysiology (EP) simulations at the organ scale with real-time performance (Pezzuto et al., 2017; Neic et al., 2017). These have been used in proof-of-concept studies to calibrate models of patient hearts to non-invasive

* Corresponding authors.

E-mail addresses: thomas.grandits@uni-graz.at (T. Grandits), karli.gillette@medunigraz.at (K. Gillette), gernot.plank@medunigraz.at (G. Plank), simone.pezzuto@unitn.it (S. Pezzuto).

¹ These authors contributed equally to this work.

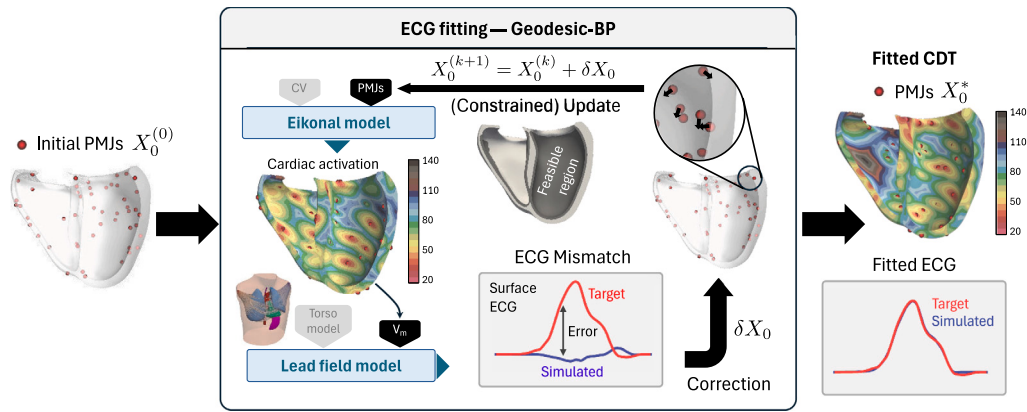


Fig. 1. Geodesic-BP: fast definition of a CDT from the surface ECG. Geodesic-BP (Grandits et al., 2024) optimizes the distribution of PMJs until the mismatch between recorded and simulated ECG is minimized. Physiological constraints for the PMJs are automatically imposed during the optimization process.

clinical ECG data using both sampling (Pezzuto et al., 2021; Gillette et al., 2021b; Camps et al., 2024; Álvarez Barrientos et al., 2025) and optimization approaches (Grandits et al., 2021a, 2024). As such, the grand challenge at the very core of functional twinning remains – to fit the model’s high dimensional parameter space from limited clinical, ideally non-invasively acquired, data to accurately reproduce clinical recordings like-for-like with high fidelity in a robust, unique and scalable manner.

A main objective is to infer the electrical activation sequence of the ventricles – the main pumping chambers of the heart – from a patient’s surface ECG, and to replicate the sequence in a physiologically accurate model of electrical wavefront propagation and the associated ECG (specifically, the QRS complex) (Pezzuto et al., 2021; Grandits et al., 2021a; Gillette et al., 2022; Li et al., 2022; Grandits et al., 2024; Camps et al., 2024). The ventricular activation sequence and its reflection in the QRS complex observed on the body surface is driven by the ventricular conduction system referred to as HPS that initiates the activation of the ventricles. The HPS comprises the bundle of His that receives atrial signals via the atrio-ventricular node, a left and right bundle branch that splits into fascicles attached to the Purkinje network, a fast-conducting network of Purkinje fibers that permeates both the endocardial and sub-endocardial tissue (Spach et al., 1963; Myerburg et al., 1972; Vigmond and Stuyvers, 2016). The Purkinje network is coupled to the ventricular myocardium at terminal junctions, referred to as PMJs, which serve as the initiation sites of earliest ventricular activation and, thus, play a pivotal role in determining the ventricular activation pattern and the surface ECG. However, the structure of the HPS as well as the distribution of PMJs is highly patient-specific and, generally, inaccessible by non-invasive methods (Pullan et al., 2010), and, even with invasive advanced mapping methodologies (Palamara et al., 2014), only observable with limited accuracy. Owing to its importance as the pivotal structure controlling ventricular activation, and as a target for the treatment of conduction disturbances (Sharma et al., 2018), a method to unveil its structure and properties is among the most fundamental challenges in cardiac electrophysiology. However, inferring an extremely high dimensional object such as the ventricular activation sequence from very limited, sparse, and noisy data such as the ECG, constitutes an ill-posed problem. As such, it is still unclear as to which extent and accuracy the ventricular activation sequence can actually be inferred solely from the standard 12-lead ECG (Grandits et al., 2022). Consequently, the possibility that different ventricular activation maps could yield the same QRS complexes in the 12-lead ECG must be considered (Colli Franzone et al., 2014; Li et al., 2025).

Fast EP simulators, based on the Eikonal and reaction-Eikonal models, offer a way to address the identifiability challenge of inferring – ideally uniquely – the ventricular activation sequence (Colli Franzone and Guerri, 1993; Pezzuto et al., 2017; Neic et al., 2017). These

simulators allow for the rapid exploration of the parameter space to identify candidate PMJ sets by comparing simulated against recorded ECGs (Gillette et al., 2021b; Camps et al., 2024). Sampling-based methods have successfully identified ventricular activation patterns from ECG data under conditions such as focal activity (Pezzuto et al., 2022; Meisenzahl et al., 2024), bundle branch block (Pezzuto et al., 2021; Álvarez Barrientos et al., 2025), and during normal sinus rhythm (Gillette et al., 2021b; Camps et al., 2024; Cardone-Noott et al., 2016; Barber et al., 2021). However, given the enormous number of samples required, these methods are feasible only for a small number of parameters or when paired with fast emulators (Pezzuto et al., 2022; Salvador et al., 2023; Camps et al., 2024). Here, the HPS is often approximated by a small number of PMJs combined with a fast endocardial layer (Pezzuto et al., 2021). In general though, sampling-based approaches and emulators do not scale well as the number of parameters increases (Larson et al., 2019), thus they are limited in their ability to infer the ventricular conduction system in a more general setting.

In this work, we leverage Geodesic-BP, a fast, gradient-based method for identifying PMJs from ECG data (Grandits et al., 2024). (See Fig. 1 for an overview of Geodesic-BP.) Geodesic-BP can achieve a highly accurate fit to the ECG in under 30 min on a single high-end graphical processing unit (GPU). Note that while the method can also be computed on a CPU, the runtime increases to more than 6 h. Being gradient-based, it scales efficiently with the number of parameters and guarantees convergence to a locally optimal solution. This makes it an ideal platform for investigating the identifiability problem. In general, Geodesic-BP converges towards a local minimum of the loss function, which measures the mismatch between recorded and simulated ECG. The presence of multiple minima indicates a lack of identifiability, while the distribution of these minima in the parameter space offers insights into potential regularization strategies.

We tackle this issue by fitting the ECG of a single case several hundred times with unprecedented accuracy, using different initial parameter conditions and varying the number of ECG leads, including up to high-density BSPMs. We then quantify the uncertainty in the identification process. Our results are quantitatively validated against high-fidelity GT data generated *in silico* using a different EP simulator (Gillette et al., 2022). Finally, we propose physiologically grounded constraints for the PMJs that significantly improve the identifiability of the ventricular conduction system from the 12-lead ECG. Exact constraints from the GT model were not utilized to elucidate how physiological assumptions of the HPS may play a role in the ability to obtain an exact match in the ECG.

This is the first study demonstrating the feasibility of inferring the HPS at unprecedented accuracy from a standard clinical 12-lead ECG. Our approach produces highly accurate ECG matches with a narrow spread in uncertainty in the identified ventricular activation times that

is well below the uncertainty of measurements with the most advanced invasive mapping technologies. We believe that our novel robust and scalable optimization and forward EP approach is the key technology for creating credible CDTs with demonstrable fidelity, and, thus, for translating CDTs to clinical applications.

2. Methods

2.1. Electrophysiology model

The forward model for the ECG is based on the eikonal equation with the lead field method (Neic et al., 2017; Pezzuto et al., 2017; Gillette et al., 2021b). Considering a domain $\Omega \subset \mathbb{R}^3$ representing the active ventricular myocardium, the eikonal equation provides the cardiac LAT $\tau(\mathbf{x}) : \Omega \rightarrow \mathbb{R}$ given a symmetric, positive-definite conduction velocity tensor $\mathbf{M}(\mathbf{x}) : \Omega \rightarrow \mathbb{R}^{3 \times 3}$ and a set of boundary conditions X_0 :

$$\begin{cases} \sqrt{(\mathbf{M}(\mathbf{x}) \nabla \tau(\mathbf{x})) \cdot \nabla \tau(\mathbf{x})} = 1, & \text{in } \Omega, \\ \tau(\mathbf{x}_i) = t_i, & \text{for } (\mathbf{x}_i, t_i) \in X_0, \end{cases} \quad (1)$$

where

$$\mathbf{M}(\mathbf{x}) = v_f^2 \mathbf{f}(\mathbf{x}) \otimes \mathbf{f}(\mathbf{x}) + v_s^2 \mathbf{s}(\mathbf{x}) \otimes \mathbf{s}(\mathbf{x}) + v_n^2 \mathbf{n}(\mathbf{x}) \otimes \mathbf{n}(\mathbf{x}), \quad (2)$$

$$X_0 = \{(\mathbf{x}_i, t_i) : \mathbf{x}_i \in \bar{\Omega}, t_i \in \mathbb{R}, i = 1, \dots, N\}, \quad (3)$$

and $v_{\{f,s,n\}}(\mathbf{x})$ are the conduction velocities (CVs) in the fiber $\mathbf{f}$, sheet $\mathbf{s}$ and normal $\mathbf{n}$ direction, respectively. The set X_0 contains the PMJs $\mathbf{x}_i$ and their activation time t_i , which should satisfy the following compatibility condition:

$$t_i \leq t_j + \delta(\mathbf{x}_i, \mathbf{x}_j), \quad \text{for all } (\mathbf{x}_i, t_i), (\mathbf{x}_j, t_j) \in X_0, \quad (4)$$

where $\delta(\mathbf{x}, \mathbf{y})$ is the travel time between $\mathbf{x}$ and $\mathbf{y}$ according to Eq. (1).

The numerical approximation, previously described (Grandits et al., 2024), consists in a piecewise linear approximation of $\tau(\mathbf{x})$ on a simplicial mesh of Ω . The conduction velocity tensor is assumed piecewise constant in each element of the grid. The solution is based on a fixed-point iteration scheme where $\tau(\mathbf{x})$ at each node is updated according to the neighbor values of τ :

$$\tau^{(k+1)}(\mathbf{x}_i) = \min_{\mathbf{y} \in \partial\omega(\mathbf{x}_i)} \left\{ \tau^{(k)}(\mathbf{x}_i), \tau^{(k)}(\mathbf{y}) + \delta(\mathbf{x}_i, \mathbf{y}) \right\}, \quad (5)$$

where $\mathbf{x}_i$ is the position of the i th mesh node and $\omega(\mathbf{x}_i)$ is the set of elements sharing $\mathbf{x}_i$. Eq. (5) is applied in parallel to all nodes until convergence. The geodesic distance is computed by solving a local optimization problem on $\partial\omega(\mathbf{x}_i)$ with a fixed number of FISTA algorithm (Beck and Teboulle, 2009) iterations. When a PMJ $(\mathbf{x}_j, t_j) \in X_0$ is not a mesh node, we solve a local eikonal problem in the mesh element containing $\mathbf{x}_j$, and then assign the boundary condition $\tau(\mathbf{x}_k) = t_j + \delta(\mathbf{x}_j, \mathbf{x}_k)$ for all neighbor nodes $\mathbf{x}_k$. Finally, the compatibility condition (4) is automatically fulfilled by the algorithm, in the sense that when violated, Eq. (1) overwrites the corresponding PMJ with the correct timing. In this way, the final number of active PMJs could be lower than N . Overall, our vectorized approach is highly efficient for GPUs and it is suitable for automatic differentiation (see Section 2.3).

2.2. ECG computation

The transmembrane voltage $V_m(\mathbf{x}, t)$ during depolarization is reconstructed from the LAT $\tau(\mathbf{x})$ as follows:

$$V_m(\mathbf{x}, t; X_0) = U(t - \tau(\mathbf{x}; X_0)) = V_0 + \frac{V_1 - V_0}{2} \left[\tanh \left(2 \frac{t - \tau(\mathbf{x}; X_0)}{\epsilon} \right) + 1 \right], \quad (6)$$

where V_0 and V_1 refer to resting and plateau potential. This simplified ionic model can be derived by assuming the cell state to be modeled by a bistable equation (Keener and Sneyd, 1998, Chapter 6.2). Note that

we emphasize the parametric dependency of $V_m(\mathbf{x}, t; X_0)$ on X_0 . In all experiments we chose $V_0 = -85$ mV, $V_1 = 30$ mV, and $\epsilon = 1$ ms to closely approximate the upstroke of a human ventricular action potential.

The ECG is obtained with the lead field method (Pezzuto et al., 2017; Potse, 2018). For a single lead $l_e = 1, \dots, L$, the corresponding EGM $\mathcal{V}_{l_e}(t)$ is given by

$$\mathcal{V}_{l_e}(t; X_0) = \int_{\Omega} \mathbf{G}_i(\mathbf{x}) \nabla Z_{l_e}(\mathbf{x}) \cdot \nabla V_m(\mathbf{x}, t; X_0) d\mathbf{x}, \quad (7)$$

where $Z_{l_e}(\mathbf{x})$ is the lead field corresponding to the lead l_e and $\mathbf{G}_i$ is the intracellular conductivity tensor. (See Section 2.7 for the computation of Z_{l_e} .) We refer to the combination of all EGMs as the ECG.

For a fixed time-step Δt , we define a temporal grid $t_0, t_0 + \Delta t, \dots, t_0 + N_t \Delta t = t_{\text{end}}$ and compute $\mathcal{V}_{l_e}(t; X_0)$ as follows:

$$\mathcal{V}_{l_e}(t_k; X_0) = \mathbf{B}_{l_e} \cdot \mathbf{V}_m(t_k; X_0), \quad (8)$$

where $\mathbf{V}_m(t_k; X_0)$ is the (interpolated) transmembrane potential at time t_k and $\mathbf{B}_{l_e}$ is the vector:

$$[\mathbf{B}_{l_e}]_j = \int_{\Omega} \mathbf{G}_i(\mathbf{x}) \nabla Z_{l_e}(\mathbf{x}) \cdot \nabla \psi_j(\mathbf{x}) d\mathbf{x}, \quad (9)$$

with $\psi_j(\mathbf{x})$ the piecewise linear hat function corresponding to the mesh node $\mathbf{x}_j$, that is $\psi_j(\mathbf{x}_j) = 1$ and $\psi_j(\mathbf{x}_i) = 0$ for all $i \neq j$. Note that the vector $\mathbf{B}_{l_e}$ is constant and can be precomputed for each lead. For the temporal discretization parameter, we select $\Delta t = 0.5$ ms, and t_{end} is chosen such that $t_{\text{end}} > \Delta \text{QRS}$ holds, with ΔQRS being the duration of the entire QRS complex in the 12-lead ECG.

2.3. Model calibration via Geodesic-BP

To achieve efficient cardiac electrophysiological twinning through the surface ECG, we employ Geodesic-BP, as previously presented in Grandits et al. (2024), and briefly summarized here.

Given the recorded ECG $\hat{\mathcal{V}}_{l_e}(t)$, $l_e = 1, \dots, L$, we can pose the problem of finding an optimal set of initiation sites X_0 such that the simulated ECG $\mathcal{V}_{l_e}(t; X_0)$ matches in a least-squares sense the recorded one:

$$\min_{X_0 \in S} \frac{1}{L} \frac{1}{|\mathbb{T}|} \sum_{l_e=1}^L \sum_{k=0}^{N_t} \left(\mathcal{V}_{l_e}(t_k; X_0) - \hat{\mathcal{V}}_{l_e}(t_k) \right)^2 = \min_{X_0 \in S} \mathcal{L}(X_0), \quad (10)$$

for $|\mathbb{T}| = t_{\text{end}} - t_0$ and S being the feasible set of PMJs and $\mathcal{L}(X_0)$ is the loss function. The feasible set allows for stricter geometrical constraints to improve identifiability and is defined as follows:

$$S = S \times \{t \geq 0\}, \quad (11)$$

that is, positions $\mathbf{x}_i$ of PMJs must lie within the subdomain $S \subset \bar{\Omega}$, and their activation times t_i must be non-negative. No upper bound is imposed on t_i ; consequently, PMJs with large t_i are automatically deactivated by the algorithm due to the compatibility condition (4). The subdomain S can be either:

- (unrestricted case) the entire active myocardium, or
- (restricted case) a subendocardial band, as described in Section 2.5.

Numerically, we minimize the loss function in Eq. (10) using the gradient-based optimizer ADAM (Kingma and Ba, 2017) for 400 iterations with a learning rate of 0.75. Starting from an initial guess $X_0^{(0)} \subset S$ for the PMJs, the optimization algorithm generates a sequence $X_0^{(k)}, X_0^{(k+1)}, \dots$ of PMJs that reduces the mismatch with the targeted ECG until convergence. We denote by X_0^* the optimal set of PMJs. The update $X_0^{(k+1)}$ is based on the gradient of the loss function, computed via backpropagation – for this problem, backpropagation returns discrete geodesic paths from the PMJs, which explains the name of the algorithm – and is then projected onto S by taking the closest point in S .

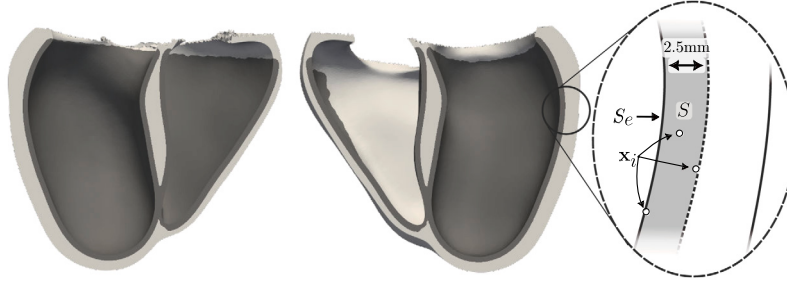


Fig. 2. Endocardial surface restrictions limits the domain of possible locations for PMJs. The PMJs are restricted to lie inside the subdomain S which is spanned by a band, equidistant to the endocardium S_e .

2.4. Sampling solutions

In general, Geodesic-BP will converge towards different optimal PMJs, X_0^* , depending on the choice of $X_0^{(0)}$, that is the initial guess for the PMJs for the optimization algorithm. We empirically quantify the variability of optimized solutions as follows. We generate 20 initial sets of PMJs by random sampling, with each set comprising 300 PMJs locations and timings. The random sampling of $X_0^{(0)}$ is as follows: each PMJ has initial position, x_i , uniformly distributed on the boundary of the feasible domain ∂S using `trimesh` (Dawson-Haggerty et al., 2019), and t_i uniformly distributed between t_0 and t_{end} . Note that all sites and timings are drawn independently. By default, the number of PMJs is set to $N = 300$, unless otherwise stated. Each of them is optimized by Geodesic-BP to minimize the mismatch to the recorded GT ECG.

2.5. Geometrical constraints for PMJs

In the restricted case, PMJs must lie inside the subendocardial band S , which has been chosen based on the known structure of the HPS from histo-anatomical studies. As shown in Fig. 2, S is the region comprising all points within a given distance $d_{\text{PMJ}} = 2.5$ mm from an endocardial surface $S_e \subset \partial\Omega$:

$$S = \{x \in \bar{\Omega} : \text{dist}(x, S_e) \leq d_{\text{PMJ}}\}, \quad (12)$$

where $\text{dist}(x, S_e)$ is the minimal Euclidean distance of x from S_e .

To determine the extent of S_e , we utilized information on the coverage and density of the HPS across the endocardium. The HPS begins in the atrioventricular node and connects to a His-Bundle within the ventricular septum. To achieve synchronous activation of the left ventricle (LV) and the right ventricle (RV), the HPS further splits after the His-bundle into the left and right bundle branches that separate further into 3 and 2 fascicles, respectively (Stephenson et al., 2017; Durrer et al., 1970; Myerburg et al., 1972). Each fascicle spreads across the subendocardium (Myerburg et al., 1972) and has a fractal-like structure as there is a merging of Purkinje fibers in addition to bifurcations (Vigmond and Stuyvers, 2016). The HPS is generally less dense in the RV than LV with limited coverage towards the base and in the inferior free wall of the RV (Stephenson et al., 2017; Myerburg et al., 1972), leading to delayed activation (Durrer et al., 1970). Therefore, the surface S_e : (1) lies within $\approx 90\%$ of the apico-basal extent, i.e. excluding a rim of 10% apico-basal extent underneath the ventricular base, and (2) must not be located within the RV inferior wall. This is consistent with the known restrictions from the GT model. In terms of intramural depth of PMJs, histological evidence suggests that Purkinje fibers in the HPS reside mostly sub-endocardially, with a potential transmural penetration of $< 30\%$ of the wall width (Vigmond and Stuyvers, 2016). To avoid compromising the generalizability of the method, the exact geometric constraints according to the PMJ depth underlying the GT model (detailed later in Section 2.8) were not exploited. Instead, a general depth of 2.5 mm globally over the entire

endocardial domain was selected and deemed as permissible based on ventricular wall thicknesses in the general population (Sjögren, 1971; Prakash, 1978). To note, the topology and the conduction velocity of the HPS are not available to the inverse problem in any form.

2.6. Pseudo-bidomain computations

In order to assess the fidelity of our algorithm on the whole torso, we utilize the pseudo-bidomain equation to compute the extracellular potentials on the torso surface. The extracellular potentials $\phi_0(x, t)$ in the torso $\Omega_0 \subset \mathbb{R}^3$ are based on the pseudo-bidomain equation (Bishop and Plank, 2011). Given $V_m(x, t)$ in the active myocardium, for each time $t \in [t_0, t_{\text{end}}]$ we solve the following elliptic problem:

$$\begin{cases} -\text{div}(\mathbf{G}\nabla\phi) = \text{div}(\mathbf{G}_i\nabla V_m), & x \in \Omega, \\ -\text{div}(\mathbf{G}_0\nabla\phi_0) = 0, & x \in \Omega_0, \\ \phi = \phi_0, & x \in \Gamma_H, \\ \mathbf{G}\nabla\phi \cdot \mathbf{n} - \mathbf{G}_0\nabla\phi_0 \cdot \mathbf{n} = \mathbf{G}_i\nabla V_m \cdot \mathbf{n}, & x \in \Gamma_H, \\ \mathbf{G}_0\nabla\phi_0 \cdot \mathbf{n} = 0, & x \in \Gamma_T, \end{cases} \quad (13)$$

where $\mathbf{G} = \mathbf{G}_e + \mathbf{G}_i$ is the bulk conductivity, for $\mathbf{G}_i, \mathbf{G}_e$ being the intra-/extracellular conductivity tensors respectively, $\phi(x, t)$ is the extracellular potential in the myocardium Ω , $\Gamma_H = \bar{\Omega} \cap \bar{\Omega}_0$ is the heart-torso interface, and $\Gamma_T = \partial\Omega_0 \setminus \Gamma_H$ is the torso surface. Since the solution is defined up to a constant, we impose the following constraint (Colli Franzone et al., 2014):

$$\int_{\Gamma_T} \phi(x, t) dx = 0. \quad (14)$$

The intracellular and extracellular conductivities ($\mathbf{G}_i$ and $\mathbf{G}_e$ respectively) within the ventricles were based on Roberts and Scher (1982) at values of $g_{i,f} = 0.34 \text{ S m}^{-1}$, $g_{e,f} = 0.12 \text{ S m}^{-1}$, $g_{i,s} = g_{i,n} = 0.06 \text{ S m}^{-1}$, and $g_{e,s} = g_{e,n} = 0.08 \text{ S m}^{-1}$. The atrial conductivities were tuned to values of $g_{i,f} = 1.02 \text{ S m}^{-1}$, $g_{e,f} = 3.72 \text{ S m}^{-1}$, $g_{i,s} = g_{i,n} = 0.22 \text{ S m}^{-1}$, and $g_{e,s} = g_{e,n} = 2.77 \text{ S m}^{-1}$ according to conductivity ratios in Roberts and Scher (1982) as reported in Nagel et al. (2022) and Gillette et al. (2022). All remaining conductivities in the torso, $\mathbf{G}_0$, were assigned the nominal values reported in Keller et al. (2010), such that the torso, blood pools, and lungs have isotropic conductivities of 0.22, 0.7, and 0.0389 S m^{-1} respectively.

Eq. (13) is numerically discretized with linear finite elements on a tetrahedral mesh of the torso (see Section 2.8). The corresponding linear system is solved with the conjugate gradient method with the orthogonalization of the residual with the linear constraint (14) at the discrete level (Bochev and Lehoucq, 2005).

2.7. Lead fields

Since the ECG or the BSPM are sparse evaluations of the torso potential, $\phi_0(x, t)$, it is convenient to adopt the lead field formulation (Potse,

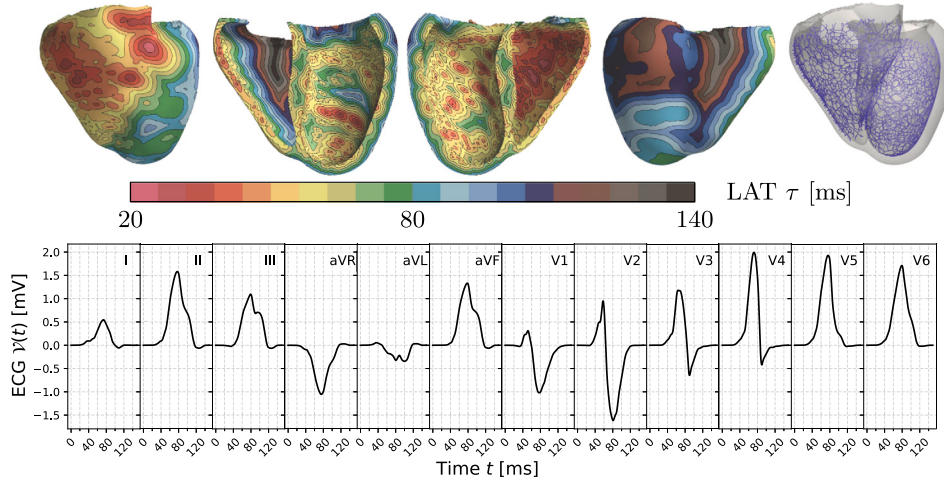


Fig. 3. The *in silico* GT solution generated from the physiologically-detailed HPS. The LAT map τ is shown together with the HPS in blue (top). The bottom row shows the corresponding, calculated 12-lead ECG.

2018). The EGM for a given lead l_e , $\mathcal{V}_{l_e}(t)$, is generally defined as follows:

$$\mathcal{V}_{l_e}(t) = \sum_e w_e \phi_0(\mathbf{x}_e, t), \quad (15)$$

where $\mathbf{x}_e \in \Gamma_T$ are the electrode positions and w_e are the corresponding weights. The lead field $Z_{l_e}(\mathbf{x})$ is defined as the solution of the following problem:

$$\begin{cases} -\operatorname{div}(\mathbf{G} \nabla Z_{l_e}) = 0, & \mathbf{x} \in \Omega, \\ -\operatorname{div}(\mathbf{G}_0 \nabla Z_0) = 0, & \mathbf{x} \in \Omega_0, \\ Z_{l_e} = Z_0, & \mathbf{x} \in \Gamma_H, \\ \mathbf{G} \nabla Z_{l_e} \cdot \mathbf{n} - \mathbf{G}_0 \nabla Z_0 \cdot \mathbf{n} = 0, & \mathbf{x} \in \Gamma_H, \\ \mathbf{G}_0 \nabla Z_0 \cdot \mathbf{n} = \sum_e w_e \delta_{\mathbf{x}_e}(\mathbf{x}), & \mathbf{x} \in \Gamma_T, \end{cases} \quad (16)$$

where $\delta_{\mathbf{x}_e}$ is the Dirac measure on Γ_T and $Z_0(\mathbf{x})$ is the lead field in the torso. Note that we are only interested in $Z_{l_e}(\mathbf{x})$, that is the lead field in the heart.

Formally, Eq. (16) corresponds to Eq. (13) with a different right hand side. Thus, we impose the constraint in Eq. (14) to the solution, yielding to the compatibility condition $\sum_e w_e = 0$ on the weights. To keep the ECG amplitude in clinical ranges in the GT model, the computed lead fields were further scaled by a factor of 0.32. This scaling overcomes discrepancies in amplitudes stemming from cardiac sources within the biophysical model. Conductivity values for lead field computation are the same as described earlier in Section 2.6.

2.8. Ground truth model

To test the identifiability of ECG-based personalization, we utilize a state-of-the-art subject-specific biophysically detailed model of the ventricles leveraging a topologically realistic model of the HPS (see Fig. 3). The model had been calibrated to replicate the ECG of this healthy subject with high fidelity (Gillette et al., 2022).

The acquisition of the geometrical model and ECG has been previously described elsewhere (Gillette et al., 2022, 2021b). Briefly, two magnetic resonance images were acquired sequentially in the single male subject within an approved magnetic resonance imaging (MRI) study. The two MRI scans were acquire sequentially: (1) a 4-stack torso MRI, and (2) a 3D whole-heart cardiac MRI. Before MRI acquisition, raw ECGs were recorded at the ten electrode locations, $\mathbf{x}_{l_e}$, in a 12-lead ECG configuration. Electrodes were MRI-compatible and left intact during acquisition to facilitate recovery in the geometric model.

A convolutional neural network was deployed for automatic cardiac segmentation from the 3D whole-heart MRI scan (Payer et al., 2018), and the torso was segmented using semi-automatically intensity threshold approaches in Seg3D (Computing and Institute, 2016). In a combined segmentation, a finite-element volumetric mesh with tetrahedral elements of approximately 1253 μm resolution within the ventricles and up to 2280 μm in the torso, atria, blood pools, and lungs was generated using *meshtool* (Neic et al., 2020).

Ventricular activation was facilitated through a physiologically and topologically realistic HPS (Fig. 3) created assuming physiological knowledge attained experimentally within both humans and other mammalian species (Stephenson et al., 2017; Durrer et al., 1970; Myerburg et al., 1972) more thoroughly detailed above in Section 2.5. The constructed HPS was discretized to give a spatial resolution of 482 μm . There were a total of 907 PMJs in the HPS facilitating the sites of earliest activation within the ventricles. PMJs were configured to reside in up to 5% transmurally from the endocardium for all fascicles, apart from up to 50% transmurally within the RV moderator band to give a realistic QRS complex (Gillette et al., 2021a). To account for electrotonic loading and associated anterograde and retrograde conduction delays, PMJs were coupled to the ventricular mesh using a radius of 1981 μm to ensure nodal capture of 10 adjacent nodes. A total of 8587 nodes were selected as coupled PMJs. PMJ penetration depths were computed as the closest distance to the endocardial surface.

The CV within the HPS was prescribed at a value of 2.0 m s^{-1} (Kassebaum and Van Dyke, 1966). Modification in CV to certain branches in the HPS was made to ensure earliest activation corresponded with ventricular activation as detailed in previous work (Gillette et al., 2021b). In contrast to the previously reported setup (Gillette et al., 2022), the CV in the remaining ventricular myocardium was prescribed values of $v_f = 0.61 \text{ m s}^{-1}$ and $v_n = v_s = 0.225 \text{ m s}^{-1}$ (Grandits et al., 2024).

2.8.1. BSPM vest generation

To test the effect of denser torso electrode coverage, we equipped the anatomical torso model with an *in silico* BSPM vest. These vests, commonly found in electrocardiographic imaging (ECGI) technologies, should provide denser recordings and potentially better reconstructions (Webber et al., 2023; Ghanem et al., 2005) and are also commonly found in explanted torso tank experiments (Calder et al., 2018). We employ a grid-based design, similar to the cited studies, with a varying amount of electrodes on the front and back of the torso. In Fig. 4, we show the generated electrode positions of the artificial vest for the tested 32, 64 and 128 electrodes. For the lead field computation (Section 2.7), we assume all electrodes to be unipolar w.r.t. the WCT, marked in red.

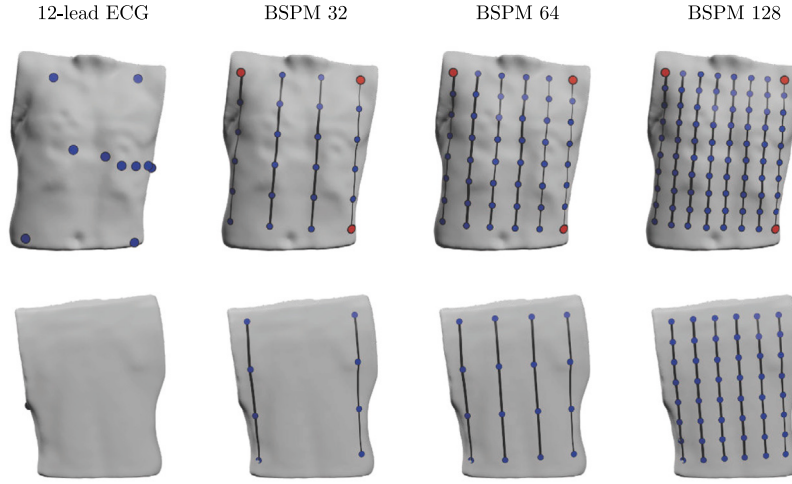


Fig. 4. Electrode locations of the 12-lead ECG (left) compared to BSPM configurations comprising 32, 64 and 128 electrodes from an anterior (top) and posterior (bottom) view. For each BSPM electrode the uni-polar lead field was computed using the WCT as reference. Electrodes for computing the WCT are shown in red.

2.9. Evaluation

The ability of the Geodesic-BP method to identify the ventricular activation sequence from the clinical 12-lead ECG and the goodness of fit of the associated ECG is evaluated by comparing against the known GT solution, and by measuring the variability of the solution as a function of initial conditions.

2.9.1. Fidelity metrics

The fidelity of the signal reconstruction at the body surface is measured for the ECG as the root mean squared deviation between computed and GT ECGs in mV and in the interval $\mathbb{T} = [t_0, t_{\text{end}}]$:

$$\text{dist}_{\mathcal{V}}(\mathcal{V}, \hat{\mathcal{V}}) = \sqrt{\frac{1}{|\mathbb{T}| N_e} \sum_{t \in \mathbb{T}} \int_{\Gamma_e} (\mathcal{V}_e(t) - \hat{\mathcal{V}}_e(t))^2 dt}, \quad (17)$$

and, analogously, for the BSPM the difference between two BSPMs ϕ_i , ϕ_j over the whole torso surface Γ_T is quantified by:

$$\text{dist}_{\phi}(\phi_i, \phi_j) = \sqrt{\frac{1}{|\Gamma_T| |\mathbb{T}|} \int_{\mathbb{T}} \int_{\Gamma_T} (\phi_i(\mathbf{x}, t) - \phi_j(\mathbf{x}, t))^2 d\mathbf{x} dt}, \quad (18)$$

where $|A|$ is the measure of the set A . The difference between two reconstructed LAT maps τ_i , τ_j in ms is measured as:

$$\text{dist}_{\tau}(\tau_i, \tau_j) = \sqrt{\frac{1}{|\Omega|} \int_{\Omega} (\tau_i(\mathbf{x}) - \tau_j(\mathbf{x}))^2 d\mathbf{x}}. \quad (19)$$

2.9.2. Variability and parameter relevance

The variability between multiple solutions is quantified by computing point-wise variations of the solutions. For this purpose, consider a set of LAT solutions $\tau_1(\mathbf{x}), \dots, \tau_N(\mathbf{x})$. We define the point-wise mean, τ_{μ} , and standard deviation, τ_{σ} , as

$$\tau_{\mu}(\mathbf{x}) = \frac{1}{N} \sum_i \tau_i(\mathbf{x}), \quad (20)$$

$$\tau_{\sigma}^2(\mathbf{x}) = \frac{1}{N} \sum_i (\tau_i(\mathbf{x}) - \tau_{\mu}(\mathbf{x}))^2. \quad (21)$$

The average deviation on the heart is given by $\bar{\tau}_{\sigma} := \frac{1}{|\Omega|} \int_{\Omega} \tau_{\sigma}(\mathbf{x}) d\mathbf{x}$ in ms. The mean and standard EGM for a single electrode – $\mathcal{V}_{\mu}(t)$ and $\mathcal{V}_{\sigma}(t)$ respectively – are defined in the same way.

The importance of the parameters on the actual solution can also be computed numerically: For a single PMJ (x_i, t_i) , we can compute the region of influence (ROI), that corresponds to the total influence of the PMJ on the solution τ in mm^3 . To this end, we use the LAT derivative to compute the total influence of the PMJ on the solution

$\text{ROI}_i = \int_{\Omega} \partial_{t_i} \tau(\mathbf{x}) d\mathbf{x}$. We call PMJs with no influence on the solution ($\text{ROI}_i = 0$) inactive. More information on this quantity and its derivation can be found in [Appendix A](#).

2.9.3. Experimental protocols

Different *in silico* experimental scenarios were considered to investigate the fidelity of ECG calibration and the identifiability of the HPS by varying physiological constraints as well as the density of observed data. The following protocols were implemented where the Geodesic-BP optimizer was employed to find a set of PMJs by minimizing the mismatch to the given GT ECG:

- No restrictions were imposed on the location of initiation sites, with permissible locations over the entire ventricular domain;
- Physiological constraints were imposed restricting the permissible domain to subendocardial regions;
- Using the same physiological constraints, denser observations beyond the ECG were provided in the form of BSPMs of variable density, using between 16 to 128 recording sites (see [Fig. 4](#));
- The number of initiation sites as the only hyperparameter of the optimization algorithm was sampled to determine its impact upon fidelity of the reconstructed ECG and the identifiability of the ventricular activation maps.

2.10. Implementation aspects

Implementation aspects of the optimization algorithm Geodesic-BP have been reported in detail previously ([Grandits et al., 2024](#), II-E, Implementation aspects). In the present work, the originally proposed algorithm was accelerated by computationally optimizing the code for solving the local problem ([Grandits et al., 2024](#), Algorithm 1), yielding a reduction in runtime of a single iteration from ≈ 16 s down to 6 s.

Geodesic-BP was implemented in Python and uses the NumPy ([Harris et al., 2020](#)) and PyTorch ([Paszke et al.](#)) packages. For the finite element computations scikit-fem ([Gustafsson and McBain, 2020](#)) was used. Simulation of the GT electrophysiology model, and the verification of computed activation sequences and associated ECG traces were carried out using a biophysically detailed high fidelity reaction-eikonal model ([Neic et al., 2017](#)) as provided by the established cardiac electrophysiology simulator CARPentry ([Vigmond et al., 2008](#)). For visualization, projection and additional 3D computations, PyVista, TriMesh, VTK ([Sullivan and Kaszynski, 2019](#); [Dawson-Haggerty et al., 2019](#); [Schroeder et al., 2006](#)) and Blender ([Blender Online Community, 2024](#)) were also utilized.

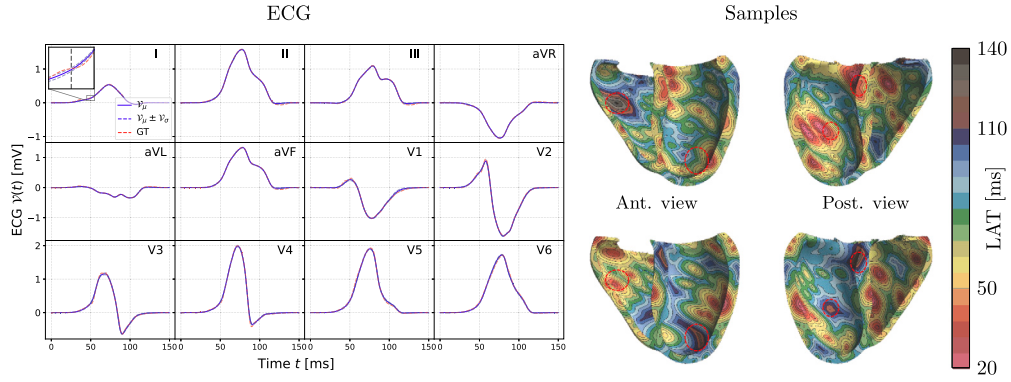


Fig. 5. Identifiability problems of inverse ECG methods. Left panel: Using Geodesic-BP, the identification of optimal PMJs locations and timings to fit a given ECG (GT) can be achieved with high fidelity. The ECG distribution obtained from 20 optimization runs with different initializations forms a tight envelope around the ECG to be reconstructed (left, $\mathcal{V}_o \pm \mathcal{V}_e$). Right panel: The two samples with the largest difference in LAT are shown that reveal significant variability in the solution space which is indicative of limited identifiability in the general unrestricted case. We highlight a few of the major differences in LAT (red dashed ellipses). This prompts for quantification of this variability and for *a-priori* constraints to reduce the non-uniqueness of the solution space.

3. Results

3.1. Identifiability in the general case

From a theoretical standpoint, there is no guarantee that the HPS governing ventricular activation can be uniquely identified from the surface ECG. Optimization algorithms such as Geodesic-BP might converge towards different local minima of the loss function, depending on the initial positions and timings of the PMJs. Here, we empirically quantify the variability of optimized solutions in the unrestricted case, without imposing any physiological constraints on the permissible positions of PMJs, and by randomly sampling the initial guess for the PMJs in the optimization algorithm (see Section 2.4).

Optimization results using Geodesic-BP for fitting the ECG are shown in Fig. 5 (left panel) where the distribution obtained from 20 optimized ECGs ($\mathcal{V}_o, \mathcal{V}_e$) is overlaid on the GT ECG we aim to recover. The tight envelope around the measured ECG demonstrates that Geodesic-BP is able to fit the ECG with very high fidelity without scaling. The maximum absolute error between optimized and GT ECG was $<2.8 \times 10^{-2}$ mV (relative error 5.098 930 131 663 843 %) according to (17) (average: 2.07×10^{-2} mV/4.066 672 407 563 584 %). Similarly, the Pearson correlation coefficient of the ECGs of all samples w.r.t. the GT was >0.994 . Convergence is also rapidly achieved with dist_V falling below 1×10^{-1} mV within ≤ 100 iterations for most samples (see also Fig. 11).

However, the low errors observed in the ECG did not necessarily correspond to small errors in the ventricular activation map τ . This is illustrated in Fig. 5 (right panel) where the two cases with the most extreme difference (dist_τ) in the activation map are shown. The variability in reconstructed position of PMJs was significant between these two samples, as readily evidenced by fundamentally different initial activation sites. For instance, a site of earliest activation in the LV mid-anterior endocardium in one run (top) is a site of latest activation in another run (bottom). Quantitatively, the absolute error in LAT was 23.12 ms (average between the samples: 18.32 ms).

While the 12-lead ECG was very similar across all samples, a more pronounced variability was observed in the BSPM, as shown in Fig. 6. Again, we show the two BSPMs that were most different according to (18) (maximum absolute difference: 0.11 mV), together with the GT BSPM. It is worth noting that these two samples with maximum distance in BSPM shown in Fig. 6 are not the same samples that yielded a maximum distance in the activation maps shown in Fig. 5.

Overall, the dipole-shaped torso potential was well-captured by all samples, indicating that the overall activation pattern was similar across all samples. The least correlated areas were found in the sternal region of the BSPM, where reconstructed BSPMs exhibited more

complex patterns than the GT. Selecting one point in this region shows different extracellular potentials between the two samples ϕ_i, ϕ_j and the GT ϕ_{GT} (bottom panel of Fig. 6). The correlation between the extracellular potentials at this unseen point was comparatively low, with correlation coefficients against the GT potentials of only 0.69 and 0.64, respectively.

3.2. Identifiability under physiological constraints

Unrestricted optimization with permissible PMJs locations over the entire ventricular domain led to significant errors in the reconstruction of the ventricular activation sequence τ , and to non-physiological activation sequences. We investigated therefore whether imposing constraints based on physiological *a priori* knowledge, as described in Section 2.5, can be effective in reducing the reconstruction error and enhancing identifiability.

In Fig. 7, the model closest to the mean τ_μ (top) and variability models τ_σ (bottom) are shown. We show the 12-lead and 128-electrode BSPM both in the restricted and unrestricted settings. With restrictions, the average error in endocardial activation improved relative to the GT, particularly in the RV inferior wall. Non-physiological early activation in the basal and epicardial regions as seen in Fig. 5 is partially mitigated when restrictions are enforced, and more consistent with GT, resulting in a more physiological transmural activation pattern and a later activation of basal regions.

Imposing physiological restrictions and increasing the density of observations effectively reduce regions of pronounced variability. This is reflected in an average deviation $\bar{\tau}_\sigma$, indicated in the top right corner of the variability models, which is always lower in the restricted setting. Deviations ranged from 12.13 ms in the unrestricted case with only a 12-lead ECG as observation down to 8.38 ms in the restricted case with a high density BSPM. Interestingly, an excellent match of the surface ECG was reached even though the physiological restrictions imposed during the reconstruction did not exactly coincide with the prescriptions made during the generation of the GT model. A geometric cutoff value of 2.5 mm in the GT model, as defined in Section 2.5, resulted in 86% capture of the PMJ nodes, with those exceeding 2.5 mm all residing in the RV septum and free wall. A maximum penetration value of 4.3 mm was reached, well above the cutoff value of 2.5 mm used during the optimization from the ECG.

3.3. Identifiability with higher density observations

Observation in Section 3.1 indicates a perfect match at all ECG electrode locations, and an overall close agreement in the reconstructed BSPMs, but deviations are witnessed for unseen positions on the torso

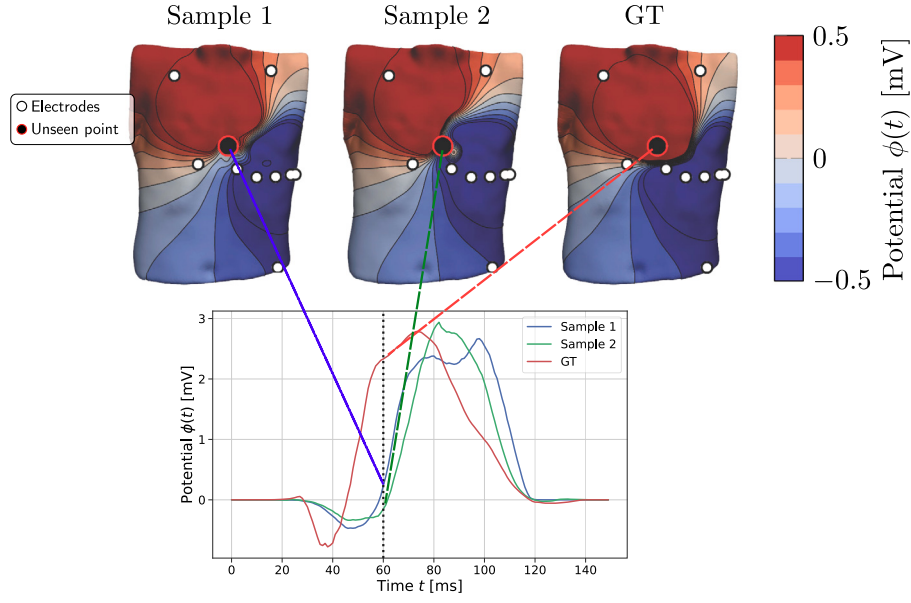


Fig. 6. Shown are the two BSPMs of maximum distance among the 20 samples next to the sought-after GT solution at a single instant in time ($t = 60$ ms, top), after normalization with respect to the mean unipolar potential (see Section 2.6). Differences in potential fields are witnessed in space across the body surface, as well as over time, when compared at a single unseen electrode location (bottom panel). At all ECG electrode locations used for optimization no differences are apparent, all potential traces are predicted with approximately zero loss (see Fig. 5, left panel).

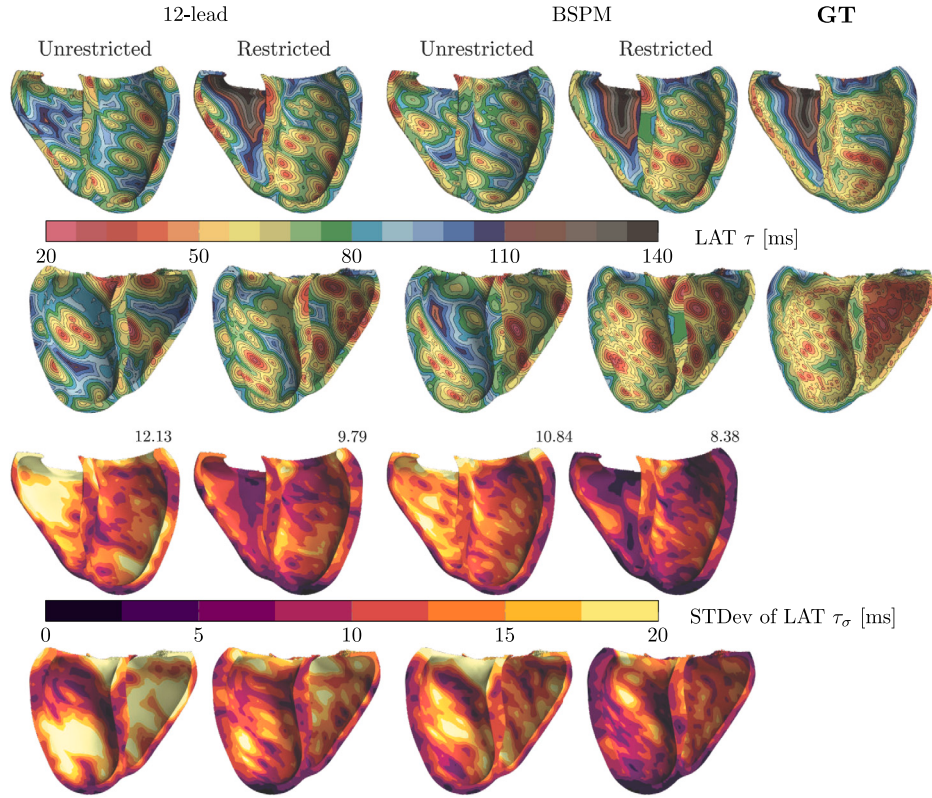


Fig. 7. Preview of the distribution of the 20 samples, reconstructed from 12-lead ECG and BSPM with 128 electrodes as observations, both with and without physiological constraints. We visualize the sample most closely representing the mean τ_p (top 2 rows) along with the deviation between the samples τ_σ (bottom 2 rows, see Section 2.9 for the exact definitions). The average deviation over the entire domain, $\bar{\tau}_\sigma$, is indicated at the top right corner of each τ_σ model.

where reconstructed and GT BSPM do not match. We investigate therefore whether an increase in electrode density on the torso is a suitable remedy to further improve BSPM reconstruction and identifiability of the LAT map τ , as suggested by the achieved reduction in regions of high variability in Fig. 7. Using higher density BSPM observations

led to a considerable reduction in the reconstruction error over the torso, from 9.67×10^{-2} mV down to 4.27×10^{-2} mV on average (see Fig. 8, left panel). However, this was less effective for improving the reconstruction of the ventricular activation sequence τ where only marginal improvements were witnessed, with errors decreasing from

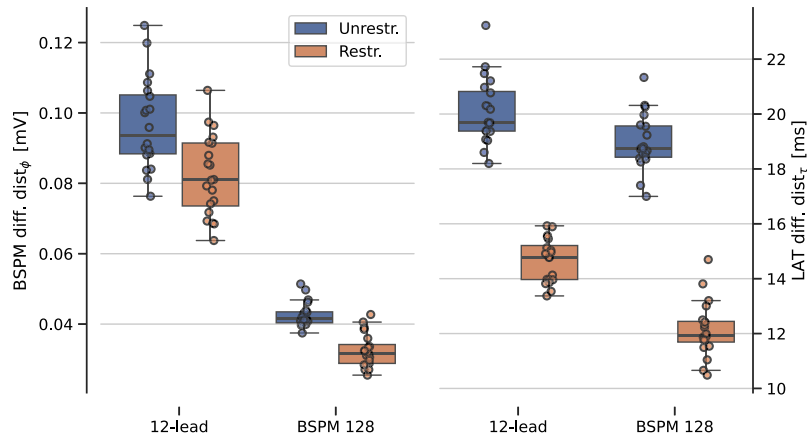


Fig. 8. Comparison between pseudo-bidomain solutions on the torso in terms of errors in potential reconstruction dist_ϕ (18) (left panel) and in the ventricular activation sequence dist_τ (19) (right panel). Each pair of boxplots shows the errors for unrestricted (blue) and restricted (brown) cases, respectively. Higher density observations led to a significant improvement in the reconstruction of the BSPM, but impact on the reconstruction of the ventricular activation map τ was marginal.

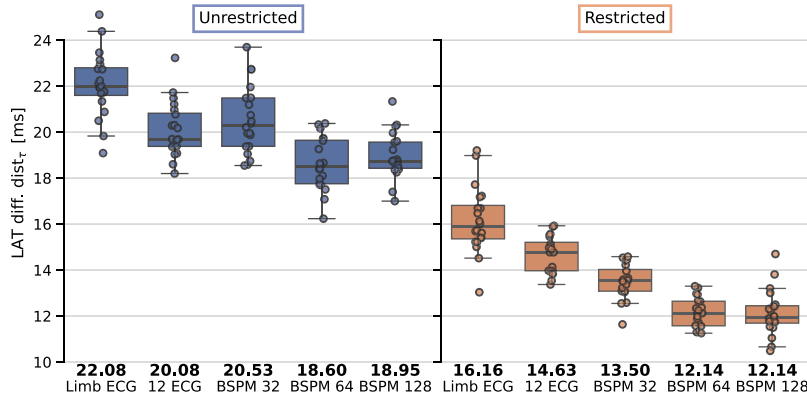


Fig. 9. Comparison between LATs as reconstructed with an increasing number of torso electrodes, both for ignoring (left panel) and enforcing (right panel) physiological restrictions. For each boxplot, the average dist_τ with respect to the GT of the 20 samples is shown as a number at the bottom line.

20.08 ms down to 18.95 ms on average (Fig. 8, right panel). As such, imposing physiological constraints is much more effective in reducing the reconstruction error in terms of dist_τ than increasing the density of observations. With physiological restrictions an average dist_τ error of 14.63 ms and 12.14 ms was achieved for 12-lead ECG and BSPM reconstructions, respectively.

A further differentiation of the impact due to observation density versus physiological constraints is shown in Fig. 9. The quality of the reconstructions of the ventricular activation sequence (dist_τ) is compared for increasing observation density from 4 (limb leads) to 128 recording sites (BSPM vest), comprising limb-lead and 12-lead ECG as well as BSPM vests with increasing electrode density (Section 2.8.1) with and without physiological constraints. Increasing the number of electrodes improves the reconstruction of the activation map τ , as the error in dist_τ is decreased from an average 22.08 ms down to 18.60 ms. In addition to the number of electrodes their placement is also a relevant factor, as indicated by the slightly better reconstruction from the 12-lead ECG over the higher density 32-electrode grid-based BSPM vest where the placement of the 12-lead ECG electrodes is denser in the proximity of the heart than the strict grid-based 32-electrode BSPM vest. Further increasing the density of electrodes of the BSPM vests past 64 electrodes is only marginally beneficial for the reconstruction error, at the cost of slightly larger variability in the samples. However, as noted before, the major improvement in terms of dist_τ results from imposing physiological constraints as seen in Fig. 8. With these the error in dist_τ decreases with electrode density from 16.16 ms down to 12.14 ms.

3.4. Hyperparameter sensitivity - the number of PMJs

Results obtained with optimization algorithms are sensitive to the choice of hyperparameters. In Geodesic-BP – since we are only using the ECG in this study as a target in (10) – the only hyperparameter to be chosen is the number of PMJs. These determine the number of earliest activation sites in the ventricles and, as such, the ability to approximate the ventricular activation map τ . The effect of the number of PMJs upon the fidelity of reconstruction of the ECG and the activation map τ was investigated in terms of dist_γ and dist_τ by fitting to the ECG with a variable number of PMJs, ranging from 1 to 5000, with imposed physiological constraints. Results are summarized in Fig. 10.

When using too few PMJs (<20), the optimizer was unable to achieve a match of sufficient fidelity, neither in terms of the ECG (correlation <0.8, $\text{dist}_\gamma > 2.4 \times 10^{-1}$ mV) nor the ventricular activation ($\text{dist}_\tau > 3 \times 10^1$ ms). From 100 to 500 PMJs, differences in terms of dist_γ between the models essentially disappeared: With a difference of 2.7006×10^{-2} mV and a correlation of 0.998 visually identical reconstructions of the 12-lead ECG were obtained. For even higher numbers of PMJs $N > 500$, errors further improved in fitting ECG, but only with marginal gains in LAT errors. Furthermore, the optimization was highly susceptible to perturbations in the ECG and the initial selection of the PMJs prior the optimization process. Overall, several PMJs had no or low contribution to the activation. With an initial $N = 300$ PMJs, only 23% (or ≈ 70) of them were responsible for activating 95% of the myocardium. For comparison, with $N = 5000$ initial sites, this number dropped to 10.9% (≈ 545) at the end of the optimization

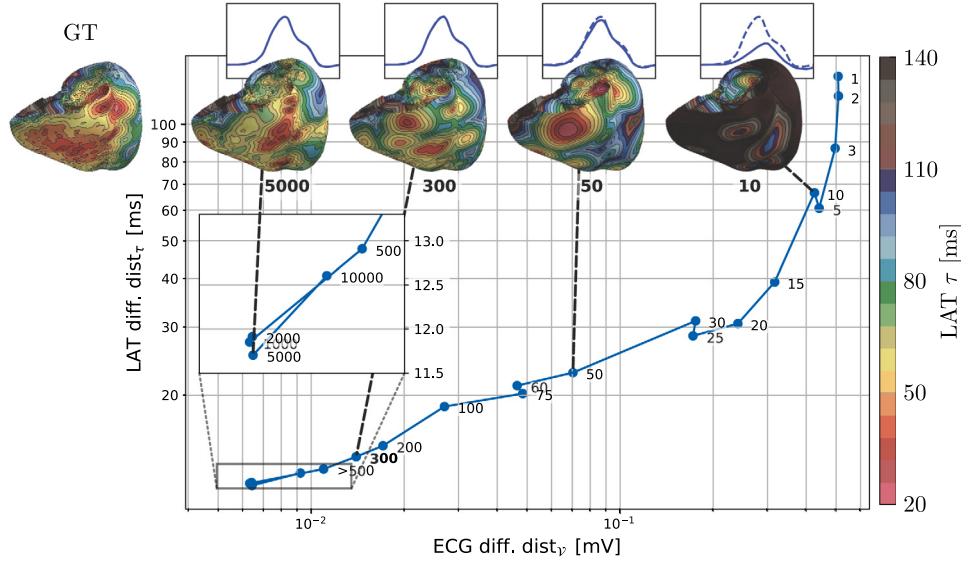


Fig. 10. Hyperparameter study of the number of PMJs. The 12-lead ECG was fitted using a variable number of initial PMJs and the error in reconstructing the ECG and the activation map τ was measured against the GT model in terms of dist_v and dist_τ . A zoom-in on the results for $N \geq 500$ is shown in the inset. In the top panel optimization results are shown for a number of PMJs of $N \in \{10, 50, 300, 5000\}$, comprising the reconstructed LAT maps and the reconstructed Einthoven II ECG (solid) next to the GT ECG (dashed).

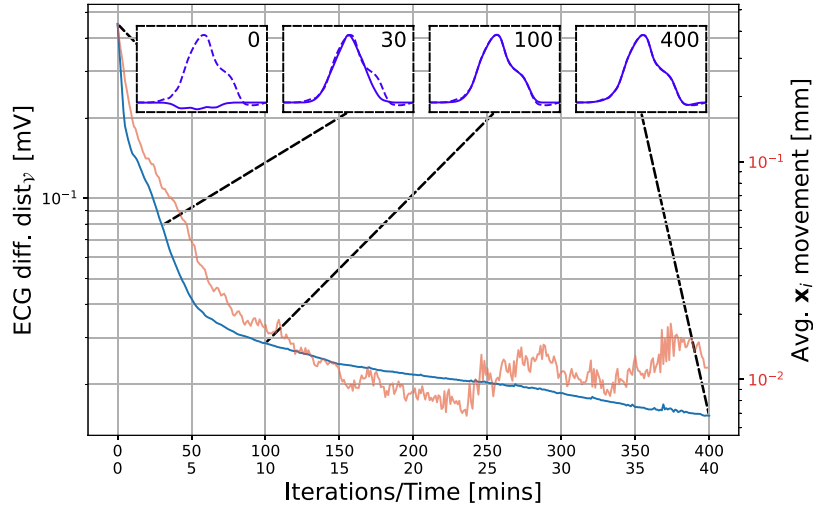


Fig. 11. Convergence history of Geodesic-BP: We show the evolution of the solution in terms of the ECG on the left y-axis (logarithmic), over the iterations (first row) and approximate computational time (second row) on the x-axis. The top 4 plots show the computed lead II ECG in the current iteration (solid) next to the GT ECG (dashed). Additionally, we show the averaged movement of the initial sites x_i w.r.t. the last iteration in red (right y-axis, also in logarithmic scale).

process. Inactive PMJs for $N = 300$ and $N = 5000$ were 62.33% and 78.5%, respectively. These numbers were calculated using the ROI defined in [Appendix A](#).

4. Discussion

In this work, we have demonstrated the ability of a novel approach for constructing CDTs of human ventricular electrophysiology with unprecedented fidelity and speed using only non-invasive clinical data – the 12-lead ECG and tomographic images. The superiority of our approach is based on its efficiency, robustness, and accuracy in reproducing clinically recorded signals without scaling that cannot be matched by any other current state-of-the-art methodology. Our findings indicate that incorporating histo-anatomical knowledge on the ventricular conduction system into our fitting approach facilitates an accurate recovery of LAT only with the clinical 12-lead ECG. Even in the most complex scenario of the Purkinje-mediated ventricular

activation during normal sinus rhythm, there is limited need for high-density BSPM data that are, in general, clinically not available. This novel optimization technique represents a significant advancement in generating credible CDTs in a scalable manner and with demonstrable fidelity. Our approach holds considerable promise for translating CDTs into clinical practice.

We provide evidence that CDTs cannot be uniquely identified from surface ECG recordings, even when using high-density BSPM. In fact, multiple markedly distinct activation patterns can predict the same surface ECG, within a tolerance level comparable to noise. As a consequence, quantifying the uncertainty in the reconstruction process is crucial for clinical applications. In this study, we show that the variability in reconstruction can be significantly reduced by imposing physiological constraints on the permissible domain for PMJs.

Our study further proved that variability in the LAT reconstruction is more effectively reduced by using *a priori* knowledge in the form of constraints than by increasing the density of observations. Specifically, when constructing a CDT, high-density BSPM offers only marginal

benefits compared to the standard 12-lead ECG. Although this may seem counter intuitive at first, our analysis revealed that in a population of CDTs all fitted to the same 12-lead ECG, the residual variability in the BSPM is predominantly confined to a narrow region around the sternum. Accurately resolving the spatio-temporal evolution of potential fields in closer proximity of the heart, including non-dipole components of the field, would require advanced BSPM systems capable of higher spatial resolutions.

Our method recovers the ventricular conduction system by optimizing the location and timing of PMJs within a subendocardial domain – defined on the basis of histo-anatomical *a priori* knowledge. In contrast, other methods focus on modeling the entire HPS, which can be personalized to match 12-lead ECG or electro-anatomical mapping (EAM) data (Camps et al., 2024; Álvarez Barrientos et al., 2025; Barber et al., 2021). Given the histological evidence and current understanding of the HPS (see Section 2.8), it is reasonable to generate it using a procedural approach, such as tree generation algorithms (Sahli Costabal et al., 2016) or constrained optimization methods (Berg et al., 2023). In these approaches, the position and timing of PMJs are fully determined by the tree's topology and the assumed CV. No such Purkinje restriction is in place for the PMJs created with our method, thus allowing for a more flexible placement and simpler manipulation of PMJs as compared to a topological representation of a Purkinje network. However, for a fully mechanistic representation in a CDT an explicit topological model of the HPS is required to facilitate an accurate prediction of ventricular activation and ECGs under other conditions the CDT was not calibrated for such as pacing. In our approach a suitable Purkinje network that produces an equivalent ventricular activation sequence must be constructed for a given set of PMJs in a post-processing step after optimization. The construction of such HPS models from PMJs is readily achieved for lower dimensional approximations of the HPS such as assuming a five fascicular HPS to activate a fast conducting subendocardial layer, as has been shown previously (Gillette et al., 2021a), but a robust reconstruction of a HPS to match the fine-grained activation pattern as produced with our approach, with a number of PMJs $N \geq 5$ has not been reported yet.

A crucial differentiating factor of our method is the use of gradient information in the fitting procedure. Other methods lack this information which necessitates computationally expensive sampling techniques to optimize the QRS complex of the ECG. Even when using the fastest ECG forward models able to predict ECGs with close to real-time performance (Neic et al., 2017) or even faster (Pezzuto et al., 2017), these methods often require many hours to compute or result in sub-optimal ECG fits. Surrogate models based on Gaussian process regression (Pezzuto et al., 2022) or neural networks (Salvador et al., 2023) are promising options to further increase by one or two orders of magnitude the forward solver, but their construction is inherently tied to sampling in the parameter space. Furthermore, defining surrogate models in generic geometries is still an open challenge.

The performance of technologies for calibrating CDTs is a key factor determining the application scope. Our method is computationally expensive, but the implementation is heavily optimized to take advantage of GPU computations, thus making it very fast in comparison to other similar methods. The absolute execution time of each run depends mostly on the longest geodesic path in the mesh, which is related to the number of active PMJs and the time needed to compute the projections. All samples for $N = 300$ take less than 30 min on a NVidia RTX 4090 for a single optimization run of 400 iterations as described in Section 2.3. As shown in Fig. 11, 100 iterations are often sufficient to achieve a good fit of the ECG. To note, the “elbow” point in the ECG fit is around 100 iterations, and also the movement of the PMJs decrease rapidly, partly because many sites deactivate, but also since the gradient magnitude decreases. In general, a single iteration step takes less than 6 s, which is comparable to the cost of running a forward simulation.

For all experiments conducted in this study the initial number of PMJs was chosen as $N = 300$, justified by the insights gleaned from

the hyperparameter study in Section 3.4. Since the PMJs are uniformly initialized over the entire time range and admissible domain, a large fraction of PMJs is inactive at the beginning of the optimization. The number of PMJs suggested in Section 3.4 may appear excessively large in comparison to other studies (Gillette et al., 2021b; Grandits et al., 2020; Cardone-Noott et al., 2016; Camps et al., 2024) that report only 5–7 PMJs. However, this is readily explained by a fundamental difference in the underlying model assumption that builds on a fast-conducting subendocardial layer, aiming to mimic the fast isotropic activation mediated by the terminal Purkinje network of the HPS (Myerburg et al., 1972). Similar studies using geodesics report even higher numbers of PMJs to achieve a good match with endocardial electro-anatomical mapping data (Cárdenes et al., 2015), and studies that do not rely on fast-conducting layers report numbers in the range of 11–51 PMJs (Barber et al., 2021). This is in agreement with our findings, showing the requirement of at least ≥ 50 PMJs to effectively match a given QRS complex in the ECG in the absence of a fast conducting layer.

The most important factor for achieving a high fidelity reconstruction of both ECG and activation sequence was the usage of physiological constraints detailed in Section 2.5 that greatly improved the reconstruction quality. While exact knowledge on the structure of the HPS could be, in principle, prescribed according to the GT model, this is not the case in real world applications when CDTs are built from patient data. Applying physiological constraints to real patient data is not straightforward as the exact structure of the HPS, as well as the distribution and behavior of PMJs within the ventricular, is not well understood in the wider population. Even less is known on the inter-individual variability. To elucidate the effects that unknown or improper assumptions of the HPS may play in the ability to obtain an exact match in the ECG, exact constraints from the GT model were not utilized. Namely, the coverage of endocardial layer S_e during optimization coincided with the GT model, but a singular PMJ penetration depth d_{pmj} of 2.5 mm was deployed. Regardless of the generalized assumption in the PMJ penetration depth d_{pmj} , a perfect match could be obtained for the ECG of the simulated GT model exhibiting robustness in the optimization method.

Further exploration of alternative geometrical constraints in real world applications when CDTs are built from patient data is thus needed. Alternative values for PMJ depth could be prescribed as ventricular wall thicknesses are highly variable within the healthy population, but range between 4–12 mm in the LV (Sjögren, 1971) and 2–5 mm in the RV (Prakash, 1978) during diastole. Furthermore, sparsity of the HPS in the RV inferior wall was deployed based on histological studies (Stephenson et al., 2017), but this may not agree with full coverage of the RV inferior wall with Purkinje fibers (Myerburg et al., 1972). A possibility is also to reformulate the inverse problem in a Bayesian framework, with a strong prior distribution for the HPS, for instance based on rule-based or generative methods (Álvarez Barrientos et al., 2025).

Moreover, at the discrete level of the advanced GT model used in this study, the information on the PMJ depth is spatially highly variable. The terminal PMJs of the Purkinje network are resistively coupled to the ventricular myocardium within a prescribed radius and minimum number of connections. This accounts for electrotonic loading and associated anterograde and retrograde conduction delays (Boyle et al., 2010). With the coarser mesh resolution of around 1.2 mm, a spatial variability at the scale of the mesh resolution is inevitable.

This paper only focused on the optimization of PMJs for a varying number of electrodes, but always assumed knowledge of the anatomy, lead fields and CV tensor. However, even in this restricted scenario, optimization of only the PMJs remains an ill-posed task as we have shown that requires strong constraints even for the already physics-restricted eikonal model. A further extension to optimize the CV tensor is possible from a methodological point-of-view (Grandits et al., 2020), but is guaranteed to further expand the space of possible solutions

and would require additional regularization considerations. For instance, additional information may be based on imaging or EAM data, which can be used to reconstruct the anisotropic structure of the tissue (Grandits et al., 2021b; Lubrecht et al., 2021; Ruiz-Herrera et al., 2022).

A further limitation is the various anatomical simplifications inherent in the process of anatomical model generation where structures pertaining to the non-compact myocardium including trabeculation, papillary muscles, or the moderator band are assigned to the blood pool. As such, a significant discrepancy arises between the relatively smooth endocardial surfaces in the model and the highly structured and rugged surfaces *in vivo* in a patient. Moreover, these ignored structures are tightly linked to the function of the HPS. For instance, the root regions of papillary muscles are activated by the Purkinje network, and the moderator band in the RV encloses a fascicle of the HPS (Gettes and Surawicz, 1968; Walton et al., 2018). These are major confounding factors as the optimization of PMJ locations is carried out within a sub-endocardial space that may be strikingly different between model and *in vivo* in a patient. Building such highly detailed anatomical models that accurately represent the non-compact myocardium is feasible (Plank et al., 2009) and can be achieved also with routine clinical imaging. These effects require further investigation, but this was beyond the scope of this study.

In this work, we have not considered the repolarization phase and the corresponding T-wave. In principle, our methodology can be easily extended to optimize specific repolarization parameters in the forward model (Gillette et al., 2021b; Camps et al., 2025).

In conclusion, in this paper we extensively validated our recent method Geodesic-BP for creating CDT from the surface ECG and discussed the identifiability and uniqueness in recovering LAT maps. While the ECG reconstruction can be achieved in a reliable manner, the quality of the LAT reconstruction highly depends on the restrictions put onto the PMJs, the initialization of the parameters, and the number of electrodes. According to our findings, the restrictions were the most important factor to improve the overall quality of the results and minimize variability between the reconstructions.

CRedit authorship contribution statement

Thomas Grandits: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Conceptualization. **Karli Gillette:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Gernot Plank:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Simone Pezzuto:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Region of influence (ROI)

In order to optimize problem in (10) we compute in each iteration of the optimization algorithm the solution τ and its gradient $\nabla_{(x_i, t_i)} \tau$ for each PMJ (x_i, t_i) in one backpropagation. The gradient is used in the optimization to match the ECG, but doubles as a way to compute the influence of a PMJ on the total solution. To better understand the concept, consider the LAT at a point $x \in \Omega$, which could be equally defined as the distance (in geodesic terms) from the closest initial site to the point x , i.e.

$$\tau(x) := \min_i t_i + \int_0^1 \gamma_i(t) dt \quad (A.1)$$

where γ_i is the geodesic path between x_i and x . Using (A.1), the derivative of each point w.r.t. t_i readily follows:

$$\frac{\partial \tau}{\partial t_i}(x) = \begin{cases} 1 & \text{if } (x_i, t_i) \text{ activates } x \\ 0 & \text{else} \end{cases} \quad (A.2)$$

In EP terms, (A.2) can be interpreted as finding for each point x in the domain its closest initial site (x_i, t_i) (excluding equidistant boundary regions with measure 0), which is responsible for the activation of x . Using (A.2), we can give a mathematically and logically sound quantitative definition of the ROI for each initial site (x_i, t_i) :

$$ROI_i = \int_{\Omega} \frac{\partial \tau}{\partial t_i}(x) dx, \quad (A.3)$$

which is measuring the volume of tissue that is activated by the initial site (x_i, t_i) . The computation of all ROIs can be performed using a single backpropagation of $\int_{\Omega} \tau(x) dx$. Note that initial sites with $ROI_i = 0$ can exist, which just means that they do not activate any tissue and will not be optimized by the gradient-based optimization. This is also consistent with the fact that their presence or absence does not change the computed solution τ . We call an initial site (x_i, t_i) with $ROI_i = 0$ simply an *inactive initial site*. Further information on the relation between the method of characteristics and the eikonal equation can be found in Carmo (1992) and Grandits et al. (2021a).

Appendix B. Supplementary data

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.media.2025.103641>.

References

- Álvarez Barrientos, F., Salinas-Camus, M., Pezzuto, S., Sahli Costabal, F., 2025. Probabilistic learning of the Purkinje network from the electrocardiogram. *Med. Image Anal.* 101, <https://doi.org/10.1016/j.media.2025.103640>.
- Barber, F., Langfield, P., Lozano, M., García-Fernández, I., Duchateau, J., Hocini, M., Haissaguerre, M., Vigmond, E., Sebastian, R., 2021. Estimation of personalized minimal Purkinje systems from human electro-anatomical maps. *IEEE Trans. Med. Imaging* 40, 2182–2194.
- Beck, A., Teboulle, M., 2009. A fast iterative shrinkage-thresholding algorithm for linear inverse problems. *SIAM J. Imaging Sci.* 2, 183–202. <https://doi.org/10.1137/080716542>.
- Berg, L.A., Rocha, B.M., Oliveira, R.S., Sebastian, R., Rodriguez, B., de Queiroz, R.A.B., Cherry, E.M., Dos Santos, R.W., 2023. Enhanced optimization-based method for the generation of patient-specific models of Purkinje networks. *Sci. Rep.* 13, 11788.
- Bishop, M.J., Plank, G., 2011. Bidomain ECG simulations using an augmented monodomain model for the cardiac source. *IEEE Trans. Bio-Med. Eng.* 58, <https://doi.org/10.1109/TBME.2011.2148718>.
- Bishop, M., Plank, G., 2025. Stochastic behaviour of arrhythmia induction in virtual heart models suggests caution in offering clinical insights. *Nat. Cardiovasc. Res.*
- Blender Online Community, 2024. Blender - a 3D Modelling and Rendering Package. Blender Foundation, Blender Institute, Amsterdam, URL <http://www.blender.org>.

- Bochev, P., Lehoucq, R.B., 2005. On the finite element solution of the pure Neumann problem. *SIAM Rev.* 47, 50–66.
- Boyle, P.M., Deo, M., Plank, G., Vigmond, E.J., 2010. Purkinje-mediated effects in the response of quiescent ventricles to defibrillation shocks. *Ann. Biomed. Eng.* 38, 456–468. <http://dx.doi.org/10.1007/s10439-009-9829-4>.
- Calder, S., O'Grady, G., Cheng, L.K., Du, P., 2018. Torso-tank validation of high-resolution electrocardiography (ECG): Forward modelling, methodology and results. *Ann. Biomed. Eng.* 46, 1183–1193. Publisher: Springer.
- Camps, J., Berg, L.A., Wang, Z.J., Sebastian, R., Riebel, L.L., Doste, R., Zhou, X., Sachetto, R., Coleman, J., Lawson, B., et al., 2024. Digital twinning of the human ventricular activation sequence to clinical 12-lead ECGs and magnetic resonance imaging using realistic Purkinje networks for in silico clinical trials. *Med. Image Anal.* 94, 103108.
- Camps, J., Wang, Z.J., Doste, R., Berg, L.A., Holmes, M., Lawson, B., Tomek, J., Burrage, K., Bueno-Orovio, A., Rodriguez, B., 2025. Harnessing 12-lead ECG and MRI data to personalise repolarisation profiles in cardiac digital twin models for enhanced virtual drug testing. *Med. Image Anal.* 100, 103361. <http://dx.doi.org/10.1016/j.media.2024.103361>.
- Cárdenes, R., Sebastian, R., Soto-Iglesias, D., Berrueto, A., Camara, O., 2015. Estimation of Purkinje trees from electro-anatomical mapping of the left ventricle using minimal cost geodesics. *Med. Image Anal.* 24, 52–62.
- Cardone-Noott, L., Bueno-Orovio, A., Mincholé, A., Zenzemi, N., Rodriguez, B., 2016. Human ventricular activation sequence and the simulation of the electrocardiographic QRS complex and its variability in healthy and intraventricular block conditions. *EP Eur.* 18, iv4–iv15.
- Carmo, M.P.D., 1992. *Riemannian Geometry*. Springer.
- Cluitmans, M.J., Plank, G., Heijman, J., 2024. Digital twins for cardiac electrophysiology: state of the art and future challenges. *Herzsch. Elektrophys.* 35, 118–123. <http://dx.doi.org/10.1007/s00399-024-01014-0>.
- Colli Franzone, P., Guerri, L., 1993. Spreading of excitation in 3-d models of the anisotropic cardiac tissue. I. Validation of the eikonal model. *Math. Biosci.* 113, 145–209. [http://dx.doi.org/10.1016/0025-5564\(93\)90001-Q](http://dx.doi.org/10.1016/0025-5564(93)90001-Q).
- Colli Franzone, P., Pavarino, L.F., Scacchi, S., 2014. *Mathematical Cardiac Electrophysiology*. Vol. 13, Springer.
- Computing, S., Institute, I., 2016. Seg3d: Volumetric image segmentation and visualization. URL <http://www.seg3d.org>.
- Corral-Acero, J., Margara, F., Marciniak, M., Rodero, C., Loncaric, F., Feng, Y., Gilbert, A., Fernandes, J.F., Bukhari, H.A., Wajdan, A., Martinez, M.V., Santos, M.S., Shamohammadi, M., Luo, H., Westphal, P., Leeson, P., DiAchille, P., Gurev, V., Mayr, M., Geris, L., Pathmanathan, P., Morrison, T., Cornelussen, R., Prinzen, F., Delhaas, T., Doltra, A., Sitges, M., Vigmond, E.J., Zacur, E., Grau, V., Rodriguez, B., Remme, E.W., Niederer, S., Mortier, P., McLeod, K., Potse, M., Pueyo, E., Bueno-Orovio, A., Lamata, P., 2020. The Digital Twin to enable the vision of precision cardiology. *Eur. Heart J.* 41, 4556–4564. <http://dx.doi.org/10.1093/eurheartj/ehaa159>.
- Crozier, A., Augustin, C., Neic, A., Prassl, A., Holler, M., Fastl, T., Hennemuth, A., Bredies, K., Kuehne, T., Bishop, M., et al., 2016. Image-based personalization of cardiac anatomy for coupled electromechanical modeling. *Ann. Biomed. Eng.* 44, 58–70.
- Dawson-Haggerty, et al., 2019. Trimesh. URL <https://trimesh.org/>.
- Durrer, D., Van Dam, R.T., Freud, G., Janse, M.J., Meijler, F.L., Arzbacher, R.C., 1970. Total excitation of the isolated human heart. *Circulation* 41, 899–912.
- Gettes, L., Surawicz, B., 1968. Effects of low and high concentrations of potassium on the simultaneously recorded Purkinje and ventricular action potentials of the perfused pig moderator band. *Circ. Res.* 23, 717–729. <http://dx.doi.org/10.1161/01.RES.23.6.717>.
- Ghanem, R.N., Jia, P., Ramanathan, C., Ryu, K., Markowitz, A., Rudy, Y., 2005. Noninvasive electrocardiographic imaging (ECGI): comparison to intraoperative mapping in patients. *Hear. Rhythm.* 2, 339–354. Publisher: Elsevier.
- Gillette, K., Gsell, M.A., Bouyssier, J., Prassl, A.J., Neic, A., Vigmond, E.J., Plank, G., 2021a. Automated framework for the inclusion of a his–Purkinje system in cardiac digital twins of ventricular electrophysiology. *Ann. Biomed. Eng.* 49, 3143–3153. <http://dx.doi.org/10.1007/s10439-021-02825-9>.
- Gillette, K., Gsell, M.A., Prassl, A.J., Karabelas, E., Reiter, U., Reiter, G., Grandits, T., Payer, C., Stern, D., Urschler, M., Bayer, J.D., Augustin, C.M., Neic, A., Pock, T., Vigmond, E.J., Plank, G., 2021b. A framework for the generation of digital twins of cardiac electrophysiology from clinical 12-lead ECGs. *Med. Image Anal.* 71, 102080. <http://dx.doi.org/10.1016/j.media.2021.102080>.
- Gillette, K., Gsell, M.A., Stocchi, M., Grandits, T., Neic, A., Manning, M., Scherr, D., Roney, C.H., Prassl, A.J., Augustin, C.M., et al., 2022. A personalized real-time virtual model of whole heart electrophysiology. *Front. Physiol.* 13, 860. <http://dx.doi.org/10.3389/fphys.2022.907190>.
- Grandits, T., Efland, A., Pock, T., Krause, R., Plank, G., Pezzuto, S., 2021a. GEASI: Geodesic-based earliest activation sites identification in cardiac models. *Int. J. Numer. Methods Biomed. Eng.* 37, e3505. <http://dx.doi.org/10.1002/cnm.3505>.
- Grandits, T., Gillette, K., Neic, A., Bayer, J., Vigmond, E., Pock, T., Plank, G., 2020. An inverse Eikonal method for identifying ventricular activation sequences from epicardial activation maps. *J. Comput. Phys.* 419, 109700. <http://dx.doi.org/10.1016/j.jcp.2020.109700>.
- Grandits, T., Pezzuto, S., Lubrecht, J.M., Pock, T., Plank, G., Krause, R., 2021b. PIEMAP: Personalized inverse eikonal model from cardiac electro-anatomical maps. In: Puyol Anton, E., Pop, M., Sermesant, M., Campello, V., Lalande, A., Lekadir, K., Suñesiaputra, A., Camara, O., Young, A. (Eds.), *Statistical Atlases and Computational Models of the Heart. M & Ms and EMIDEC Challenges*. In: *Lecture Notes in Computer Science*, Vol. 12592, Springer, Cham, pp. 76–86. http://dx.doi.org/10.1007/978-3-030-68107-4_8, arXiv:2008.10724.
- Grandits, T., Pezzuto, S., Plank, G., 2022. Smoothness and continuity of cost functionals for ECG mismatch computation. *IFAC-Pap.* 55, 181–186.
- Grandits, T., Verhulsdonk, J., Haase, G., Efland, A., Pezzuto, S., 2024. Digital twinning of cardiac electrophysiology models from the surface ECG: a geodesic backpropagation approach. *IEEE Trans. Biomed. Eng.* 71, 1281–1288. <http://dx.doi.org/10.1109/TBME.2023.3331876>.
- Gustafsson, T., McBain, G.D., 2020. Scikit-fem: A Python package for finite element assembly. *J. Open Sour. Softw.* 5, 2369. <http://dx.doi.org/10.21105/joss.02369>.
- Harris, C.R., Millman, K.J., van der Walt, S.J., Gommers, R., Virtanen, P., Cournapeau, D., Wieser, E., Taylor, J., Berg, S., Smith, N.J., Kern, R., Picus, M., Hoyer, S., van Kerkwijk, M.H., Brett, M., Haldane, A., del Río, J.F., Wiebe, M., Peterson, P., Gérard-Marchant, P., Sheppard, K., Reddy, T., Weckesser, W., Abbasi, H., Gohlke, C., Oliphant, T.E., 2020. Array programming with NumPy. *Nature* 585, 357–362. <http://dx.doi.org/10.1038/s41586-020-2649-2>, number: 7825 Publisher: Nature Publishing Group.
- Kassebaum, D.G., Van Dyke, A.R., 1966. Electrophysiological effects of isoproterenol on Purkinje fibers of the heart. *Circ. Res.* 19, 940–946.
- Keener, J.P., Sneyd, J., 1998. *Mathematical Physiology*. Vol. 1, Springer.
- Keller, D.U., Weber, F.M., Seemann, G., Dössel, O., 2010. Ranking the influence of tissue conductivities on forward-calculated ECGs. *IEEE Trans. Biomed. Eng.* 57, 1568–1576.
- Kingma, D.P., Ba, J., 2017. Adam: A method for stochastic optimization. <http://dx.doi.org/10.48550/arXiv.1412.6980>, arXiv:1412.6980.
- Larson, J., Menickelly, M., Wild, S.M., 2019. Derivative-free optimization methods. *Acta Numer.* 28, 287–404.
- Laubenbacher, R., Mehrad, B., Shmulevich, I., Trayanova, N., 2024. Digital twins in medicine. *Nat. Comput. Sci.* 4, 184–191.
- Li, L., Camps, J., Banerjee, A., Beetz, M., Rodriguez, B., Grau, V., 2022. Deep computational model for the inference of ventricular activation properties. In: Camara, O., Puyol-Antón, E., Qin, C., Sermesant, M., Suñesiaputra, A., Wang, S., Young, A. (Eds.), *Statistical Atlases and Computational Models of the Heart Regular and CMR Motion Challenge Papers*. In: *Lecture Notes in Computer Science*, Springer Nature Switzerland, Cham, pp. 369–380. http://dx.doi.org/10.1007/978-3-031-23443-9_34.
- Li, L., Camps, J., Rodriguez, B., Grau, V., 2025. Solving the inverse problem of electrocardiography for cardiac digital twins: A survey. *IEEE Rev. Biomed. Eng.* 18, 316–336. <http://dx.doi.org/10.1109/RBME.2024.3486439>.
- Lubrecht, J.M., Grandits, T., Gharaviri, A., Schotten, U., Pock, T., Plank, G., Krause, R., Auricchio, A., Pezzuto, S., 2021. Automatic reconstruction of the left atrium activation from sparse intracardiac contact recordings by inverse estimate of fiber structure and anisotropic conduction in a patient-specific model. *EP Eur.* 23, i63–i70. <http://dx.doi.org/10.1093/europace/eaab392>.
- Meisenzahl, C., Gillette, K., Prassl, A.J., Plank, G., Sapp, J.L., Wang, L., 2024. Boatmap: Bayesian optimization active targeting for monomorphic arrhythmia pace-mapping. *Comput. Biol. Med.* 182, 109201.
- Myerburg, R.J., Nilsson, K., Gelband, H., 1972. Physiology of canine intraventricular conduction and endocardial excitation. *Circ. Res.* 30, 217–243.
- Nagel, C., Espinosa, C.B., Gillette, K., Gsell, M.A., Sánchez, J., Plank, G., Dössel, O., Loewe, A., 2022. Comparison of propagation models and forward calculation methods on cellular, tissue and organ scale atrial electrophysiology. *IEEE Trans. Biomed. Eng.* 70, 511–522.
- Neic, A., Campos, F.O., Prassl, A.J., Niederer, S.A., Bishop, M.J., Vigmond, E.J., Plank, G., 2017. Efficient computation of electrograms and ECGs in human whole heart simulations using a reaction–eikonal model. *J. Comput. Phys.* 346, 191–211. <http://dx.doi.org/10.1016/j.jcp.2017.06.020>.
- Neic, A., Gsell, M.A., Karabelas, E., Prassl, A.J., Plank, G., 2020. Automating image-based mesh generation and manipulation tasks in cardiac modeling workflows using meshtool. *SoftwareX* 11, 100454.
- Niederer, S.A., Sacks, M.S., Girolami, M., Willcox, K., 2021. Scaling digital twins from the artisanal to the industrial. *Nat. Comput. Sci.* 1, 313–320.
- Palamara, S., Vergara, C., Catanzariti, D., Faggiano, E., Pangrazzi, C., Centonze, M., Nobile, F., Maines, M., Quarteroni, A., 2014. Computational generation of the Purkinje network driven by clinical measurements: the case of pathological propagations. *Int. J. Numer. Methods Biomed. Eng.* 30, 1558–1577.
- Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., Chanan, G., Killeen, T., Lin, Z., Gimselshin, N., Antiga, L., Desmaison, A., Kopf, A., Yang, E., DeVito, Z., Raison, M., Tejani, A., Chilamkurthy, S., Steiner, B., Fang, L., Bai, J., Chintala, S., PyTorch: An imperative style, high-performance deep learning library.
- Payer, C., Stern, D., Bischof, H., Urschler, M., 2018. Multi-label whole heart segmentation using CNNs and anatomical label configurations. In: *Statistical Atlases and Computational Models of the Heart. ADCD and MMWHS Challenges: 8th International Workshop, STACOM 2017, Held in conjunction with MICCAI 2017, Quebec City, Canada, September (2017) 10–14, Revised Selected Papers*. Springer, pp. 190–198. http://dx.doi.org/10.1007/978-3-319-75541-0_20.

- Pezzuto, S., Kal'avský, P., Potse, M., Prinzen, F.W., Auricchio, A., Krause, R., 2017. Evaluation of a rapid anisotropic model for ECG simulation. *Front. Physiol.* 8, 265. <http://dx.doi.org/10.3389/fphys.2017.00265>.
- Pezzuto, S., Perdikaris, P., Costabal, F.S., 2022. Learning cardiac activation maps from 12-lead ECG with multi-fidelity Bayesian optimization on manifolds. *IFAC-Pap.* 55, 175–180. <http://dx.doi.org/10.1016/j.ifacol.2022.09.091>.
- Pezzuto, S., Prinzen, F.W., Potse, M., Maffessanti, F., Regoli, F., Caputo, M.L., Conte, G., Krause, R., Auricchio, A., 2021. Reconstruction of three-dimensional biventricular activation based on the 12-lead electrocardiogram via patient-specific modelling. *EP Eur.* 23, 640–647. <http://dx.doi.org/10.1093/europace/euab330>.
- Plank, G., Burton, R.A.B., Hales, P., Bishop, M., Mansoori, T., Bernabeu, M.O., Garny, A., Prassl, A.J., Bollensdorff, C., Mason, F., et al., 2009. Generation of histologically representative models of the individual heart: tools and application. *Philos. Trans. A Math. Phys. Eng. Sci.* 367, 2257–2292, Publisher: The Royal Society..
- Potse, M., 2018. Scalable and accurate ecg simulation for reaction–diffusion models of the human heart. *Front. Physiol.* 9, 370. <http://dx.doi.org/10.3389/fphys.2018.00370>.
- Prakash, R., 1978. Determination of right ventricular wall thickness in systole and diastole. echocardiographic and necropsy correlation in 32 patients.. *Heart* 40, 1257–1261.
- Pullan, A.J., Cheng, L.K., Nash, M.P., Ghodrati, A., MacLeod, R., Brooks, D.H., 2010. The inverse problem of electrocardiography. In: Macfarlane, P.W., Oostrom, A. Van, Pahlm, O., Kligfield, P., Janse, M., Camm, J. (Eds.), *Comprehensive Electrocardiology*. Springer, London, pp. 299–344. http://dx.doi.org/10.1007/978-1-84882-046-3_9.
- Roberts, D.E., Scher, A.M., 1982. Effect of tissue anisotropy on extracellular potential fields in canine myocardium in situ.. *Circ. Res.* 50, 342–351, Publisher: Am Heart Assoc..
- Ruiz-Herrera, C., Grandits, T., Plank, G., Perdikaris, P., Sahli Costabal, F., Pezzuto, S., 2022. Physics-informed neural networks to learn cardiac fiber orientation from multiple electroanatomical maps. *Eng. Comput.* 38, 3957–3973. <http://dx.doi.org/10.1007/s00366-022-01709-3>, arXiv:2201.12362.
- Sahli Costabal, F., Hurtado, D.E., Kuhl, E., 2016. Generating Purkinje networks in the human heart. *J. Biomech.* 49, 2455–2465.
- Salvador, M., Kong, F., Peirlinck, M., Parker, D.W., Chubb, H., Dubin, A.M., Marsden, A.L., 2023. Digital twinning of cardiac electrophysiology for congenital heart disease. <http://dx.doi.org/10.1101/2023.11.27.568942>, bioRxiv 2023.11.27.568942.
- Schroeder, W., Martin, K., Lorensen, B., 2006. *The Visualization Toolkit*, fourth ed. Kitware, NY.
- Sharma, P.S., Dandamudi, G., Herweg, B., Wilson, D., Singh, R., Naperkowski, A., Koneru, J.N., Ellenbogen, K.A., Vijayaraman, P., 2018. Permanent his-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Hear. Rhythm.* 15, 413–420.
- Sjögren, A., 1971. Left ventricular wall thickness determined by ultrasound in 100 subjects without heart disease. *Chest* 60, 341–346.
- Spach, M.S., Huang, S.-n., Ayers, C.R., 1963. Electrical and anatomic study of the Purkinje system of the canine heart. *Am. Heart J.* 65, 664–673. [http://dx.doi.org/10.1016/0002-8703\(63\)90129-7](http://dx.doi.org/10.1016/0002-8703(63)90129-7).
- Stephenson, R.S., Atkinson, A., Kottas, P., Perde, F., Jafarzadeh, F., Bateman, M., Iaizzo, P.A., Zhao, J., Zhang, H., Anderson, R.H., et al., 2017. High resolution 3-dimensional imaging of the human cardiac conduction system from microanatomy to mathematical modeling. *Sci. Rep.* 7, 7188.
- Sullivan, C.B., Kaszynski, A., 2019. Pyvista: 3D plotting and mesh analysis through a streamlined interface for the Visualization Toolkit (VTK). *J. Open Sour. Softw.* 4, 1450. <http://dx.doi.org/10.21105/joss.01450>, publisher: The Open Journal..
- Sung, E., Prakosa, A., Zhou, S., Berger, R.D., Chrispin, J., Nazarian, S., Trayanova, N.A., 2022. Fat infiltration in the infarcted heart as a paradigm for ventricular arrhythmias. *Nat. Cardiovasc. Res.* 1, 933–945.
- Vigmond, E., Dos Santos, R.W., Prassl, A., Deo, M., Plank, G., 2008. Solvers for the cardiac bidomain equations. *Prog. Biophys. Mol. Biol.* 96, 3–18. <http://dx.doi.org/10.1016/j.pbiomolbio.2007.07.012>.
- Vigmond, E.J., Stuyvers, B.D., 2016. Modeling our understanding of the his-Purkinje system. *Prog. Biophys. Mol. Biol.* 120, 179–188.
- Walton, R.D., Pashaei, A., Martinez, M.E., Constantin, M., Duchateau, J., Bear, L., Cros, C., Pascarel-Auclerc, C., Guo, Y., Benoist, D., Dubes, V., Faye, N.R., Chaigne, S., Dupuis, S., Détaille, D., Pourtau, L., Pasdois, P., Brette, F., Rogier, J., Labrousse, L., Hocini, M., Vigmond, E.J., Haissaguerre, M., Bernus, O., 2018. Compartmentalized structure of the moderator band provides a unique substrate for macroreentrant ventricular tachycardia. *Circ.: Arrhythmia Electrophysiol.* 11, e005913. <http://dx.doi.org/10.1161/CIRCEP.117.005913>, publisher: American Heart Association..
- Webber, M., Joy, G., Bennett, J., Chan, F., Falconer, D., Shiwani, H., Davies, R.H., Krausz, G., Tanackovic, S., Guger, C., et al., 2023. Technical development and feasibility of a reusable vest to integrate cardiovascular magnetic resonance with electrocardiographic imaging. *J. Cardiovasc. Magn. Reson.* 25, 73, Publisher: Springer..