



Reconstructing ventricular activation sequences from epicardial data: Insights from Geodesic Back-Propagation optimization in porcine models

Lindsay C.R. Tanner^{a,b,c,d,*}, Anna Busatto^{a,b,c,d,1}, Thomas Grandits^d, Jake A. Bergquist^{a,b,c}, Brian Zenger^e, Simone Pezzuto^f, Gernot Plank^{g,h}, Rob S. MacLeod^{a,b,c}, Karli Gillette^{a,c,g}

^a Scientific Computing and Imaging Institute, University of Utah, Salt Lake City, UT, United States of America

^b Nora Eccles Cardiovascular Research and Training Institute, University of Utah, Salt Lake City, UT, United States of America

^c Department of Biomedical Engineering, University of Utah, Salt Lake City, UT, United States of America

^d Department of Mathematics and Scientific Computing, University of Graz, Graz, Austria

^e Department of Medicine - Cardiovascular Division, Washington University in St. Louis School of Medicine, Saint Louis, MO, United States of America

^f Department of Mathematics, University of Trento, Trento, Italy

^g Division of Biophysics and Medical Physics, Gottfried Schatz Research Center, Medical University of Graz, Graz, Austria

^h BioTechMed-Graz, Graz, Austria

ARTICLE INFO

Keywords:

Cardiac digital twin
Ventricular activation
His-Purkinje system
Geodesic Back-Propagation
Cardiac electrophysiology modeling
Epicardial mapping

ABSTRACT

Cardiac digital twins (CDTs) are emerging as powerful tools in personalized medicine, providing subject-specific models to simulate and understand cardiac function. A central challenge in constructing CDTs is accurately personalizing the structure and function of the His-Purkinje system (HPS), which determines ventricular activation. In this study, we leveraged a novel modified Geodesic-BP method to infer early activation sites (EASs) from epicardial activation times. The EASs can then serve as a surrogate for Purkinje-myocardial junctions, facilitating anterograde ventricular activation. We used both experimental porcine ($N = 5$) and synthetic ($N = 5$) datasets of epicardial activation times measured or assigned to locations on an electrode sock. For both datasets, we optimized for initial estimates of 5, 50, 100, and 200 EASs and assessed output variability by repeating the inference process 10 times. Assessments were based on matching the predicted activation times at both the epicardial locations and from intracardiac measurements made with multielectrode needles, and throughout the ventricular myocardium for the synthetic dataset. The algorithm could consistently recover global ventricular activation patterns from epicardial data alone. For the experimental dataset, the minimum and maximum mean absolute differences were 0.19 ms and 3.86 ms on the epicardial sock and 2.65 ms and 10.69 ms for the needles. For the synthetic dataset, the corresponding values were 0.13 ms and 2.81 ms on the sock and 2.42 ms and 14.07 ms throughout the ventricular myocardium. However, discrepancies between the epicardial surface and intramural myocardium, overfitting of EASs, and variability across repeated runs revealed key limitations. These findings highlight both the overall potential and current limitations of inferring EASs using the proposed optimization approach. They demonstrate the feasibility of deriving informative activation patterns from limited data, while underscoring the need to incorporate stronger physiological priors and anatomical constraints. Ultimately, our results motivate future efforts to refine simulation-based personalization frameworks, improve robustness, and enhance the physiological realism of CDTs for more accurate and reliable applications.

1. Introduction

Cardiac digital twins (CDTs) have emerged as a transformative technology in cardiology, offering detailed, subject-specific computational replicas of cardiac structure and function to enable personalized and precise diagnosis, prognosis, and therapy planning [1–4]. Central to

the vision of CDTs is the accurate personalization and inference of the numerous parameters underlying the biophysical models from standard clinical measurements. Therein also lies the major challenge in this endeavor, one example of which is the characterization of the ventricular activation sequence during normal sinus rhythm. Ventricular activation

* Correspondence to: 72 S Central Campus Dr, Salt Lake City, UT 84112, United States of America.

E-mail address: lindsay.c.r.tanner@utah.edu (L.C.R. Tanner).

¹ These authors contributed equally to this research.

is predominantly governed by the His-Purkinje system (HPS), a rapidly conducting fiber network terminating in Purkinje-myocardial junctions (PMJs) that facilitate the earliest activation sites (EASs) within the ventricles [5–7]. The anatomical configuration and electrophysiological behavior of the HPS play a crucial role in shaping activation dynamics, arrhythmia maintenance, and retrograde conduction properties [8,9].

Despite its physiological importance, inferring the PMJ locations and subsequent ventricular activation for CDT applications remain challenging tasks [1,10]. Foremost among these challenges is the limited accessibility of high-resolution anatomical or functional data in both experimental and clinical practice [11,12], which limits our understanding of the electrical properties of the HPS [13]. As a result, computational models of cardiac electrophysiology often rely on replicating the predominant breakthrough of the Durrer-based five primary fascicles of the HPS described in the literature as long ago as the 1970's [14]. More recent methods have turned to inverse modeling techniques, inferring HPS structures [15] or numerous EASs [16] from ECGs and BSPMs [17], or activation maps [18]. These iterative inverse approaches are enabled by fast and efficient solvers for the eikonal equation, which enables rapid simulations of cardiac activation [19,20]. Probabilistic frameworks have further improved model plausibility by generating ensembles of feasible HPS configurations constrained by data [21], and generative models have emerged to synthesize realistic ventricular activation [16]. Validation of these optimization techniques, however, is necessary to assess the reliability of HPS reconstruction for generating accurate CDTs for potential clinical applications. This is particularly important because inverse reconstructions in cardiac modeling applications (e.g., ECG Imaging) are challenging, as they are known to be ill-posed and ill-conditioned [10, 13,16]. Furthermore, the problem is inherently non-unique, leading to multiple ventricular activation sequences that can produce remarkably similar 12-lead ECGs [10,13].

To our knowledge, no studies to date have performed volumetric validation of HPS-inferred activation sequences based on independent data, *i.e.*, not used in the optimization process. Most validation efforts have relied on torso surface ECG morphologies, which offer limited spatial insight and do not assess volumetric accuracy within the myocardium [16]. A few landmark studies have compared noninvasively reconstructed epicardial and endocardial activation times from electrocardiographic imaging (ECGI), showing promising surface-level agreement—but they still lacked validation against independent intramural recordings [22]. More recently, ventricular simulations coupled with pre-clinical models have begun to estimate conduction velocities and validate wavefront reconstructions using volumetric datasets [23–25]. However, these efforts focused on ectopic activity and therefore lack the anatomical specificity and defined activation breakthrough points characteristic of the HPS [23]. This gap highlights a critical need for benchmarks that can test the predictive fidelity of His-Purkinje personalization methods within CDTs.

In this study, we evaluated an enhanced approach for inferring EASs from the cardiac conduction system using epicardial activation times, with a particular focus on assessing the reconstruction of volumetric activation times. The optimization process employed a modified version of the Geodesic-BP method, developed initially to estimate EASs from epicardial data [18]. This method determines the spatial and temporal characteristics of EASs within the ventricular myocardium by minimizing discrepancies between optimized simulations and observed epicardial activation patterns. More recently, the approach has been further refined and extended to incorporate torso ECG data [16]. We applied the method to geometric models and epicardial sock electrode activation times from five invasive porcine experiments. To evaluate the accuracy of activation reconstruction beyond the epicardial sock, we compared optimized simulated activation timings with intramural needle electrode recordings, which were omitted from the optimization. We further validated this approach by testing its ability to recover

activation patterns from synthetic epicardial sock data generated using five prescribed EASs aligned with HPS fascicles described in the literature [14]. By integrating computational modeling [15,26] with *in situ* electrical recordings, our framework provides a link between simulation and physiological measurements. Leveraging insights from generative modeling [16], this methodology overcomes key limitations of ECG-based techniques and enhances the physiological fidelity of personalized CDTs by comparing to invasive experimental signals.

2. Methods

2.1. Experimental dataset

Before describing the details of the optimization approach, we outline the experiments that provided the input data and the validation.

2.1.1. *InSitu* experiment setup

The experimental model used in this study has been previously described in Zenger et al. [27]. Briefly, midline sternotomies were performed on five anesthetized Yucatan minipigs (male, approximately 30 kg) to expose the anterior surface of the heart. Each animal was instrumented with both epicardial and intramural electrode arrays for high-resolution electrical mapping. The intramural electrodes consisted of custom-made plunge needles, each containing 10 electrodes spaced 1.6 mm apart along the shaft. For each animal, 20–30 plunge needles were inserted into the myocardium within the perfusion territory of the left anterior descending (LAD) coronary artery, with 5–10 mm spacing between epicardial entry sites. To capture epicardial potentials, a high-density 247-electrode sock array was placed over the ventricular surface, providing an approximate resolution of 6.6 mm² and 10 mm inter-electrode spacing. Following electrode placement, the thoracic cavity was closed and any residual air evacuated, and recordings were delayed for one hour to allow recovery from needle insertion before sinus rhythm electrograms were collected. Bioelectric signals were recorded simultaneously using a custom-built digital multiplexer system at a sampling rate of 1 kHz, with appropriate gain settings and low-pass filtering [27]. All animal procedures were approved by the University of Utah Institutional Animal Care and Use Committee (protocol #20-11001, approved 11/23/2020) and conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

2.1.2. Experiment processing

Geometric model generation: After euthanasia, the hearts were excised, filled with dental alginate to preserve internal structure, fixed in formalin, and scanned via computed tomography (CT). Using Seg3D (www.sci.utah.edu/software/seg3d), geometric segmentations were created for the intramural needles, left and right ventricles, and blood pools. Finite element meshes with a target mean edge length of 700 μ m were generated using Cleaver (www.sci.utah.edu/software/cleaver) [28,29]. The five anatomical models derived from these scans are referred to as Geometries A through E. Myocardial fiber orientations were assigned using a rule-based method incorporating fiber (α) and helix (β) angles defined on the endocardium and epicardium [30]. Specifically, α was set to 60° at the endocardium and –60° at the epicardium, while β was assigned values of –35° and 0°, respectively [31,32].

Geometric registration: At the end of each experiment, the positions of selected sock electrodes and intramural needle insertion points were digitized using a MicroScribe 3D digitizer (Revware Inc., Raleigh, NC). These digitized points were registered to the CT space via an affine transformation, using the common locations of digitized and imaged intramural needles. The transformed sock points were snapped to the myocardial surface using a nearest-neighbor approach. To register the full set of sock electrodes, a nominal sock mesh, created by manually stretching the sock over a heart model and digitizing each individual electrode, was first adjusted along the apical-basal axis to match vertical electrode spacing. This nominal mesh was then aligned with the

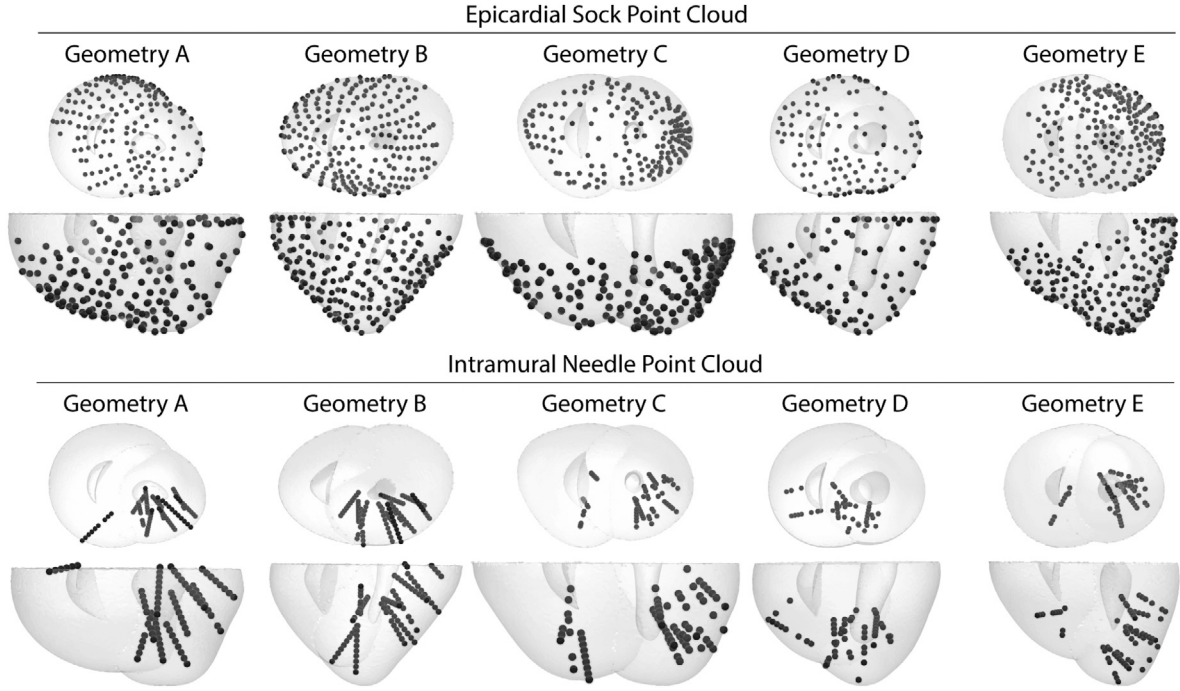


Fig. 1. Electrode locations for Geometries A through E (columns). The top panel shows the epicardial sock electrodes, showing two views per experiment: the ventricular base (top) and the anterior surface (bottom). The bottom panel shows intramural needle electrode locations with matching views: base (top) and anterior (bottom).

CT-derived heart mesh using correspondence-driven iterative closest point (ICP) registration, followed by geodesically constrained radial basis deformation as previously described [33].

For each geometry (A–E), spatial correspondence was established by identifying the closest point on the biventricular mesh to each electrode location from the sock and plunge needle datasets using *meshtool* [34]. The resulting geometric models thus represented distinct distributions of electrode locations across the epicardial surface and throughout the myocardial wall, as shown in Fig. 1. Electrode count summaries for each geometry are provided in Table 1.

Signal processing. Electrical recordings were processed using the open-source software PFEIFER (<https://github.com/SCIInstitute/PFEIFER>) [35]. Signals were baseline-corrected, filtered (amplitude-normalized 11th-order rational transfer function), and annotated for temporal landmarks on a beat-by-beat basis. Electrodes exhibiting excessive noise, no detectable physiological response, or inconsistent behavior relative to neighbors were manually reviewed and excluded from the analysis. As a result, the number of valid time signals (and activation times) for the experiments ranged from 111–218. For each dataset, a global root mean squared signal was computed separately for the sock and intramural arrays and used to identify fiducials around the QRS complex. Local activation times were then computed based on the time of the maximum negative deflection ($dV/dt_{\min}$) within the QRS complex and checked for accuracy. For visualization only, activation times were interpolated using *meshtool* based on the spatial distribution of the epicardial sock electrodes.

2.2. Eikonal method

Activation sequences were calculated with CARPentry using the eikonal approximation framework [19] controlled using the openCARP framework [36]. In this approach, the arrival time of the activation wavefront, denoted by t_a , is computed within the myocardial Ω based on a spatially varying orthotropic velocity field represented by the tensor $\mathbf{V}(\mathbf{x})$, with initial activation times t_0 at locations Γ . The governing

Table 1

Number of intramural needle electrodes (column 1) and epicardial sock electrodes (column 2) used in five experiments (Geometry A–E). Each row corresponds to a different experimental geometry.

	# of intramural electrodes	# of epicardial electrodes
Geometry A	101	205
Geometry B	113	218
Geometry C	72	183
Geometry D	56	111
Geometry E	73	190

equations for this model are defined as:

$$\begin{cases} \sqrt{\nabla t_a^T \mathbf{V} \nabla t_a} = 1 & \text{in } \Omega, \\ t_a = t_0 & \text{in } \Gamma, \end{cases} \quad (1)$$

where Ω denotes the myocardial tissue, and t_a is a scalar field representing the time at which the activation wavefront arrives at position $\mathbf{x}$. The tensor $\mathbf{V}(\mathbf{x})$ is a symmetric, positive-definite 3×3 matrix encoding the squared conduction velocities along orthotropic fiber directions: longitudinal (l), transverse (t), and sheet (s). This tensor is given by:

$$\mathbf{V} = v_l^2 ll^T + v_t^2 tt^T + v_s^2 ss^T. \quad (2)$$

A homogeneous longitudinal conduction velocity of 100 cm/s and off-axis velocities at $\frac{1}{2}$ of the longitudinal velocity [23] were set in the entirety of the myocardium. These conduction velocity values are in agreement with experimental porcine studies [23–25,37].

2.3. Geodesic backpropagation algorithm

We employed a Geodesic-BP algorithm modified to optimize EASs from activation times across an epicardial sock, with methodology described by Grandits et al. (2020) and Grandits et al. (2025) [16,18]. To summarize, given target epicardial activation times $\hat{t}_a(\mathbf{x}_{\text{epi}})$ for epi =

$1, \dots, L$, an optimal set of initiation sites X_0 , both location and stimulus time, are found such that simulated activation times $t_{a,X_0}(\mathbf{x}_{\text{epi}})$ best match the targets in a least-squares sense:

$$\min_{X_0 \in S} \frac{1}{L} \sum_{\text{epi}=1}^L \left(t_{a,X_0}(\mathbf{x}_{\text{epi}}) - \hat{t}_a(\mathbf{x}_{\text{epi}}) \right)^2 = \min_{X_0 \in S} \mathcal{L}(X_0), \quad (3)$$

where S is the feasible set of EASs, and $\mathcal{L}(X_0)$ denotes the loss function. The loss function in Eq. (3) is minimized using the ADAM optimizer [38], run for 400 iterations with a learning rate of 0.75. Starting from an initial set of early activation site (including both location and stimulus time) guesses $X_0^{(0)}$, iterative updates to the solution $X_0^{(0)}, X_0^{(1)}, \dots, X_0^{(k+1)}, \dots$ are made until convergence to an optimal set X_0^* . Gradients are computed via back-propagation, which traces discrete geodesic paths from the EASs. The feasible set S includes all EASs within the entire myocardial volume, *i.e.*, from endocardium to epicardium, with non-negative activation times t_i . No upper bound is enforced on t_i , allowing the algorithm to naturally deactivate EASs with large initiation times. For each optimization run, initial EAS positions $\mathbf{x}_i$ are sampled uniformly throughout the myocardium using the `trimesh` library [39]. Corresponding activation times t_i were drawn from a uniform distribution between t_0 and $\max_{\text{epi}} \hat{t}_a(\mathbf{x}_{\text{epi}})$. Computation of activation from the EASs within Geodesic-BP was performed using an iterative optimization procedure to approximate the eikonal model (Section 2.2).

2.4. Optimization of experimental epicardial data

We deployed the Geodesic-BP method in Section 2.3 using 4 different, randomly selected sets of candidate EASs: 5, 50, 100, and 200 locations each with its own stimulus time. We repeated this process with each of the 5 different geometric models from the experimental studies. The goal of each optimization was to minimize the discrepancy between the inferred and ground-truth epicardial sock activation times. We repeated the inference process using the Geodesic-BP method 10 times for all EAS setups, *i.e.*, we performed a different random selection of initial EAS locations and stimulus times. The goal of the repeated optimizations was to assess the variability in the solution.

To evaluate the performance of the optimization method, we distinguished between training and validation data. Epicardial sock activation times were used as input to the optimization process, effectively serving as training data to determine the best-fit activation sequence. In contrast, intramural needle activation times were withheld from the optimization and used exclusively for validation, allowing us to assess the accuracy of the reconstructed activation sequences independently. Accuracy was quantified by computing the absolute differences between experimentally measured and optimized activation times at each location. Point-wise means and standard deviations were computed over all solutions, both throughout the myocardial volume and at the epicardial points.

2.5. Optimization of synthetic epicardial data

We also evaluated the ability of the Geodesic-BP algorithm to recover a synthetically generated activation sequence based on five early activation areas first reported by Durrer et al. and often used in cardiac applications [26,40–42]. Synthetic simulations offer an opportunity to evaluate the optimization of EAS locations and stimulus times, albeit under controlled conditions that involve assigning values to generate the activation times used in the optimization [26]. Durrer-like ground truth activation sequences were calculated with CARPentry using the eikonal approximation framework [19,43] controlled using the open-CARP framework [36], described in Section 2.2. This simulation was repeated for each experimental geometry, using the equivalent five stimulus sites based on previous studies by Gillette et al. using the universal ventricular coordinate system [26,30]. Table 2 contains a summary of the EAS details.

Table 2

Early activation sites used for synthetic ground truth eikonal simulations of sinus ventricular activation.

Parameter	z	ρ	ϕ	v
$b_{lv,s,f}$	0.61	0.0	0.73	−1
$b_{lv,p,f}$	0.47	0.0	−1.36	−1
$b_{lv,a,f}$	0.82	0.0	1.94	−1
$b_{rv,s,f}$	0.72	1.0	−0.04	−1
$b_{rv,mod}$	0.63	0.0	0.21	+1

As with the examples from the measured values, we provided the optimizer with the 5 different geometric models (A–E) and the synthetic epicardial activation times at the same locations as the values measured with the sock and then conducted the same steps: ten repeated selections of 5, 50, 100, and 200 EAS locations and stimulus times. To generate the synthetic activation times on the experimental epicardial sock, we mapped each sock electrode to the nearest simulated activation time. For all optimizations, we omitted additional noise to the synthetic data, as the goal of this study was to evaluate how well the method could recover ground truth information under ideal conditions, where all input parameters were fully known and controlled.

For the optimization setup with 5 EASs, we captured the variability in the EAS locations across trials. We performed constrained k-means clustering on the EAS locations produced by the 10 randomly selected starting locations. The constraints ensured that each cluster contained exactly 10 points. From the resulting clusters, we calculated the point-wise differences within every cluster of points and summarized the results as minimum, maximum, and average intra-cluster distances. Additionally, for the optimization setups with 5 and 200 EASs, we constructed histograms of the stimulus start times to capture the variability between setups.

3. Results

3.1. Optimization from measured activation times

For each of the five geometric models, we used between 111–218 measured epicardial sock activation times (see Table 1) as input to the modified Geodesic-BP algorithm that we optimized for 10 sets of 5, 50, 100, and 200 initial EASs, as detailed in Section 2.4. Fig. 2 presents an overall performance metric as the mean absolute differences between measured and inferred activation times for both the epicardial sock and intramural needles. For the epicardial sock results, we observed a general decrease in mean absolute difference with increasing numbers of EASs. In contrast, no consistent trend was observed in the intramural needle results. Notably, Geometry D, Run 6 with 200 EASs yielded the lowest mean absolute difference (0.44 ms) on the epicardial sock, while Geometry E, Run 0 with 5 EASs, exhibited the highest (3.86 ms). Interestingly, although this sample had the worst accuracy on the epicardial sock, it produced the lowest mean absolute difference in the intramural needle data (7.18 ms). Similar patterns were seen in Geometry E, Run 4, with 50 EASs and Geometry B, Run 1 with 50 EASs. Conversely, some runs with the highest intramural error achieved the lowest epicardial sock error, including Geometry A, Run 7 with 100 EASs, Geometry A, Run 2 with 200 EASs, and Geometry C, Run 2 with 200 EASs.

Fig. 3 shows visualizations of the experimental ground truth, optimized simulation, and corresponding difference maps for the best- and worst-performing optimizations: Geometry D, Run 6 with 200 EASs (minimum average absolute difference) and Geometry E, Run 0 with 5 EASs (maximum average absolute difference), respectively. Results are shown on both anterior and posterior views of the epicardial surface. In the best-performing optimization, the experimental activation pattern appears smoother than the optimized result, though both coarsely share similar regions of mid-activation (blue) and late activation (brown) on

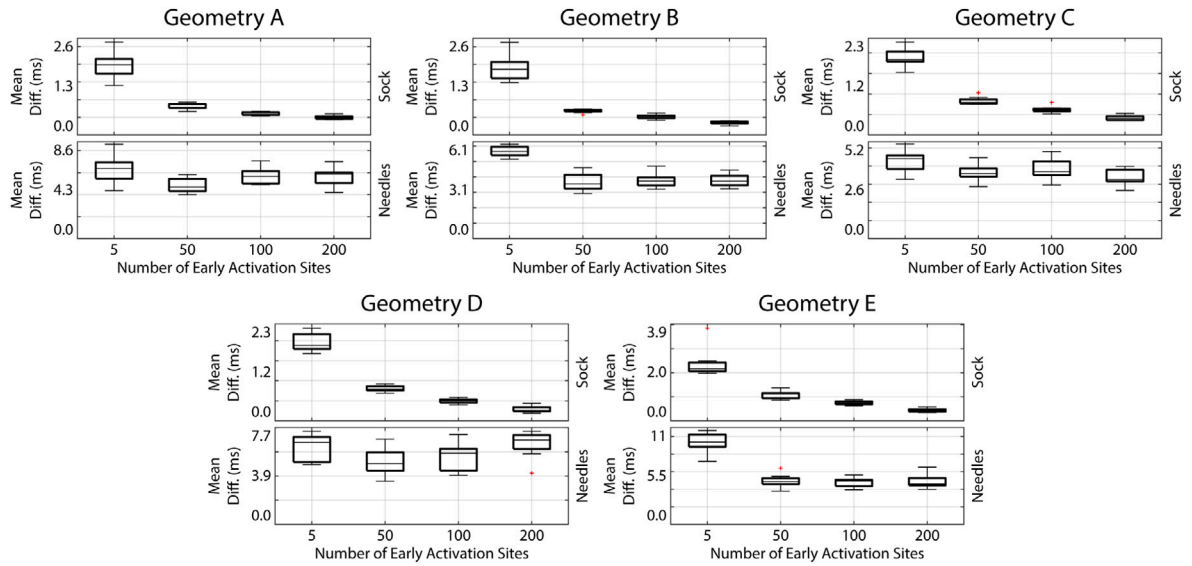


Fig. 2. Box plots of mean absolute differences. Mean absolute differences between optimized and experimental activation times are shown for measurements from the epicardial socks (top) and intramural needle electrodes (bottom) across five different experiments. The x-axis indicates the number of optimized EASs: 5, 50, 100, and 200.

the anterior and posterior surfaces, respectively. In contrast, the worst-performing optimization shows little to no spatial similarity between the experimental and optimized activation patterns. The difference maps also highlight localized temporal discrepancies between the optimized and experimental data, and they range from 0–4 ms in the best-performing case and up to 15 ms in the worst.

Fig. 4 shows the spatial distribution of initiation sites for Geometry D in the best-performing run (minimum average absolute difference) and Geometry E in the worst-performing run (maximum average absolute difference), each selected from optimizations initialized with 5, 50, 100, and 200 EASs. Some EASs activated after the initial stimulus, as discussed in Section 2.3; these sites functioned as acceleration sites to help match epicardial sock activation patterns. In the best-performing 5-EAS case, two sites, one near 0 ms (pink) and one near 14 ms (orange), were clustered on the endocardial surface. In contrast, the worst-performing case shows a more scattered distribution throughout the myocardium. As the number of EASs increased, initiation times became more temporally staggered and spatially distributed across the myocardium. The colors of the spheres in the figure indicate delayed activation, with later-onset sites corresponding to those that provided acceleration. Notably, the number of such acceleration sites generally increased with the number of initial EASs.

Fig. 5 summarizes the mean activation times and corresponding standard deviations across 10 optimization runs for Geometry E, comparing optimizations initialized with 5 and 200 EASs. In the mean activation maps, the 5 EASs case exhibited a marginally higher maximum activation time (54 ms) compared to the 200 EASs case (49 ms). Moreover, activation times throughout the myocardium were generally lower in the 5 EASs case, as indicated by increased regions of blue and green, while the 200 EASs case displayed more widespread late activation (browns). In terms of variability, the 5 EASs case showed a slightly larger maximum standard deviation (11 ms) than the 200 EASs case (8 ms). For both EAS setups, regions of elevated variability were localized primarily on the endocardial surface and within the intramural volume, as indicated by concentric isochrones transitioning from blue to brown. The 200 EASs case exhibited more spatially patchy patterns in both the mean and standard deviation maps, closely resembling the variability observed in individual (non-averaged) optimized simulations.

3.2. Optimization from synthetic activation times

For each geometry, we conducted a simulation of synthetic activation with 5 EASs based on the 1970 Durrer report [14]. A subset of the resulting epicardial activation times served as the input to the Geodesic-BP algorithm using the same paradigm as for the measured epicardial sock activation times, as detailed in Section 2.5. Fig. 6 presents the mean absolute differences for both the epicardial sock and across all the nodes in the heart volume. As with the case derived from the measured values, we observed a general decrease in mean absolute difference with increasing numbers of EASs. In contrast, within the heart volume, we observed a general increase in mean absolute difference with increasing number of EASs. Notably, Geometry D, Run 0 with 200 EASs yielded the lowest mean absolute difference (0.13 ms) on the epicardial sock, while Geometry D, Run 9 with 5 EASs exhibited the highest (2.81 ms).

Fig. 7 presents the synthetic ground truth, optimized simulation, and corresponding difference maps for the best- and worst-performing optimizations based on the epicardial sock activation times: Geometry D, Run 0 with 200 EASs (minimum average absolute difference across the epicardial sock) and Geometry D, Run 9 with 5 EASs (maximum average absolute difference across the epicardial sock), respectively. Results are shown from both anterior and posterior views of the epicardial surface. Even in the best-performing optimization, the synthetic ground truth activation pattern is more spatially coherent and less patchy compared to either optimized result, which, in fact, more closely resembles each other than they do the ground truth. Both display similar regions of late activation (brown) across the epicardial surface and coarsely resemble the patterns of the ground truth case. Intramural activation patterns reveal a similar trend to that observed from the measured intramural needles, *i.e.*, that neither case performs well, but that better epicardial sock agreement is paired with worse intramural fit. These patterns are further reflected in the difference maps, where there was increased error (blue) on the endocardium, including the endocardial surface and throughout the septum. For the best-performing case, absolute differences were higher (up to 51 ms) than for the worst-performing case (40 ms).

Fig. 8 illustrates the spatial distribution of initiation sites on Geometry D for the best- and worst-performing run optimizations initialized with 5, 50, 100, and 200 EASs. In the 5-EAS case, the best-performing run had two early stimuli (approximately 0 ms, shown in pink), while

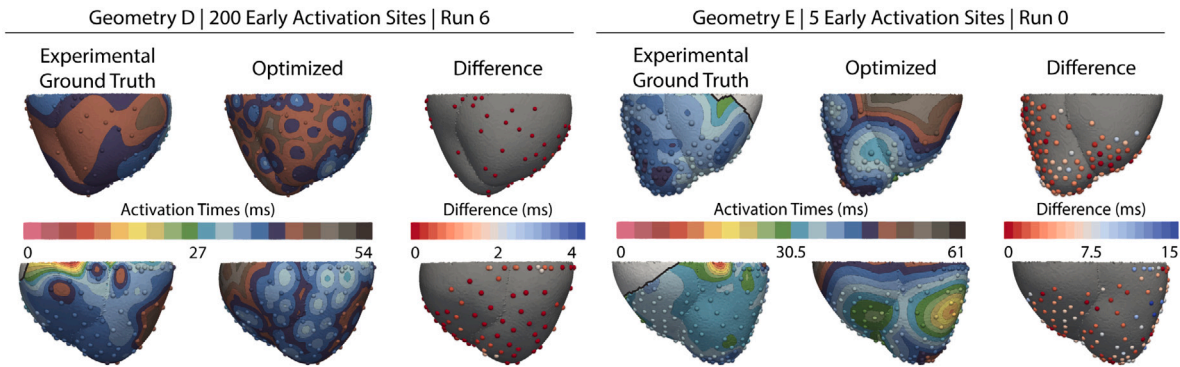


Fig. 3. Epicardial surface activation maps and corresponding difference maps for the best-performing (Geometry D, Run 6 with 200 EASs) and worst-performing (Geometry E, Run 0 with 5 EASs) optimizations. The best and worst performances correspond to the minimum and maximum mean absolute differences on the epicardial sock. The columns show, from left to right: the experimental ground truth, the optimized simulation, and the absolute differences in activation times between experimental and optimized cases. The first and second rows display posterior and anterior views of the epicardial surface, respectively. Spheres indicate the locations of the sock epicardial electrodes and are colored according to either activation time or absolute difference in activation time, depending on the column. Activation time color bars range from 0–54 ms for the best case and 0–61 ms for the worst case. The color bars for absolute differences ranged from 0–4 ms for the best case and 0–15 ms for the worst case.

the worst-performing run had only one. The remaining sites in both cases activated around 15 ms, deviating from the prescribed 0 ms onset of the ground truth configuration we imposed. In the best-performing run, three sites were located on the subendocardial surface, whereas in the worst-performing run, only one site was subendocardial and one was even positioned on the epicardial surface. Both the best- and worst-performing runs represent a departure from the expected subendocardial confinement of EASs. As the number of EASs increased, the stimulus initiation times became more temporally dispersed and spatially distributed throughout the myocardium. In some cases, the earliest stimulus was delayed until approximately 20 ms, significantly later than the 0 ms onset prescribed in the synthetic ground truth simulation.

Fig. 9 summarizes the mean activation times and corresponding standard deviations across 10 optimization runs for Geometry D, comparing optimizations initialized with 5 and 200 EASs. For both the 5 and 200 EASs, the maximum activation time was 53 ms. However, activation times throughout the myocardium were generally lower in the 5 EASs case, as indicated by increased regions of blue and green, while the 200 EASs case displays more widespread late activation (browns). In terms of variability, the 5 EASs case showed a larger maximum standard deviation (12 ms) than the 200 EASs case (7 ms). For both EAS setups, regions of elevated variability were localized primarily on the endocardial surface. The 200 EASs case exhibited more spatially patchy patterns in both the mean and standard deviation maps, closely resembling the variability observed in individual (non-averaged) optimized simulations.

Table 3 summarizes the minimum, maximum, and average intra-cluster distances for each cluster across all geometries. Geometry D exhibited the smallest intra-cluster distance (0.3 mm), while Geometry E exhibits the largest intra-cluster distance (36.6 mm). Across all geometries, the average distances ranged from 7.8 mm (Geometry C) to 12.8 mm (Geometry D). Fig. 10 shows the distributions of stimulus start times for each geometry. Across all geometries, the 200 EASs optimization setup consistently resulted in later stimulus start times compared to the 5 EASs setup.

4. Discussion

In this study, we deployed a novel modified Geodesic-BP method [16,18] to optimize the earliest sites of ventricular activation from high-resolution epicardial sock activation data collected during normal sinus rhythm in five porcine experiments [44]. We evaluated the model’s capacity to reconstruct activation beyond the epicardial surface, comparing recovered volumetric activation times with intramural

Table 3
Minimum, maximum, and mean intra-cluster distances (in mm) across all five geometries (A–E). Values represent the spatial spread of clustered stimulus points across 10 optimization runs per geometry when using five initiation sites.

Distance (mm)	Geom. A	Geom. B	Geom. C	Geom. D	Geom. E
Minimum	0.4	0.3	0.3	0.3	0.6
Maximum	28.6	20.8	30.3	33.4	36.6
Mean	9.3	7.8	7.8	12.8	11.8

needle electrode recordings withheld from the optimization process. We also tested the algorithm’s ability to recover activation patterns from synthetic epicardial sock data generated from 5 EASs placed along known HPS fascicles [14]. The motivation for this study was twofold. First, there is the profound paucity of knowledge regarding the anatomical and physiological details of the HPS, particularly its variability across subjects, where EAS serves as a functional replacement for the PMJs in the context of personalized CDTs [5–7,45,46]. Second, inverse optimization methods face a fundamental limitation that multiple optimized HPS configurations can produce nearly indistinguishable activation patterns, rendering the inverse problem under-determined in cardiac electrophysiology and complicating personalization [10,16]. Validation is therefore critical to ensure reliability when deploying CDTs for clinical application and use. Overall, this methodology integrated computational modeling [26] with *in situ* and synthetic electrical recordings to explore a strategy that replaces explicit modeling of inaccessible details of the HPS with a functional equivalent suitable for eventual clinical translation.

Our key findings from this study are as follows: first, we found that the optimization process using the Geodesic-BP efficiently reproduced the ventricular activation sequence on the epicardial surface from activation times sampled at 111–218 locations on an epicardial sock with modest fidelity (maximum mean absolute difference of 3.9 ms). However, the complex activation patterns lacked physiological realism, with excessive simultaneous breakthroughs beyond what occurs in the heart, likely due to missing regularization or physiological constraints in the optimization. Note that the known physiology of HPS structures in humans lends itself to tighter physiological constraints than in porcine data, as discussed later in the limitations. More critically, our optimization failed to simultaneously recover both epicardial activation patterns and intramural needle activation timings (Figs. 3 and 7). There are several putative explanations for this poor performance, especially unavoidable geometric errors (see Section 4.1), rather than inherent limitations of the optimization method itself.

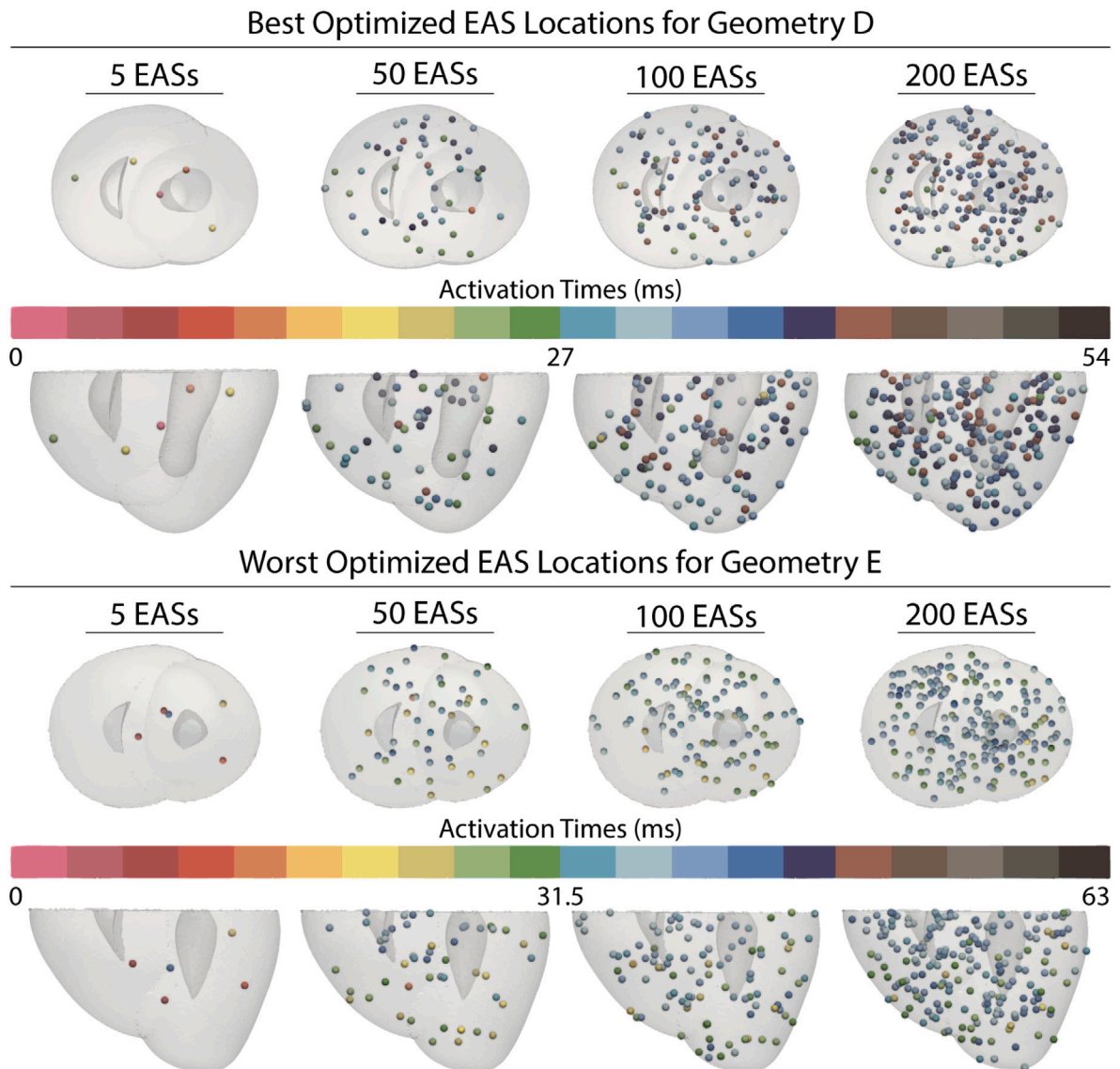


Fig. 4. Optimized initiation and acceleration sites for experimental activation times. The top row shows the runs with the best-performing (minimum mean absolute difference on the epicardial sock) optimized EAS locations on Geometry D, while the bottom row shows the runs with the worst-performing (maximum mean absolute difference on the epicardial sock) optimized EAS locations on Geometry E, each selected from initializations with 5, 50, 100, and 200 EASs. In each panel, color-coded spheres indicate the optimized stimulus (EAS) sites, with color representing activation start time. The top and bottom rows display basal and anterior views of the myocardium, respectively, both shown as transparent volumes. Activation times ranged from 0–54 ms in the best-performing run and 0–63 ms in the worst-performing run, as indicated by the color bar.

The second notable finding is that increasing the number of EASs used to seed the optimization only marginally improved errors in epicardial sock predictions, while producing activation sequences that lacked physiological realism, a likely sign of overfitting (Figs. 3 and 7. In contrast, optimizing from fewer EAS seed points resulted in highly variable outcomes, which diminished the reliability of the inference (Table 3). A further source of concern was the substantial variability that occurred across the 10 different optimized runs with randomized initialization in the synthetic dataset. These observations highlight critical limitations and trade-offs associated with this optimization approach, underscoring the need for physiology-based constraints on the number and location of EASs, as well as the smoothness of cardiac activation patterns.

Across all five geometries, the optimized simulations coarsely reproduced the global epicardial activation patterns observed in the ground truth experimental and synthetic epicardial maps, as shown in Figs. 3 and 7. For example, in Fig. 7 (Geometry D, Run 0 with 200 EASs,

top panel), both the synthetic ground truth and optimized simulations display regions of late activation (>42 ms, colored in shades of brown) near the posterior basal and anterior apical left ventricle, as well as the posterior apical and anterior basal right ventricle. Regions of mid-activation (30 ms, colored in shades of blue) appear near the posterior basal and anterior apical ventricular junctions, with central zones of even earlier activation (25 ms, shown in green) nested within. Overall, both the anterior and posterior epicardial surfaces show consistent wavefront propagation patterns, and the reconstructed epicardial activation sequences effectively captured the main features of ventricular depolarization. These findings suggest that epicardial activation data alone can provide sufficient information to personalize epicardial activation based on the placement and timing of EAS using a simplified eikonal model of propagation. However, the optimizer is not explicitly constrained, meaning it may place EASs in locations that could directly reproduce the epicardial pattern.

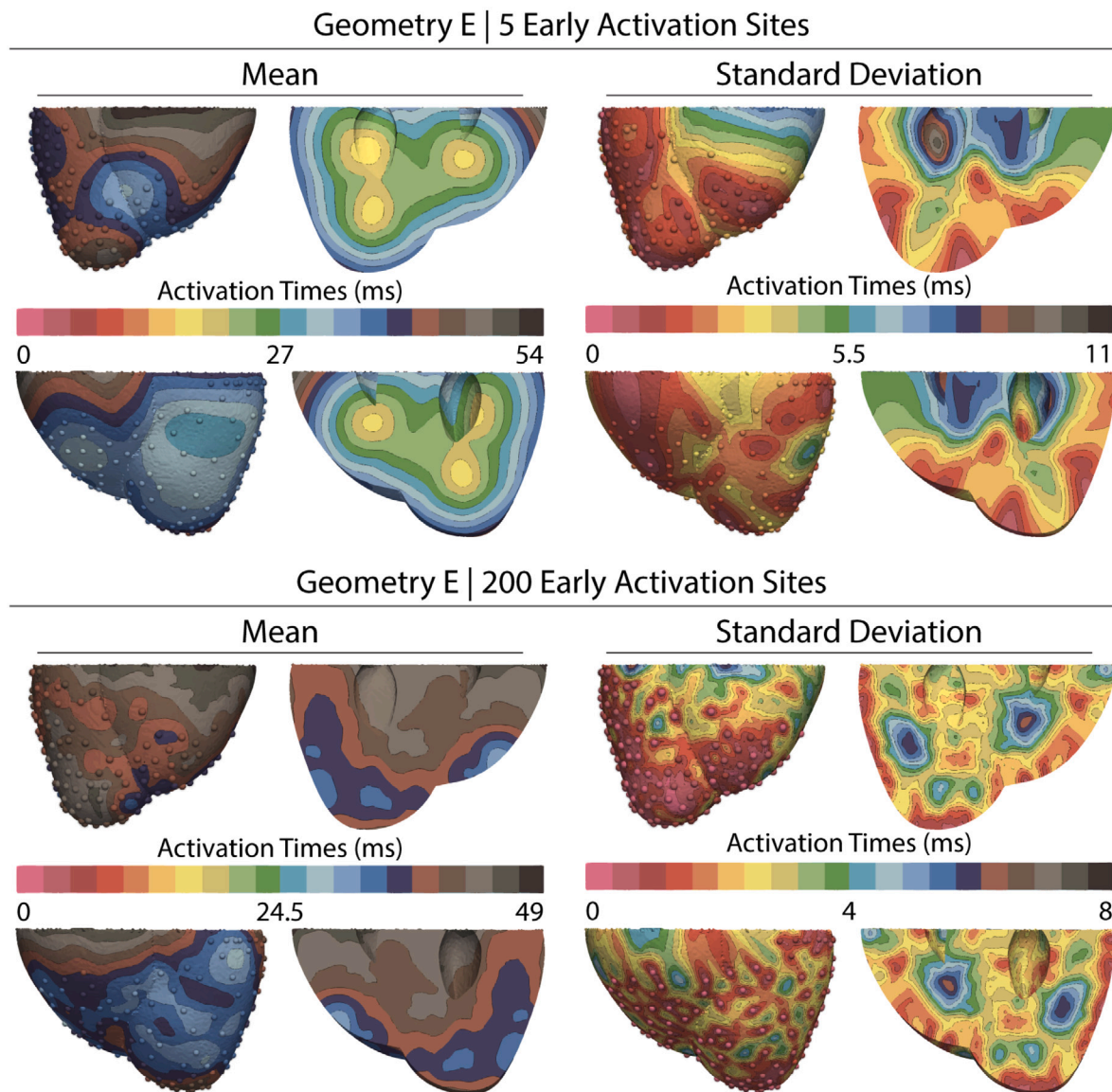


Fig. 5. Epicardial and intramural maps of mean activation times and corresponding standard deviations for Geometry E. The top panel shows results for 5 EASs, and the bottom panel shows results for 200 EASs. In each panel, the first row presents the posterior view, and the second row presents the anterior view. Columns from left to right display: (1) mean activation times on the epicardial surface, (2) mean activation times on an intramural cut plane, (3) standard deviations on the epicardial surface, and (4) standard deviations on the cut plane. The color of the spheres corresponds to the mean activation time in the first and second columns, and to the standard deviation in the third and fourth columns, matching the corresponding epicardial sock recordings. For 5 EASs, mean activation times range from 0–54 ms and standard deviations range from 0–11 ms. For 200 EASs, mean activation times ranged from 0–49 ms and standard deviations from 0–8 ms.

The optimization results were much less convincing when viewed from the context of intramural activation, *e.g.*, throughout the myocardium. Examples of these inadequacies include Figs. 3 and 7. In some geometries, such as Geometry D, Run 0 with 200 EASs, the absolute differences between the optimized simulation and the synthetic ground truth intramural activation times exceeded 50 ms, as shown in Fig. 7. These differences are clinically and experimentally relevant, as they may obscure conduction abnormalities or misrepresent the spatial extent of early activation zones. Another example of the discrepancy between the epicardial and intramural optimization results arose with Geometry E, Run 0, with 5 EASs, exhibiting the highest error on the epicardial sock while simultaneously achieving the lowest error on the intramural needles. We also see the opposite trend, where the lowest error on the epicardial sock simultaneously resulted in the highest error on the intramural needles.

When comparing optimization results seeded at 5 and 200 locations in the cases of fully synthetic activations initiated from 5 defined locations, the 200 EASs setup created a closer match at the epicardium despite the fact that the synthetic ground truth incorporated only 5 stimulus sites. For instance, in Geometry D, the 5 EASs optimization yielded a maximum mean absolute difference of 2.81 ms on the epicardium. In contrast, 200 EASs reduced this error to 0.33 ms. However, the larger value of activation times of many of the inferred EASs showed that the additional locations did not act as initiation sites, but rather as acceleration points to help the optimized simulation better fit the observed data, as shown in Figs. 8, and 10. This finding raises the possibility that the optimization process may not be identifying physiologically plausible early activation sites, but instead is introducing non-physiological patch-like stimuli to locally reduce the error. Such behavior suggests that the current formulation may be overfitting the data rather than accurately recovering the underlying physiological

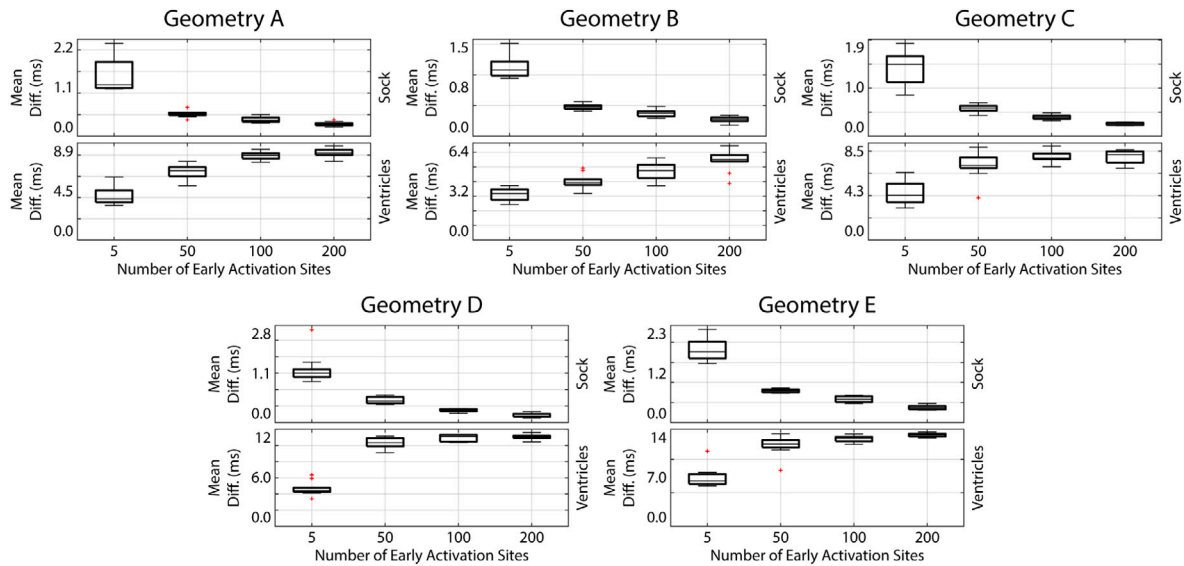


Fig. 6. Box plots of mean absolute differences. Mean absolute differences between optimized and synthetic activation times are shown for measurements from the epicardial socks (top) and for the ventricles (bottom) across five different experiments. The x-axis indicates the number of optimized EASs (5, 50, 100, and 200); note that the number of ground truth EAS remains constant.

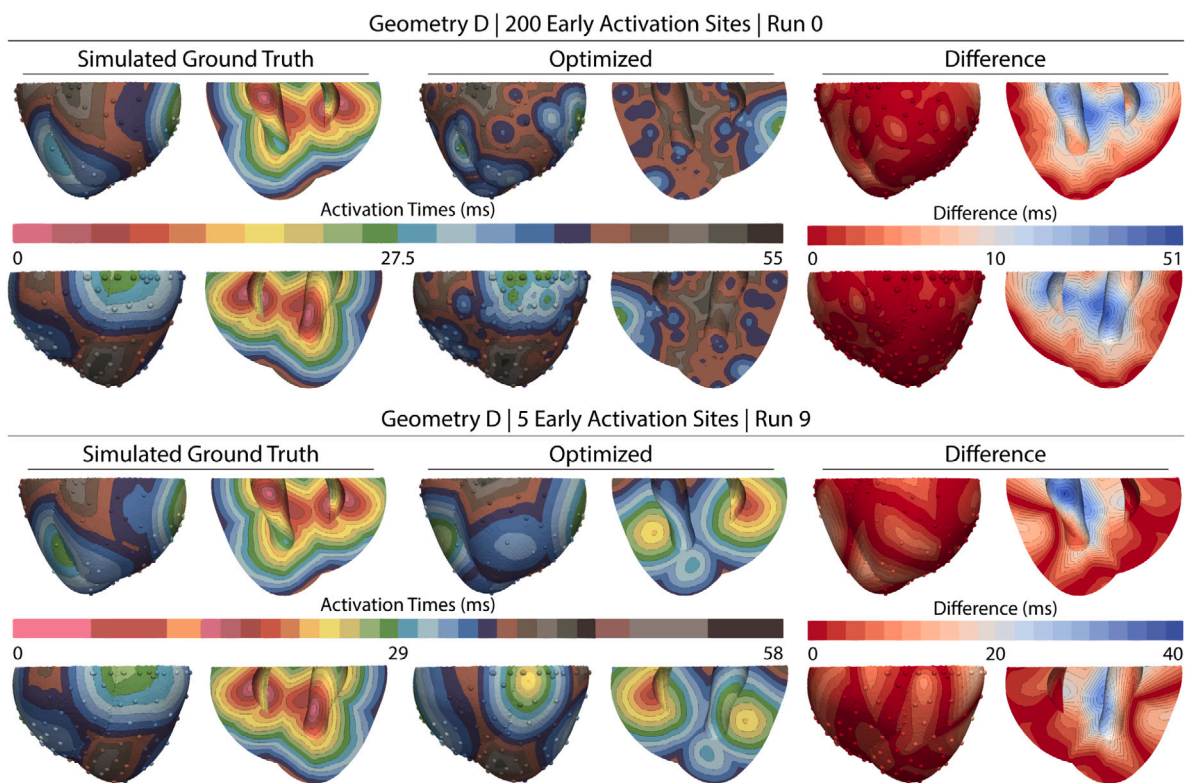


Fig. 7. Ventricular activation maps and corresponding difference maps for the best-performing (Geometry D, Run 0 with 200 EASs) and worst-performing (Geometry D, Run 9 with 5 EASs) optimizations. The best and worst performances correspond to the minimum and maximum mean absolute differences on the epicardial sock. The columns show, from left to right: the synthetic ground truth on the epicardium (column 1) and intramurally (column 2), the optimized simulation on the epicardium (column 3) and intramurally (column 4), and the absolute differences between synthetic and optimized activation times on the epicardium (column 5) and intramurally (column 6). The first and second rows display posterior and anterior views of the epicardial surface, respectively. Spheres indicate the locations of the sock epicardial electrodes and are colored according to either activation time or absolute difference in activation time, depending on the column. Activation time color bars range from 0–55 ms for the best case and 0–58 ms for the worst case. Color bars for absolute differences ranged from 0–51 ms for the best case and 0–40 ms for the worst case.

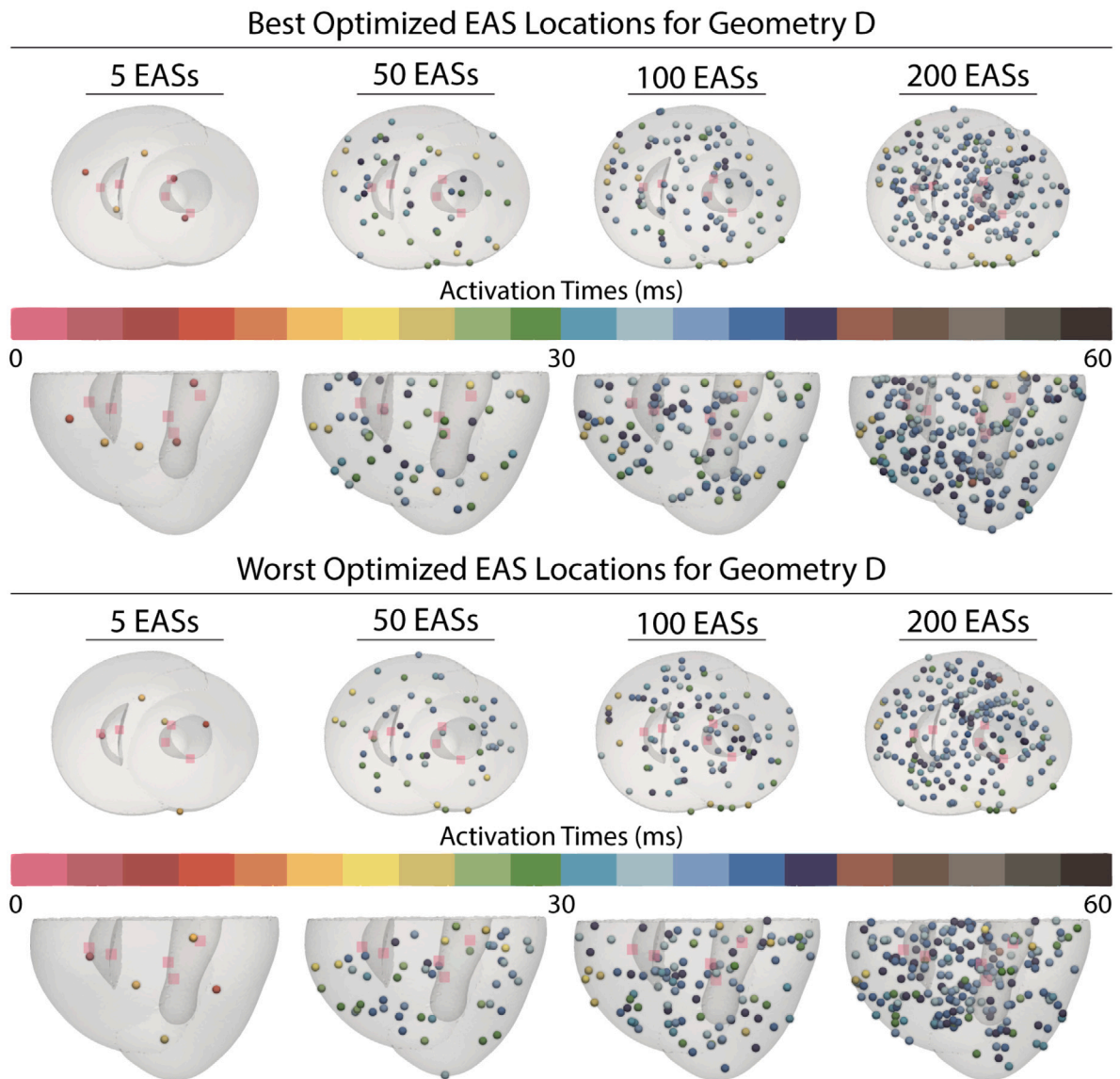


Fig. 8. Optimized initiation and acceleration sites for synthetic activation times. The top row shows the runs with the best-performing (minimum mean absolute difference on the epicardial sock) optimized EAS locations and the bottom row shows the runs with the worst-performing (maximum mean absolute difference on the epicardial sock) optimized EAS locations on Geometry D, each selected from initializations with 5, 50, 100, and 200 EASs. In each panel, color-coded spheres indicate the optimized stimulus (EAS) sites, with color representing activation time. Additionally, color-coded cubes indicate the Durrer ground truth stimulus sites, with color representing activation time (all sites are pink, 0 ms). The top and bottom rows display basal and anterior views of the myocardium, respectively, both shown as transparent volumes. Activation times ranged from 0–60 ms, as indicated by the color bar.

activation pattern. Introducing a constraint that penalizes increases in stimulus start times would discourage reliance on acceleration sites and encourage the optimization to accurately identify the early activation sites.

Furthermore, the 5 EASs setups show substantial variability across the different optimized runs, which were initiated from random initial guesses. As shown in Table 3, the maximum distance between corresponding optimized points can reach up to 36.6 mm, a clinically significant difference. While the mesh resolution (700 μm) may contribute to the minimum observed variability, the overall variability is substantial, suggesting that mesh generation has minimal impact on these results. We would also expect variability in the specific locations of the 200 EASs across different optimization runs, even if the resulting activation times are less variable. However, a consistent point-by-point comparison across such a large number of sites was not feasible.

Moreover, in Figs. 5 and 9, there were standard deviations of the activation sequence up to 12 ms throughout the myocardium for the

5 EASs setup and 7 ms for 200 EASs setup. This level of variability suggests that the optimization algorithm may struggle to consistently converge on similar solutions, especially with a lower number of EASs. This inconsistency may arise from the deterministic nature of the optimization algorithm used in Geodesic-BP, which relies on local gradient-based search strategies and is sensitive to initial guesses. Such methods can converge to different local minima across runs, particularly when the number of early activation sites (EASs) is small relative to the complexity of the ventricular activation landscape, which is highly non-convex and spatially heterogeneous.

Overall, these findings highlight the importance of incorporating intramural validation data when evaluating model performance, particularly in the context of CDTs intended for diagnostic or therapeutic applications. While epicardial or intramural activation values may appear accurate in isolation, there is no guarantee of fidelity across the ventricles as a whole, nor a unique mapping between epicardial

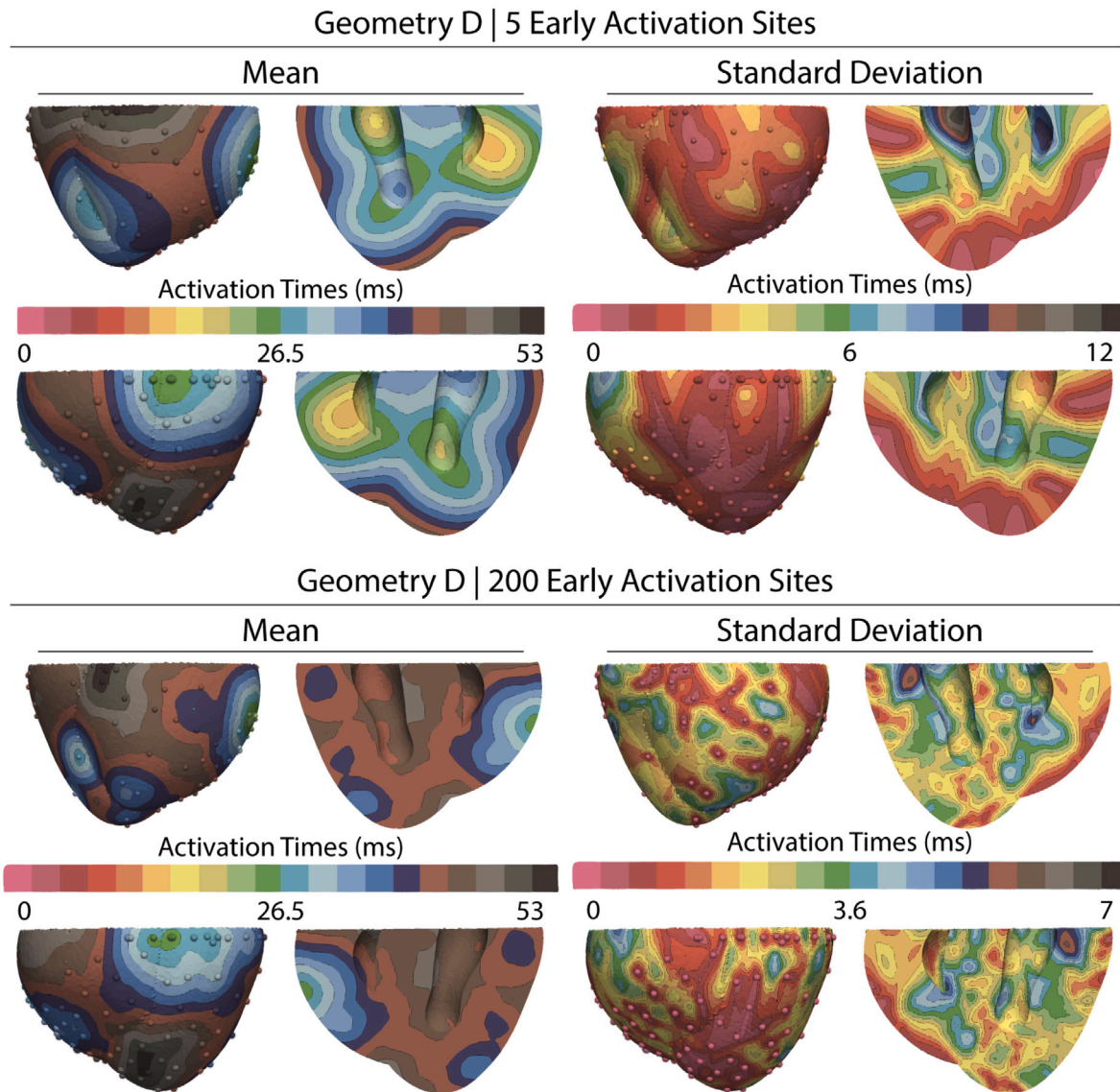


Fig. 9. Epicardial surface and intramural maps of mean activation times and corresponding standard deviations for Geometry D. The top panel shows results for 5 EAS, and the bottom panel shows results for 200 EASs. In each panel, the first row presents the posterior view, and the second row presents the anterior view. Columns from left to right display: (1) mean activation times on the epicardial surface, (2) mean activation times on an intramural cut plane, (3) standard deviations on the epicardial surface, and (4) standard deviations on the cut plane. The color of the spheres corresponds to the mean activation time in the first and second columns, and to the standard deviation in the third and fourth columns, matching the corresponding epicardial sock recordings. For the 5 EASs case, mean activation times range from 0–53 ms and standard deviations range from 0–12 ms. For the 200 EASs case, mean activation times ranged from 0–53 ms and standard deviations from 0–7 ms.

and intramyocardial activation. There are fundamental limitations in surface mapping techniques that prevent the revelation of myocardial events that generate them. Such a lack of uniqueness reveals the need to apply great care when extracting deeper meaning from superficial mapping data, whether measured or estimated using ECGI methods. For diagnosing conduction behaviors that occur within the subepicardium, the accuracy of the epicardial approach may be sufficient. However, for applications requiring detailed whole-heart conduction modeling, such as arrhythmia risk assessment or localization of premature ventricular contractions, validation must extend throughout the entire myocardium, not just on the epicardium or endocardium where data are typically available. Our results show that while epicardial activation can be accurately matched, significant discrepancies can remain intramurally, highlighting the necessity of full volumetric validation.

4.1. Limitations

The presented implementation of the Geodesic-BP method performs limited optimization of EASs underlying the ventricular activation sequences stemming from the HPS. While EASs and corresponding activation times were adjusted, the underlying topology of the HPS was not explicitly modeled or constrained, which may limit the physiological realism of the inferred activation sequences under pacing conditions. In particular, Purkinje-myocardium junctions were not explicitly modeled, restricting our ability to assess their interactions with the surrounding myocardium. Previous studies have either reconstructed HPS structures from EASs obtained via endocardial mapping [47] or performed simultaneous optimization of a physiologically detailed HPS [21,48], highlighting alternative approaches for capturing these effects.

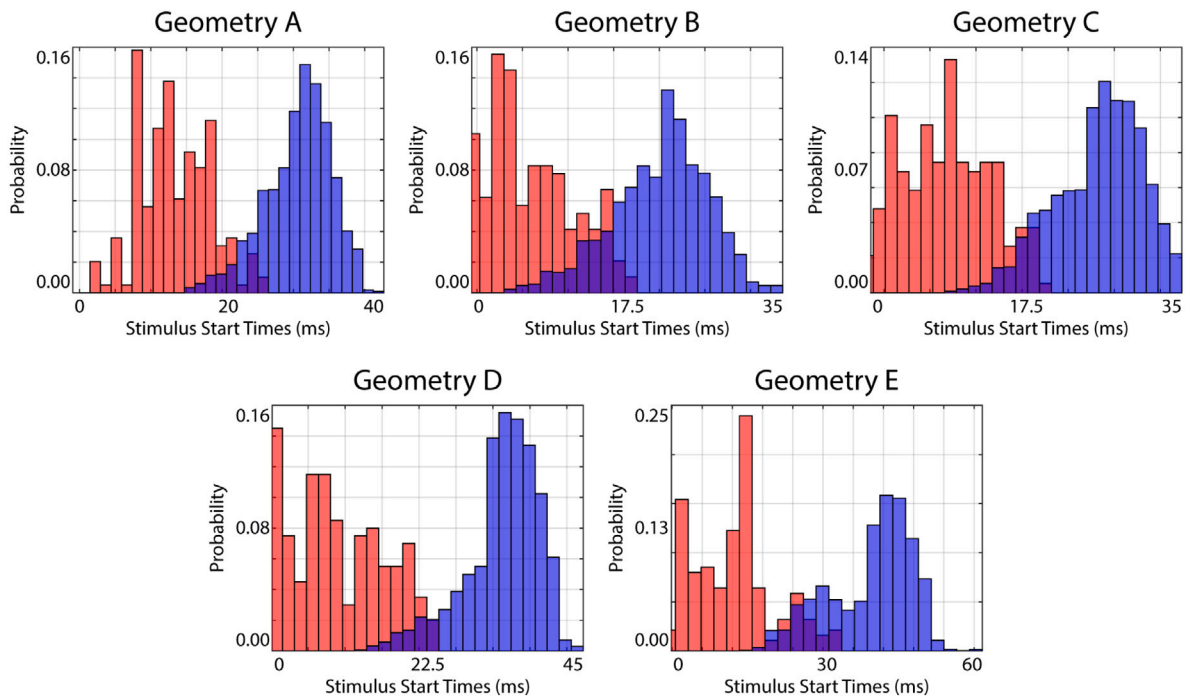


Fig. 10. Histograms of stimulus start times for Geometries A–E. Each panel displays the distribution of start times across 10 optimization runs for a given geometry. Red bars correspond to the 5 EASs optimization setup, and blue bars correspond to the 200 EASs optimization setup.

Our models assumed a homogeneous conductivity tensor, which may obscure more complex, regionally variable activation patterns. Although the synthetic dataset was set to match the conduction velocity used in the optimization, accurately measuring conduction velocity in experimental data is challenging, especially across the full volumetric myocardial wall [23–25,37]. We used values from previous studies with the same setup, but did not implement region- or patient-specific velocities [23]. Our analysis focuses on relative activation patterns and differences across conditions, which are preserved even when conductivity is uniform. Additional information from imaging or electro-anatomical data could be used to reconstruct the anisotropic nature, or by extending Geodesic-BP to optimize the conduction velocity tensor simultaneously [16].

Furthermore, experimental conduction velocities were fixed during inference rather than being optimized alongside EAS locations and timings. Other studies have simultaneously optimized conduction velocities along with EAS locations, which could improve reconstruction accuracy [49–52]. While fixing velocities could contribute to the observed inaccuracies in experimental intramural activation patterns, similar discrepancies were also seen in the synthetic dataset, where conduction velocities were identical to the assumed model, indicating that other factors, such as the number of EASs or the ill-posed nature of the optimization, also play a role. Future work could incorporate conduction velocity optimization to further enhance intramural reconstruction and improve the physiological plausibility of inferred activation sequences.

Furthermore, our underlying eikonal model did not allow for capturing complex propagation dynamics such as re-entrant circuits or multiple interacting wavefronts, despite performing well under near-normal conditions. These phenomena involve intricate interactions between wavefronts, tissue heterogeneities, and refractory properties [53], which are currently not represented. Capturing them would require more detailed biophysical models, such as reaction-diffusion models that incorporate curvature-dependent conduction, recovery dynamics, and potentially patient- or region-specific tissue properties. Reaction-diffusion models are not ideal for optimization due to their high computational cost. However, eikonal-based solvers capable

of capturing re-entrant behavior more closely resembling reaction-diffusion models have recently been developed [54]. As such, our conclusions are most applicable to scenarios where activation remains relatively organized and may not generalize to highly arrhythmic or structurally abnormal hearts.

To inform and validate our computational framework, we employed porcine heart models, which offer valuable anatomical and physiological parallels to the human heart. Prior experimental investigations have characterized the structure and variability of the HPS across species, revealing key differences in the distribution of Purkinje fibers. In pigs, Purkinje fibers extend through the ventricular wall toward the epicardium [55–57], whereas in humans, the network is largely confined to the endocardium [8,55,58]. This anatomical distinction, which could be encoded as physiological constraints under optimization, such as the location and stimulus times of the EAS, underscores the need for caution when extrapolating findings from porcine models to human applications.

In the experimental setup, several sources of geometric error could have affected the accuracy of the resulting early activation predictions. First, because these experiments involved beating hearts, the epicardial sock electrodes could shift position, sometimes by as much as 25 mm, and needle electrodes might be pushed outward. Second, by the end of the experiment, the arrested heart often became severely deformed, generating substantial errors in the measurements of electrode position, a problem only exacerbated by the fixation process that preceded *ex vivo* imaging. Finally, registration errors between the electrode arrays (epicardial sock and intramural needles) and the image-based anatomical geometries introduced further distortions that could result in spatial inaccuracies in the activation maps. Although we took extreme care to minimize these sources of error (see 2.1.2), even small misalignments can compromise the spatial fidelity of the resulting activation maps, particularly in the context of an ill-conditioned inverse problem. Such inaccuracies may lead to local discrepancies between recorded and optimized activation patterns, especially in regions with dense electrode coverage or steep activation gradients. Additionally, geometric errors can distort the inferred stimulus locations and timing, potentially influencing both mean activation times and variability across optimization runs. Future work incorporating revised experimental methods

to preserve heart shape and improved registration techniques – such as image-guided electrode localization or more robust landmark-based alignment methods – could help reduce these errors and improve model accuracy.

4.2. Conclusion

Taken together, these results indicate a persistent challenge in the broader efforts of applying digital twin and ECGI approaches to replicate early activation in specific subjects [26,59]. While the inference method was capable of achieving some agreement with epicardial-level signals, the resulting myocardial activations were highly unphysiological and erroneous. Hence, a significant gap remains in adapting the underlying mechanisms driving this method to the conditions in the heart. We have illustrated two different novel forms of validation that can be applied to further approaches to this highly relevant problem if digital twin methods are to become clinically useful. Possible improvements to this method should include setting physiological constraints on the EASs and then exploring the necessary hyperparameters involved, potentially through uncertainty quantification.

CRediT authorship contribution statement

Lindsay C.R. Tanner: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anna Busatto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Thomas Grandits:** Writing – review & editing, Software, Resources, Methodology, Data curation, Conceptualization. **Jake A. Bergquist:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Brian Zenger:** Writing – review & editing, Data curation. **Simone Pezzuto:** Writing – review & editing, Resources, Data curation, Conceptualization. **Gernot Plank:** Writing – review & editing, Validation, Software, Methodology. **Rob S. MacLeod:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Karli Gillette:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics statement

All animal procedures were approved by the University of Utah Institutional Animal Care and Use Committee (protocol #20-11001, approved 11/23/2020) and were conducted in accordance with the Guide for the Care and Use of Laboratory Animals. No human subjects were involved in this research; therefore, informed consent and related ethical approvals were not required.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used Microsoft Copilot and ChatGPT in order to improve the readability and language of the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Funding

The research leading to these results received funding from the National Institutes of Health, United States under grant agreements P41 GM103545, R24 GM136986, T32 HL007576, and U24EB029012, the National Science Foundation Graduate Research Fellowship Program, the Austrian Science Fund, Austria (ESP 592), and the Nora Eccles Harrison Foundation for Cardiovascular Research.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rob MacLeod reports financial support was provided by National Institutes of Health. Rob MacLeod reports financial support was provided by Nora Eccles Harrison Foundation for Cardiovascular Research. Jake Bergquist reports financial support was provided by National Institutes of Health. Lindsay Tanner reports financial support was provided by National Science Foundation. Karli Gillette reports financial support was provided by Austrian Science Fund. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Computational support for this research came from the Center for Integrative Biomedical Computing (www.sci.utah.edu/cibc).

Data availability

The experimental and simulated data that support the findings of this study are not publicly available, but are available from the corresponding author upon reasonable request.

References

- [1] P. Bhagirath, M. Strocchi, M.J. Bishop, P.M. Boyle, G. Plank, From bits to bedside: entering the age of digital twins in cardiac electrophysiology, *Europace* 26 (12) (2024) euae295.
- [2] G. Coorey, G.A. Figtree, D.F. Fletcher, V.J. Snelson, S.T. Vernon, D. Winlaw, S.M. Grieve, A. McEwan, J.Y.H. Yang, P. Qian, et al., The health digital twin to tackle cardiovascular disease—a review of an emerging interdisciplinary field, *NPJ Digit. Med.* 5 (1) (2022) 1–12.
- [3] J. Corral-Acero, F. Margara, M. Marciniak, C. Rodero, F. Loncaric, Y. Feng, A. Gilbert, J.F. Fernandes, H.A. Bukhari, A. Wajdan, M.V. Martinez, M.S. Santos, M. Shamohammedi, H. Luo, P. Westphal, P. Leeson, P. DiAchille, V. Gurev, M. Mayr, L. Geris, P. Pathmanathan, T. Morrison, R. Cornelussen, F. Prinzen, T. Delhaas, A. Doltra, M. Sitges, E.J. Vigmond, E. Zacur, V. Grau, B. Rodriguez, E.W. Remme, S. Niederer, P. Mortier, K. McLeod, M. Potse, E. Pueyo, A. Bueno-Orovio, P. Lamata, The “Digital Twin” to enable the vision of precision cardiology, *Eur. Heart J.* 41 (48) (2020) 4556–4564.
- [4] M.J. Cluitmans, G. Plank, J. Heijman, Digital twins for cardiac electrophysiology: state of the art and future challenges, *Herzschrittmachertherapie+ Elektrophysiologie* 35 (2) (2024) 118–123.
- [5] R.J. Myerburg, K. Nilsson, H. GELBAND, Physiology of canine intraventricular conduction and endocardial excitation, *Circ. Res.* 30 (2) (1972) 217–243.
- [6] C. Ramanathan, P. Jia, R. Ghanem, K. Ryu, Y. Rudy, Activation and repolarization of the normal human heart under complete physiological conditions, *Proc. Natl. Acad. Sci. USA* 103 (16) (2006) 6309–6314.
- [7] A. Atkinson, S. Inada, J. Li, J.O. Tellez, J. Yanni, R. Sleiman, E. Abd Allah, R.H. Anderson, H. Zhang, M.R. Boyett, et al., Anatomical and molecular mapping of the left and right ventricular his–purkinje conduction networks, *J. Mol. Cell. Cardiol.* 51 (5) (2011) 689–701.
- [8] E.J. Vigmond, B.D. Stuyvers, Modeling our understanding of the His-Purkinje system, *Recent Developments in Biophysics & Molecular Biology of Heart Rhythm*, *Prog. Biophys. Mol. Biol.* 120 (1) (2016) 179–188.
- [9] M.M. Scheinman, Role of the His-Purkinje system in the genesis of cardiac arrhythmia, *Hear. Rhythm.* 6 (7) (2009) 1050–1058.
- [10] L. Li, J. Camps, B. Rodriguez, V. Grau, Solving the Inverse Problem of Electrocardiography for Cardiac Digital Twins: A Survey, 2024, arXiv preprint [arXiv:2406.11445](https://arxiv.org/abs/2406.11445).
- [11] C.M. Costa, A. Neic, K. Gillette, B. Porter, J. Gould, B. Sidhu, Z. Chen, M. Elliott, V. Mehta, G. Plank, C.A. Rinaldi, M.J. Bishop, S.A. Niederer, Left ventricular endocardial pacing is less arrhythmogenic than conventional epicardial pacing when pacing in proximity to scar, *Hear. Rhythm.* 17 (8) (2020) 1262–1270.
- [12] C. Mendonca Costa, P. Gemmell, M.K. Elliott, J. Whitaker, F.O. Campos, M. Strocchi, A. Neic, K. Gillette, E. Vigmond, G. Plank, R. Razavi, M. O'Neill, C.A. Rinaldi, M.J. Bishop, Determining anatomical and electrophysiological detail requirements for computational ventricular models of porcine myocardial infarction, *Comput. Biol. Med.* 141 (2022) 105061.

- [13] A. Pullan, L. Cheng, M. Nash, D. Brooks, A. Ghodrati, R. MacLeod, The inverse problem of electrocardiography, in: P. Macfarlane, A. van Oosterom, O. Pahlm, P. Kligfield, M. Janse, J. Camm (Eds.), *Comprehensive Electrocardiology*, Springer Verlag, London, UK, 2010, pp. 299–344.
- [14] D. Durrer, R. van Dam, G. Freud, M. Janse, F. Meijler, R. Arzbaecher, Total excitation of the isolated human heart, *Circ.* 41 (1970) 899–912.
- [15] F.S. Costabal, D.E. Hurtado, E. Kuhl, Generating Purkinje networks in the human heart, *J. Biomech.* 49 (12) (2016) 2455–2465.
- [16] T. Grandits, K. Gillette, G. Plank, S. Pezzuto, Accurate and efficient cardiac digital twin from surface ECGs: Insights into identifiability of ventricular conduction system, *Med. Image Anal.* (2025) 103641.
- [17] M.J. Boonstra, R.W. Roudijk, R. Brummel, W. Kassenberg, L.J. Blom, T.F. Oostendorp, A.S.J.M. Te Riele, J.F. van der Heijden, F.W. Asselbergs, P. Loh, P.M. van Dam, Modeling the His-Purkinje Effect in Non-invasive Estimation of Endocardial and Epicardial Ventricular Activation, *Ann. Biomed. Eng.* 50 (3) (2022) 343–359.
- [18] T. Grandits, K. Gillette, A. Neic, J. Bayer, E. Vigmond, T. Pock, G. Plank, An Inverse Eikonal Method for Identifying Ventricular Activation Sequences from Epicardial Activation Maps, *J. Comput. Phys.* 419 (2020) 109700.
- [19] A. Neic, F.O. Campos, A.J. Prassl, S.A. Niederer, M.J. Bishop, E.J. Vigmond, G. Plank, Efficient computation of electrograms and ECGs in human whole heart simulations using a reaction-eikonal model, *J. Comput. Phys.* 346 (2017) 191–211.
- [20] S. Pezzuto, P. Kal'avský, M. Potse, F.W. Prinzen, A. Auricchio, R. Krause, Evaluation of a Rapid Anisotropic Model for ECG Simulation, *Front. Physiol.* 8 (2017) 265.
- [21] F. Álvarez-Barrientos, M. Salinas-Camus, S. Pezzuto, F.S. Costabal, Probabilistic Validation of the purkinje network from the electrocardiogram, *Med. Image Anal.* (2025) 103460.
- [22] P. Oosterhoff, V.M. Meijborg, P.M. van Dam, P.F. van Dessel, C.N. Belterman, G.J. Streekstra, J.M. de Bakker, R. Coronel, T.F. Oostendorp, Experimental Validation of Noninvasive Epicardial and Endocardial Activation Imaging, *Circ.: Arrhythmia Electrophysiol.* 9 (8) (2016) e004104.
- [23] W. Good, K. Gillette, B. Zenger, J. Bergquist, L. Rupp, J. Tate, D. Anderson, M. Gsell, G. Plank, R. MacLeod, Estimation and validation of cardiac conduction velocity and wavefront reconstruction using epicardial and volumetric data., *IEEE Trans. Biomed. Eng.* 68 (11) (2021) 3290–3300.
- [24] T.I. Wilhelm, T. Lewalter, J. Fischer, J. Reiser, J. Werner, C. Baumgartner, L. Gleirscher, P. Hoppmann, K. Kupatt, K. Tiemann, et al., Electroanatomical conduction characteristics of pig myocardial tissue derived from high-density mapping, *J. Clin. Med.* 12 (17) (2023) 5598.
- [25] A. Lee, R. Denman, H. Haqqani, Ventricular ectopy in the context of left ventricular systolic dysfunction: risk factors and outcomes following catheter ablation, *Hear. Lung Circ.* 28 (3) (2019) 379–388.
- [26] K. Gillette, M.A. Gsell, J. Bouyssier, A.J. Prassl, A. Neic, E.J. Vigmond, G. Plank, Automated framework for the inclusion of a His-Purkinje system in cardiac digital twins of ventricular electrophysiology, *Ann. Biomed. Eng.* 49 (12) (2021) 3143–3153.
- [27] B. Zenger, W. Good, J. Bergquist, B. Burton, J. Tate, L. Berkenbile, V. Sharma, R. MacLeod, Novel experimental model for studying the spatiotemporal electrical signature of acute myocardial ischemia: a translational platform., *J. Physiol. Meas.* 41 (1) (2020) 015002.
- [28] CIBC, Seg3D, 2016, Seg3D: Volumetric Image Segmentation and Visualization. Scientific Computing and Imaging Institute (SCI), Download from: <http://www.seg3d.org>.
- [29] CIBC, 2015, Cleaver: A MultiMaterial Tetrahedral Meshing Library and Application. Scientific Computing and Imaging Institute (SCI), Download from: <http://www.sci.utah.edu/software.html>.
- [30] J. Bayer, A.J. Prassl, A. Pashaei, J.F. Gomez, A. Frontera, A. Neic, G. Plank, E.J. Vigmond, Universal ventricular coordinates: A generic framework for describing position within the heart and transferring data, *Med. Image Ana.* 45 (2018) 83–93.
- [31] D.D. Streeter Jr, H.M. Spotnitz, D.P. Patel, J. Ross Jr, E.H. Sonnenblick, Fiber orientation in the canine left ventricle during diastole and systole, *Circ. Res.* 24 (3) (1969) 339–347.
- [32] H. Lombaert, J.-M. Peyrat, P. Croisille, S. Rapacchi, L. Fanton, F. Chieriet, P. Clarysse, I. Magnin, H. Delingette, N. Ayache, Human atlas of the cardiac fiber architecture: study on a healthy population, *EEE TMI* 31 (7) (2012) 1436–1447.
- [33] J.A. Bergquist, W.W. Good, B. Zenger, J.D. Tate, R.S. MacLeod, GRÖMeR: A pipeline for geodesic refinement of mesh registration, in: *Lecture Notes in Computer Science*, Vol. 11504, Springer Verlag Functional Imaging and Model of the Heart (FIMH), 2019, pp. 37–45.
- [34] A. Neic, M.A. Gsell, E. Karabelas, A.J. Prassl, G. Plank, Automating image-based mesh generation and manipulation tasks in cardiac modeling workflows using meshTool, *SoftwareX* 11 (2020) 100454.
- [35] A. Rodenhauser, W. Good, B. Zenger, J. Tate, K. Aras, B. Burton, R. MacLeod, PFEIFER: Preprocessing framework for electrograms intermittently fiducialized from experimental recordings, *J. Open Source Softw.* 3 (21) (2018) 472.
- [36] G. Plank, A. Loewe, A. Neic, C. Augustin, Y.-L. Huang, M.A. Gsell, E. Karabelas, M. Nothstein, A.J. Prassl, J. Sánchez, G. Seemann, E.J. Vigmond, The open-CARP simulation environment for cardiac electrophysiology, *Comput. Methods Programs Biomed.* 208 (2021) 106223.
- [37] A.G. Kleber, M.J. Janse, F. Wilms-Schopmann, A. Wilde, R. Coronel, Changes in conduction velocity during acute ischemia in ventricular myocardium of the isolated porcine heart., *Circulation* 73 (1) (1986) 189–198.
- [38] D.P. Kingma, J. Ba, Adam: A method for stochastic optimization, 2017, ArXiv.
- [39] P. Dawson-Haggerty, et al., Trimesh, 2019, (Accessed: 01 May 2025) <https://trimesh.org/>.
- [40] M. Potse, Mathematical modeling and simulation of ventricular activation sequences: implications for cardiac resynchronization therapy, *J. Cardiovasc. Transl. Res.* 5 (2) (2012) 146–158.
- [41] J.P. Cranford, T.J. O'Hara, C.T. Villongco, O.M. Hafez, R.C. Blake, J. Loscalzo, J.-L. Fattebert, D.F. Richards, X. Zhang, J.N. Glosli, et al., Efficient computational modeling of human ventricular activation and its electrocardiographic representation: A sensitivity study, *Cardiovasc. Eng. Technol.* 9 (3) (2018) 447–467.
- [42] L. Myklebust, G. Monopoli, G. Balaban, E.W. Aabel, M. Ribe, A.I. Castrini, N.E. Hasselberg, C. Bugge, C. Five, K. Haugaa, et al., Stretch of the papillary insertion triggers reentrant arrhythmia: an in silico patient study, *Front. Physiol.* 15 (2024) 1447938.
- [43] E. Vigmond, R.W. Dos Santos, A. Prassl, M. Deo, G. Plank, Solvers for the cardiac bidomain equations, *Prog. Biophys. Mol. Biol.* 96 (1–3) (2008) 3–18.
- [44] B. Zenger, J.A. Bergquist, A. Busatto, W.W. Good, L.C. Rupp, V. Sharma, R.S. MacLeod, Tipping the scales of understanding: An engineering approach to design and implement whole-body cardiac electrophysiology experimental models, *Front. Physiol.* 14 (2023) 10.
- [45] M.S. Spach, S.-n. Huang, C.R. Ayers, Electrical and anatomic study of the purkinje system of the canine heart, *Am. Heart J.* 65 (5) (1963) 664–673.
- [46] R. Lazzara, N. El-Sherif, B. Befeler, B.J. Scherlag, Regional refractoriness within the ventricular conduction system. An evaluation of the "gate" hypothesis., *Circ. Res.* 39 (2) (1976) 254–262.
- [47] R. Cárdenes, R. Sebastian, D. Soto-Iglesias, A. Berrueto, O. Camara, Estimation of Purkinje trees from electro-anatomical mapping of the left ventricle using minimal cost geodesics, *Med. Imag. Anal.* 24 (1) (2015) 52–62.
- [48] J. Camps, L.A. Berg, Z.J. Wang, R. Sebastian, L.L. Riebel, R. Doste, X. Zhou, R. Sachetto, J. Coleman, B. Lawson, et al., 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 (2024) 103108.
- [49] S. Pezzuto, P. Perdikaris, F.S. Costabal, Learning cardiac activation maps from 12-lead ECG with multi-fidelity Bayesian optimization on manifolds, 10th Vienna International Conference on Mathematical Modelling MATHMOD 2022, IFAC-PapersOnLine 55 (20) (2022) 175–180.
- [50] L. Li, J. Camps, A. Banerjee, M. Beetz, B. Rodriguez, V. Grau, Deep computational model for the inference of ventricular activation properties, in: *International Workshop on Statistical Atlases and Computational Models of the Heart*, Springer, 2022, pp. 369–380.
- [51] T. Grandits, K. Gillette, A. Neic, J. Bayer, E. Vigmond, T. Pock, G. Plank, An inverse Eikonal method for identifying ventricular activation sequences from epicardial activation maps, *J. Comput. Phys.* 419 (2020).
- [52] S. Giffard-Roisin, T. Jackson, L. Fovargue, J. Lee, H. Delingette, R. Razavi, N. Ayache, M. Serresant, Noninvasive personalization of a cardiac electrophysiology model from body surface potential mapping, *IEEE Trans. Biomed. Eng.* 64 (9) (2016) 2206–2218.
- [53] P.M. Boyle, M.J. Murphy, T.V. Karathanos, S. Zahid, R.C. Blake III, N.A. Trayanova, Termination of re-entrant atrial tachycardia via optogenetic stimulation with optimized spatial targeting: insights from computational models, *J. Physiol.* 596 (2) (2018) 181–196.
- [54] C. Barrios Espinosa, J. Sánchez, S. Appel, S. Becker, J. Krauß, P. Martínez Díaz, L. Unger, M. Houillon, A. Loewe, A cyclical fast iterative method for simulating reentries in cardiac electrophysiology using an eikonal-based model, *Eng. Comput.* (2025) 1–24.
- [55] D.J. Dossdall, K.-A. Cheng, J. Huang, J.S. Allison, J.D. Allred, W.M. Smith, R.E. Ideker, Transmural and Endocardial Purkinje Activation in Pigs Preceding Local Myocardial Activation after Defibrillation Shocks, *Hear. Rhythm. : Off. J. Hear. Rhythm. Soc.* 4 (6) (2007) 758–765.
- [56] J. Tranum-Jensen, A.A. Wilde, J.T. Vermeulen, M.J. Janse, Morphology of electrophysiologically identified junctions between Purkinje fibers and ventricular muscle in rabbit and pig hearts., *Circulation* (1991).
- [57] R.L. Hamlin, R.R. Burton, S.D. Leverett, J.W. Burns, Ventricular activation process in minipigs, *J. Electrocardiol.* 8 (2) (1975) 113–116.
- [58] M.C. De Almeida, F. Lopes, P. Fontes, F. Barra, R. Guimaraes, V. Vilhena, Ungulates heart model: a study of the Purkinje network using India ink injection, transparent specimens and computer tomography, *Anat. Sci. Int.* 90 (4) (2015) 240–250.
- [59] J. Sánchez, I. Llorente-Lipe, C.B. Espinosa, A. Loewe, I. Hernández-Romero, J. Vicente-Puig, S. Ros, F. Atienza, A. Carta-Bergaz, A.M. Climent, M.S. Guillem, Enhancing premature ventricular contraction localization through electrocardiographic imaging and cardiac digital twins, *Comput. Biol. Med.* 190 (2025) 109994.