Validation of Intramural Wavefront Reconstruction and Estimation of 3D Conduction Velocity

Wilson W. Good[1], Karli Gillette[2], Jake A. Bergquist[1], Brian Zenger[1], Jess Tate[1], Gernot Plank[2], Rob S. MacLeod [1]

[1] Scientific Computing and Imaging Institute, Biomedical Engineering, University of Utah, Salt Lake City, UT, USA

[2] Institute of Biophysics, Medical University of Graz, Graz, Austria

Abstract

Introduction: *Changes in conduction velocity are indicative of a wide variety of cardiac abnormalities yet measuring conduction velocity is challenging, especially within the myocardial volume. In this study we investigated a novel technique to reconstruct activation fronts and estimate three-dimensional (3D) conduction velocity (CV) from experimental intramural recordings.*

Methods: *Our method is based on irregularly sampled electrograms from within the myocardium, which we capture in experiments using intramural needle electrodes. From the electrograms we reconstruct the activation profile, which we use to compute the gradient of the activation times and a series of streamlines. Onto these streamlines we then map the activation times to estimate 3D conduction velocity along the streamline. To assess the accuracy of our reconstruction techniques, we utilized the CARPentry simulation platform, which calculated the activation times throughout the region sampled by the intramural needles. We then compared our simulated activation times to those we reconstructed. We also used CARPentry's simulations to validate our estimation of 3D CV.*

Results: *The reconstructed activation times agreed closely with simulated values, with an average RMSE of* $0.65ms$ *and* 89% *percent of the volume with errors* $< 1ms$*. We found close agreement between the CVs calculated using reconstructed versus simulated activation times. Across the reconstructed stimulations sites we saw an average CV of* $459cm/s$ *with a standard deviation of* $131cm/s$ *versus* $435cm/s$ *with a standard deviation of* $132cm/s$ *with simulated data.*

Discussion: *This study used simulated datasets to validate our methods for reconstructing 3D activation fronts and estimating conduction velocities. Our results indicate that our method allows accurate reconstructions from sparse measurements, thus allowing us to examine changes in activation induced by experimental interventions such as acute ischemia, ectopic pacing, or drugs.*

1. Introduction

Changes in conduction velocity are indicative of a wide variety of cardiac abnormalities yet measuring conduction velocity is challenging, especially within the myocardial volume. In this study we investigated a novel activation reconstruction approach and a method to estimate three-dimensional (3D) conduction velocity (CV). Cardiac CV is often studied under a range of interventions but rarely in three dimensions, nor at the level of resolution achieved in this study.[1,2] Changes in conduction velocity are indicative of a wide variety of cardiac arrhythmias that can lead to sudden cardiac death (SCD). The short time frame between the onset of symptoms and the cessation of cardiac function complicates the study of SCD clinically. Therefore, the use of large animal experiments in which high density electrical recordings can be made in the intramural space are essential to improve our understanding of dynamic electrical events that may ultimately result in SCD. The approach introduced in this study will provide a means to study the formation of these arrhythmias by estimating regional differences in CV throughout a three-dimensional region sampled by intramural needle electrodes.

A key challenge in evaluating the accuracy of activation reconstruction techniques is obtaining gold standard data. There is no feasible approach to obtaining the necessary resolution with direct measurement, at least with the coverage necessary for useful experiments. To generate data for validation we applied the CARPentry simulation platform [3] to perform whole heart simulations of image-based models based on our experimental preparations. By using the same geometry, we could identify the nodes in the CARP model corresponding to the measurement sites and then compare simulated and reconstructed activation time values [3,4].

With the reconstruction accuracy established we could also use CARPentry to evaluate a novel technique for estimating conduction velocity at high spatial resolution

within the heart volume. This techniques utilizes the gradient of activation times and a series of streamlines to compute 3D CV throughout the region sampled by the intramural needles. The flexibility of the CARPentry environment allowed us also to generate activation sequences from a range of pacing sites and thus comprehensively evaluate our reconstruction and estimation approaches.

2. Methods

2.1. Wavefront Reconstruction and Estimation of 3D Conduction Velocity

This study used intramural plunge needles, replicating the experimental placement and density, to approximate the conduction velocity (CV) throughout the convex hull using the reconstructed activation sequences. The activation times simulated on the intramural plunge needles were reconstructed using a radial basis function (RBF) that interpolated the activation times into the convex hull. Using the reconstructed activation times the gradient of activation is estimated and used to compute a series of streamlines. The seed points for around 2000 streamlines were uniformly distributed throughout the convex hull and were parametrized to ascend the local gradient.The geodesic distance along the streamline was sampled along with the activation time differences at $3mm$ increments to compute conduction velocity along the streamlines. The values were then smoothed using a simple three element box filter over the length of each streamline. The RBF interpolation, gradient estimation, and streamline generation were all performed using the SCIRun problem solving environment (www.sci.utah.edu/cibc-software/scirun.html). An example of these streamlines, with activation times mapped onto them, can be seen in Figure 2.

2.2. Experimental Preparation

The data used for this study was acquired during a series of large animal experiments carried out to study the electrophysiological response to acute myocardial ischemia and a number of other pathologies.[1, 5, 6]To provide measurements for this study, we conducted a series of experiments using 20–40 transmural plunge needles, each with 10 unipolar electrodes roughly uniformly distributed within the myocardial tissue of the perfusion bed in which ischemia was induced through restriction of coronary flow and elevated heart rates[5]. Figure 1 shows a schematic diagram of a typical intramural needle with $5 - -10\ mm$ between each needle. The region sampled by the needles is referred to in this study as the 'convex hull' and is the enclosed volume created by the spatial distribution of the intramural needles.

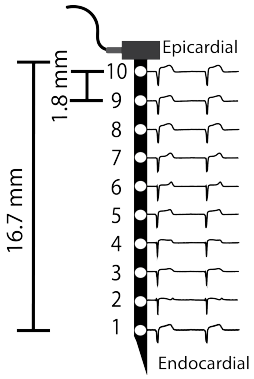

Figure 1. Schematic of an intramural plunge needle used in our experiments. Example signals captured at each depth are located to the right of each electrode. The first electrode is 0.5 mm below the epicardial surface. Typically 20–30 of these needles are placed into the perfusion bed of the LAD

2.3. Computational Model Creation and Simulation

To generate the validation data, we generated image-based models of the experimental preparation in similar manner to that outlined by Burton *et al.*[7], and processed in the CARPentry environment to produce a computational simulation of cardiac activation. Rule-based fiber orientations were then incorporated and experimental positions of the needle placements were localized to nodal points on the mesh. CARPentry was then used to simulate an eikonal wave activation sequence from an initial stimulus point with prescribed CVs of 60, 40, and 20 cm/s along the principal, sheer, and normal fiber orientations, respectively [4]. The CV values were chosen to give activation times within the physiological range for canines. To analyze the accuracy of reconstruction into the volume of the convex hull we stimulated wavefronts from five locations throughout the myocardium. The range of stimulation sites was intended to probe the effect of different wavefront shapes on the reconstruction accuracy throughout the convex hull as well as the estimation of conduction velocity.

Below is a list of stimulation sites analyzed for this study:

- **Stimulation A:** Epicardial stimulation in a region of the convex hull with a low density of sampling electrodes.
- **Stimulation B:** Midmyocardial stimulation in a region of the convex hull with a low density of sampling electrodes.
- **Stimulation C:** Posterior endocardial stimulation far outside of the convex hull in the posterior endocardial region of the heart.
- **Stimulation D:** Midmyocardial stimulation in a region

of the convex hull with a high density of sampling electrodes.

• **Stimulation E:** Endocardial stimulation in a region of the convex hull with a high density of sampling electrodes.

From these simulations, we replicated the reconstruction of activation and estimation of CV, comparing the results with the simulated values throughout the volume defined by the needle electrodes. Statistical metrics included the root-mean-square error (RMSE) and the percentage of the hull below $1ms$ of error. Furthermore, the average 3DCV and standard deviation were calculated throughout the reconstructed convex hull as well as the simulated hull.

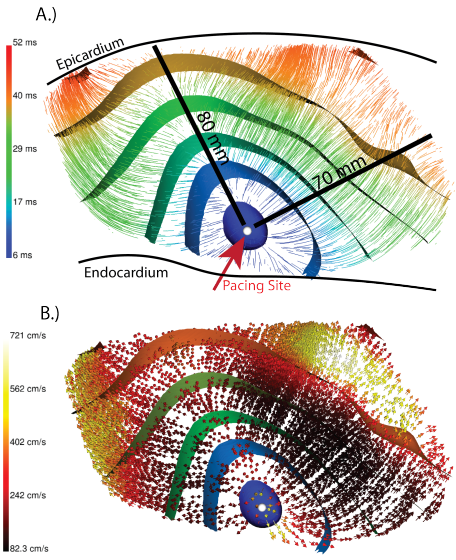

Figure 2. A two-dimensional cut plane of a simulation of a point stimulation at an endocardial region within the convex hull created by our intramural needles. The location of stimulus is indicated by the white sphere. A.) A series of isochrons marked at $7, 13, 20, 30, 38, 45ms$ with streamlines navigating the field with activation times mapped onto the streamlines. The pacing site and estimations of the epicardial and endocardial boundaries are indicated. B.) The same isochrons are indicated in A but with 3D conduction velocity vectors mapped in the field. The vectors are scaled and colored by conduction velocity magnitude.

3. Results

The reconstructed activation times compared to the calculated activation times had an average RMSE across the five stimulations of $0.65ms$ with 89% of the convex hull volume showing an error of less than $1\ ms$. Figure 3 shows the intramural needle electrodes and the region of the convex hull that has interpolation error greater than $1ms$. We thresholded the convex hull to visualize the region with error greater than $1ms$ and then mapped the distance between that thresholded volume and the closest measurement locations. We see that the largest errors occur in regions of the cardiac tissue 1.5–3 cm away from the electrodes. Stimulation C, the posterior stimulation, resulted in the greatest error, with RMSE = 1.00 ms.

We analyzed the estimated 3DCVs from both the simulated and reconstructed activation times to investigate the level of confidence at which 3DCV can be estimated with the resolution achieved during our experiments. We found that the CVs were calculate using the reconstructed activation times agreed with the CVs estimated using the simulated convex hull. The CVs estimated using the reconstructed data typically overestimated the CV found using the simulated data by around 20-30 cm/s. This overestimate

Table 1. RBF-based interpolation error within the convex hull formed by the intramural needles and mean 3DCV for the simulated and reconstructed stimulation site.

Stim. Site	RMSE (ms)	Under Thresh.	Simulated CV (cm/s)	Reconstructed CV (cm/s)
A	0.63	89.53%	421 ± 127	446 ± 126
B	0.65	88.97%	431 ± 125	451 ± 125
C	1.00	79.77%	482 ± 142	511 ± 145
D	0.55	92.56%	408 ± 125	427 ± 127
E	0.44	95.13%	433 ± 141	457 ± 130

4. Discussion

The purpose of this study was to evaluate the accuracy with which we could reconstruct the activation front in an experimental setting throughout the region measured by the intramural needles. Furthermore, this study will allow us to gain an understanding of the range and variability to expect in the computation of 3D CV. This study leveraged the advantages of cardiac computational modeling to validate the current activation wavefront reconstruction techniques using simulated datasets. This study also showed the feasibility of using the volumetric activation front to compute conduction velocity throughout the sampled region.

The ability to accurately reconstruct the activation wavefront and estimate CV has promising appeal for the study of various pathologies that perturb the wavefront. With our results suggesting RMS errors at the level of 1 ms or less, even subtle changes should be visible with this combination of centimeter scale resolution of the needle electrodes and this novel reconstruction approach. We have begun to apply this combination to experiments in which we induced acute ischemia and have found the largest errors to lie under the left anterior descending artery, which is also

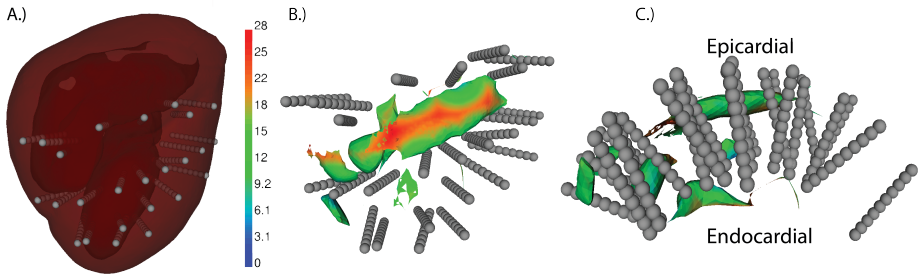

Figure 3. The computational model used to evaluate reconstruction of the activation front within the convex hull of the needles. A.) The whole heart model showing the relative positioning of the intramural plunge needles. B.) The intramural needles with a volume rendering of the region within the convex hull exhibiting interpolation error greater than $1ms$. Mapped onto this regions is a distance map from the closest intramural electrode to each node exhibiting error greater than $1ms$. C.) This is the same geometry as viewed in B but seen from a inferior visage.

one of least well sampled regions because of challenges of placing needles close to the artery.

The ability to accurately measure CV in the myocardium opens many opportunities in the study of arrhythmias, for example, those that arise in the acute phases of ischemia and other cardiac pathologies that one may induce in experiments. A second broad application of these approaches is in the interplay between fiber orientation and propagation in different regions of the heart. Figure 2 shows that even a relatively simple wavefront undergoes a very complex anisotropic activation that introduces a large range in the computed values of CV's. Since the intramural needles allow both pacing and recording, one can envision studies in which pacing from different sites and then measuring (and reconstructing) propagation could lead to as yet unexplored aspects of the spread of excitation.

Limitations in this study have to do primarily with the fact that our validation was based on simulations. There are unavoidable features of the heart used in an experiments that will not be captured faithfully in a geometric model and even the most sophistical simulations of propagation have known deviations from reality. In future studies the volume surrounding the needle electrode locations will be modified in order to better represent concave regions on the endocardium and capture tissue structure obtained from postmorten MRI scans. We will also review the errors that arise using the eikonal assumptions of the CARPentry simulations by comparing with full bidomain simulations conducted on the same geometric models.

Acknowledgments

Support for this research comes from the NIH NIGMS Center for Integrative Biomedical Computing (www.sci.utah.edu/cibc), NIH NIGMS grant no. P41GM103545, the Nora Eccles Treadwell Foundation for Cardiovascular Research.

References

[1] Good WW, Erem B, Zenger B, Coll-Font J, Brooks DH, MacLeod RS. Temporal performance of laplacian eigenmaps and 3d conduction velocity in detecting ischemic stress. Journal of electrocardiology 2018;.

[2] Barnette AR, Bayly PV, Zhang S, Walcott GP, Ideker RE, Smith WM. Estimation of 3-d conduction velocity vector fields from cardiac mapping data. IEEE transactions on biomedical engineering 2000;47(8):1027–1035.

[3] Vigmond E, Dos Santos RW, Prassl A, Deo M, Plank G. Solvers for the cardiac bidomain equations. Progress in biophysics and molecular biology 2008;96(1-3):3–18.

[4] Neic A, Campos FO, Prassl AJ, Niederer SA, Bishop MJ, Vigmond EJ, Plank G. Efficient computation of electrograms and ecgs in human whole heart simulations using a reaction-eikonal model. Journal of computational physics 2017;346:191–211.

[5] Aras K, Burton B, Swenson D, MacLeod R. Spatial organization of acute myocardial ischemia. Journal of electrocardiology 2016;.

[6] Zenger B, Good WW, MacLeod RS. Electrocardiographic comparison of dobutamine and bruce cardiac stress testing with high resolution mapping in experimental models ;.

[7] Burton BM, Aras KK, Good WW, Tate JD, Zenger B, MacLeod RS. A framework for image-based modeling of acute myocardial ischemia using intramurally recorded extracellular potentials. Annals of biomedical engineering 2018;1–12.

Address for correspondence:

Name: **Wilson William Good**
Full postal address: **SCI Institute, University of Utah, 72 Central Campus Dr, Salt Lake City, UT 84112**
E-mail address: **wgood@sci.utah.edu**