Activation Time Imaging in the Presence of Myocardial Ischemia: Choice of Initial Estimates for Iterative Solvers

Walther HW Schulze, Danila Potyagaylo, Olaf Dössel

Institute of Biomedical Engineering, Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

Abstract

In this work, a simulation study is performed that demonstrates how activation times of cardiac action potentials can be reconstructed from body surface potential maps (BSPMs).

An extrasystole is simulated in the ventricles, which are affected by myocardial ischemia or necrosis, and the related BSPM is calculated. Initial estimates are required for iterative algorithms that solve the related non-linear reconstruction problem. As a good initial estimate is essential for a proper reconstruction, the robustness of two methods is tested against the influence of pathological conditions: the critical times method and a linear time-integral based method.

While the first method extrapolates activation times into inactive tissue in this study, the latter carves out ischemic or necrotic tissue as homogeneous regions. In an outlook, a concept for the combination of both methods is proposed.

1. Introduction

In this study, we solve the inverse problem of electrocardiography for the activation times of cardiac transmembrane potentials. The clinical application of a reliable method would allow cardiologists to perform a non-invasive pre-inverventional diagnosis of cardiac diseases.

The performance of activation time imaging has been demonstrated both *in silico* and in clinical scenarios [1–3]. In recent clinical studies of our group, we faced a myocardium that was significantly affected by scar tissue. When applied under these circumstances, we found that the iterative solver by Fischer et al. [2] did not deliver good enough results, although it had previously been the most reliable in simulation studies. Final results of this method are strongly governed by the provided initial estimate.

This work hence investigates whether myocardial scar tissue is likely to affect the solution of two methods that produce initial estimates: the critical times method by Huiskamp et al. [3] (as used in [2]) and a linear time-integral based method [4, 5].

We demonstrate that both methods react differently, and in an outlook, a combination of both approaches is then proposed that could compensate for the weaknesses of the individual solvers.

2. Methods

2.1. Anatomical model

The anatomical model of a healthy volunteer is produced by segmentation of an MRI dataset into several tissue classes of specific conductivity. For a coarse grid of nodes in the myocardial volume, a lead field matrix is then calculated that relates the transmembrane potential at the specific heart nodes to their corresponding electrocardiogram, which is measured at 64 points on the body surface.

2.2. Simulation setup

A ventricular extrasystole is simulated in the anatomical model of the heart using a cellular automaton (see Fig. 1), and the related BSPM is calculated using the bidomain model [6] (see 2 and 3). Tissue is locally affected by myocardial ischemia using an implementation of the ischemia model by Weiss et al. [7] into the automaton, see Loewe et al. [8]. Effects of extracellular hyperkalemia, acidosis and hypoxia are simulated, leading to an increase in resting membrane voltage and a reduction in duration and amplitude of action potentials, as well as a decrease of conduction velocity. Transmural heterogeneities are taken into account. To facilitate a clear characterization of effects, a central ischemic zone radius of $22.2\,\mathrm{mm}$ was chosen, where the pathological deviations reach full extent, and a border zone of $2.8\,\mathrm{mm}$ radius, over which the ischemic zone factor [8] has a linear decrease. To simulate necrotic tissue, action potentials of the healthy simulation are set to zero, without further adaptations of the excitation spread in a radius of again $22.2\,\mathrm{mm}$.

The methods under assessment assume the given BSPM is constrained to the interval of the QRS for normal sinus rhythm activation, i.e., the assumption is that the elec-

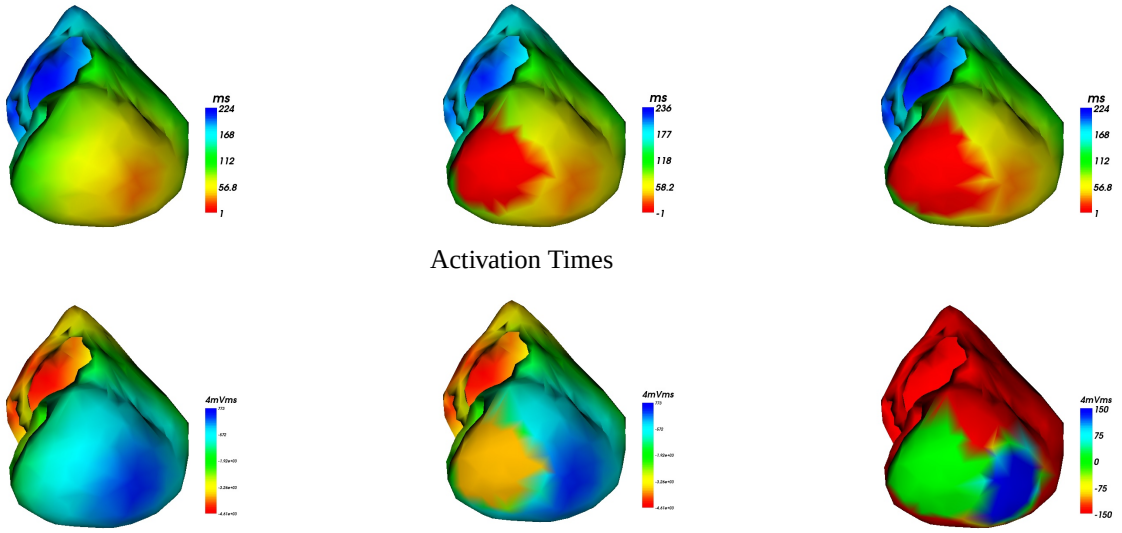

Figure 1. Ground truth, simulated beat. LV/RV: left/ right ventricle, MI: myocardial ischemia, NEC: necrosis. Upper row: time of first surpassing of $-40\,\mathrm{mV}$, else -1 (if staying below). Lower row: TMV-integral over QRS.

trocardiogram only contains effects of cardiac depolarization. The simulated BSPM is therefore truncated to the end of the depolarization seen in the simulation, which is at $232\,\mathrm{ms}$ (see Fig. 2 and Fig. 3).

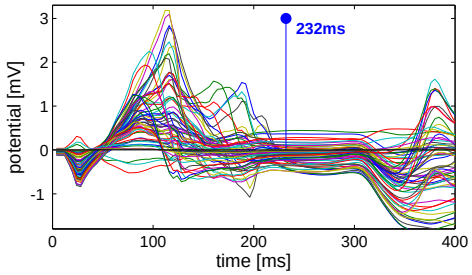

Figure 2. ECG of the beat with myocarial ischemia (MI)

2.3. The linear inverse problem

Forward calculations in electrocardiography can be formulated as a linear expression

$$Ax = b, \tag{1}$$

where A is the leadfield matrix and b and x are the vectors of the BSPM and cardiac transmembrane voltages at the respective electrode positions and heart nodes.

The inverse problem of calculating x from the BSPM is solved using the Tikhonov method that minimizes the

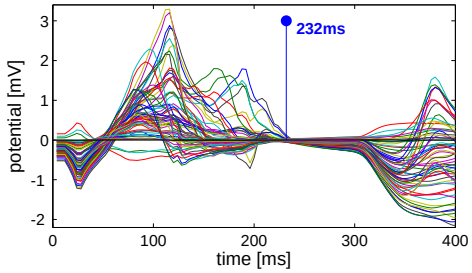

Figure 3. ECG of the beat with necrosis (NEC)

L2-norms of both the residual and a regularization term:

$$\hat{x} = \arg\min_{\mathrm{x}} \left\{ \|\mathrm{Ax} - \mathrm{b}\|_2^2 + \lambda^2 \|\mathrm{L}(\mathrm{x} - \mathrm{x}_0)\|_2^2 \right\}, \tag{2}$$

where λ is the regularization factor, L a discretized Laplace operator and x_0 is a solution estimate.

2.4. Iterative solvers for activation time imaging

Contrary to the linear inverse problem of imaging transmembrane voltages, the non-linear relationship between activation times of transmembrane voltages and BSPMs does not have a closed-form solution. Activation times are therefore reconstructed using iterative solvers. Fischer and Modre et al. [2, 9] propose methods that start with an ini-

tial estimate and then minimize a cost term with respect to a vector of activation times. For the iteration, a sigmoidal time-course model with efficiently-to-compute partial activation times derivatives is then used to establish a relationship between transmembrane voltages and their activation times. This study focuses only on the initital estimate for such solvers.

2.5. Initial estimates

To start the iterative solvers, an initial reconstruction is required. That initial guess has significant impact on the final solution, since the non-linear cost function has multiple local minima. This study explores both the critical times method by Greensite and Huiskamp and a linear time-integral based method.

2.5.1. Critical times method

Greensite and Huiskamp [3] found a well-posed formulation of the inverse problem, which reliably produces activation times (critical times) for the spatial extrema of activation times (critical points). Critical points can be identified as singularities of $M_0^{k_T}(i)$, where

$$M_0^k(i) = \left| 1 - \sum_{r=1}^{r_{eff}} \langle\, \alpha_i, U_r^{[0,k]} \,\rangle^2 \right|^{-1} \tag{3}$$

and where i is the heart nodes index, k_T is the time index that corresponds to the end of QRS, $\langle\ ,\ \rangle$ is the inner product, $U_r^{[0,k]}$ is the spatial eigenfunction in the singular value decomposition of $B = [b_0, \ldots, b_k]$, $\alpha_i = \frac{a_i}{\|a_i\|_2^2}$, where a_i is the i-th column of the leadfield matrix A.

When computing the representation of a source i in the BSPM $M_0^k(i)$ over time, a significant upstroke can be seen at the time of depolarization. This behaviour is used to compute the activation times of critical points. For details see Sect. II in [3].

The method assumes that action potentials have the time-course of a Heaviside function, which is approximately true during the QRS-phase of the ECG. Under this assumption, the method is theoretically proven in [3] to work for critical points on the heart surface. In the paper, it is then also used to compute activation times for nodes on the heart surface that lie between critical points. These times can be considered interpolations of the activation times found at the critical points. In this work, activation times are also reconstructed in the volume of the myocardium, meaning another extension of the interpolation. As the interpolation is based on the correlation of BSPM-signals, it does not necessarily lead to physiological spatial distributions of activation times in the heart.

2.5.2. Linear time-integral based method

When Eq. 1 is integrated over time,

$$A\tilde{x} := A \int_0^T x\, dt = \tilde{b} := \int_0^T b\, dt, \tag{4}$$

the solution of the inverse problem according to Eq. 2 yields the area under the time-course of transmembrane voltages [4]. Under the assumption of similar action potential curves that are continuously rising, $\tilde{x}$ can also be interpreted as activation sequence [5] or as activation time relative to the end of the integration interval T in the case of $x(t)$ resembling a Heaviside function [4].

When making the Heaviside assumption, Eq. 4 can be written as

$$A\Delta_x(T - \tau) \approx A \int_0^T x\, dt = \tilde{b} \approx t_s \sum_{k=1}^{k_T} b_k, \tag{5}$$

where T is the interval length of the QRS, t_s the sampling interval and Δ_x and τ are the amplitude (assumption in this study is $\Delta_x = 90\,\mathrm{mV}$) and onset time of the Heaviside function. This can be written as:

$$A\hat{\tau} = A(\tau - T) = -\frac{t_s}{\Delta_x} \sum_{k=1}^{k_T} b_k := \hat{b}, \tag{6}$$

After Eq. 6 is solved with the method in Eq. 2 and regularization constraints on $\hat{\tau}$, the offset in $\hat{\tau}$ and at the same time wrong assumptions in Δ_x can be eliminated by scaling the range of the resulting activation time distribution to that of the BSPM signal in b:

$$\tau_{i,\mathrm{scaled}} = 1 + T \frac{\hat{\tau}_i - \min\limits_i \hat{\tau}_i}{\max\limits_i \hat{\tau}_i - \min\limits_i \hat{\tau}_i}. \tag{7}$$

2.5.3. Combined method

In the following, an approach for the combination of both methods is proposed that uses results of the critical times method as a reference where considered reliable (critical points) and inherits the benefits of regularization from the time-integral method. To identify reliable points, function $M_0^k(i)$ of Eq. 3 is evaluated for $k = k_T$ [3]. A binary weighting vector s is then established, which is 1 for reliable heart nodes, else 0. To test the method, heart nodes i are considered reliable if

$$\frac{M_0^{k_T}(i) - \min\limits_i M_0^{k_T}(i)}{\max\limits_i M_0^{k_T}(i) - \min\limits_i M_0^{k_T}(i)} > 0.2, \tag{8}$$

a threshold that needs to be adjusted through statistical analysis in future applications. Critical times that are

produced as in Sect. 2.5.1 are added as τ_{crit} to the cost function of the integral-based method in Sect. 2.5.2 with a strong and case-independent weighting parameter of $\beta = 10000$ (greater values led to numerical instabilities):

$$\hat{\tau} = \arg\min_{\hat{\tau}} \left\{ \|\mathrm{A}\hat{\tau} - \hat{\mathrm{b}}\|_2^2 + \lambda^2 \|\mathrm{L}\hat{\tau}\|_2^2 + \beta^2 \|\hat{\tau} - \tau_{\mathrm{crit}}\|_2^2 \right\} \tag{9}$$

3. Results

The critical times method (Fig. **??**) produces a reconstruction that corresponds qualitatively well to the simulations in Fig. 1, but that lacks some of its smoothness (see small artifacts in yellow area) and that fails to produce the exact time range for both early and late activations. Activation times are extrapolated into central ischemic or necrotic areas, preventing the tissue properties from being visible.

The time-integral based method (Fig. **??**) complies with the time range due to automatic adaptation in Eq. 7 and shows results which are almost of the same quality as for the first method. In areas of ischemia or necrotic tissue, however, homogeneous artifacts of very late or early activation are present. These are in good correspondence with the time-integrals in Fig. 1, which reflects that in both cases, the pathological tissue had mostly constant potentials around a low resting membrane voltage for the ischemia ($< 60\,\mathrm{mV}$) and $0\,\mathrm{mV}$ for the necrosis. The artifacts are present also on the endocardium in the same colour and even more expressed in the ischemia case when the ECG is taken from the QRS-T interval. The combination of the methods (Fig. 2.5.2) does not yet lead to better results in this stage of implementation.

4. Discussion and conclusions

The choice of proper initial estimates for iterative solvers in activation time imaging is still an issue, especially in the presence of myocardial ischemia or necrosis. Both methods rely on the Heaviside function as basic assumption, which is unrealistic for the pathological case. Previous studies show that methods based on the uniform double layer are incapable of dealing with old infarctions (see [10]). This single-case study however suggests that the critical times method is stable in the presence of pathological tissue, but ignores it. The time-integral based method on the other hand characterizes the pathological tissue properties correctly in terms of the voltage integral, which is an artifact when being interpretated as activation time. The results suggest that the Heaviside function is favourable for robust results in the active tissue when pathologies are present, but that more attention to the course of action potentials should be given for the area-specific characterization of tissue. Results of this single-case study should not be interpreted as statistically strong, and further investigation is required to substantiate the conclusions.

Acknowledgements

This project was funded by the German Research Foundation under grants DO637/10-1 and DO637/13-1.

References

[1] Ramanathan C, Ghanem RN, Jia P, Ryu K, Rudy Y. Noninvasive electrocardiographic imaging for cardiac electrophysiology and arrhythmia. Nat Med 2004;10:422–428.

[2] Fischer G, Pfeifer B, Seger M, Hintermuller C, Hanser F, Modre R, Tilg B, Kremser C, Roitinger FX, Hintringer F. Computationally efficient noninvasive cardiac activation time imaging. Methods of Information in Medicine 2005; 44:674.

[3] Huiskamp G, Greensite F. A new method for myocardial activation imaging. IEEE Trans Biomed Eng 1997;44:433–446.

[4] Geselowitz DB. Use of time integrals of the ecg to solve the inverse problem. IEEE Trans Biomed Eng 1985;32:73–75.

[5] Dössel O, Jiang Y, Schulze WHW. Localization of the origin of premature beats using an integral method. In International Journal of Bioelectromagnetism 2011; 13: 178–183.

[6] Geselowitz DB, Miller TW. A bidomain model for anisotropic cardiac muscle. Annals of Biomedical Engineering 1983;11:191–206.

[7] Weiss DL, Ifland M, Sachse FB, Seemann G, Dössel O. Modeling of cardiac ischemia in human myocytes and tissue including spatiotemporal electrophysiological variations. Biomedizinische Technik 2009;54:107–125.

[8] Loewe A, Schulze WHW, Jiang Y, Wilhelms M, Dössel O. Determination of optimal electrode positions of a wearable ecg monitoring system for detection of myocardial ischemia: a simulation study. Computing in Cardiology 2011; 38: 741–744.

[9] Modre R, Tilg B, Fischer G, Wach P. Noninvasive myocardial activation time imaging: a novel inverse algorithm applied to clinical ecg mapping data. IEEE Trans Biomed Eng 2002;49:1153–1161.

[10] Oostendorp T, Nenonen J, Korhonen P. Noninvasive determination of the activation sequence of the heart: application to patients with previous myocardial infarctions. Journal of Electrocardiology 2002;35 Suppl:75–80. ISSN 0022-0736.

Address for correspondence:

Institute of Biomedical Engineering
Karlsruhe Institute of Technology
Kaiserstr. 12, 76131 Karlsruhe, Germany
publications@ibt.kit.edu