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Decomposition of Fractionated Local Electrograms Using an Analytic Signal Model Based on Sigmoid Functions

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Abstract

Microstructural heterogeneities in cardiac tissue, such as embedded connective tissue secondary to fibrosis, may lead to complex patterns of electrical activation which are reflected in a fractionation of extracellularly recorded electrograms. The decomposition of such electrograms into nonfractionated components is expected to provide additional information to allow a more precise classification of the microstructural properties adjacent to a given recording site. For this sake an analytic signal model is introduced in this study which is capable of reliably identifying extracellular waveforms associated with sites of initiating, free running, and terminating or colliding activation wavefronts. Using this signal model as a template a procedure is developed for the automatic decomposition of complex fractionated electrograms into nonfractionated components. The decomposition method has been validated using electrograms obtained from 1D and 2D computer simulations in which all relevant intracellular and extracellular quantities are accessible at a very high spatio-temporal resolution and can be manipulated in a controlled manner. Fractionated electrograms were generated in these models by incorporating microstructural obstacles which mimicked inlays of connective tissue. Using this signal model fractionated electrograms emerging from microstructural heterogeneities in the submillimeter range with latencies between components down to 0.6 ms can be decomposed.

Keywords

cardiac near field; complex fractionated atrial electrogram; computer model; fibrosis; heart

Introduction

Spatial heterogeneity in electrical activation of the heart plays a major role in the genesis of unidirectional blocks which may lead to the formation of reentrant arrhythmias [1, 2]. Such conduction heterogeneities arise, on one hand, due to spatial variation in cellular dynamics and, on the other hand, due to discontinuities in tissue structure. In the normal healthy heart these heterogeneities are omnipresent due to numerous factors such as heterogeneous expression of gap junctions, varying electrotonic loads as imposed by anatomical complexities, and differences in the makeup of myocytes. In the aging or diseased heart, however, these heterogeneities may be exacerbated. Structural diseases such as fibrosis

which are thought to play a pivotal role in arrhythmogenesis [3], increase the fraction of connective tissue which separates neighboring myocytes and thus forms local barriers for propagating depolarization wavefronts. As a consequence, wavefronts propagate along more tortuous pathways which is reflected in an apparently slower propagation of wavefronts at a macroscopic size scale. This link between microfibrosis-induced complex excitation patterns and electrogram fractionation has been investigated recently in an elegant computer simulation study [4]. Experimental techniques for studying activation patterns at a cellular size scale are feasible, but achieving a sufficiently high spatio-temporal resolution is challenging. Typically, such studies rely on densely packed multielectrode sensor arrays with fast data acquisition which allow to resolve local propagation patterns [5]. The locality of such extracellularly recorded signals at any given site, however, may be tainted by activations occurring with a certain delay in adjacent tissue which interfere with the local signal via electrotonic interaction through the volume conductor surrounding the tissue. In the case of sufficiently large delays these electrotonic interactions are manifested in a fractionation of extracellularly recorded electrograms [6, 7]. Therefore, the characterization of local propagation based on such datasets requires dedicated signal processing methods.

During uniform propagation electrograms are not fractionated, but the shape of waveforms may vary as well. In the case of a free running activation along a cable-like muscle strand, the waveform of the corresponding electrogram $\Phi(t)$ during the depolarization phase is fairly symmetric, i.e. it shows a biphasic shape with similar magnitude of positive and negative phase. Close to an initiation site of wave propagation, the positive amplitude of $\Phi(t)$ is reduced, whereas close to a sealed end or a wavefront collision site, the negative amplitude is diminished [8]. The temporal derivative of $\Phi(t)$, $\dot{\Phi}(t)$, shows a single negative deflection which is why these signals are referred to as nonfractionated electrograms. This is not the case during discontinuous conduction where multiple deflections in $\dot{\Phi}(t)$ may occur which is referred to as electrogram fractionation [9]. Since this is caused by the presence of multiple current sources which differ in strength, distance to the recording site, and activation time, such fractionated local electrograms can also be viewed as superpositions of nonfractionated components.

The decomposition of fractionated electrograms enables the analysis of the individual nonfractionated components in terms of amplitude, waveform symmetry, and - for multisite recordings - local conduction velocity and direction of propagation. The number of nonfractionated components and their waveform characteristics can be used to classify the microstructural composition of the tissue in the adjacency of the recording site. In a first step towards this goal a method for decomposing fractionated electrograms into nonfractionated components is presented.

The objectives of this article are i) to introduce an analytic signal model of a nonfractionated unipolar local electrogram $\Phi(t)$ during depolarization, ii) to use an optimization procedure to fit a template signal $\Phi_m(t)$, created by means of this signal model, to a given waveform $\Phi(t)$, iii) to identify if and to which degree a given waveform $\Phi(t)$ is fractionated, and iv) to decompose fractionated electrograms by repeated fitting and subtracting of templates. To test and validate signal model and processing, normal and fractionated noise free

electrograms were simulated with a 1D computer model of a strand of myocytes and a 2D model of a sheet of cardiac tissue in which electrode configuration and distance to the tissue surface matched with a previously described experimental setup for measuring the cardiac electric near field [5]. The key advantage of using a computer model is that all relevant factors implicated in the genesis of electrograms such as the exact excitation patterns and the distribution of current sources in the tissue are known with high accuracy. To gauge the robustness of the method, noise of the same characteristics as observed under experimental conditions was added.

Methods

Signal Model

The template $\Phi_m(t)$, centered at $t = 0$ consists of four sigmoid functions: The positive phase of the biphasic waveform $\Phi_m(t)$ is created by multiplication of the rising function $s_{PR}(t)$ and the falling function $s_{PF}(t)$. Likewise, the negative phase consists of $s_{NR}(t)$ and $s_{NF}(t)$. The function $\Phi_m(t)$ is described by four parameters $[a \ b \ c \ d]^T$, where b , c , and d determine the waveform of the sigmoids and a scales the overall function.

$$\begin{aligned}\Phi_m(t) &= a (s_{PR}(t) s_{PF}(t) - s_{NR}(t) s_{NF}(t)) \\ s_{PR}(t) &= \frac{b}{1 + \exp(-tb)} \\ s_{PF}(t) &= \frac{c \exp(-tc)}{1 + \exp(-tc)} \\ s_{NR}(t) &= \frac{c}{1 + \exp(-tc)} \\ s_{NF}(t) &= \frac{d \exp(-td)}{1 + \exp(-td)}\end{aligned}$$

Figure 1 illustrates the generation of $\Phi_m(t)$ and shows the modeling of starting, free running, and terminating or colliding waveforms by variation of $[a \ b \ c \ d]^T$.

Curve Fitting

The task of finding the set of the four parameters $[a \ b \ c \ d]^T$ for which $\Phi_m(t)$ best fits a given waveform $\Phi(t)$ was solved by nonlinear curve fitting in least-squares sense using the Trust-Region-Reflective method (MATLAB function `lsqcurvefit`) [10]. The waveform $\Phi_m(t)$ was centered at the local activation time (LAT) of $\Phi(t)$. The duration between maximum and minimum of $\Phi(t)$, henceforth termed depolarization time t_{dep} , was determined. $\Phi(t)$ was windowed around LAT using a rectangular window of $t_W = 4 \ t_{dep}$ length. Start coefficients $[a_1 \ b_1 \ c_1 \ d_1]^T$, minimum coefficients $[a_l \ b_l \ c_l \ d_l]^T$, and maximum coefficients $[a_h \ b_h \ c_h \ d_h]^T$ were calculated from (t) following empirically established rules (see Table 1). The maximum number of function evaluations was chosen to be 2000, the termination tolerance for the function value was set to $tol = \Phi_{pp} 10^{-4}$.

Computer Simulations

Monodomain computer simulations were performed to be able to precisely control, modify, and observe all parameters at a high spatio-temporal resolution which are relevant to the genesis of extracellular electrograms. Model geometries were discretized at a spatial resolution of $25 \mu\text{m}$ using hexahedral finite elements [11]. Cellular dynamics was

represented using either the Lindblad et al. model (LMCG) [12] of a rabbit atrial myocyte or the Mahajan-Shiferaw model (MSH) [13] of a rabbit ventricular myocyte. An operator splitting technique was employed to be able to treat the parabolic diffusion term and the reaction term separately [14], where temporal discretization relied on a Crank-Nicholson scheme and a Rush-Larsen scheme for parabolic PDE's and ODE's, respectively. Extracellular potential waveforms $\Phi(t)$, $t = 0 \dots N-1$, were recovered according to [15] at a temporal resolution of $10 \mu\text{s}$ which corresponds to a sampling frequency of 100 kHz. The volume conductor surrounding the cardiac tissue was assumed to be homogeneous with a conductivity of $1 \text{ S} \cdot \text{cm}^{-1}$ and infinite extent. All computer simulations were performed with the Cardiac Arrhythmia Research Package (CARP) [16].

Two setups were considered. The first setup consisted of two 20 mm long strands of myocytes where the distance z between *strand 2* and recording site could be varied (Figure 2 (a)). The weighting of two propagating sources on the extracellular potential Φ at the recording position was separately analyzed by applying a point-like stimulus of 1 ms duration either to *strand 1* or to *strand 2*. Φ was obtained by adding the contributions Φ_1 and Φ_2 of the two strands.

The second setup modeled a 2D anisotropic sheet of tissue of $4 \text{ mm} \times 1.25 \text{ mm}$ in which obstacles were embedded to mimic the effect of microfibrosis upon excitation patterns at a microscopic size scale (Figure 2 (b)). Longitudinal to transverse conductivity ratio was set to 9.158 [17]; longitudinal conduction velocity was $0.7 \text{ m} \cdot \text{s}^{-1}$. Two rectangular non-conducting obstacles of $500 \mu\text{m} \times 50 \mu\text{m}$, oriented parallel to the fibers were embedded at a distance of $100 \mu\text{m}$ in the center of the tissue sheet, mimicking inlays of interstitial connective tissue. Point-like stimulation of 1 ms duration was applied to the lower left corner of the sheet to induce an elliptic wavefront which propagates towards the obstacles in an oblique direction. To mask the influence of borders, an area of $1 \text{ mm} \times 0.3 \text{ mm}$ at the center of the sheet was extracted for signal analysis.

Evaluation of the Curve Fitting

First, the ability of the proposed signal model to represent a wide range of nonfractionated electrograms was tested using synthetic data generated with the 1D computer model where only *strand 2* was activated while *strand 1* remained quiescent.

Test of Curve Fitting

Extracellular potentials were computed at positions I, II, and III, representing starting, free running, and terminating propagation. Further, experiments were repeated with *strand 2* being moved away from the recording sites, by $z = 50, 250$, and $500 \mu\text{m}$, to account for shape variations of Φ due to the changed weighting of the sources. To ensure general usability, this experiment was performed with both atrial and ventricular myocyte models [12, 13].

Goodness of Fit

The goodness of fit was quantified by 1.) the sum of the squared errors sse_{Φ} calculated as

$$sse_{\Phi} = \frac{\sum_{t=0}^{N-1} (\Phi_m(t) - \Phi(t))^2}{\sum_{t=0}^{N-1} (\Phi(t))^2}$$

where N is the length of the sequences $\Phi(t)$ and $\Phi_m(t)$ and 2.) the Pearson product-moment correlation coefficient r between $\Phi(t)$ and $\Phi_m(t)$. Likewise, $sse_{\dot{\Phi}}$ and $r_{\dot{\Phi}}$ were determined for the temporal derivative $\dot{\Phi}(t)$. For studies with noisy signals Φ the following parameters were evaluated: 1.) Amplitude $A = \max \Phi - \min \Phi$, 2.) symmetry $a = (\max \Phi - |\min \Phi|)/A$, $a \in [-1, 1]$, $a = 0$ for a symmetric biphasic waveform [18, 19], and 3.) depolarization duration t_{dep} . A , a , and t_{dep} were compared to the respective parameters B , b , and t_{dep_m} determined from Φ_m .

Decomposition of Fractionated Electrograms

The decomposition of fractionated electrograms was performed in two steps:

Estimation of the fractionation index and local activation times—

The fractionation index (FI) indicates the number of superimposed events within $\Phi(t)$. FI and local activation times (LAT's) were determined using a template based algorithm [20]. A template $\Phi_T(t)$ with the length of $t_w = 16 t_{dep}$ was created by means of the introduced signal model using the coefficients $[abcd]^T = [\Phi_{pp}/4 \quad 2\Phi_{max}/\Phi_{pp} \quad |\dot{\Phi}_{min}|/\Phi_{pp} \quad 2|\dot{\Phi}_{min}|/\Phi_{pp}]$.

Symbols are explained in Table 1. $\Phi_T(t)$ was differentiated with respect to time ($\dot{\Phi}_T$). Φ was bidirectionally lowpass filtered (FIR, order 100, cutoff frequency $f_C = 1.5$ kHz) and temporally differentiated. A window of length t_w was extracted around the maximum negative peak of this derivative $\dot{\Phi}$. The cross correlation function $c_{\dot{\Phi}\dot{\Phi}_T}(\tau)$ of $\dot{\Phi}$ and $\dot{\Phi}_T$ was computed in the frequency domain. From the second derivative of $c_{\dot{\Phi}\dot{\Phi}_T}(\tau)$ with respect to Φ , peaks with a magnitude above 20 % of the maximum peak were identified. The number of peaks as well as their instants and magnitudes relative to the maximum peak were determined. These values represent FI, the vector of local activation times, and the vector of magnitudes.

Repeated application of curve fitting procedure—In case $FI > 1$ the curve fitting was carried out in n iterations $i = 1 \dots n$. Hence the curve fitting procedure was applied n FI times centered at the local activation time LAT_k , $k = (j - 1 \bmod FI) + 1$, $j = 1 \dots n$ FI. Window size and termination tolerance for the optimization procedure were adapted as follows: $t_w = t_{dep} 2^{2(i-1)}$, $tol = \Phi_{pp} 10^{-(i+3)}$. After each iteration j , $\Phi_{m,j}(t)$ was modeled using the determined coefficients. For $i=1$ the coefficients for the FI components were determined

by fitting the signal model into $\Phi_j = \Phi - \sum_{k=1}^{j-1} \Phi_k$. For $i > 1$ the curve fitting was done for

$\Phi_j = \Phi - \sum_{k=l}^{FI} \Phi_{m,k}$, $l = FI(i-2) + k$, $l = j - FI$. Because the subtraction of modeled components might alter the LAT's, prior to the curve fitting the respective LAT was adjusted. The resulting components are $\Phi_{m,(n-1)FI+1} \dots \Phi_{m,n FI}$. Figure 3 shows the

decomposition procedure for $n=3$. With increasing i the fit improves, i.e. sse decreases and r increases. For the choice of n a trade-off between goodness of fit and computation time has to be made. In the following, $n=5$ was chosen.

All procedures were developed using MATLAB [10], including Optimization, Signal Processing, Statistical, and BioSig [21] toolboxes.

Evaluation of the Decomposition of Fractionated Electrograms—The setup consisting of two 1D strands of myocytes was used to synthesize fractionated electrograms Φ_{12} in a well controlled manner by superposition of two nonfractionated waveforms Φ_1 and Φ_2 (Figure 5 (a)). Two parameters which limit the successful decomposition of fractionated electrograms were taken into consideration: 1) the difference LAT between the local activation times of Φ_1 and Φ_2 , and 2) the difference in the distance between recording site and the sources of Φ_1 and Φ_2 , respectively. The components Φ_1 and Φ_2 were recorded at site II, with only either *strand 1* or *strand 2* being stimulated. The minimum distance of 50 μm between recording site and strand corresponds to the distance between electrodes and tissue surface of the sensors described in [5]. Φ_2 was computed with *strand 2* being located at distances $z = 50 \dots 300 \mu\text{m}$ in steps of 5 μm , which resulted in an amplitude ratio between Φ_2 and Φ_1 , A_2/A_1 , in the range of 1 to 0.24.

The depolarization time of Φ_1 , t_{dep1} was 0.94 ms, whereas the depolarization time of Φ_2 , t_{dep2} constantly increased from 0.94 to 1.8 ms with increasing z . The difference in LAT (ΔLAT) was varied by temporally shifting Φ_2 with respect to Φ_1 from 0.5 to 3 ms in steps of 0.1 ms. The resulting fractionated electrogram Φ_{12} was decomposed with the described procedure to recover the nonfractionated components Φ_{m1} and Φ_{m2} as well as their sum Φ_{m12} . To evaluate the goodness of fit, the amplitudes B_1 and B_2 , the symmetry factors b_1 and b_2 , and the depolarization times t_{dep1} and t_{dep2} of Φ_{m1} and Φ_{m2} were compared to the values A_1 , A_2 , a_1 , a_2 , t_{dep1} , and t_{dep2} , respectively, obtained from Φ_1 and Φ_2 . For each distance z and each parameter (B_1 , B_2 , b_1 , b_2 , t_{dep1} , and t_{dep2}), the minimum values of

LAT were determined above which the chosen error tolerance of $\pm 20\%$ for amplitude and depolarization time, and ± 0.2 for the symmetry factor, were not exceeded.

To examine the robustness of the decomposition method against noise, for each z and LAT Gaussian white noise with amplitudes according to experimental values [22] was regenerated 100 times and added to Φ_{12} before the decomposition procedure was performed. The mean values μ and standard deviations σ of B_1 , B_2 , b_1 , b_2 , t_{dep1} , and t_{dep2} were calculated and compared to the corresponding values A_1 , A_2 , a_1 , a_2 , t_{dep1} , and t_{dep2} . Again, the minimum values of LAT were determined above which $\mu \pm \sigma$ did not exceed the chosen error tolerance. The respective values were denoted $\text{LAT}_{\min, B1}$, $\text{LAT}_{\min, B2}$, $\text{LAT}_{\min, b1}$, $\text{LAT}_{\min, b2}$, $\text{LAT}_{\min, t_{dep1}}$, and $\text{LAT}_{\min, t_{dep2}}$.

Application of the Decomposition Procedure—In order to obtain fractionated electrograms with a fractionation index $1 \leq \text{FI} \leq 3$ the model of a 2D tissue sheet with two embedded elongated microobstacles was employed. As shown in previous computer simulation studies, for fractionated electrograms to occur not only the presence of conduction obstacles, but also their orientation with respect to the direction of propagation

matters [23]. That is, wavefronts propagating aligned with the axis of an elongated obstacle do not produce any relevant fractionation. Therefore, a stimulus site was chosen to induce propagation in an oblique direction relative to the alignment of the obstacle, to ensure sufficiently large delays in activation time between the split wavefronts. In a grid of $25 \mu\text{m}$ lateral length spanning an area of approximately $1 \text{ mm} \times 0.3 \text{ mm}$, 602 extracellular potentials $\Phi(t)$ were computed at a distance $z = 50 \mu\text{m}$.

Results

Evaluation of the Curve Fitting

Figure 4 shows the simulated waveforms Φ using the LMCG model, the waveforms Φ_m modeled with the introduced signal model, and the residual $e_\Phi = \Phi_m - \Phi$ at the beginning, in the middle, and at the end of the cable at three different distances z . Table 2 shows the goodness of fit, as quantified by sse_Φ and r_Φ as well as $sse_{\dot{\Phi}}$ and $r_{\dot{\Phi}}$ for electrograms generated with the LMCG and the MSH model, respectively. The window length for the evaluation of sse and r was chosen $3t_{dep}$ centered around the LAT.

Evaluation of the Decomposition of Fractionated Electrograms

The synthesis of fractionated electrograms Φ_{12} from the components Φ_1 and Φ_2 and the decomposition into Φ_{m1} and Φ_{m2} is illustrated in Figure 5 (a).

Figure 5 (b) displays FI for the range of $0.5 \leq \text{LAT} \leq 1 \text{ ms}$ and $50 \leq z \leq 300 \mu\text{m}$. The minimum value of LAT for which $\text{FI}=2$ is detected is 0.6 ms for $50 \leq z \leq 95 \mu\text{m}$, then increases with increasing z .

For $\text{LAT} = 1 \text{ ms}$ three sites A), B), and C) with $z = 50, 100, \text{ and } 250 \mu\text{m}$, respectively, were selected. Φ_1 , Φ_2 , and Φ_{12} as well as Φ_{m1} , Φ_{m2} , and Φ_{m12} for sites A), B), and C) are plotted in Figure 5 (c). In point C), $\text{FI}=1$ was detected and therefore only Φ_{m1} was modeled.

For each z , Figure 5 (d) shows the respective minimum LAT for which the parameters B_1 , b_1 , and t_{dep1} , determined from Φ_{m1} , have an error which is within the given tolerance band. $\text{LAT}_{min,B1} = 0.7 \text{ ms}$ for all values of z , whereas $\text{LAT}_{min,b1}$ and $\text{LAT}_{min,t_{dep1}}$ slightly increase with increasing z .

In Figure 5 (e), LAT for the parameters determined from the second component Φ_{m2} are given. From 0.7 ms for $z = 50 \mu\text{m}$, $\text{LAT}_{min,B2}$, $\text{LAT}_{min,b2}$, and $\text{LAT}_{min,t_{dep2}}$ increase with increasing z .

Application of the Decomposition Procedure

Figure 6 shows the results for the 2D setup with two embedded obstacles. Isochrones based on local activation time were calculated from transmembrane voltages (Figure 6 (a)), which remained nonfractionated throughout the entire observation area, including the vicinity of the obstacles. Their density and curvature reflect the substantial variations in local conduction velocity and direction of propagation around the obstacles. The activation wavefront remained largely undisturbed until encountering with the lower left corner of

obs1 which led to acceleration of propagation due to reduced electrotonic load downstream and reduced wavefront curvature.

The bold isochrone demonstrates the split of a wavefront into three components, α , β , and γ . For recordings at sites **p₃** and **p₁₃** on top of *obs1* and *obs2*, the wavefront components pass by with delays of roughly 0.7 – 0.8 ms between α and β as well as between β and γ which is responsible for the fractionation of Φ .

In the vicinity of the obstacles extracellular potentials Φ at $z = 50 \mu\text{m}$ were fractionated, showing either 2 or 3 distinct components (Figure 6 (c)). Within the observation area numbers of with FI=1, 2, and 3 were 199 (33%), 120 (20%), and 283 (47%), (N=602). The goodness of fit parameters and their distribution are shown in Figure 6 (d)-(g).

Discussion

De Bakker and Wittkamp have comprehensively listed the various reasons for complex extracellular electrograms [7]. Apart from measurement artifacts, the specified reasons for fractionated electrograms can mathematically be considered as caused by the superposition of nonfractionated electrograms. This forms the conceptual basis of the presented decomposition algorithm.

Physical phenomena underlying the genesis of the cardiac transmembrane current waveform can be approximated very well by exponential functions. That is, the product of the functions $s_{PR} \times s_{PF}$ represents the capacitive discharge of the cell membrane and $-s_{NR} \times s_{NF}$ the super-threshold phase during the activation which is driven by the fast influx of sodium.

Exponential functions have been used previously to model bioelectric signals. For instance, Chouvarda et al. used a modified Morita function to model the waveform of transmembrane current in a cardiac muscle fiber [24], or van Veen et al. used exponential functions to represent single fiber action potentials of skeletal muscles [25]. For us, however, the described templates turned out to be not sufficiently versatile for the purpose of modeling the various shapes of local extracellular potential waveforms during depolarization as the dedicated signal model presented in this work. Fractionated electrograms have been analyzed by means of template matching and decomposition techniques. To detect fibrillation electrograms Houben et al. created a library of 128 single and double potentials [26]. Furthermore, continuous wavelet transform was used to analyze fibrillation electrograms [27]. A procedure to fit and subtract waveforms which is similar to the one presented in this work was done by Censi et al. to assess P-wave morphology in atrial fibrillation electrograms [28].

Evaluation of the Curve Fitting

Figure 4 and Table 2 clearly demonstrate the suitability of the introduced signal model for representing a wide variety of waveform shapes of nonfractionated electrograms, including starting, free running, and terminating/colliding wavefronts at different distances from the current sources. As expected, differences in the goodness of fit between atrial and ventricular electrograms were negligible. The noticeable residuals e_Φ in the case of a starting

wavefront, as shown in the left panels of Figure 4, are due to the stimulus artifact which coincides with the depolarization. In the used computer simulation setup this stimulus artifact is inevitable, whereas in electrograms representing starting activation wavefront at sites of tissue expansions, such effects would not occur.

Evaluation of the Decomposition of Fractionated Electrograms

Determination of Fractionation Index FI—We have found that the template based decomposition method presented in this study offers a more robust approach for quantifying the presence and degree of fractionation as compared to previously applied methods such as a simple threshold peak counting within the temporal derivative of $\Phi(t)$ where the choice of the threshold for deciding which peaks to include may cause a significant bias. Further, this novel decomposition approach allows to detect electrogram fractionation down to smaller differences in LAT's of the wavefront components causing the fractionation. Figure 5 (b) shows that the minimum LAT above which two contributing components can be discriminated, i.e. FI=2, increases with z . The minimum LAT that could be resolved was 0.6 ms at $z = 50 \mu\text{m}$, i.e. when both sources were located $50 \mu\text{m}$ away from the point of observation. The corresponding durations of depolarization of Φ_1 and Φ_2 were $t_{dep1} = t_{dep2} = 0.94$ ms. Using the peak counting method a minimum LAT of only 1 ms could be resolved (figures are not shown here). As shown in Figure 6 (a), local delays in activation caused by microobstacles can be expected in the range of 0.7 ms which is below the separability threshold of the peak counting method, thus underlining the benefits of the presented method. However, a thorough evaluation of the multitude of peak counting approaches in the literature as well as an optimization of the presented method e.g. in terms of template coefficients, has not been done.

Determination of Parameters from Decomposed Signals—Figure 5 (d) and (e) demonstrate that with increasing z the minimum LAT for which the errors of amplitude B , symmetry factor b , and duration of depolarization t_{dep} remain within the given tolerance increases, i.e. the separability decreases. This is due to the broadening of Φ_2 with z , caused by the relative reduction in weight given to local sources (compare Figure 4). The error tolerances for B , b , and t_{dep} ($\pm 20\%$, ± 0.2 , and $\pm 20\%$, respectively) were arbitrarily chosen. We suppose that during in-vitro experiments the chosen values represent the required accuracy to allow a clear qualitative classification of the micropropagation. Once a fractionated electrogram is decomposed, the parameters B and t_{dep} of the decomposed signals may allow to discriminate between local and distant activations, while the parameter b may allow to discriminate between starting, free running, and terminating/colliding wavefronts.

The presented decomposition method enables the estimation of these parameters with the required accuracy, even if they are masked within a fractionated electrogram.

Robustness against Noise—The minimum LAT's in Figure 5 (d) and (e) were calculated for noisy waveforms. The respective values for noise free waveforms (not shown) differ only marginally for the parameters obtained from Φ_{m2} for $z > 200 \mu\text{m}$, i.e. the

minimum LAT's are slightly lower, which suggests that the decomposition method is also well suited for electrograms recorded under experimental conditions.

Limitations

The curve fitting and the decomposition procedure for fractionated electrograms have been developed as methods for detailed analysis of local electrograms during sinus rhythm. The main goal has been to extract information from fractionated electrograms, which allows to elucidate propagation mechanisms and characterize tissue structure at a microscopic scale.

The suitability of the methods has been demonstrated for a microscopic size scale. It has not yet been investigated whether the method is applicable to electrograms as recorded at a larger size scale, for instance, intracardiac electrograms as recorded with clinical mapping systems. We have successfully applied the method to electrograms recorded experimentally from rabbit atria, however, not yet performed a careful validation of the decomposition method in an experimental context. For elucidating the basic principles underlying the presented method the use of computer simulation seems to be more appropriate, since all relevant contributing factors such as tissue structure and source distribution are exactly known with high spatio-temporal resolution which cannot be achieved with any concurrent experimental methodology.

Although the decomposition procedure has not been optimized in terms of computation time, the entire procedure, when applied to electrograms of a length of 5000 samples, never lasted longer than 1 s for FI=2 and number of iterations $n=5$, when executed on a standard desktop computer (Dell Optiplex 960). Despite the current performance lags real-time by roughly a factor of 5, it is expected that the method may be suited for on-line processing of local electrograms with additional careful code optimizations.

The most important limiting parameter underlying the presented decomposition method is the time difference LAT between the local activation times of two concurrent activation events relative to their duration of depolarization t_{dep} . If LAT is large enough the decomposition can be achieved more easily by windowing Φ , i.e. by temporal segmentation of the waveform into its components.

Another limiting parameter for a successful decomposition is the maximum value of FI (FI_{max}). In this work, the decomposition has been examined for $FI_{max}=3$. Experimental recordings ($n = 249$) taken from the endocardium of five rabbit atria during sinus rhythm showed distribution of FI=1, FI=2, and FI=3 of 63.9 %, 26.9 %, and 9.2 %, respectively [29]. Although a decomposition is feasible for $FI>3$, the interpretation of the resulting components becomes difficult.

Relevance for Electrophysiological Experiments

Pad size and inter-electrode spacing of multi-electrode sensor arrays and their distance to the bioelectric sources determine whether or not individual depolarization events can be resolved. Multi-electrode sensors with pad sizes of $18 \mu\text{m}$ and inter-electrode spacings of $50 \mu\text{m}$ allow to detect the presence of multiple wavefronts in the submillimeter range [5] at a distance $z = 50 \mu\text{m}$ away from the tissue surface.

From multiple simultaneously recorded electrograms, direction and velocity of propagating wavefronts can be determined in the case of nonfractionated electrograms [15]. The application of the decomposition method to fractionated multivariate local electrograms enables estimating local velocities and directions of each individual nonfractionated component. Thus, it is expected that this method allows the following additional characterizations of the microstructure at the recording site:

1. Classification of the microstructural makeup of fibrotic tissue such as a) longitudinally separating inlays of connective tissue, as in patchy fibrosis [30], b) crossing fibers, and c) microscopic obstacles leading to a zig-zag course of propagation.
2. Detection of components representing starting or terminating/colliding wavefronts. Thus, discontinuities in the underlying structure of the tissue, which are considered to be potential sites for unidirectional conduction block [31], may be revealed.

Conclusion

An analytic signal model for nonfractionated local unipolar electrograms has been introduced which allows to model a wide range of electrogram waveforms. Based on this signal model, a procedure for the decomposition of fractionated local electrograms has been presented which allows a detailed characterization of the microstructural makeup of the tissue at a given recording site in terms of the number of individual components and their morphological properties.

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Abbreviations

CARP	Cardiac Arrhythmia Research Package
FI	fractionation index
LAT	local activation time
LMCG	Lindblad et al. model
MSH	Mahajan-Shiferaw model

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Figure 1. Modeling of depolarization waveform $\Phi_m(t)$, $t = -5 \dots 5$ ms in steps of 0.01 ms
Panels (a)-(f) illustrate the composition of $\Phi_m(t)$ (h) by sigmoid functions $s_{PR}(t)$, $s_{PF}(t)$, $s_{NR}(t)$, and $s_{NF}(t)$. The coefficients for the sigmoids are indicated in panels (a), (b), (d), and (e). Panels (g)-(i) show resulting waveforms representing starting, free running, and terminating or colliding activation wavefronts and respective parameters $[a \ b \ c \ d]^T$.

Figure 2. Computer simulation setups

(a) Two 20 mm long strands of myocytes stimulated at $x = 0$ mm. Recording positions ($\times$) at the beginning (I, $x = 0$ mm), in the middle (II, $x = 10$ mm), and at the end of the strands (III, $x = 20$ mm) at a fixed distance of $50 \mu\text{m}$ from *strand 1* and a variable distance z from *strand 2*. (b) 2D sheet of tissue with embedded obstacles *obs1* and *obs2*, stimulated at the lower left corner. Fiber orientation is aligned with the x -axis. The observation area demarcated with dashed line was considered for signal analysis. Recording positions are $50 \mu\text{m}$ above the surface of the tissue. Dimensions are given in μm .

Figure 3. Decomposition of a fractionated waveform consisting of two components at the local activation times LAT_1 and LAT_2 , respectively; number of iterations $n=3$

For better visibility, the graphs show the development of the temporal derivatives of simulated waveform $\dot{\Phi}$ and modeled waveform $\dot{\Phi}_m$. The decomposition starts by fitting in the signal model at LAT_1 (panel $j=1$). The modeled waveform $\Phi_{m,1}$ is subtracted from Φ and LAT_2 is adapted before curve fitting centered at LAT_2 is performed ($j=2$). The third row shows the result of the fitting procedure after each iteration i . The diagram below displays the changes in error (sse) and correlation coefficient r between the simulated waveform Φ and the modeled waveform Φ_m (sse_{Φ} and r_{Φ}), as well as between their derivatives $\dot{\Phi}$ and $\dot{\Phi}_m$ ($sse_{\dot{\Phi}}$ and $r_{\dot{\Phi}}$).

Figure 4. Modeling of nonfractionated depolarization waveforms

Simulated waveforms Φ (blue line), modeled waveforms Φ_m (red), and residuals e_Φ (green) at start (recording position I: $x = 0$ mm), middle (II: $x = 10$ mm), and end of the strand (III: $x = 20$ mm) at distances $z = 5, 250$, and $500 \mu\text{m}$. The amplitude scales are arbitrary and different for different z .

Figure 5. Limitations for the decomposition of fractionated local electrograms

(a) Principle of synthesizing fractionated electrograms Φ_{12} by adding Φ_1 and Φ_2 as evoked by *strand 1* and *strand 2* and decomposing into Φ_{m1} and Φ_{m2} . (b) Fractionation index (FI) for the range of ΔLAT and z . (c) Φ_1 , Φ_2 , and Φ_{12} as well as Φ_{m1} , Φ_{m2} , and Φ_{m12} for points A, B, and C. (d) ΔLAT_{min} : Lower limit of ΔLAT for which the errors of amplitude B_1 , symmetry b_1 , and depolarization time t_{dep1} determined from Φ_{m1} go below the given tolerances ($\pm 20\%$ for B and t_{dep} , ± 0.2 for b). (e) ΔLAT_{min} for parameters B_2 , b_2 , and t_{dep2} determined from Φ_{m2} .

Figure 6. Spatial distribution of electrogram fractionation of Φ caused by microobstacles
 (a) Isochrones of local activation time derived from transmembrane voltages. The bold isochrone highlights wavefront fragmentation into three components α , β , and γ . (b) Temporal derivatives $\dot{\Phi}$ from local electrograms recorded at positions $\mathbf{p}_1 - \mathbf{p}_{15}$. Amplitude scales are arbitrary. (c) Fractionation index of Φ (FI). (d), (e) Sum of squared errors of Φ (sse_{Φ}) and $\dot{\Phi}$ ($sse_{\dot{\Phi}}$). (f), (g) Correlation coefficient of Φ (r_{Φ}) and $\dot{\Phi}$ ($r_{\dot{\Phi}}$).

Table 1
Choice of start, minimum, and maximum coefficients for the curve fitting process.

Coefficient	Related property	Initialization	Minimum value	Maximum value
a	Φ_{pp} : amplitude of $\Phi(t)$	$a_1 := \frac{\Phi_{pp}}{2}$	$a_l := \frac{\Phi_{pp}}{400}$	$a_h := 4 \cdot \Phi_{pp}$
b	Φ_{max} : magnitude of positive phase of $\Phi(t)$	$b_1 := \frac{\Phi_{max}}{\Phi_{pp}}$	$b_l := \frac{1}{1000} \frac{\Phi_{max}}{\Phi_{pp}}$	$b_h := 20 \frac{\Phi_{max}}{\Phi_{pp}}$
c	$ \dot{\Phi}_{min} $: magnitude of negative phase of $\dot{\Phi}$	$c_1 := 5 \frac{ \dot{\Phi}_{min} }{\Phi_{pp}}$	$c_l := \frac{1}{5} \frac{ \dot{\Phi}_{min} }{\Phi_{pp}}$	$c_h := 20 \frac{ \dot{\Phi}_{min} }{\Phi_{pp}}$
d	$ \Phi_{min} $: magnitude of negative phase of $\Phi(t)$	$d_1 := \frac{ \Phi_{min} }{\Phi_{pp}}$	$d_l := \frac{1}{1000} \frac{ \Phi_{min} }{\Phi_{pp}}$	$d_h := 20 \frac{ \Phi_{min} }{\Phi_{pp}}$

Table 2
Goodness of sse_{Φ} , r_{Φ} of Φ and $sse_{\dot{\Phi}}$, $r_{\dot{\Phi}}$ of derivative $\dot{\Phi}$, for nonfractionated Φ obtained from computer simulations using atrial (LMCG) and ventricular (MSH) kinetic models at recording sites I, II, and III.

	$z(\mu\text{m})$	I: $x = 0$ mm sse_{Φ} , r_{Φ} / $sse_{\dot{\Phi}}$, $r_{\dot{\Phi}}$	II: $x = 10$ mm sse_{Φ} , r_{Φ} / $sse_{\dot{\Phi}}$, $r_{\dot{\Phi}}$	III: $x = 20$ mm sse_{Φ} , r_{Φ} / $sse_{\dot{\Phi}}$, $r_{\dot{\Phi}}$
LMCG	500	0.197, 0.904 / 0.281, 0.85	0.011, 1 / 0.003, 0.999	0.008, 0.998 / 0.031, 0.984
	250	0.111, 0.944 / 0.367, 0.795	0.009, 1 / 0.003, 0.999	0.006, 1 / 0.015, 0.993
	5	0.041, 0.98 / 0.587, 0.651	0.009, 1 / 0.006, 0.997	0.009, 0.997 / 0.031, 0.986
MSH	500	0.022, 0.99 / 0.231, 0.889	0.018, 1 / 0.008, 0.997	0.061, 0.97 / 0.179, 0.9
	250	0.032, 0.984 / 0.334, 0.82	0.018, 1 / 0.006, 0.998	0.069, 0.988 / 0.07, 0.963
	5	0.025, 0.987 / 0.449, 0.742	0.008, 0.999 / 0.019, 0.991	0.075, 0.998 / 0.025, 0.997