Optimizing Multiscale Entropy Approach for Rotor Core Identification using Simulated Intracardiac Electrograms

Vasanth Ravikumar[1] and Elena G. Tolkacheva[2], *Member, IEEE*

***Abstract*— Atrial Fibrillation (AF) is most common sustained cardiac arrhythmia and a precursor to many fatal cardiac conditions. Catheter ablation, which is a minimally invasive treatment, is associated with limited success rates in patients with persistent AF. Rotors are believed to maintain AF and core of rotors are considered to be robust targets for ablation. Recently, multiscale entropy (MSE) was proposed to identify the core of rotors in ex-vivo rabbit hearts. However, MSE technique is sensitive to intrinsic parameters, such as scale factor and template dimension, that may lead to an imprecise estimation of entropy measures. The purpose of this research is optimize MSE approach to improve its accuracy and sensitivity in rotor core identification using simulated EGMs from human atrial model. Specifically, we have identified the optimal time scale factor (τ_{opt}) and optimal template dimension (T_{opt}) that are needed for efficient rotor core identification. The τ_{opt} was identified to be 10, using a convergence graph, and the T_{opt} (~20 ms) remained the same at different sampling rates, indicating that optimized MSE will be efficient in identifying core of the rotor irrespective of the signal acquisition system.**

Keywords – Atrial Fibrillation, Multiscale Entropy, Rotor

INTRODUCTION

Atrial Fibrillation (AF) is the most common type of cardiac arrhythmia prevalent in United States and is associated with increased risk of stroke and precursor to other fatal cardiac diseases. According to an estimate in 2014, 2.7 to 6.1 million people in the United States are afflicted by AF [1, 2]. Recent scientific studies indicate the presence of localized sources (electrical rotors) is responsible for sustaining AF in both animals and humans [3, 4].

Catheter ablation, which is a minimally invasive therapy for AF termination, is shown to have an increased success rate in patients with intermittent AF, where the triggered activity is originated close to the pulmonary vein (PV) regions [5, 6]. However, in the case of persistent AF, core of rotors may arise outside the PV regions, thus decreasing the success of AF ablation therapy [7]. Hence, it is important to identify targets for ablation outside the PV region to improve the success of catheter-based ablation therapy.

Conventional mapping for AF ablation is challenging, because clinical intracardiac electrograms (EGMs) may not always represent local activation, thus leading to false identification of AF maintenance sites. On the other hand, non-contact methods may distort the EGMs recorded, thus leading to poor signal to noise ratio [2, 8]. Currently used electro-anatomical mapping techniques for identification of ablation sites, such as local activation time, complex fractionated EGMs and dominant frequency (DF), are known to have limitations that prevent the accurate identification of the cores of rotors, due to noise, misleading phase and signal distortion [9].

Recently, we proposed to use a multi-scale entropy (MSE) approach to improve identification of the core of the rotor [11]. We validated this technique in *ex-vivo* animal experiments, in which high-resolution optical mapping was used to visualize electrical activity in the hearts. We demonstrated that MSE approach is not only able to accurately identify the cores of both stationary and meandering rotors in ex-vivo rabbit hearts [10, 11], but also is robust with respect to reduced spatial and temporal resolutions [11]. Therefore, it was suggested that MSE can potentially be implemented on intracardiac clinical EGMs. However, further optimization is required for MSE approach to have better performance.

We have developed an optimized MSE approach to improve its accuracy and sensitivity in rotor core identification using simulated EGMs from human atrial model. First, we identified the optimal time scale factor (τ_{opt}). Then using the τ_{opt} measured, optimal template dimension (T_{opt}) that is needed for efficient rotor core identification is evaluated. Then we show that optimized MSE will be efficient in identifying core of the rotor irrespective of the EGM signal acquisition system.

I. METHODS

A. *Numerical Simulations:*

Electrical activity in a 25x25mm isotropic human atrial tissue model was simulated using an extended model that incorporates both fibroblasts and myocytes, as previously published [12]. A bi-layer anatomical model was adopted, in which fibroblasts are aligned on top and in a parallel matrix to a monolayer of myocytes. The extra-cellular potential, φ_e, and the transmembrane voltage (V_m), were modeled using the bi-domain coupled equations [13].

The local number of fibroblasts connected to a single myocyte was adjusted to maintain and simulate a stationary sustained rotor. The rotor was induced using the S1 S2 stimulations as suggested in [13]. The 25x25mm 2-dimensional (2D) map is represented by a 100x100 pixel image with each pixel containing V_m signals for a 1.7 second time period. Fig 1a shows the 2D V_m map for the numerically simulated stationary rotor.

*Research supported by National Science Foundation DCSD 1662250 grant (EGT), and Institute for Engineering in Medicine grant (EGT).

1 V. Ravikumar is with the Department of Electrical Engineering, University of Minnesota, Minneapolis, MN 55455 USA. (Phone: 612-624-4122; e-mail: ravik014@umn.edu).

2 E.G. Tolkacheva is with the Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455 USA. (Phone: 612-624-4122; e-mail: talkacal@umn.edu).

B. "True" core identification:

The core of the rotor is the spatial area around which the rotational electrical activity sustains in the heart during AF and other arrhythmias. The "true" core of the rotor was determined as demonstrated previously [14], by implementing Hilbert transform over entire duration of the movie and identifying the phase singularity (PS) points based on numerical simulation of V_m obtained previously. Fig. 1b shows the location of the "true" core of the rotors (white colored area) for the simulated stationary rotor.

C. Simulated Unipolar EGMs:

Simulated unipolar EGMs (UniEGMs) were obtained from the numerical simulations by the summation of V_m dipoles weighted by the direction $\vec{r}$ and distance r with respect to the measuring point using 2D linear gradient $\vec{\nabla}$ [12], under the assumption of a homogeneous, unbounded and quasistatic substrate. The UniEGMs are computed at each pixel location assuming the measuring point to be at the current pixel and the reference is assumed to be at infinite distance:

$$UniEGM = \sum_{\vec{r}} \left(\frac{\vec{r}}{r^3}\right) . \vec{\nabla} V_m \qquad (1)$$

Fig. 2 a,b show representative examples of simulated V_m and UniEGMs signals at the same pixel location indicated by a yellow * in Fig.1a, respectively. It is to be noted that the V_m signal has information content in repolarization phase indicated by the red part of the zoomed in signal whereas the information is diminished or absent in the UniEGMs signal during the repolarization. The sampling rate of the signals was 1000 samples per second.

D. MSE Approach:

The MSE approach is briefly described below (see [10] for more details).

Let $x = \{x_1, x_2, \ldots, x_N\}$ represent the EGM time series of length N.

The moving average time series z^{τ}, is calculated for the chosen time scale factor "τ" as

$$z_j^{\tau} = \frac{1}{(2\tau+1)} \sum_{i=j}^{2\tau+1} x_i, \qquad (2)$$

where $1 \leq j \leq N - \tau$ and $i = 1,2,3\ldots, N$

Template vectors $y_k^m(\delta)$ with dimension m and delay δ are constructed from at z^{τ} each specific τ as the following:

$$y_k^m(\delta) = \{z_k^{\tau}\, z_k^{\tau} + \delta \ldots z_k^{\tau} + (m-1)\delta\}, \qquad (3)$$

where $1 \leq k \leq N - m\delta$.

The Euclidian distance $d_{ij}^m(\delta)$ for each template vector pairs is calculated using infinity norm and matched template vector pairs are computed based on a tolerance threshold r, chosen to be 0.2 times standard deviation of EGM. The total number of matched pair vectors is denoted by n (m, δ, r). MSE is calculated as follows:

$$MSE = -\ln\left(\frac{n(m+1,\delta,r)}{n(m,\delta,r)}\right) \qquad (4)$$

E. Quantitative measures of core identification:

The sensitivity and specificity of the MSE approach was calculated by comparing the "true" core of the rotor with the core of rotor identified by the MSE technique. The equations for sensitivity and specificity are as follows:

$$Sensitivity = \frac{TP}{TP+FN}, \qquad (8)$$

$$Specificity = \frac{TN}{TN+FP}, \qquad (9)$$

where True Positive (TP) are the points that are identified as a core both by MSE approach and by a PS analysis (see "true" core of the rotor in Fig.1b); True Negative (TN) are the points that are identified as a periphery of the rotor both by MSE and PS analysis; False Negative (FN) are the points that are identified as a "true" core of the rotor by the PS analysis, but not by the MSE approach; and False Positive (FP) are the points that are identified as a core of the rotor by MSE, but not by the PS analysis. The specificity was maintained to be above 90% in all further analysis, to keep the false core identifications at the minimum.

F. Analysis at different sampling rates:

We investigated the efficacy of MSE optimization procedure with respect to different sample rate, since different signal acquisition systems have different sampling rates when recording clinical EGM signals. For this, the UniEGMs were resampled at different sampling rates (500, 1000, 1500 and 2000 samples/second), and optimal τ (τ_{opt}) was calculated for each sampling rate using the convergence graph (sensitivity vs τ plot). τ_{opt} was defined as the maximum τ for which the sensitivity does not increase by more than 0.01% when compared to the next τ. The dimension of template vector y_k^m (see Eq. 3) was set such that it is equal to 2τ+1. The optimal template dimension (T_{opt}) needed under different sampling rates of input EGMs was identified to evaluate the robustness of the optimized MSE for different EGM acquisition systems.

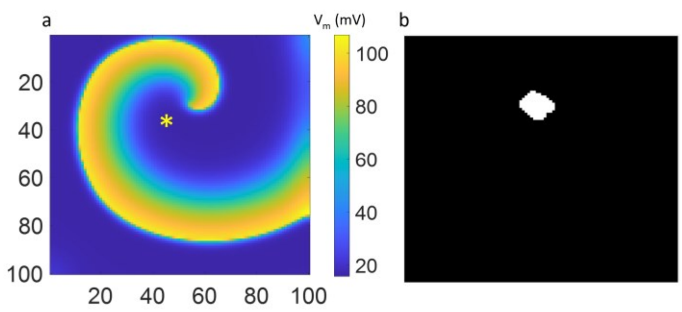

Figure 1. (a) 2D V_m map of the simulated stationary rotor. (b) The "true" core of the rotor indicated by the white area.

II. RESULTS

A. Rotor Identification at different τ:

Fig. 3 shows the 2D MSE map at τ = 1, that was obtained using the simulated UniEGMs for the stationary rotor and the white boundary encloses the identified core. The core is identified as previously done in [11]. The identified core is clearly smaller in comparison to the "true" core of the rotor in Fig. 1b.

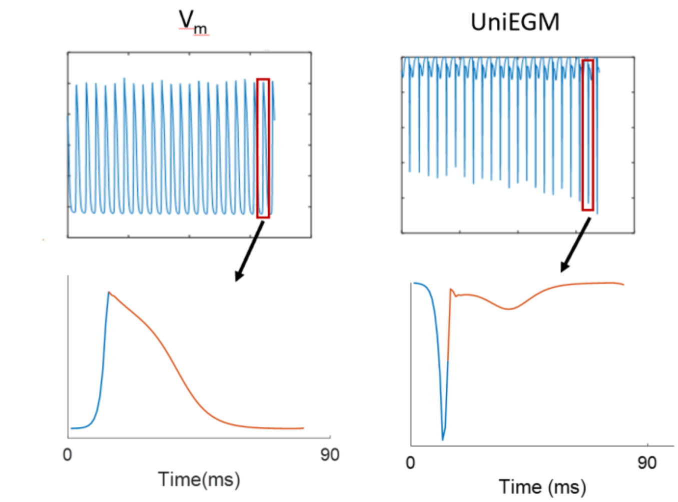

Figure 2. Representative examples of V_m at one pixel (see yellow * Fig. 1.) along with a single period cycle (left). Representative examples of UniEGM at the same pixel along with a single period cycle (right). Red line segment in zoomed images show the repolarization phase.

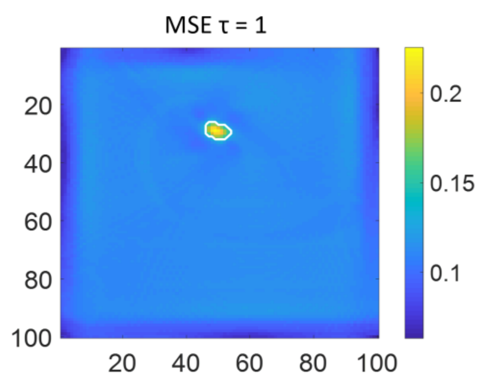

Figure 3. 2D MSE Map for the simulated stationary rotor using UniEGMs at $\tau = 1$. Core enclosed by white boundary.

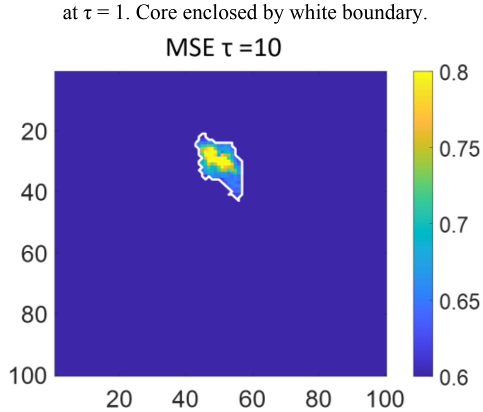

Figure 4. 2D MSE Map for the simulated stationary rotor using UniEGMs at $\tau = 10$. Core enclosed by white boundary

Fig. 4 shows the 2D MSE map at $\tau = 10$, that was obtained using the simulated UniEGMs for the stationary rotor and the white boundary encloses the identified core. The identified core is closer in size to the "true" core of the rotor in comparison to $\tau = 1$ identification.

B. Optimization of rotor core identification

The sensitivity of MSE in identification of the core of the stationary rotor at a sampling rate of 1000 is shown in Fig. 5 as a function of τ. Note that the sensitivity is low at small τ, and increases as τ increases, converging at ~ 93%.

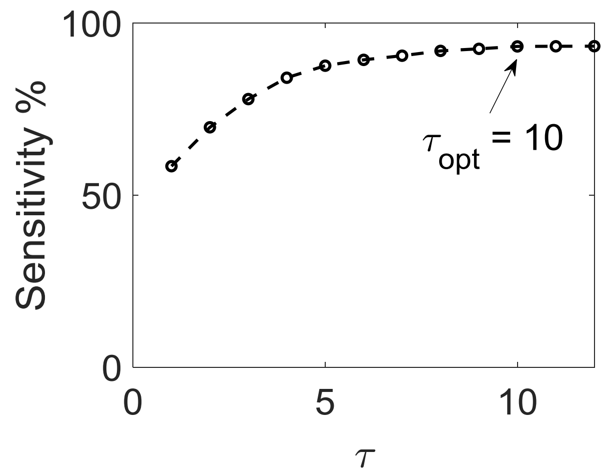

Figure 5. Sensitivity as function of τ in stationary rotor core identification using the MSE approach. Sensitivity converges at ~93% with τ_{opt} =10.

The τ_{opt} was calculated to be 10 because the percentage increase in sensitivity for the next τ was not significant. Further, larger the τ, number of computations required for calculating MSE increases, thus, reducing the computational efficiency.

C. τ_{opt} at different sampling rates

TABLE 1 τ_{OPT} AT DIFFERENT SAMPLING RATES

Sampling Rates (samples/s)	τ_{opt}	T_{opt} *(ms)*
500	4	18
1000	10	21
1500	15	21
2000	19	19

Table 1. shows the τ_{opt} obtained at each sampling rate and the corresponding T_{opt}. It is evident that in each case T_{opt} has very similar time lengths. This indicated that the optimized MSE captures the same critical complexity of a signal irrespective of the sampling rate of the inputs. Thus, optimization technique eliminates the effect of sampling rate on the MSE analysis results and helps identify critical complexity of the UniEGMs. Therefore, here we present a robust method for rotor core identification irrespective of the sampling rate of the input signals in use.

III. Discussion

In this work, we developed an optimization of the MSE approach to improve its accuracy and sensitivity in cores identification using simulated EGMs from human atrial model. Specifically, we have identified the optimal time scale factor (τ_{opt}) and optimal template dimension (T) that are needed for efficient rotor core identification. The τ_{opt} was identified using a convergence graph and the T_{opt} remained the same at different sampling rates, indicating that optimized MSE will be efficient in identifying core of the rotor irrespective of the signal acquisition system.

Previously the MSE approach was used to differentiate AF from normal sinus rhythms using a single lead ECG signals [10]. It was also used for identification of core of rotors in ex-vivo rabbit hearts [11]. In these studies, the τ_{opt} was 3 and 2, respectively. But the signals used for the rotor core detection has different morphology and complexity compared to the EGM signals that are usually used in clinical settings. From Fig. 2, it is clear that the information content in the repolarization phase of the V_m signal is missing or diminished in the UniEGMs. This causes changes in the complexity of the signals measured by the MSE approach. Therefore, the optimization step was important and implemented to identify the τ_{opt} of MSE approach for rotor core identification using UniEGMs.

The sensitivity measures are computed to evaluate the performance of the MSE method in identification of rotor cores with respect to the different τ. The sensitivity measures help in identifying the percentage of true spatial area of the core that is identified by our MSE method. High specificity value represents the minimization of false core identifications, that is peripheral areas that are falsely identified to be the core. High specificity value is desired, to reduce the number of false identification of cores thus decreasing the probability of ablating peripheral spatial area of the rotors. Hence, throughout our analysis we have always maintained the specificity value to be above 90%.

For complete AF termination the conduction block must extend from the core region to at least one of the unexcited boundaries of the rotational site. This can be achieved by performing a linear conduction block that extends from core of the rotational site to the periphery. The optimized MSE approach clearly distinguishes between the core of the rotor and its periphery using UniEGMs, this will enable us to identify the core region and an unexcitable boundary and perform an ablation that leads to successful AF termination.

IV. Conclusion

Optimization of MSE is important for the successful identification of core of the rotors using the EGM signals. Further, validation of this approach is required in persistent AF patients using clinically recorded EGM signals, which will lead us towards identification of possible active sites that cause AF and improve the catheter ablation therapy.

Acknowledgements

We thank Dr. Sharon Zlochiver who helped us with the simulations of stationary rotor and the Human atrial model.

This work was supported by the NSF DCSD 1662250 (E.G.T.); IEM grants from University of Minnesota (E.G.T.).

References

[1] Ganesan, A. N., Kuklik, P., Lau, D. H., Brooks, A. G., Baumert, M., Lim, W. W., Thanigaimani, S., Nayyar, S., Mahajan, R., Kalman, J. M., Roberts-Thomson, K. C., and Sanders, P., 2013, "Bipolar Electrogram Shannon Entropy at Sites of Rotational Activation Implications for Ablation of Atrial Fibrillation", Circ. Arrhythmia Electrophysiol., 6(1), pp. 4857.

[2] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study." JAMA. 2001; 285:23702375.

[3] Pandit, S. V., and Jalife, J., 2013," Rotors and the Dynamics of Cardiac Fibrillation," Circ. Res., 112(5), pp. 849862.

[4] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659666.

[5] Zaman, J. A. B., Peters, N. S., Narayan, S. M." Rotor mapping and ablation to treat atrial fibrillation". Current Opinion in Cardiology, 30(1), 2432 (2015).

[6] Haissaguerre M, Shah DC, Jais P, Hocini M, Yamane T, Deisenhofer I, Garrigue S, Clementy J. Mapping-guided ablation of pulmonary veins to cure atrial fibrillation. American Journal of Cardiology 2000;86.

[7] Willems S, Drewitz I, Steven D, Hoffmann BA, Meinertz T, Rostock T. Interventional therapy of atrial fibrillation: possibilities and limitations. Dtsch Med Wochenschr. 2010 Mar; 135 Suppl 2: S48-54.

[8] Chou CC, Chang PC, Wen MS, Lee HL, Chen TC, et al. "Epicardial ablation of rotors suppresses inducibility of acetylcholine induced atrial fibrillation in left pulmonary vein-left atrium preparations in a beagle heart failure model." J Am Coll Cardiol (2011) 58: 158-166.

[9] Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel W-J, et al. (2012d) "Treatment of Atrial Fibrillation by the Ablation of Localized Sources: The Conventional Ablation for Atrial Fibrillation with or Without Focal Impulse and Rotor Modulation (CONFIRM) Trial." J Am Coll Cardiol 60: 628-636.

[10] Arunachalam SP, Kapa S, Mulpuru SK, Friedman PA, Tolkacheva EG. Improved Multiscale Entropy Technique with Nearest-Neighbor Moving-Average Kernel for Nonlinear and Nonstationary Short-Time Biomedical Signal Analysis. J Healthc Eng. 2018.

[11] E. M. Annoni, S. P. Arunachalam, S. Kapa, S. K. Mulpuru, P. A. Friedman and E. G. Tolkacheva, "Novel Quantitative Analytical Approaches for Rotor Identification and Associated Implications for Mapping," in IEEE Transactions on Biomedical Engineering, vol. 65, no. 2, pp. 273- 281, Feb. 2018.

[12] Greisas A, Zafrir Z, Zlochiver S. Detection of abnormal cardiac activity using principal component analysis -- a theoretical study. IEEE Transactions on Biomedical Engineering. 2015; 62: 154-164.

[13] MacCannell KA, Bazzazi H, Chilton L, Shibukawa Y, Clark RB, Giles WRA. Mathematical Model of Electrotonic Interactions between Ventricular Myocytes and Fibroblasts. Biophysical Journal. 2007; 92: 4121–4132.

[14] Unger L, Rottmann M, Seemann G, Dossel O. Detecting phase singularities and rotor center trajectories based on the Hilbert transform of intraatrial electrograms in an atrial voxel model. Current Directions in Biomedical Engineering, 2015: 1: 38-41.