Nonlinear measures characterize atrial fibrillatory dynamics generated using fractional diffusion

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Abstract— **Computational simulations are used as tool to study atrial fibrillation and its maintaining mechanisms. Phase analysis has been used to elucidate the mechanisms by which a reentry is generated. However, clinical application of phase mapping requires a signal preprocessing stage that could affect the activation sequences. In this work we use the fractional diffusion equation to generate fibrillatory dynamics, including stable and meandering rotors, and multiple wavelets, by varying the order of the spatial fractional derivatives obtaining different complexity levels of propagation in a 2D domain. We applied nonlinear measures to characterize the propagation patterns from electrograms. Our results show that electroanatomical maps constructed using approximate entropy and multifractal analysis, are able to detect the tip of stable and meandering rotors, and to mark the occurrence of collisions and wave breaks. Application of these signal processing techniques to clinical practice is feasible and could improve atrial fibrillation ablation procedures.**

Keywords— **atrial fibrillation, nonlinear measures, rotors, phase analysis, fractional diffusion**

I Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia observed in clinical practice [1]. There is experimental and theoretical evidence that complex propagating patterns during an AF episode, are derived from spiral waves of self-organized and high-frequency drivers known as rotors [2]. Phase maps have been widely used to elucidate the mechanisms by which a rotor is generated. However phase analysis requires high spatial resolution and an additional signal conditioning stage that could lead to changes in activation sequence [3].

Computational models are used as tool to study rotors and other arrhythmogenic mechanisms [4], including ectopic foci and multiple wavelets. In order to simulate complex propagation patterns, electrophysiological heterogeneity is implemented by varying the parameters of the cellular model, and coupling the system using standard difussion equation, which implies an elaborated design of the cardiac model. Fractional calculus generalizes the standard diffusion equation by letting the order of the spatial derivative be a real number. It has been reported that through this approach, different propagation dynamics can be obtained [5]. However, studies of systems involving cardiac membrane formalisms are scarce.

In this work, we simulated episodes of fibrillatory propagation using fractional reaction-difussion equation and Fenton-Karma cardiac celular model. Irregularity maps were built applying nonlinear measures, such as approximate entropy (ApEn) [6] and multifractal analysis (MF) [7], calculated from virtual unipolar electrograms (EGM). By applying a dynamical approach, our results evinced that nonlinear measures were able to characterize complex propagating patterns using phase analysis as gold standard method.

II Materials and Methods

We designed a cardiac excitable tissue through a 2D regular domain of cardiomyocytes. Action potential (AP) propagation was implemented using fractional diffussion operator which involves spatial fractional derivatives. Complexity of fibrillatory dynamics was controlled varying the order of the spatial derivative. We performed phase singularity (PS) tracking to quantify complexity of propagation. EGM from each simulated episode were calculated and their degree of irregularity was measure using ApEn and MF.

A *Electrophysiological computational model*

Propagation of AP was modeled using 2D isotropic fractional diffusion equation:

$$\frac{\partial U}{\partial t} = D\left(\frac{\partial^{\alpha} U}{\partial x^{\alpha}} + \frac{\partial^{\alpha} U}{\partial y^{\alpha}}\right) - (I_{ion} + I_{stim}) \qquad (1)$$

where U is the transmembrane potential, I_{stim} is the stimulus current, and x and y the spatial variables. The ionic current i_{ion} was defined by Fenton-Karma membrane formalism [8]. Fractional derivative order α was varied within the interval

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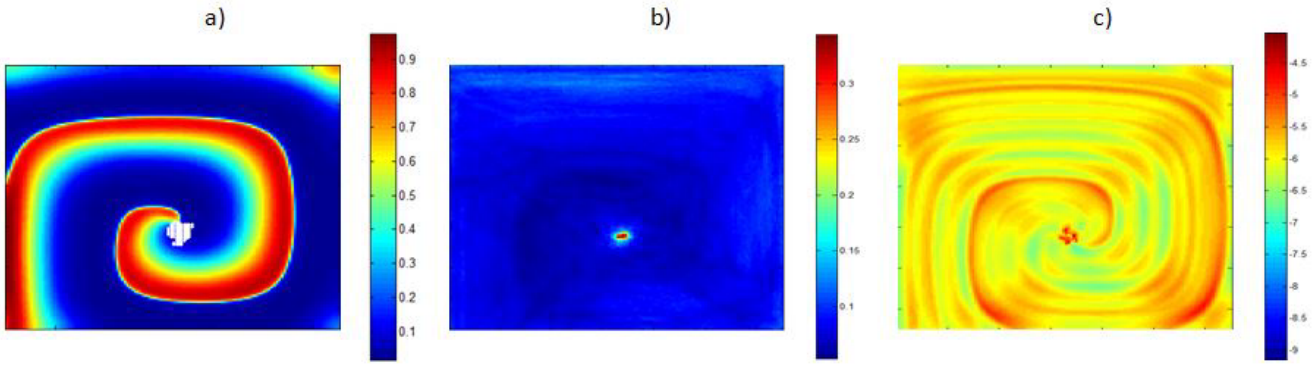

Fig. 1: Atrial Fibrillatory episode (AF1P3) is sustained by a stable clockwise rotor. a)Simulated episode, the white path represents the phase singularity. b) Irregularity map of approximate Entropy. c) Irregularity map of Multifractal index.

[1,2]. Diffusion coefficient D was fixed to obtain a conduction velocity of 60 cm/s for $\alpha = 2$.

B *Tissue domain and stimulation protocol*

Atrial tissue was represented by a $2x2\ cm^2$ domain, discretized into a $130x130$ mesh. Fibrillatory episodes were generated through $S1-S2$ protocol. $S1$ was a train of five pulses at the left boundary of the tissue. $S2$ was a single pulse applied after $S1$, at the inferior half of the middle vertical line of the domain.

C *Phase singularity detection*

Phase analysis provides information about the propagation dynamics by representing the state of the system as a phase angle, revealing mechanistic aspects of fibrillatory events [9]. If a functional reentry is present, the spatial distribution of phase will contain one or more singularities, which are points surrounded by tissue with phases ranging from $-\pi$ to π.The phase singularity (PS) marks a region where the phase is undefined. We obtained the phase maps from membrane potentials and singularity tracking was implemented using the topologic charge formulation [10].

D *Electrograms, approximate entropy and multifractal analysis*

Unipolar EGM were calculated as the extracellular potential Φ_e registered at the point r':

$$\Phi_e(r') = -\frac{1}{4\pi}\frac{\sigma_i}{\sigma_e}\iiint \nabla U \cdot \nabla\left(\frac{1}{r'-r}\right) dxdydz \qquad (2)$$

where r corresponds to a source point, and σ_i y σ_e are the intra and extracellular conductivities, respectively. Calculated EGM have temporal resolution of 1 ms. 16900 registry points (130x130) were located 0.1 mm above the tissue.

Fractionation levels in EGM were assessed using approximate entropy (ApEn) and multifractal analysis (MF). ApEn is a nonlinear statistic proposed by Pincus [6]. Calculation of $ApEn(N,m,r)$ depends on three parameters: number of data points N, embedding dimension m and threshold r. $ApEn(500,3,0.30)$ was used as reported in a previous work [11].

Multifractal h-fluctuation index (hFI) was implemented accordingly with the parameters defined in [12]. The hFI extracts information for the shape of the singularity spectrum $f(\alpha)$ which is a generalization of fractal dimension when statistical scaling is characterised by different Hurst exponents.

EGM irregularity maps were generated considering a 500 points window applied to each EGM signals in order to calculate ApEn and MF-a. Maps of both measures were built applying their respective ranges to a color scale.

E *Numerical methods*

Fractional diffusion equation was numerically solved using a semi-spectral approach, in which spatial variables in equation 1 were transformed into the frequency domain, time derivative was discretized using Euler method and inverse-transforming to the spatial domain [13]. Time step was fixed to 0.01 ms.

III Results

A *Simulated fibrillatory episodes*

Three fibrillatory episodes were generated using values of α equal to 1.3, 1.4 and 1.5, Referred to hereinafter as AF1p3,

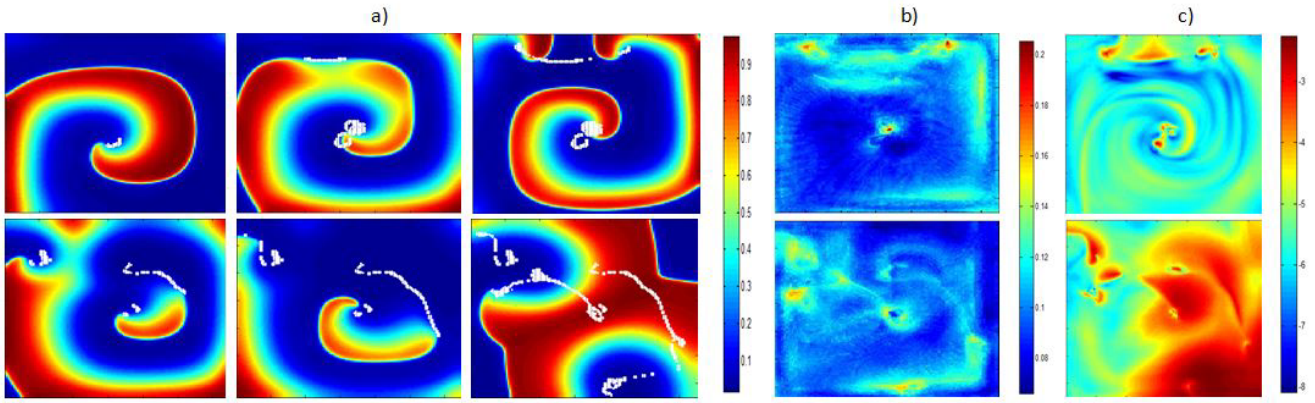

Fig. 2: Atrial fibrillatory episode (AF1P4) initiate with a clockwise rotor which breaks in several waves leading to new microreentrants. Top and bottom rows correspond to two consecutive 500 ms of simulation. a)Simulated episode, the white path represents the phase singularity. b) Irregularity map of approximate Entropy. c) Irregularity map of Multifractal index.

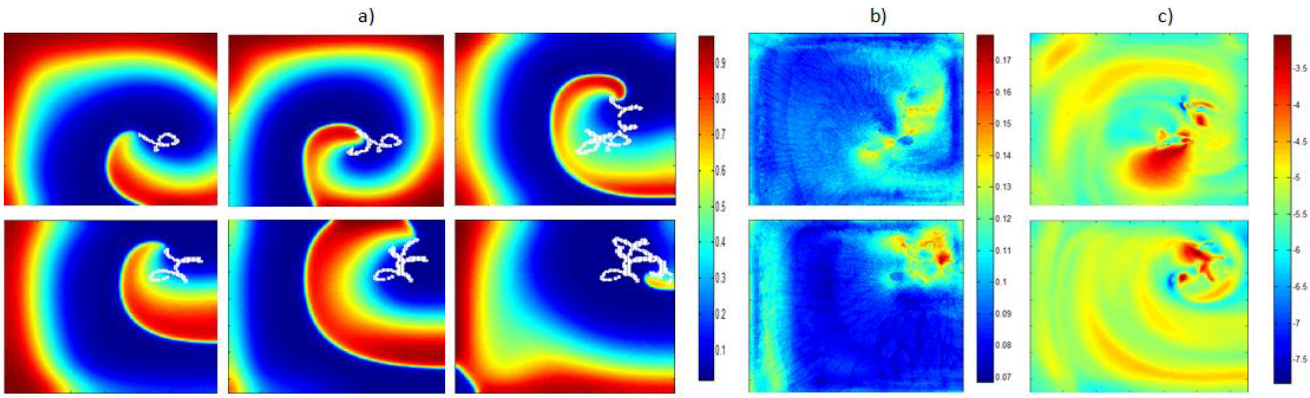

Fig. 3: Atrial Fibrillatory episode (AF1P5) is sustained by a meandering rotor. Top and bottom rows correspond to two consecutive 500 ms of simulation. a)Simulated episode, the white path represents the phase singularity. b) Irregularity map of approximate Entropy. c) Irregularity map of Multifractal index.

AF1p4 and AF1p5, respectively. AF1p3 is sustained by a stable clockwise rotor (Figure 1a). AF1p4 initiate with a clockwise rotor which breaks in several waves leading to new microreentrants (Figure 2a). AF1p5 is sustained by a meandering rotor. (Figure 3a). Phase maps were generated for each episode. Figures 1a, 2a and 3a mark the location of the PS motion as a white path. AF1p4 contains a scattered distribution of PS paths, compared to AF1p3 and AF1p5; marking fibrillatory dynamics of greater complexity. In Figures 2 and 3, top and bottom rows correspond to two consecutive 500 ms of simulation.

B Nonlinear meausures maps

Irregularity maps were generated for 1000 ms of each simulation. For episode AF1p3: ApEn detects the core of stable rotor through highest ApEn values (Figure 1b); while high hFI values mark the core and the profile of spiral propagation (Figure 1c). For episode AF1p4: within the first 500 ms interval, highest ApEn and hFI values (top Figure 2b-c) detect the cores of microreentrants waves (top-right Figure 2a); within the second 500 ms interval, the core of a microreentrant wave is also highlighted by high ApEn values, while middle ApEn values (bottom Figure 2b) correspond with the path of the singularity (bottom-right Figure 2a). For episode AF1p5: highest ApEn and hFI values (Figure 3b-c) highlight the meandering path of the rotor core (Figure 3a). Moreover, hFI depicts the spiral propagation of the AP.

IV Discussion

In this study, we performed computational simulations to generate three fibrillatory episodes with different AP prop-

agation complexity, by implementing fractional reaction-diffusion equation. Currently, phase mapping come up as primary technique for characterizing fibrillatory propagation. In order to obtain proper phase calculation, monophasic recordings are needed [3]. Since membrane potentials are available from computational simulations, phase map analysis is straightforward. However, for clinical procedures, phase analysis requires a EGM preprocessing stage that can affect the activation patterns [3, 9]. A recent clinical phase mapping study [14] shows controversial results, due to its non-disclosed signal preprocessing methods [15] and non-reproducibility. Thus phase analysis feasibility requires further validation.

In this work, we applied phase analysis for relating nonlinear measures outcomes with arrhythmogenic mechanisms. We show that quantification of EGM complexity using nonlinear measures can reveal mechanistic aspects of fibrillatory events. We showed that ApEn and MF maps contain information about the propagating patterns: ApEn values can be related with complex propagation where the highest values correspond with rotor tips; while intermediate values highlight waves shock and wave breaks. From MF maps, rotation direction can be defined together with the location of rotor tips. Thus, characterization of fibrillatory conduction dynamics is possible through nonlinear measures. Moreover, ApEn and MF can be applied to signals obtained using commercial register systems [16], therefore their clinical application is feasible.

V Conclusions

Our findings evince that fractional calculus can be used to generate arrhythmogenic mechanisms and these propagation patterns can be characterized trough nonlinear measures such as ApEn and MF. Future studies are needed to translate these results to clinical procedures.

Conflict of Interest

The authors declare that they have no conflict of interest.

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