

Fractional Diffusion Modulates distribution of Action Potential Duration in Fibrotic Atrial Strands

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Abstract

Background: *Fibroblast proliferation, as a component of the fibrotic process, plays a role in structural remodeling, but also can alter the electrophysiology of the cardiomyocytes.* **Aim:** *To study the action potential duration dispersion (dAPD) in fibrotic atrial strands, where fibroblasts exerts both, structural and electrical influence on the propagation, using a fractional diffusion model.* **Methods:** *The Courtemanche model of human atrial cell is implemented under chronic atrial fibrillation (AF) remodeling conditions. The atrial strands are designed as 1D domains, having a fibrotic portion localized in the middle. Fibrosis is modeled taking into account an electrical component, implemented by coupling a number of fibroblasts to a single cardiomyocyte, and a structural component, implemented through a q -order fractional derivative.* **Results:** *The variations of q define two dAPD dispersion regimes. For $q < 1.4$, the fibrosis density and the number of fibroblast per cardiomyocyte do not alter the dAPD. For $q \geq 1.4$, the dAPD depends on the fibrosis spatial characteristics.* **Conclusion:** *This study shows that the structural component of fibrosis, modeled using fractional diffusion, modulates the spatial dAPD in a domain including electrical coupling of cardiomyocytes and fibroblasts, under chronic AF conditions.*

1. Introduction

Atrial fibrillation (AF) is characterized by rapid and complex electrical activation patterns. The arrhythmia involves several processes and interactions that determine the conditions for the genesis and sustaining of the AF [1]. A commonly observed factor among AF patients is fibrosis which has been related to the AF perpetuation [2]. It is recognized that fibrosis can exert a remodeling action that alters the atrial electrophysiological and propagation properties of the tissue. Still, the underlying mechanisms

of this interplay are not fully understood [1].

Computational models have provided insight into the fibrosis effects on the atrial conduction [3]. However, the simulation outcomes depends on the considered aspects for representing the fibrotic process [4]. In this work, a fibrosis model is proposed that includes the electrical remodeling exerted by fibroblasts coupled to cardiomyocytes and the structural remodeling implemented by applying a fractional diffusion operator in the monodomain diffusion equation. Fractional calculus generalizes the classical integer order derivatives for real or complex orders [5]. Recent works in cardiac electrophysiology modeling account the fractional derivative order as the degree of structural heterogeneity in healthy ventricular [6] tissue and in atrial remodeled tissue due to chronic AF [7]. Thus, the aim of this work is to assess properties of a fractional order diffusion operator under the presence of cardiomyocytes and fibroblasts, as a model of fibrosis.

2. Methods

2.1. Atrial fibrillation electrical remodeled strands

The Courtemanche human atrial formalism is applied for modeling the membrane ionic kinetics. The electrical remodeling due to atrial fibrillation is implemented by varying specific ionic conductances as follows: the transient outward potassium current and the L-type calcium current are reduced by 35%, the ultra-rapid potassium current is reduced by 51%, and the rectifier potassium current is increased by 110%. These modifications are in accordance with the experimental data [8]. Cholinergic effects are included by integrating the acetylcholine current into the Courtemanche atrial model [9].

2.2. Fibrosis model

The fibrotic domain is represented by the combination of electrical and structural remodeling components. Fibrosis electrical remodeling is implemented through fibroblasts-cardiomyocyte (FCM) coupling. For this purpose, the Maleckar atrial fibroblast model [10] is applied. A single cardiomyocyte is electrically coupled to N_f fibroblasts through gap junctions of 3 nS of conductance. The number of fibroblasts N_f varies from 2 to 100. The FCM systems are randomly distributed within the fibrotic domain with densities of 10%, 30% and 100%. For fibrotic densities of 10% and 30%, 10 patterns are generated. Figure 1 shows an example of each case. The blue segments represent FCM systems, while the yellow segments represent cardiomyocytes. The non-fibrotic domains are defined between the 1 and 2 cm and between 2 and 3 cm. In this manner, atrial strands coated with fibroblasts are represented.

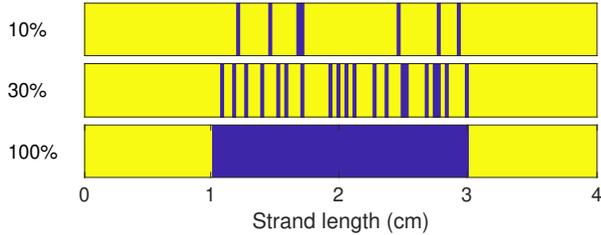


Figure 1. Atrial strands with different densities of fibrosis.

The structural remodeling accounts for the complexity of a fibrotic pattern. A spatial fractional order derivative is used in the reaction-diffusion equation for modeling electrical propagation as follows:

$$\frac{\partial u}{\partial t} = \rho \frac{\partial^q u}{\partial x^q} - \frac{1}{C_m} I_{ion}, \quad (1)$$

where u is the transmembrane potential, ρ is diffusion coefficient, C_m is the membrane capacitance and I_{ion} is the transmembrane current described by the Courtemanche model. The derivative order q is a real number between 1 and 2. The closer the q value is to 1, the greater the structural complexity of the strand [6]. Thus, the fibrotic structural remodeling is controlled through the q value.

2.3. Simulation setup and electrophysiological measurements

The numerical solution to equation (1) is calculated by splitting the operator. The spatial fractional derivative is solved by applying a semi-spectral scheme [11]. The temporal derivatives are solved using the explicit Euler method with a time step of 10^{-2} ms.

The atrial strands are designed as 1D domains of 4 cm in length and discretized at $312.4 \mu\text{m}$. Propagation is gen-

erated by pacing the left end of the strand at a basic cycle length of 400 ms. Action potential duration (APD) is defined at 90% of repolarization. The APD dispersion (dAPD) is calculated as the difference between the maximum and the minimum APD after ten pacing stimuli.

3. Results

The effect of the proposed fibrosis model on the action potential is shown in Figure 2. The curve $N_f = 0$ (dashed line) corresponds to the case where the atrial strand does not undergo electrical remodeling due to fibrosis. The FCM coupling without structural remodeling ($q = 2$), significantly reduces the APD and increases the resting membrane potential as N_f increases. However, when q decreases the effect on the APD is diminished, prevailing the N_f effect to increase the cardiomyocyte resting potential.

The distribution of the APD within the atrial strand is analyzed through the dAPD value. The Figure 3 depicts the dAPD versus the q values at different fibrosis densities for fixed values of N_f . The 10% and 30% curves are constructed using the dAPD boxplots registered from the 10 distinct patterns. The case of 0% fibrosis represents a strand without fibroblasts. It can be seen that the dAPD depends on the degree of structural remodeling and the fibrosis density for $q \geq 1.4$. The dAPD remains approximately invariant for $q < 1.4$.

From the results in Figure 2, the resting potential is affected by the number of fibroblasts per cardiomyocyte within the fibrotic domain. The behavior of the membrane potential is analyzed in the non-fibrotic domain. The resting potential is registered at 0.5 cm outside the fibrotic domain. The Figure 4 shows the resting potential values for the variations of q . For $q = 2$, the resting potential outside the fibrotic domain remains invariant to the changes of fibrosis configuration. However, as q decreases the resting potential increases and its specific value depends on the fibrosis density and N_f .

4. Discussion

In this study, a model of fibrosis that combines electrical and structural remodeling, specifically related with the fibrotic process, is assessed. The results suggest that the APD and its spatial distribution is modulated by the interaction of both fibrotic remodeling processes. Such modulation is defined by the extent of electrical and structural remodeling interacting within the strand.

Experimental reports show that the FCM coupling modifies the morphology of the cardiomyocyte action potential by electrotonic interactions [12, 13]. These changes in the shape of the action potential have been studied using computational models where the APD decrease as the number of coupled fibroblasts increase [10, 14]. This APD short-

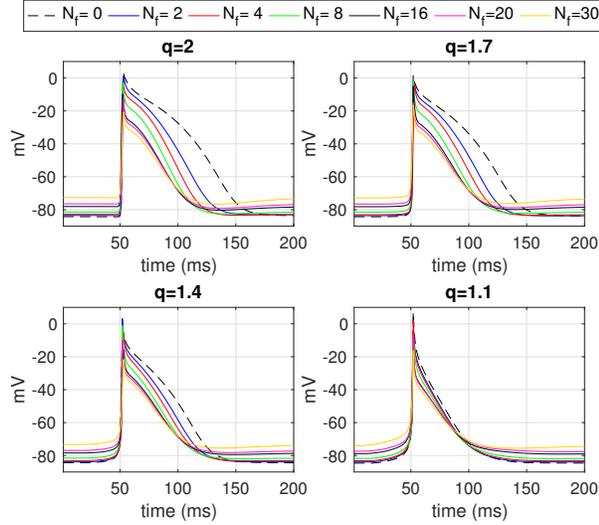


Figure 2. Action potential registered at a point containing a FCM system with distinct values of N_f . Four representative values of the fractional derivative order q are shown.

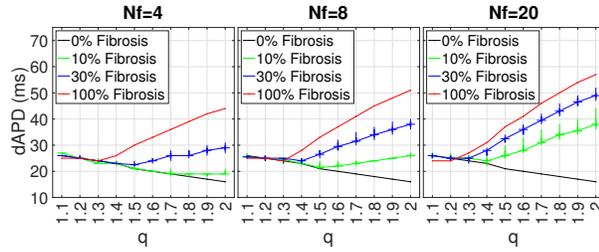


Figure 3. Curves depicting the relation between dAPD and q keeping N_f fixed. Three representative values of N_f are shown.

ening is also observed in this work, however, conjugating the fibrosis electrical and structural remodeling under the proposed design, modifies the APD behavior at different scales. At cellular level, higher degrees of structural remodeling (q is close to 1) have a major role in the APD shortening than the electrical remodeling (the FCM systems) and viceversa. At a mesoscopic level, the dAPD exhibits two regimes: having a high degree of structural remodeling ($q < 1.4$) yields a dAPD approximately independent to the FCM systems configuration. Having an intermediate and low degree of structural remodeling ($q \geq 1.4$) yields an dAPD dependence to the electrical remodeling.

The fibrosis and structural and electrical remodeling have been observed experimentally [3, 15]. The results obtained in this work suggest a complex interaction between them. Specifically, the described APD behavior could lead to an increment of the APD heterogeneity within the atria which could have proarrhythmic implications [16, 17].

It is worth noting that, although the electrophysiologi-

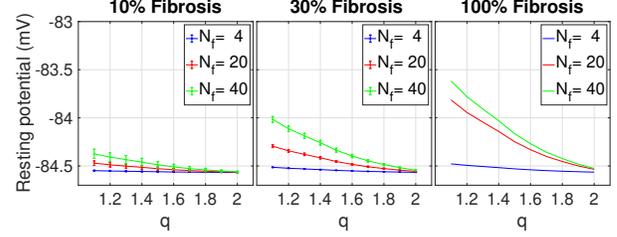


Figure 4. The resting membrane potential registered outside the fibrotic domain versus the fractional derivative order q . Three representative values of N_f are shown for each fibrotic density.

cal influence of the fibroblasts on the cardiomyocyte APD is reduced at high degrees of structural remodeling, they do modify the resting membrane potential which does not occur with the structural remodeling alone. Thus, a model of fibrosis composed only by the q -order derivative is not equivalent to a model that includes the FCM coupling besides the fractional derivative. Experimental studies have shown that dense fibrotic regions are not arrhythmogenic by themselves but the surrounding tissue presents conduction alterations and arrhythmogenic susceptibility [18, 19]. The distribution of the resting membrane potential described in this work presents long range interactions: the resting potential outside the fibrotic domain increases with the FCM density and the number of fibroblast per cardiomyocyte. This characteristic is related with the fractional derivative which is a non-local operator. Thus, the proposed model is able to reproduce the conditions that can establish a proarrhythmic scenario.

5. Conclusion

A model of fibrosis that includes a fractional derivative operator for representing the structural remodeling combined with the electrical remodeling exerted by fibroblast is presented. The model surmises that both remodeling processes play a role in the modulation of the cardiomyocytes action potential. This interaction can support the AF genesis and maintenance.

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