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A note on stress-driven anisotropic diffusion and its role in active deformable media

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ABSTRACT

We introduce a new model to describe diffusion processes within active deformable media. Our general theoretical framework is based on physical and mathematical considerations, and it suggests to employ diffusion tensors directly influenced by the coupling with mechanical stress. The proposed generalised reaction-diffusion-mechanics model reveals that initially isotropic and homogeneous diffusion tensors turn into inhomogeneous and anisotropic quantities due to the intrinsic structure of the nonlinear coupling. We study the physical properties leading to these effects, and investigate mathematical conditions for its occurrence. Together, the mathematical model and the numerical results obtained using a mixed-primal finite element method, clearly support relevant consequences of stress-driven diffusion into anisotropy patterns, drifting, and conduction velocity of the resulting excitation waves. Our findings also indicate the applicability of this novel approach in the description of mechano-electric feedback in actively deforming bio-materials such as the cardiac tissue.

1. Introduction

Excitable media, whether of biological type or not, represent complex nonlinear systems which are often of electrochemical nature, and can typically be coupled to several multi-physical factors as heat transfer or solid and/or fluid mechanics. A remarkable example is the heart, where nonlinear bioelectrical waves propagate on a complex anatomical medium undergoing large mechanical deformations and facing strong interactions with biological fluids. More precisely, cardiac contraction results from the combination of a complex emerging behaviour where subcellular ion dynamics induce the overlapping of protein filaments, rapidly scaling up to both the cellular and tissue scales through a process known as excitation-contraction coupling and, as main topic of the present work, its reverse effect known as the *mechano-electric feedback* (MEF) (Kaufmann and Theophile, 1967; Kohl and Sachs, 2001). Studying the spatiotemporal dynamics of excitation waves in the heart is of paramount importance in the understanding of a large class of processes including depolarisation, repolarisation and period doubling bifurcations occurring in the transition towards chaotic regimes (arrhythmias) (Chen et al., 2017; Das et al., 2014; Tran et al., 2009).

Still in the context of cardiac dynamics, a large number of experimental data is available to describe ionic and electrophysiological processes at many spatio-temporal scales. However, due to diverse technical reasons, a common practice is to biochemically suppress any mechanical feedback to record these data, implying that any back-reacting effect intrinsically due to electromechanical interactions is systematically neglected. Nevertheless, the importance of understanding the interplay between the reaction-diffusion (RD) dynamics with mechanical deformation is quite clear, and a recent growing interest in refining a companion mathematical model for the dynamics of higher complexity models has been observed (Quinn, 2014; 2015; Quinn et al., 2014; Ravelli, 2003). Even though several subcellular contributors to cardiac MEF have been extensively studied (as for instance, stretch-activated ion channels (Ward et al., 2008)), their proper and consistent integration into tissue-level models has remained a challenging task; further having a very limited clinically-translatable application and validation.

In the last fifteen years, the relation between cell or tissue-based electrophysiology models with mechanical deformation of soft tissues has been formulated in terms of active stress (Nash and Panfilov, 2004), active strain (Cherubini et al., 2008;

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Gizzi et al., 2015; Nobile et al., 2012), with the addition of stretch-activated currents (Panfilov and Keldermann, 2005; Panfilov et al., 2007; Quinn and Kohl, 2013; Trayanova et al., 2011), or recently combined with either membrane capacitance changes (De Oliveira et al., 2015), or with inertial effects (SahliCostabal et al., 2017). However, in all of these works the key physical ingredient ruling the spatio-temporal dynamics of the membrane potential, i.e. the diffusion (in this context, the conductivity tensor), has been commonly considered independent of mechanical deformation when related with the current configuration of the body. Even if general constitutive prescriptions suggesting a possible interaction were advanced (Nash and Panfilov, 2004), the resulting MEF coupling due to the pull back operation has been confirmed to be rather small (De Oliveira et al., 2013; Rossi et al., 2014; Sahli Costabal et al., 2017; Whiteley et al., 2007) (which somewhat justifies the search for other means of describing MEF mechanisms). It is clear that further understanding in this regard is required, possibly using dedicated experimental approaches via fluorescence optical mappings. However these techniques still require advancements of more sophisticate motion tracking algorithms.

Processes related to MEF have a fundamental role in a wide variety of *passive* physical systems. Notable examples comprise corrosion (Zheng et al., 2015), rock anisotropy (Johnson and Rasolofosaon, 1996), glass transition (Cohen, 1989), dissolution phenomena (Miller-Chou and Koenig, 2002), electromigration (Wang and Suo, 1997), hydrogen trapping (Chêne, 2008), as well as swelling effects (Hong et al., 2009). Clear evidence for the existence of such a coupling in biological systems has also been recently observed in strain-dependent oxygen diffusivity in cartilage (Jackson et al., 2009; Yuan et al., 2009), and in transcription factors within the cell nucleus (Nava et al., 2016). Regarding the specific context of active biological media, connections forming gap junctions in cardiomyocytes (and associated to intercellular communication and mesoscale diffusion) have been recently discussed in terms of their mechano-sensitive properties (Salamhe and Dhein, 2013). Furthermore, a quantitative analysis on the specific effects of stretch into connexins in terms of hemichannels has been experimentally verified in a number of different cellular preparations (Bao et al., 2004; Cherian et al., 2005).

In the perspective of the present work, an important number of experimental studies have demonstrated key MEF effects in ventricular myocardium and atrial tissue (see e.g. Quinn et al., 2014; Ravelli, 2003 for an extended review). Specific applications include atria arrhythmias, where basically three main results are available. First, the spatiotemporal distribution of atrial excitation depends strongly on the anatomical substrate (Ravelli et al., 2005). Secondly, upon mechanical loading (stretching), the conduction velocity of the excitation wave decreases, a beat-to-beat interval variability appears, early afterdepolarisations, ectopic excitations and a higher vulnerability to atrial fibrillation are present (Masé and Ravelli, 2008). Third, atrial tissue undergoes multiple high frequency and unstable rotors (spiral waves) when subject to constant and variable stretch states (Yamazaki et al., 2009). Experimental evidence of MEF has also been studied during ventricular loading, indicating a strong relationship between variations in the conduction velocity and strain anisotropy (De Oliveira et al., 2015; Franz et al., 1989; Lab, 1978; Mills et al., 2011).

The fact that electrical properties of solids undergo intrinsic modifications due to (even infinitesimal) deformations has been a subject of study since several decades (see e.g. the classical volume by Landau et al. on the electrodynamics of continuous media (Landau et al., 1984, pp. 69)). These changes suggest the representation of the corresponding models using strain-dependent (or also stress-dependent) dielectric tensors. In particular, this dependency in turn affects the electromagnetic dynamics by enforcing inhomogeneous and anisotropic patterns in structures that were not necessarily so. Experimental evidence supports the main present assumption that electrical conductivity (hereafter referred as diffusion for the case at hand) depends on deformation. Therefore, and thanks to first principles, one can readily Taylor-expand a given diffusion tensor in terms of the deformation quantities.

In this note we present a novel formulation for the description of soft active deformable media within the context of coupled reaction-diffusion-mechanics systems, and employ nonlinear cardiac dynamics as a main motivating example. At this point we highlight that the concept of stress-assisted diffusion has been originally formulated for generalised composite media (see Aifantis, 1980; Klepach and Zohdi, 2014; Miehe et al., 2014; Weitsman, 1987 and the references therein), but many resemblances exist with respect to the active deformation of soft tissues (De Vita et al., 2017). Most notably, here we have found that an anisotropic and inhomogeneous diffusivity is naturally induced by mechanical deformations, thus affecting the nonlinear dynamics of the spatiotemporal excitation wave. This important fact implies that the present formulation can recover and generalise a large class of electromechanical models based on basic FitzHugh-Nagumo-type descriptions (Aliev and Panfilov, 1996; Panfilov and Keldermann, 2005). The most relevant additional parameters are here the weights accompanying the stress when incorporated into the diffusion tensors, and therefore we study the plausibility of specific choices in the model parameter space. Our assessment is conducted for stretched tissues, focusing on appropriate physical indicators as conduction velocity, propagation patterns and spiral dynamics, and also carefully identifying conditions leading to the stability of the coupled system.

2. A stress-assisted electromechanical model

We centre our investigation on an active stress RD model describing qualitative non-oscillatory properties of cardiac tissue supporting stable propagation of excitation waves (Nash and Panfilov, 2004; Panfilov and Keldermann, 2005). We frame our modelling into finite elasticity, where one identifies the relationship between material (reference) and spatial (deformed) coordinates, indicated by X_I and x_j, respectively, via the smooth map $x_j(X_I)$ that determines then the deformed position of a point x_j originally located at X_I. We indicate with J the Jacobian of the map. In the deformed configuration the proposed equations read:

$$\frac{\partial V}{\partial t} = \frac{\partial}{\partial x_i} d_{ij}(\sigma_{ij}) \frac{\partial V}{\partial x_j} + I_{\text{ion}}, \quad \frac{\partial r}{\partial t} = f(V, r)\,, \tag{2.1}$$

$$\frac{\partial T_a}{\partial t} = \epsilon(V)(k_{T_a} V - T_a), \quad \frac{\partial \sigma_{ij}}{\partial x_i} = 0\,, \tag{2.2}$$

with constitutive prescriptions for the RD system (Panfilov and Keldermann, 2005)

$$I_{\text{ion}} = -kV(V-a)(V-1) - rV\,, \tag{2.3a}$$

$$f(V, r) = \left(\eta + \frac{\mu_1 r}{\mu_2 + V}\right)(-r - kV(V - b - 1))\,, \tag{2.3b}$$

and for incompressible isotropic materials ($J = 1$)

$$\sigma_{ij} = 2c_1 b_{ij} - 2c_2 b_{ij}^{-1} - p\delta_{ij} + T_a \delta_{ij}\,, \tag{2.4}$$

$$d_{ij}(\sigma_{ij}) = D_0 \delta_{ij} + D_1 \sigma_{ij} + D_2 \sigma_{ik}\sigma_{kj}\,. \tag{2.5}$$

Eq. (2.1) provides a non-dimensional, two-variables RD model where V represents the transmembrane potential and r is the recovery variable, whose dynamics is prescribed by Eqs. (2.3). The term $kV(V-a)(V-1)$ controls the fast processes regulated via the