

ELECTROMECHANICAL COUPLING IN CARDIAC DYNAMICS: THE ACTIVE STRAIN APPROACH*

D. AMBROSI[†], G. ARIOLI[†], F. NOBILE[†], AND A. QUARTERONI[‡]

Abstract. The coupling between cardiac mechanics and electric signaling is addressed in a nonstandard framework in which the electrical potential dictates the active *strain* (not *stress*) of the muscle. The physiological and mathematical motivations leading us to this choice are illustrated. The propagation of the electric signal is assumed to be governed by the FitzHugh–Nagumo equations, rewritten in material coordinates with a deforming substrate; the solution is compared with the rigid case, and differences in celerity and width of a pulse are discussed. The role of viscoelasticity is pointed out. We show that the stretching of coordinates is insufficient to originate electromechanical feedback; nevertheless, it can increase the energy of a perturbation enough to produce a traveling pulse: an energy estimate and numerical evidence are reported. To support these conclusions, numerical simulations in two dimensions show the interplay between electric propagation and mechanical strain.

Key words. elasticity, cardiac mechanics, electromechanical coupling, FitzHugh–Nagumo equations

AMS subject classifications. 74F, 92C10

DOI. 10.1137/100788379

Introduction. The mathematical modeling of the cardiac activity is a longstanding research field; to some extent it provides the paradigm of a complex system, as it incorporates several mathematical issues that are already challenging by themselves. Without even mentioning the social relevance of the problem, we resume below a partial list of the issues that characterize the mathematical modeling of the heart (see [20] for a review of the subject).

- The cardiac mechanics are nonlinear: the heart tissue undergoes large deformations, and viscoelasticity is relevant, as the time scale of a single heart beat is on the order of the relaxation time of the material.
- Geometrical data, material parameters, and boundary conditions are complex, and, at least in vivo, they are affected by a severe uncertainty.
- There is a complex fluid-solid interaction between the heart pump and the blood, involving nontrivial matching of boundary conditions with the global vascular network.
- The dynamics of the electric potential is nonlinear, and more than one equilibrium value exists.
- The cardiac deformation involves an active contribution, due to the fiber contraction, and a passive one, mainly due to elastin and collagen.
- The mechanics as well as the electric signal propagation are anisotropic, as they are dictated by the fiber's orientation.

*Received by the editors March 11, 2010; accepted for publication (in revised form) February 10, 2011; published electronically April 13, 2011. This work was supported by the ERC Advanced Grant *Mathcard* (227058).

<http://www.siam.org/journals/siap/71-2/78837.html>

[†]MOX-Dipartimento di Matematica, Politecnico di Milano, piazza Leonardo da Vinci 32, 20133 Milano, Italy (davide.ambrosi@polimi.it, gianni.arioli@polimi.it, fabio.nobile@polimi.it).

[‡]MOX-Dipartimento di Matematica, Politecnico di Milano, piazza Leonardo da Vinci 32, 20133 Milano, Italy, and CMCS, Modeling and Scientific Computing, Ecole Polytechnique Federale de Lausanne, CH-1015, Lausanne, Switzerland (Alfio.Quarteroni@epfl.ch).

- Time scales span a large range: the time scale of the electric signal is typically 50 ms, while the mechanical wavelength is one order of magnitude bigger. On long time scales (on the order of weeks) the heart remodels; i.e., it has the ability to grow, resorb material, and modify its shape according to its functionality.

The theoretical modeling of the cardiac activity is both a longstanding topic and a very active field of current research; in this paper we do not have the ambition to face the mathematical modeling of a heart in toto; we rather focus on the electromechanical coupling only. Our aim is to keep the mathematical complexity of the finite elasticity and electric models at a minimum, while the mutual coupling is addressed in quite a general way.

The application of the principles of force balance to living matter features a specific difficulty: living tissues not only *passively* balance external loads (as in rubber, for instance), but they *actively* deform. This ability of the living matter is usually taken into account in mechanical models at the level of a prescribed active stress that contributes to the overall tensional state. The constitutive prescription of the active stress is then a delicate issue. In the relevant literature it is usually addressed by an additive decomposition of the standard (passive) stress and the active one; the latter is to be constitutively specified [20].

In this paper we follow the alternative idea proposed by Cherubini and coworkers [3]: the fiber contraction driving the depolarization of the cardiomyocyte rewrites in the mechanical balance of forces as a prescribed active *deformation*, rather than as an additive contribution to the stress. This approach has its very roots in plasticity, and it has already been successfully exploited in biomechanics to explain the emergence of residual stress in arteries and their stress-driven remodeling ability [18]. The idea of a multiplicative decomposition of the tensor gradient of deformation directly incorporates the microlevel information on the fiber contraction in the kinematics, without the intermediate transcription of their role in terms of stress. Conversely, the strain energy of the biological material now depends at an inner level on the activation potential, and the algebraic aspects of the theory become more complicated. This and other issues are discussed in the paper.

The first section of the paper is devoted to a discussion of the pros and cons underlying an *active strain* approach to cardiomechanics. The model is then derived in detail, and a comparison with the well-established model by Panfilov, Keldermann, and Nash [15] is discussed at the end of section 3. When neglecting viscoelasticity effects and abstaining from introducing an additive stretch activated current in the potential balance, the equations turn out to be simple enough that some formal analysis can be carried out: explicit form, celerity, and width of traveling fronts is found in a one-dimensional model problem, and a sufficient condition for the emergence of a pulse from a perturbation is derived.

Numerical simulations are collected in sections 6 and 7. The one-dimensional simulations exemplify the theory exposed above, while some two-dimensional results show the potential ability of the model to approach more complex geometries.

1. Mechanics. We consider the heart as a hyperelastic body subject to external loads and active deformation that originate a strain field. The motion of the point \mathbf{X} at time t is therefore defined by the vectorial map $\mathbf{x} = \mathbf{x}(\mathbf{X}, t)$ from the initial (relaxed) configuration to the current one. The gradient of this function is a tensor

(the tensor gradient of deformation) indicated as follows:

$$(1.1) \quad \mathbf{F} = \text{Grad } \mathbf{x}, \quad F_{ij} = \frac{\partial x_i}{\partial X_j}, \quad 1 \leq i, j \leq 3.$$

Here and in the following “Grad” and “Div” denote the gradient and the divergence operators with respect to the \mathbf{X} coordinates, respectively.

Following [3], we decompose the tensor gradient of deformation into two factors, the micro (active) and the macro (passive):

$$(1.2) \quad \mathbf{F} = \mathbf{F}_e \mathbf{F}_o.$$

The rationale of this decomposition is the following: fibers inside the muscle contract and become shorter. They form a kind of a watermark, defined in every point of the body, and the kinematics of this microstructure is accounted for by \mathbf{F}_o , a distortion that does not necessarily preserve compatibility of the body but dictates the deformation at a fiber scale. The deformation at the macroscale is measured by \mathbf{F}_e , which accounts for both the deformation of the material needed to ensure compatibility (possibly undermined by \mathbf{F}_o) and the possible tension due to external loads. Notice that, in general, neither \mathbf{F}_e nor \mathbf{F}_o is a gradient (they are not integrable), or, in other words, there exists no real motion that corresponds to fibers’ elongation without muscle contraction; indeed, (1.2) is a pure theoretical decoupling that associates the microscale dynamics to the macroscale continuum mechanics.

The lack of integrability of \mathbf{F}_e does not allow us to introduce an intermediate global configuration corresponding to a global motion; however, such a meaning can be retained in a local sense (see [13] for a detailed discussion of this issue).

We accordingly assume that the strain energy of the cardiac muscle depends only on the deformation at the macroscale

$$(1.3) \quad W = W(\mathbf{F}_e).$$

In other words, the energy storage occurs only at the macrolevel. Of course, there is a microforce that dictates the sarcomere contraction, and, as a matter of fact, much is known about the energy spent in such a process, but this force balance is immaterial in the present context because the kinematics is *directly* dictated. One could then wonder about the energy balance hidden in the present context and the corresponding nature of the forces that generate the contraction of the muscle. Without going into the details, we want to mention that here the force generated by sarcomere contraction is supposed to have a dissipative nature, and thermodynamic issues can be properly addressed [5, 19].

The bundles (pathways of electric signals) cross the heart, transmitting the signal in a short time (a few milliseconds). The electric potential then travels through the whole muscle body in a time scale on the order of one second; this propagation mainly occurs along preferential directions dictated by the orientation of the mechanical fibers—the same fibers that primarily drive the mechanical contraction. However, the charged ions also diffuse in the direction normal to the fibers, and the transverse velocity is about one half of the longitudinal velocity.

In a simple setting, one can assume that in any point \mathbf{X} the fibers are oriented according to one direction only, namely, \mathbf{n} . The unitary vector field $\mathbf{n}(\mathbf{X})$ denotes the (unique) direction of the fibers in \mathbf{X} in the relaxed state of the material. The microscale part of the deformation tensor can take the simple form

$$(1.4) \quad \mathbf{F}_o = \mathbf{1} + \gamma(v)\mathbf{n} \otimes \mathbf{n},$$

where v is the electrical potential. The activation function, to be constitutively prescribed, must be such that $\gamma > 0$ denotes elongation, and $\gamma < 0$ denotes contraction. Note that $\det(\mathbf{F}_0) = 1 + \gamma$.

The Piola stress tensor $\tilde{\mathbf{P}}$ in the locally *intermediate configuration* is obtained by Frechet derivative of the strain energy (1.3)

$$(1.5) \quad \tilde{\mathbf{P}} = \frac{\partial W}{\partial \mathbf{F}_e},$$

and it accounts for the tension due to the deformation $\mathbf{F}_e = \mathbf{F}\mathbf{F}_o^{-1}$. The corresponding force balance equation is conveniently written in the original reference configuration (spanned by the \mathbf{X} coordinates) by a pull-back (see, for instance, [11])

$$(1.6) \quad \text{Div} \left(J_o \tilde{\mathbf{P}} \mathbf{F}_o^{-T} \right) = 0,$$

to be supplemented by suitable boundary conditions.

Summarizing, the present model for the mechanics of the cardiac activity requires, from a constitutive viewpoint, a strain energy, a geometrical description of the fiber vector field \mathbf{n} , and a constitutive law $\gamma(v)$ relating the fiber contraction to the electric potential v . The strain energy can be also generalized to depend on the fiber distribution \mathbf{n} (an orthotropic material) without much relevance for our purposes.

1.1. Active stress versus active strain. The norm in biomechanics is to model the ability of living matter to reshape itself adding an *active* component of the stress to the usual passive one. Although such a standard approach has already been successfully applied to a number of examples [7, 15, 20], the alternative choice of an *active strain* adopted in the present work deserves to be explored.

As a starting remark, a simple example shows that the two approaches are not equivalent, except in the linear case or when an explicit dependence of the active stress on the strain is assumed to exist. In fact, consider a zero-dimensional spring of rest length ℓ_o and stiffness k that elongates actively to ℓ_a and is subject to the force f . The spring then elongates to ℓ so that the force balance is satisfied. Active stress and strain predict, respectively,

$$(1.7) \quad k(\ell - \ell_o) + f_a = f,$$

$$(1.8) \quad k(\ell - \ell_a) = f.$$

It is easy to see that the two theories are equivalent provided that $f_a = -k(\ell_a - \ell_o)$. On the other hand, for a cubic spring the two models rewrite as

$$(1.9) \quad k(\ell - \ell_o)^3 + f_a = f,$$

$$(1.10) \quad k(\ell - \ell_a)^3 = f,$$

and no simple relation for f_a independent of ℓ can be provided. The same comment applies in the three-dimensional case, in the absence of residual stress [10]: only when

$$(1.11) \quad \|\mathbf{F} - \mathbf{1}\| \ll 1, \quad \|\mathbf{F}_o - \mathbf{1}\| \ll 1$$

does

$$(1.12) \quad \begin{aligned} \mathbf{P}(\mathbf{F}\mathbf{F}_o^{-1}) &= \mathbf{P} \left((\mathbf{1} + (\mathbf{F} - \mathbf{1})) (\mathbf{1} + (\mathbf{F}_o - \mathbf{1}))^{-1} \right) \\ &\sim \mathbf{P} \left((\mathbf{1} + (\mathbf{F} - \mathbf{1})) (\mathbf{1} - (\mathbf{F}_o - \mathbf{1})) \right) \\ &\sim \mathbf{P} (\mathbf{1} + (\mathbf{F} - \mathbf{1}) - (\mathbf{F}_o - \mathbf{1})) \sim \mathbf{P}(\mathbf{F}) - \mathbf{P}(\mathbf{F}_o). \end{aligned}$$

After assessing that the two approaches are not equivalent, it remains to understand their pros and cons in terms of physiological correctness, mathematical stability, and numerical simplicity. From a physiological standpoint, the zero-dimensional model illustrated above is too crude when the active stress f_a and/or the active strain ℓ_a are independent on any other field. A deeper physiological insight is provided by experiments on the cell level. Accurate measurements reported by Iribe, Helmes, and Kohl [8] show definite evidence of linear dependence of the active force produced by a cardiomyocyte versus its prestretch. This cellular equivalent of the Frank–Starling effect has to be upscaled at the tissue level assuming that the active tension depends linearly on the macroscopic elongation ℓ (see [20], for example). However, this physiological behavior can be reproduced by both an active stress model (straightforwardly) and an active strain model. The validity of different macroscopic approaches to tissue contraction would be enforced by evidence that myocytes control stress or strain: a clear result in this respect would support either active stress or active strain macroscopic models. In our opinion, the striking linearity of the experimental curves makes it impossible to draw a conclusion in this respect, as all the plots can be understood in two ways. An increase of preload (prestretch, respectively) yields a linear increase in the ability to perform work (contraction, respectively).

A natural objection to the use of a multiplicative decomposition such as that in (1.2) is that it yields an algebraic complication in the equations: a closer look at (3.3) reveals that cumbersome calculations with \mathbf{F}_o occur. As a nonminor practical consequence, standard finite element codes for finite elasticity cannot be easily adopted, because the active strain acts at an inner level in the equations. Conversely, an additive active stress can be simply included in standard codes, and this may be one of the reasons that make this approach more popular.

In principle, at least, the active strain approach is more satisfactory from the modeling point of view, when the contraction of the observable fibers is included in the equations, while the active stress needs to be tuned in order that it can provide the observed deformation.

Finally, mathematical requirements of frame indifference and stability should apply. Few results are known in this respect: a recent paper by Pathmanathan et al. [16] shows that rank one ellipticity cannot be ensured when large deformations occur for a specific active stress form. The same kinds of problems are reported and addressed at a numerical level in [14]. It remains to be understood if active strain models do not face the same problem.

2. Electric activity. The electrical signal in the cardiac muscle is actually an ionic flux generated by a potential gap at a cellular or extracellular level. A broad literature exists on the modeling aspects of this process; the classical book by Keener and Sneyd [9] is an excellent introduction in this respect. However, as the focus of this work is on electromechanical coupling, we restrict our attention to the simplest equation that provides a correct qualitative dynamics for the propagation of the electric signal in a fixed domain, wherein the electric potential v satisfies a diffusion-reaction equation of FitzHugh–Nagumo type coupled with a reaction-transport equation for the gate variable w . The FitzHugh–Nagumo model written in coordinates fixed in space reads

$$(2.1) \quad \frac{\partial v}{\partial t} + \nabla \cdot (\dot{\mathbf{x}}v) - \nabla \cdot (\mathbf{D}\nabla v) = -Av(v - \alpha)(v - 1) - Aw,$$

$$(2.2) \quad \frac{\partial w}{\partial t} + \nabla \cdot (\dot{\mathbf{x}}w) = v - \frac{w}{\tau}.$$

Here \mathbf{D} is a second order positive definite diffusion tensor, A is a positive constant [9], and both v and w are defined per unit volume. The symbols ∇ and $\nabla \cdot$ denote the gradient and divergence operators in \mathbf{x} coordinates. Here and in the following, the equations are directly written in nondimensional form; typically $A \simeq \|\mathbf{D}\| \gg 1$ for a suitably defined norm of \mathbf{D} . Note that (2.1) is a balance equation for the potential, accounting for the dynamics between diffusion and transmembrane currents of ionic species, whereas (2.2) does not involve any spatial flow besides convection. The divergence term on the left-hand side represents the convective transport due to the displacement of the material itself, as can be observed by using coordinates fixed in space (usually called *spatial coordinates* or *Eulerian coordinates*). These terms are usually negligible, and, in any case, they disappear when the equations are rewritten in material coordinates.

As the interplay between active and passive tension originates a large deformation in the heart body and the elasticity equations are conveniently stated in a material coordinate system, we rewrite (2.1) in \mathbf{X} coordinates. To this aim we first rewrite (2.1) as a system of two first order equations in divergence form:

$$(2.3) \quad \frac{\partial v}{\partial t} + \nabla \cdot (\dot{\mathbf{x}}v) - \nabla \cdot (\mathbf{D}\mathbf{f}) = -Av(v - \alpha)(v - 1) - Aw,$$

$$(2.4) \quad \mathbf{f} = \nabla \cdot (v\mathbf{1}).$$

In a material frame of reference these equations rewrite as

$$(2.5) \quad \frac{\partial}{\partial t}(Jv) - \text{Div}(J(\mathbf{D}\mathbf{f})\mathbf{F}^{-T}) = -AJv(v - \alpha)(v - 1) - AJw,$$

$$(2.6) \quad J\mathbf{f} = \text{Div}(Jv\mathbf{F}^{-T}),$$

where $J = \det(\mathbf{F})$. With an abuse of notation, in (2.5) and (2.6) we denote by the same symbols functions that take the same values acting on different domains. The domains are in one-to-one relation, spanned by the \mathbf{X} and \mathbf{x} coordinates; the context clarifies the meaning. Direct substitution yields the second order equation

$$(2.7) \quad \frac{\partial}{\partial t}(Jv) - \text{Div}(\mathbf{F}^{-1}\mathbf{D}\text{Div}(J\mathbf{F}^{-T}v)) = -AJv(v - \alpha)(v - 1) - AJw$$

or

$$(2.8) \quad \frac{\partial}{\partial t}(Jv) - \text{Div}(J\mathbf{F}^{-1}\mathbf{D}\mathbf{F}^{-T}\text{Grad}v) = -AJv(v - \alpha)(v - 1) - AJw,$$

where the relation $\text{Div}(J\mathbf{F}^{-T}) = 0$ has been used (see, e.g., [11]). As a further simplification, one may consider an isotropic homogeneous diffusion: the diffusion tensor becomes just the identity one times the constant scalar coefficient D , so that (2.8) simplifies to

$$(2.9) \quad \frac{\partial}{\partial t}(Jv) - D\text{Div}(J\mathbf{C}^{-1}\text{Grad}v) = -AJv(v - \alpha)(v - 1) - AJw,$$

where $\mathbf{C} = \mathbf{F}^T\mathbf{F}$ is the right Cauchy–Green tensor.

Note that (2.9) is obtained on the basis of a coordinate transformation (from spatial to material coordinates), purely accounting for kinematics: the mapping is encoded in the gradient of deformation \mathbf{F} , which has to be provided by the balance of mechanical forces (1.6).

3. Constitutive assumptions. The constitutive assumptions in this paper are kept at a minimum degree of complexity, and, in fact, the discussion of the section above remains unaltered when applied to a reaction term on the right-hand side of (2.1) more complicated than a cubic polynomial (i.e., more complex ionic models). Following the same vein, we restrict our attention to an isotropic Mooney–Rivlin material

$$(3.1) \quad W = W(\mathbf{F}_e) = \frac{\mu}{2} (\mathbb{I} - 3) + \frac{\mu_2}{2} (\mathbb{II} - 3),$$

where \mathbb{I} and \mathbb{II} are the first and second invariants of the left Cauchy–Green tensor of \mathbf{F}_e , respectively:

$$(3.2) \quad \mathbb{I} = \text{tr}(\mathbf{F}_e \mathbf{F}_e^T), \quad \mathbb{II} = \frac{1}{2} \left((\text{tr}(\mathbf{F}_e \mathbf{F}_e^T))^2 - \text{tr}(\mathbf{F}_e \mathbf{F}_e^T)^2 \right).$$

We will consider only the case $\mu_2 = 0$, corresponding to a neo-Hookean material. It is often assumed that biological materials can only undergo isochoric motion under load. This assumption usually stems by observing that biological materials are essentially made of water. In the present framework a material is incompressible if the visible deformation \mathbf{F} satisfies the kinematic constraint $J = \det \mathbf{F} = 1$. In this respect our approach differs from Cherubini et al., who assume that $\det \mathbf{F}_e = 1$ [3]. After introducing the pressure p , the Lagrange multiplier enforcing incompressibility, a pull-back to the initial fully relaxed configuration for a neo-Hookean material, using the relation (1.6), yields the following form of the Piola tensor:

$$(3.3) \quad \mathbf{P} = J_o \frac{DW}{D\mathbf{F}_e} \mathbf{F}_o^{-T} - Jp \mathbf{F}_e^{-T} \mathbf{F}_o^{-T} = \mu J_o \mathbf{F} \mathbf{F}_o^{-1} \mathbf{F}_o^{-T} - Jp \mathbf{F}^{-T},$$

where $J_o = \det \mathbf{F}_o$.

The function γ introduced in (1.4) dictates the contraction of the cardiac muscle depending on the value of the potential. This activation is actually driven by the concentration of calcium ions and is sometimes accounted for by complicated dependencies. In this work we restrict ourselves to considering activation of the contraction proportional to the potential field, according to the following simple rule:

$$(3.4) \quad \gamma = -\beta v.$$

A typical muscle contraction involves a 30% strain, and therefore we choose the parameter $\beta \simeq 0.3$. According to this relation, γ is negative (contraction) for a positive potential difference (the depolarization phase). We are aware that such a crude coupling cannot account for well-known spatiotemporal dynamics, such as the much longer relaxation time of the mechanical contraction with respect to the width of the potential pulse (1.4); however, we decide again not to include such a delay for the time being in our model to keep the minimum degree of complexity.

Equations (1.6), (2.9), and (2.2) supplemented by the constitutive assumptions (1.4), (3.3), and (3.4) and the incompressibility constraint, together with initial and boundary conditions, provide a simple three-dimensional framework for the electrome-

chanical cardiac coupling. Summarizing, the three-dimensional model reads

$$(3.5) \quad \frac{\partial}{\partial t}(Jv) - \text{Div} (J\mathbf{F}^{-1}\mathbf{D}\mathbf{F}^{-T}\text{Grad}v) = -AJv(v - \alpha)(v - 1) - AJw,$$

$$(3.6) \quad \frac{\partial}{\partial t}(Jw) = Jv - \frac{Jw}{\tau},$$

$$(3.7) \quad \text{Div} (\mu J_o \mathbf{F}\mathbf{F}_o^{-1}\mathbf{F}_o^{-T} - Jp\mathbf{F}^{-T}) = 0,$$

$$(3.8) \quad J = 1,$$

to be supplemented by suitable initial and boundary conditions.

A comparison between the equations above and the model by Panfilov, Keldermann, and Nash [15] may help to point out how mechanics is handled in a different way and some physical and physiological mechanisms are neglected herein.

The first difference has been already discussed in depth: the potential here dictates the active strain and not the stress. The second difference is that in system (3.5)–(3.7) there is neither delay nor difference in wavelength between the electrical wave and the corresponding mechanical contraction; this effect is physiologically well known and could be easily taken into account considering the viscoelastic behavior of the substrate. Alternatively, one could consider more sophisticated models and relate the active contraction to calcium concentration, which is known to be characterized by a slower dynamics than the overall electric potential (see, e.g., [1]). The last major difference is that no stretch activated current is added on the right-hand side of (3.5) to account for the observed ability of myocytes to get electrical activation by a mechanical stretch. This effect is obtained by Panfilov and coworkers by adding a linear term in v on the right-hand side of the action potential equation (3.5), activated by a measure of the elastic strain (namely, the density, for a compressible material). Its effect is to move to the right the zeros of the third order polynomial in v to destabilize possible spiral waves as a self-originated pacemaker. While aware of these biophysical simplifications, the system (3.5)–(3.8) is simple enough to allow mathematical insight into electromechanical coupling.

4. Pulse along a fiber: The one-dimensional case. In the limit of infinitesimal strain ($\mathbf{F} \rightarrow \mathbf{1}$), the electromechanical coupling vanishes in the equation for the action potential (3.5), and it is interesting to understand to what extent the solution differs for a finite contraction of physiological magnitude. In other words, we address the question of whether such a coupling involves a significant modification in a traveling wave, when compared with the usual solution computed on fixed domains. To this aim consider the one-dimensional displacement field $x = x(X)$ along a fiber. For the sake of simplicity we take $A = 1$ in the present section. The active deformation tensor \mathbf{F}_o simply reads

$$(4.1) \quad F_o = 1 + \gamma,$$

and, assuming one-dimensional motion, the momentum equation reads

$$(4.2) \quad \left(\frac{x'}{1 + \gamma} \right)' = 0,$$

which can be immediately integrated to give

$$(4.3) \quad x' = 1 + \gamma,$$

where possible constants (depending on time only) vanish because of the boundary conditions at infinity. Back-substitution into (2.8) yields

$$(4.4) \quad \frac{\partial}{\partial t}((1 + \gamma)v) - D \frac{\partial}{\partial X} \left(\frac{1}{1 + \gamma} \frac{\partial v}{\partial X} \right) = -(1 + \gamma)v(v - \alpha)(v - 1) - (1 + \gamma)w$$

or, expanding the time derivative,

$$(4.5) \quad (1 + \gamma) \frac{\partial v}{\partial t} - D \frac{\partial}{\partial X} \left(\frac{1}{1 + \gamma} \frac{\partial v}{\partial X} \right) = -(1 + \gamma)v(v - \alpha)(v - 1) - (1 + \gamma)w - v \frac{\partial \gamma}{\partial t}.$$

We start by assuming that $\gamma(v)$ is a smooth function. Whatever the constitutive relation that provides γ in terms of v , some qualitative behaviors can be devised in (4.5). The zeroth order terms on the right-hand side are multiplied by a nonnull factor, and therefore the points of equilibrium are not modified by the electromechanical coupling. Observing that a step in the potential always produces a contraction ($\gamma \leq 0$), it follows that the twitch rereads as a greater effective diffusion in the second term on the left-hand side of (4.5). Analogously, the time derivative in the last term on the right-hand side enhances the temporal variation of the potential, since it is positive in contraction and negative in relaxation.

If the activation function is linear in the potential, we get the final problem

$$(4.6) \quad \frac{\partial}{\partial t}((1 - \beta v)v) - D \frac{\partial}{\partial X} \left(\frac{1}{1 - \beta v} \frac{\partial v}{\partial X} \right) = -(1 - \beta v)v(v - \alpha)(v - 1) - (1 - \beta v)w,$$

$$(4.7) \quad \frac{\partial}{\partial t}((1 - \beta v)w) = (1 - \beta v) \left(v - \frac{w}{\tau} \right).$$

4.1. Traveling fronts. When neglecting the recovery phase ($w = 0$), one can look for steady reaction fronts traveling at a constant speed and connecting the equilibrium states $v = 0$ and $v = 1$. In other words, we look for traveling wave solutions of the type $v = v(x - ct)$, where c is to be determined in terms of the physical parameters of the problem (the diffusion D and the equilibrium value α). Using these assumptions (4.6) rewrites as a second order boundary value problem,

$$(4.8) \quad -c(1 - 2\beta v)v' - D \left(\frac{1}{1 - \beta v} v' \right)' = -(1 - \beta v)v(v - \alpha)(v - 1),$$

supplemented by the asymptotic boundary conditions $v(-\infty) = 0$ and $v(+\infty) = 1$. We look for the solution of (4.8) in the one-parameter family of functions satisfying the first order equation

$$(4.9) \quad v' = av(1 - v)(1 - \beta v),$$

with initial condition $v(-\infty) = 0$. The parameter a represents the steepness of the front and should be fixed using (4.8). Equation (4.9) can be integrated by separation of variables; however, a simple argument demonstrates that a class of solutions is a front connecting the states $v = 0$ and $v = 1$. In fact, for $v < 1$ it is monotonically increasing and cannot overcome the threshold $v = 1$ because the derivative becomes negative therein. Therefore, the solution of the initial value problem (4.9) also satisfies the boundary conditions of the boundary value problem (4.8).

We now show that, with a suitable choice of the parameter a , the front solution of (4.9) is also a solution of the second order equation (4.8). We directly plug the relation (4.9) into the original problem, thus finding a first order algebraic polynomial in v that must be identically null. This is possible only if all the coefficients of the polynomial vanish, thus leading to the following relations:

$$(4.10) \quad a^2 = \frac{1 - 2\alpha\beta}{1 - \beta} \frac{1}{2D},$$

$$(4.11) \quad c = \frac{1 - 2\alpha}{2} \left(\frac{2D}{(1 - \beta)(1 - 2\alpha\beta)} \right)^{1/2}.$$

Note that in the case of $\beta = 0$ we recover the usual FitzHugh–Nagumo equation and the celebrated explicit hyperbolic tangent solution. A traveling front solution exists only if $\alpha\beta < 1/2$, a condition that did not show up in the case of null contraction ($\beta = 0$). As expected from the general discussion above, the front is sharper and travels faster than in the case of fixed domain.

Note that the solution $v(X, t)$ described above depends on the variable X spanning the fixed material domain; the representation of the “same” function in the physical domain $v(x(X, t), t)$ can be recovered integrating (4.3):

$$(4.12) \quad x(X, t) = X - \beta \int_{-\infty}^X v(\hat{X}, t) d\hat{X}.$$

4.2. Viscoelasticity. This simple one-dimensional setting allows an easy extension of the theory presented above to viscoelastic materials. The simplest example of a viscoelastic solid is provided by the Voigt–Kelvin model, ideally represented by a spring and a dashpot in parallel. In zero-dimensional linear elasticity the stress-strain $\sigma - \epsilon$ relation is classically represented as

$$(4.13) \quad \lambda \dot{\epsilon} + \epsilon = \sigma,$$

where λ is the relaxation time of the material and the upper dot denotes differentiation with respect to time.

In the present framework there is no external load, the strain has to be measured from the intermediate configuration, and therefore the constitutive equation (4.13) rewrites as

$$(4.14) \quad \lambda \frac{d}{dt} \left(\frac{x' - 1}{1 + \gamma} \right) + \frac{x' - 1}{1 + \gamma} = 0,$$

which is a generalization of (4.3).

Comparing λ with τ , the typical time over which the signal is nonnull, one can understand the role of viscoelasticity and appreciate the dynamics of the system at different regimes. For $\tau \gg \lambda$ we recover the fully elastic case discussed above, while for $\tau \ll \lambda$ the material does not undergo any deformation in the relevant time scale, and the limit of rigid substrate is recovered. For intermediate values, the propagating signal has a velocity and width within those of the extreme cases.

5. Initial conditions and start-up of a pulse. In this section, we derive the condition that an initial perturbation in the potential field must satisfy to start a wave that eventually takes the form of a traveling pulse of permanent shape.

A closer look at (2.9) reveals that two mechanisms of opposite nature dictate the evolution of the signal: the diffusion damps the perturbation, while the nonlinear term excites the field. It is therefore expected that a minimum energy is needed to trigger a pulse in the material, and we aim to evaluate it.

For the sake of generality, we assume here that the muscle is possibly deformed at time $t = 0$ as measured by the gradient of deformation \mathbf{F} . After some algebraic manipulations, it is found that the energy of the solution satisfies the equation

$$(5.1) \quad \frac{\partial}{\partial t} \int_{\Omega_o} \left(\frac{v^2}{2} + A \frac{w^2}{2} \right) d\Omega = -D \int_{\Omega_o} |\mathbf{F}^{-T} \text{Grad } v|^2 d\Omega - A \int_{\Omega_o} v^2(v - \alpha)(v - 1) d\Omega - A \int_{\Omega_o} \frac{w^2}{\tau} d\Omega.$$

At time $t = 0$ the energy of the solution starts growing if the following condition is satisfied:

$$(5.2) \quad A \int_{\Omega_o} v^2(v - \alpha)(1 - v) d\Omega \geq D \int_{\Omega_o} |\mathbf{F}^{-T} \text{Grad } v|^2 d\Omega,$$

where $w = 0$ at the initial time without loss of generality.

A question of clear interest is whether an electric signal can be triggered by mechanical deformation only. According to the model discussed in the present work, the answer is negative: a closer look at (2.8) reveals that no source term depends on strain only, and therefore no contraction can raise a nonzero potential.

However, for a given potential field v that does not satisfy the energy condition (5.2), a mechanical strain can induce such a modification in the derivatives of the displacement so as to originate a pulse. In fact, for a potential $v(\mathbf{X}, 0)$ too weak or too steep to originate a traveling wave, we can supposedly apply a strain externally so that the stability condition (5.2) is satisfied. This requirement takes a particularly simple form in case of homogeneous strain. Denoting by λ_{\min} the minimum (positive) eigenvalue of \mathbf{C} , we recall the inequality

$$(5.3) \quad \int_{\Omega_o} |\mathbf{F}^{-T} \text{Grad } v|^2 d\Omega = \|\mathbf{F}^{-T} \text{Grad } v\|_2^2 \leq \|\mathbf{F}^{-T}\|_2^2 \|\text{Grad } v\|_2^2 = \frac{1}{\lambda_{\min}(\mathbf{C})} \|\text{Grad } v\|_2^2.$$

It is easy to see that in the case of an externally provided homogeneous strain, a sufficient condition to originate a pulse is

$$(5.4) \quad \lambda_{\min}(\mathbf{C}) > \frac{D \int_{\Omega_o} |\text{Grad } v|^2 d\Omega}{A \int_{\Omega_o} v^2(v - \alpha)(1 - v) d\Omega}.$$

6. Numerical simulations. In this section we compare numerical results of pulse propagation in a fixed and in a deformable material. In Figure 1 we show the results of a numerical approximation of the solution of (4.6). An initial perturbation $v > \alpha$ in $x = X = 0$ gives rise to a traveling pulse here plotted at time $t = 5$. The physical parameters are $\alpha = 0.1$, $\tau = 0.2$, and $D = A = 100$. The reaction-diffusion equation is discretized by an implicit finite difference scheme, with a time step $\Delta t = 0.001$ and a spatial step $\Delta x = 1$.

The dashed line corresponds to the solution of the standard FitzHugh–Nagumo equation; the continuous line shows the solution corresponding to a coupled propagation-contraction of the domain. Notice that both solutions are represented in spatial

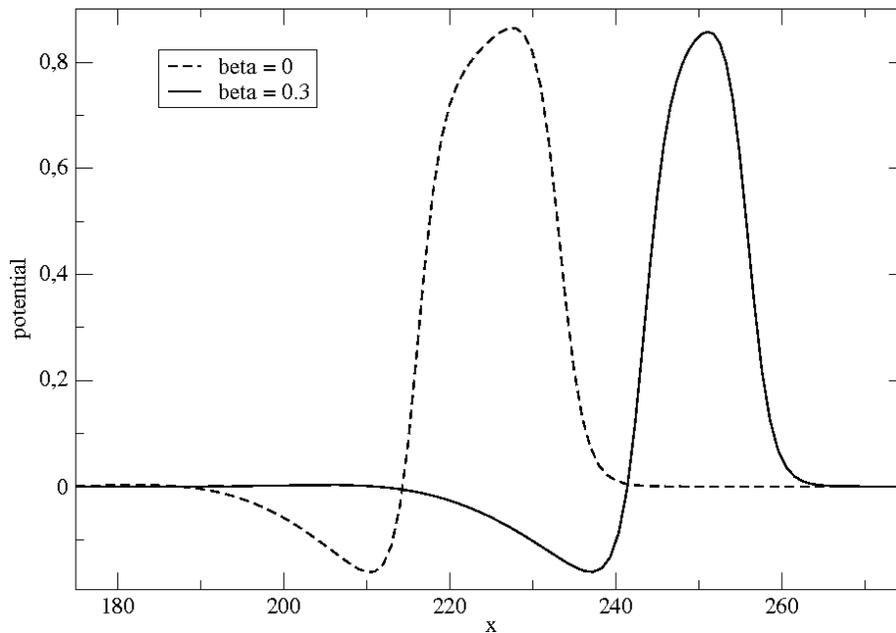


FIG. 1. Comparison between the activation potential of a traveling pulse solution of the standard FitzHugh–Nagumo equation in a fixed domain (dashed line) or a domain contracting linearly with the potential itself (continuous line). Both fields are represented versus spatial coordinates x .

coordinates x , so that in the case of contracting domain, i.e., when the dynamics of the potential is conveniently calculated in material coordinates, the solution has been pulled back to the physical coordinates by numerical integration.

The numerical results show that the coupling between the electrical signal and mechanics is important: propagating a pulse in a fixed domain yields a nonnegligible error. The computed pulse in a contracting domain exhibits a shorter width and travels faster, while preserving the same maximum and minimum values; this is in agreement with the qualitative discussion of section 4. In this specific case the difference in celerity is of order 10%, while the difference in width is about 25%.

The simulations corresponding to the results shown in Figure 2 are the same as in the previous case, except that here the initial datum is $v = 0.6$ for $-1 < x < 1$. This initial potential does not satisfy the instability condition (5.2); the numerical simulation obtained by numerical integration of the coupled electromechanical system shows that, as the corresponding energy is not sufficient to trigger a pulse, the diffusive damping prevails at the initial time, thus pushing the solution to the null stable point. Instead, if the strain is externally fixed to $x' = 1$ for a short initial time ($0 < t < 0.01$), nonlinearity prevails and the same initial condition gives rise to a traveling wave (Figure 2(b)).

7. Two-dimensional electromechanical coupling. In this section some preliminary two-dimensional numerical simulations obtained by the model discussed in the paper are illustrated. Collecting (2.2), (2.8), and (3.3), the two-dimensional problem for an incompressible neo-Hook material rewrites as

$$(7.1) \quad \text{Div} (\mu J_o \mathbf{F} \mathbf{F}_o^{-1} \mathbf{F}_o^{-T} - p \mathbf{F}^{-T}) = 0,$$

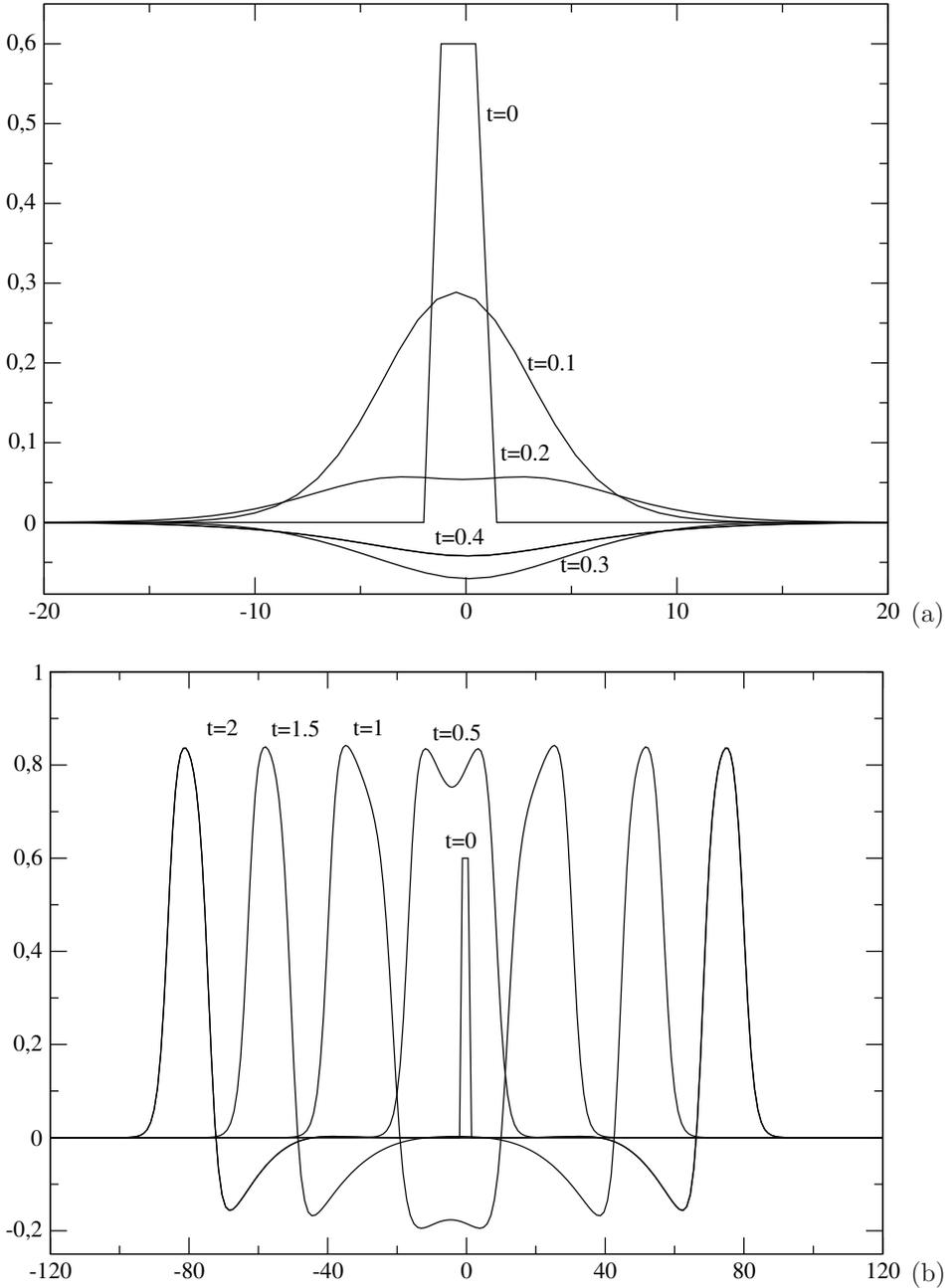


FIG. 2. Plot of the solution of (4.6), originated by the same initial conditions with and without initial stretch of the domain. An imposed fixed stretch of the boundary for a short time can give rise to a pulse (b) that is instead damped by diffusion if no external strain applies (a).

$$(7.2) \quad \frac{\partial v}{\partial t} - \text{Div} (\mathbf{F}^{-1} \mathbf{D} \mathbf{F}^{-T} \text{Grad } v) = -Av(v - \alpha)(v - 1) - Aw,$$

$$(7.3) \quad \frac{\partial w}{\partial t} = v - \frac{w}{\tau}.$$

With an abuse of notation, we denote by \mathbf{F} the plane gradient of deformation from now on.

In the simulations that follow we assume that muscle fibers are uniformly oriented in the $\mathbf{n} = (n_x, n_y)$ direction, so that the tensors rewrite as

$$(7.4) \quad \mathbf{F} = \begin{pmatrix} \frac{\partial x}{\partial X} & \frac{\partial x}{\partial Y} \\ \frac{\partial y}{\partial X} & \frac{\partial y}{\partial Y} \end{pmatrix}, \quad \mathbf{F}_o = \begin{pmatrix} 1 + \gamma n_x^2 & \gamma n_x n_y \\ \gamma n_x n_y & 1 + \gamma n_y^2 \end{pmatrix},$$

where it has been assumed that diffusion occurs along the fibers' direction only.

It is convenient to rewrite (7.1)–(7.3) in weak form:

$$(7.5) \quad \mu \int_{\Omega_o} J_o \mathbf{F} \mathbf{F}_o^{-1} \mathbf{F}_o^{-T} : \text{Grad } \phi \, d\Omega - \int_{\Omega_o} p \mathbf{F}^{-T} : \text{Grad } \phi \, d\Omega = -k \int_{\partial\Omega_o} \mathbf{u} \cdot \phi \, d\Sigma,$$

$$(7.6) \quad \int_{\Omega_o} \frac{\partial v}{\partial t} \phi \, d\Omega - D \int_{\Omega_o} \mathbf{F}^{-T} \text{Grad } v \cdot \mathbf{F}^{-T} \text{Grad } \phi \, d\Omega$$

$$(7.7) \quad = -A \int_{\Omega_o} (v(v - \alpha)(v - 1) - w) \phi \, d\Omega,$$

$$\int_{\Omega_o} \frac{\partial w}{\partial t} \phi \, d\Omega = \int_{\Omega_o} \left(v - \frac{w}{\tau} \right) \phi \, d\Omega,$$

where ϕ and ϕ are vectorial and scalar test functions, respectively. The surface integral on the right-hand side of (7.5) follows from the Robin boundary condition

$$(7.8) \quad \mathbf{P}\mathcal{N} = -k\mathbf{u} \quad \text{on } \partial\Omega,$$

where $\mathbf{u} = \mathbf{x} - \mathbf{X}$ and \mathcal{N} is the outgoing versor normal to the boundary. This boundary condition physically corresponds to an elastic resistance of the surrounding tissues proportional to the displacement with stiffness k .

The numerical simulation is carried out by a first order implicit discretization in time with fixed-point treatment of nonlinearities and linear triangular finite elements. Preliminary two-dimensional numerical simulations show the ability of the model to capture the coupled interaction between mechanics and electric signals. The computational domain we consider is a distorted ellipsoid, contained in a rectangle with size 130×180 , to be discretized by nearly 12000 nodes connected to form about 24000 triangular linear elements. The characteristic element size is chosen as the minimum spatial increment that in one-dimensional calculations allows us to capture the correct wave propagation speed ($\Delta x = 1$). The fibers are all supposed to be aligned in the same direction, parallel to the vector $(n_x, n_y) = (1, -1)$. The active strain is oriented along the fibers, while the diffusion is isotropic (see (7.4)). The latter assumption is not very relevant: a physical anisotropic diffusion has a typical ratio of 4 in the longitudinal versus transverse direction. The results differ only in the velocity of propagation.

The substrate is initially relaxed, and a perturbation in the potential of value $v = 0.9$ is located in the bottom right corner of the domain. The elastic modulus is $\mu = 1$, while all the other parameters appearing in the equations take the same values used for one-dimensional simulations. Robin boundary conditions and null flux of action potential apply on the whole perimeter of the domain, with rigidity constant $k = 1$ (see (7.8)).

The qualitative time evolution of the solution is as follows: in a few time steps, a pulse self-organizes where the initial perturbation was located and starts traveling across the domain. The results corresponding to $t = 3$ are plotted in Figure 3.

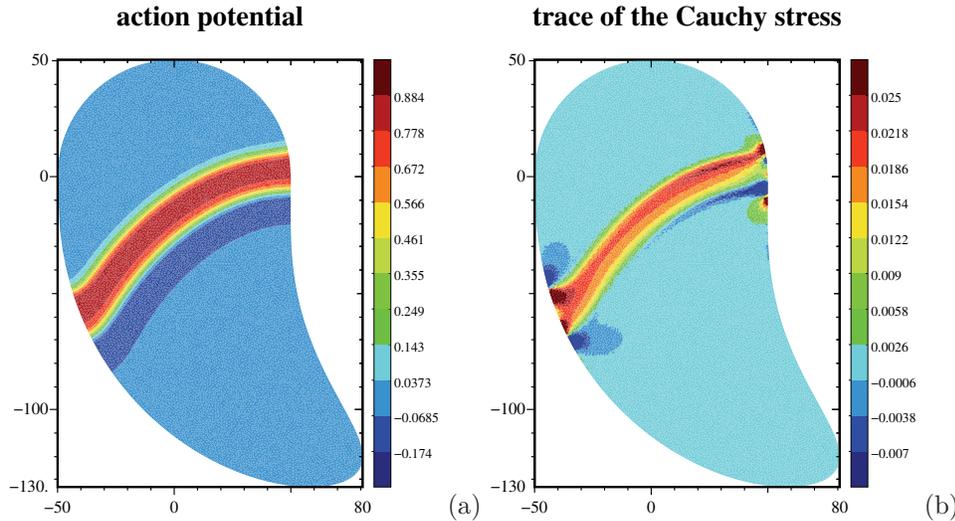


FIG. 3. Two-dimensional plots of the activation potential (a) and trace of the Cauchy stress (b) generated by an initial bump in a contractile domain. A voltage perturbation is located at the bottom right of the domain at $t = 0$.

The traveling wave of the action potential, shown in Figure 3(a), is similar to the one-dimensional case; the curvature of the front is due to non-Cartesian geometry of the domain and the almost pointwise initial conditions. The displacement of the substrate is relevant only where the action potential pulse is not small and originates the stress shown in Figure 3(b). It might be worthwhile to recall that the material we consider is incompressible and the vertical component of the strain (not shown) here plays the role of a diagnostic variable.

Concluding remarks. The mathematical modeling of the electromechanical coupling on a contractile substratum has been addressed with a careful separation between the balance equations for the elastic momentum and the action potential on one side, and the constitutive equations that prescribe their flux and sources on the other side. A precise distinction in this respect allows us to distinguish between the balance equations and the assumptions that lead to specific functional forms. Before any details on the coupling between stress and electric field are provided, the system of equations for the action potential has been rewritten in material coordinates, the most convenient of which will be used in nonlinear elasticity. This form (see (2.9)) immediately points out the feedback of strain on electric activity.

The focus of this paper is on electromechanical coupling; this is usually addressed in the relevant literature by introducing an active component of stress, depending on the electric potential, to be added to the standard one. In our opinion, other approaches deserve to be explored, according to the arguments exposed in section 1.1. Here we have directly stated the *kinematics* by imposing an active deformation of the soft tissue on the basis of the observed fibers' direction and stretch. This idea rewrites in mathematical terms in the multiplicative decomposition of the gradient of deformation adopted in the numerical modeling by Teresi et al. [3, 10]. The discussion of section 1.1 points out the difference between the two approaches and the advantages that one or the other could have in some respect. A definite comparison both from mathematical and physiological points of view is, however, still lacking.

Although there is an evident interest in applying the theory to cardiac electromechanics modeling, this paper mainly has a mathematical perspective. The physiological detail of the model is admittedly too poor, at least in two respects.

- The delay between potential upstroke and mechanical contraction is not accounted for; the same remark holds for the difference between the typical length of the action potential and the contraction, as the latter is known to be much longer. This is due to the simplicity of the voltage-strain relationship (1.4), here justified by the mathematical analysis that it allows. The expected physiological behavior can be reproduced by introducing the viscoelastic properties of the material, as discussed in section 4.2, and will be the subject of a forthcoming work.
- Despite its mathematical attractiveness, the Fitzhugh–Nagumo equation cannot provide quantitative prediction of the shape of the voltage pulses. Improvements in this respect can be obtained by including the time dynamics of ionic species. There are many models available in the literature: some of them include a large number of ionic species and are more difficult to analyze qualitatively [4, 12, 17]; other phenomenological models of the action potential [2, 6] are more attractive from this point of view as they are able to provide a quantitative prediction while keeping a small number of unknowns.

The simplicity of the assumed model allows us, however, to analyze the equations mathematically and draw some conclusions. Most of the discussion in the present paper concerns the case of a one-dimensional pulse along a fiber; however, the statements below are of general validity.

- The electromechanical coupling, as outlined in the present paper, does not modify the stability landscape of the reaction-diffusion equation: this model does not include an explicit term of stretch-activated current (as in [15]); the stretch of the domain does not affect the stability points of the action potential.
- Under quite general assumptions, traveling solutions of the FitzHugh–Nagumo equation that are well known to exist for propagation in a fixed domain still exist when introducing a coupling with the elastic strain. The celerity and steepness of a traveling front have been explicitly calculated and are generally bigger than for rigid substrates.
- Energy arguments allow us to determine the minimum strain to be applied on the substrate in order to originate a traveling wave starting from a too weak initial signal. Here, this kind of electromechanical feedback is not introduced by an explicit stretch-activated current added to the equation for the action potential, as in [15]. The physiological role of this mechanism is, however, expected to be minor: the incompressibility of the material composing the cardiac tissue does not allow large stretches so that the eigenvalue on the left-hand side of (5.4) cannot be much smaller than one.
- Preliminary two-dimensional numerical simulations confirm the ability of the model to predict at least qualitatively the electromechanical coupling.

REFERENCES

- [1] D. M. BERS, *Cardiac excitation-contraction coupling*, Nature, 415 (2002), pp. 198–205.
- [2] A. BUENO-OROVIO, E. M. CHERRY, AND F. H. FENTON, *Minimal model for human ventricular action potentials in tissue*, J. Theoret. Biol., 253 (2008), pp. 544–560.

- [3] C. CHERUBINI, S. FILIPPI, P. NARDINOCCHI, AND L. TERESI, *An electromechanical model of cardiac tissue: Constitutive issues and electrophysiological effects*, Progr. Biophys. Molec. Biol., 97 (2008), pp. 562–573.
- [4] P. COLLI FRANZONE, L. F. PAVARINO, AND G. SAVARÈ, *Computational electrocardiology: Mathematical and numerical modeling*, in Complex Systems in Biomedicine, Springer Italia, Milan, 2006, pp. 187–241.
- [5] A. DICARLO AND S. QUILIGOTTI, *Growth and balance*, Mech. Res. Commun., 29 (2002), pp. 449–456.
- [6] F. H. FENTON AND A. KARMA, *Vortex dynamics in three-dimensional continuous myocardium. Filament instability and fibrillation*, Chaos, 8 (1998), pp. 20–47.
- [7] S. GÖKTEPE AND E. KUHL, *Electromechanics of the heart: A unified approach to the strongly coupled excitation-contraction problem*, Comput. Mech., 45 (2010), pp. 227–243.
- [8] G. IRIBE, M. HELMES, AND P. KOHL, *Force-length relations in isolated intact cardiomyocytes subjected to dynamic changes in mechanical load*, Am. J. Physiol. Heart Circ. Physiol., 292 (2007), pp. 1487–1497.
- [9] J. KEENER AND J. SNEYD, *Mathematical Physiology*, Springer, New York, 1998.
- [10] P. NARDINOCCHI AND L. TERESI, *On the active response of soft living tissues*, J. Elasticity, 88 (2007), pp. 27–39.
- [11] I-SHIH LIU, *Continuum Mechanics*, Springer, New York, 2002.
- [12] C. H. LUO AND Y. RUDY, *A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes*, Circ. Res., 74 (1994), pp. 1071–1096.
- [13] A. MENZEL AND P. STEINMANN, *On configurational forces in multiplicative elastoplasticity*, Internat. J. Solids Structures, 44 (2007), pp. 4442–4471.
- [14] S. A. NIEDERER AND N. P. SMITH, *An improved numerical method for strong coupling of excitation and contraction models in the heart*, Progr. Biophys. Mol. Biol., 96 (2008), pp. 90–111.
- [15] A. V. PANFILOV, R. H. KELDERMANN, AND M. P. NASH, *Self-organized pacemakers in a coupled reaction-diffusion-mechanics system*, Phys. Rev. Lett., 95 (2005), 258104.
- [16] P. PATHMANATHAN, S. J. CHAPMAN, D. J. GAVAGHAN, AND J. P. WHITELEY, *Cardiac electro-mechanics: The effect of contraction model on the mathematical problem and accuracy of the numerical scheme*, Quart. J. Mech. Appl. Math., 63 (2005), pp. 375–399.
- [17] A. J. PULLAN, M. L. BUIST, AND L. K. CHENG, *Mathematical Modelling of the Electrical Activity of the Heart*, World Scientific, Singapore, 2005.
- [18] E. K. RODRIGUEZ, A. HOGER, AND A. MCCULLOCH, *Stress dependent finite growth in soft elastic tissues*, J. Biomechanics, 27 (1994), pp. 455–467.
- [19] J. STALHAND, A. KLARBRING, AND G. A. HOLZAPFEL, *Smooth muscle contraction: Mechano-chemical formulation for homogeneous finite strains*, Progr. Biophys. Molec. Biol., 96 (2008), pp. 465–481.
- [20] N. P. SMITH, D. P. NICKERSON, E. J. CRAMPIN, AND P. J. HUNTER, *Multiscale computational modelling of the heart*, Acta Numer., 13 (2004), pp. 371–431.
- [21] J. P. WHITELEY, M. J. BISHOP, AND D. J. GAVAGHAN, *Soft tissue modelling of cardiac fibers for use in coupled mechano-electric simulations*, Bull. Math. Biol., 69 (2007), pp. 2199–2225.