Finite element modelling of the calcium-induced contraction of cardiomyocytes based on time-lapse videomicroscopy

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Abstract: Isolated cardiac myocytes exhibit spontaneous oscillating patterns of contraction. This nonlinear dynamic behaviour is a clear landmark of the self-organizing capabilities of these cells, emerging from the coupling of intracellular calcium oscillations with the active and passive stresses generated within the cell. Starting from the analysis of time-lapse videomicroscopy sequences of cardiomyocytes contractions, we propose a finite-element analysis of these mechanical relaxation oscillations which integrates the cell rheological properties and the self-sustained spatio-temporal variation of cytosolic calcium concentrations resulting from the calcium-induced calcium release mechanism. By taking into account the cell structural anisotropy in the formulation of the active intracellular stress tensor, we successfully simulate the observed periodic variations of the cardiomyocytes morphologies, both qualitatively and quantitatively. This integrative analysis of the mechano-chemical coupling within cardiac cells may help to understand pathological rhythmic activity of normal cardiac tissue.

Key-Words: - Ca^{2+} Oscillations – Contraction – Anisotropic diffusion – Mechano-chemical Model

1 Introduction

Spontaneous intracellular Ca^{2+} oscillations in cardiac myocytes are well documented. This nonlinear dynamical behaviour results from the calcium-induced calcium release (CICR) mechanism, according which liberation of calcium from the sarcoplasmic reticulum (SR) is activated by calcium [1]. This autocatalytic process not only triggers intracellular calcium release, but also the propagation of a calcium wave which modulates the cell mechanical contraction. This mechano-chemical coupling is of particular importance since analysis of cardiomyocyte response to mechanical stress may shed light on various pathologies of the rhythmic contractility of the cardiac tissue.

However, while CICR mechanisms have been quite largely investigated through mathematical models [2], comprehensive descriptions of calcium-induced cardiomyocyte contraction, taking into account the mechanical properties and morphology of the cardiac cell, are still lacking. In this work, we propose a mechano-chemical model in which Ca^{2+} cytosolic concentrations variations and anisotropic diffusion are coupled with anisotropic cell sarcomeres contraction. Considering the model of Goldbeter et al. [3] as a basis for the modelling of the CICR mechanism, we investigate the conditions under which rhythmic cardiomyocytes contractions can occur. The simulated spatio-temporal cell contractions are then compared to time-lapse videomicroscopy sequences of spontaneously and periodically contracting isolated rat cardiac myocytes.

2 Modelling the calcium-induced cardiomyocyte contraction

2.1 From intracellular calcium oscillations to cardiomyocyte contraction

In the first step of our modelling approach, we consider for a seek of simplicity the quite well established two-variable model of Goldbeter et al. [3] as the core for self-sustained calcium oscillations. In this model, the CICR process is described by nonlinear kinetics between cytosolic Z(t) and sarcoplasmic Y(t) calcium concentrations, with rates of variation given by the differential system:

$$\frac{dY(t)}{dt} = v_2 - v_3 - k_f.Y \tag{1}$$

$$\frac{dZ(t)}{dt} = v_0 + v_1.\beta - v_2 + v_3 + k_f.Y - k.Z \tag{2}$$

In this model, $\upsilon_1\beta$ is the constant flow of calcium into the cytosol, controlled by the SR. The concentration of free cytosolic calcium Z(t) oscillates between low levels, during which Z is pumped by the SR ($\upsilon_{2\ flux}$), and high levels, characterised by the autocatalytic release of calcium υ_3 from the SR. The flux k_fY is a basal leak of

calcium into the SR, while the input flux υ_0 and efflux kZ refer to the Ca^{2+} fluxes into and out of the cell, respectively. Calcium fluxes υ_2 and υ_3 are modelled by Michaelis-Menten like reaction terms, where n, m and p represent the cooperativity degrees of the activation process, according to the relationships:

$$v_2 = V_{M2}.\frac{Z^n}{K_2^n + Z^n} \quad (3) \qquad v_3 = V_{M3}.\frac{Y^m}{K_R^m + Y^m}.\frac{Z^p}{K_A^p + Z^p} \quad (4)$$

where the positive constants V_{M2} and V_{M3} define the maximum rates of Ca^{2+} pumped into and released from the SR respectively.

In order to take into account the intracellular propagation of free calcium, we extended this CICR model by considering the anisotropic diffusion of calcium observed experimentally [4]. Starting from equation (Eq.1), the spatio-temporal variation of Z(**r**,t) at location **r** is thus given by:

$$\frac{\partial Z}{\partial t} = v_0 + v_1\beta - v_2 + v_3 + k_f Y - k.Z + \nabla.(\mathbf{D}\nabla Z) \quad (5)$$

where **D** is the diffusion tensor with components D_{ij}.

2.2 Modelling the cardiomyocyte active contraction

We assume that the total stress σ within the cardiac cell is the sum of passive elastic stresses $\boldsymbol{\sigma}_{passive}$ and active stresses $\boldsymbol{\sigma}_{active}$ generated by the contraction of acto-myosine fibers. Since the sarcomeres are oriented along the cell principal axis (x axis), we consider an anisotropic active stress tensor of the form:

$$\boldsymbol{\sigma}_{active} = \gamma(Z).T_0.\mathbf{e_x}\otimes\mathbf{e_x} \quad (6)$$

where $\gamma(Z).T_0$ is the local active cellular tension driven by the intracellular calcium concentration Z(**r**,t), $\mathbf{e_x}$ is the longitudinal x axis and $\otimes$ is the tensor product. We assume that the analytical expression of $\gamma(Z)$ is given by a Hill function of the form [5]:

$$\gamma(Z(r,t)) = \frac{Z^4}{Z_{50}^4 + Z^4} \quad (7)$$

The constitutive stress-strain relationship driving cell contraction is then given by :

$$\boldsymbol{\sigma} = \frac{E}{(1+\nu)}\left[\boldsymbol{\varepsilon} + \frac{\nu}{(1-2\nu)}Trace(\boldsymbol{\varepsilon}).\mathbf{I}\right] + \gamma(Z).T_0.\mathbf{e_x}\otimes\mathbf{e_x} \quad (8)$$

where **Id** is the identity tensor and $\boldsymbol{\varepsilon}$ the strain tensor, while E and v are the cell Young's modulus and Poisson ratio respectively. Neglecting inertial effects and volumic forces, the local mechanical equilibrium equation reads:

$$\nabla.\boldsymbol{\sigma} = \mathbf{0} \quad (9)$$

2.3 Finite element simulations of cardiomyocyte contractions.

Equations (2)-(5) are numerically solved using a finite element method (Femlab© software, Comsol) in a two-dimensional domain extracted from real cell morphology (Fig.1). The following boundary conditions are considered in the simulations: (i) zero-fluxes (Neumann) conditions on Z(**r**,t) and Y(**r**,t); (ii) zero-displacement conditions on cell nucleus and (iii) no propagation of strains through cell boundaries ($\boldsymbol{\sigma}.\mathbf{n} = \mathbf{0}$, where **n** is the vector normal to the cell membrane).

3 Results

Finite element simulations of the mechano-cellular model have been fist undertaken in order to reproduce qualitatively the observed contraction of isolated cardiomyocytes (Fig.1, left). Then, model parameters have been adjusted to get a quantitative agreement with the data extracted from the time lapse sequences.

Model parameters	Values	Units	References
υ_0	0.45	$\mu M.s^{-1}$	-
k	2.2	s^{-1}	-
k_f	0.1	s^{-1}	-
υ_1	4	$\mu M.s^{-1}$	-
V_{M2}	65	$\mu M.s^{-1}$	[3]
V_{M3}	500	$\mu M.s^{-1}$	[3]
K_2	1.2	μM	-
K_A	0.92	μM	-
K_R	3.5	μM	-
Y_0	0.1	μM	[3]
Z_0	10	μM	[3]
Z_{50}	2.5	μM	
β	0.05	-	-
D_{11}	300	$\mu m^2.s^{-1}$	[4]
D_{22}	150	$\mu m^2.s^{-1}$	[4]
D_{12}	0	$\mu m^2.s^{-1}$	[4]
D_{21}	0	$\mu m^2.s^{-1}$	[4]
E	100	kPa	-
υ	0.49	-	-
T_0	18.5	kPa	-

***Table I**: Set of biochemical and mechanical parameter values used for the model simulations (see Fig.1)*

Typically, the cell contraction periodicity is around 18sec, including a very brief cell contraction phase (1.5sec) followed by a refractory period of about 16.5 sec. This dynamical behaviour has been successfully

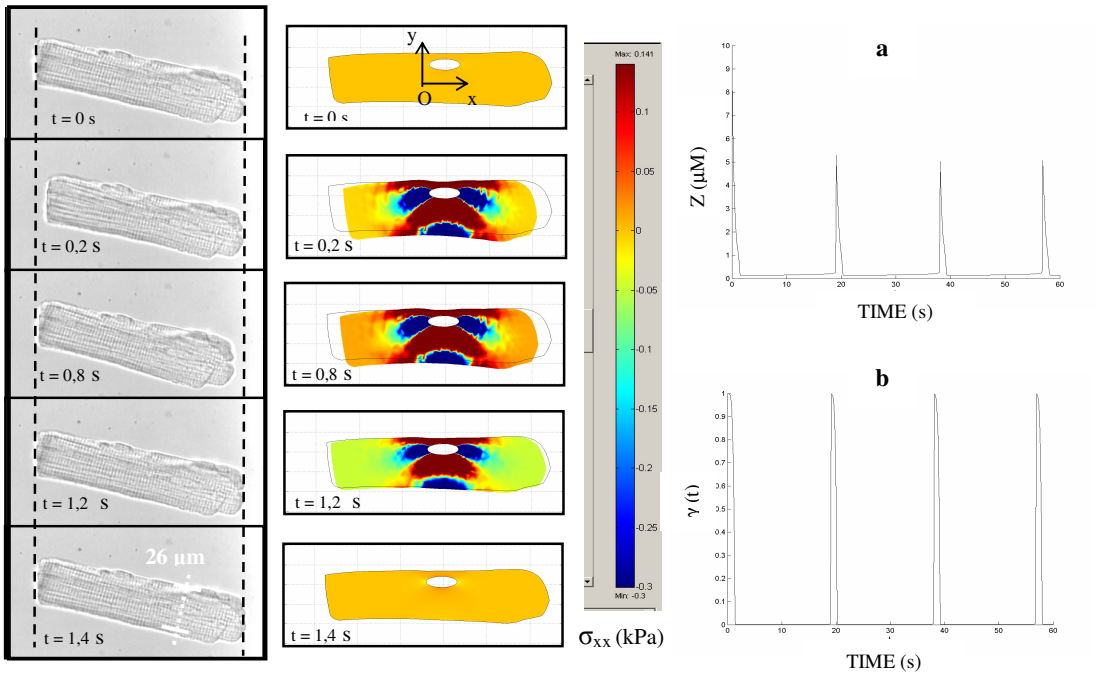

Fig.2: -left column: *Time-lapse sequence of an isolated rat cardiomyocyte contraction shown at successive times. Time t =0 sec indicates the beginning of a contraction. Experiment is achieved at room temperature to favour spontaneous cell contraction -* ***middle column*** *simulations of cell contraction (cell length~ 110 µm) and associated evolution of spatial principal stress distribution* σ_{xx}. ***Right-column: a:*** *temporal evolution of cytosolic calcium concentration Z(r,t) and.* ***b:*** *temporal evolution of variable* $\gamma(t)$ *at a given location inside the cell.*

reproduced with the parameter set reported in Table I. Furthermore, assuming that the cardiomyocyte is nearly incompressible (υ=0.49) with a Young's modulus E of 100kPa, we calculated a cell active tension T_0 of 18.5 kPa (Table I) in order to get a cell contraction amplitude of about 8µm (~7% of cell length), corresponding to the experimental data. Interestingly, maximum stress values are obtained in the central cell region (Fig.1, middle), as expected from the centripetal cell contraction.

4 Conclusion

This work proposes an original mechano-chemical model of cardiomyocyte self-sustained periodic contractions. The simulated model behaviour reproduces quite satisfactorily, both qualitatively and quantitatively, the real cell behaviour recorded by time lapse videomicroscopy. Even if a detailed discussion of the parameter values would be necessary for a further validation of the model, the present analysis already provides a general framework for investigating how modifications of intracellular calcium kinetics, cardiac cell rheological properties or contractility could lead to abnormal cell dynamics, with direct consequences on cardiac tissue contractility and cardiac rhythm.

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