Mathematical Modelling of Cardiac Mechanoenergetics

J. Engelbrecht[1], M. Vendelin[1,2]

[1] Tallinn Technical University, Centre for Nonlinear Studies, Estonia
je@ioc.ee
[2] Université J. Fourier, Laboratory of Fundamental and Applied Bioenergetics, France markov@ioc.ee

It has been shown how to bridge the physiological descriptions to continuum mechanics using the formalism of internal variables. Due to the complicated microstructure of cardiac tissues, these internal variables are switched in successively forming a hierarchy. The stress developed in the myocardium is separated into active and passive parts. The passive stress depends upon the elastic properties of fibres, the active stress, according to the Huxley model, depends on triggering the myofibrils due to Ca^{2+} signals. Overall, the process includes a three-level hierarchy of internal variables. The test problems, such as isometric contraction, Adenosin-Tri-Phosphate (ATP) consumption, etc. have shown good matches with experimental results. The numerical calculations based on FEM are presented for the left ventricle, modelled geometrically as a spheroid.

1 Introduction

The complexity of living tissues and cells is a challenge for modelling various biophysical and biochemical processes. The progress of *in silico* modelling shows the strength of a bio-mathematical approach supported by large-scale computing techniques. There are several reviews which reflect the recent results in this fast progressing research; see Kohl et al. (2000), Kolston (2000), Humphrey (2003), van Leeuwen and Aerts (2003), etc. The most promising results are obtained by integrating macro- and microbehaviour of tissues. Here macrobehaviour is understood for an organ or tissue as a whole and microbehaviour for the behaviour and processes of its constituents, including the processes in cells. Such a matching of physiology and continuum theory leads to a comprehensive description of tissues and their assemblies with predictive power and a wide range of *in silico* experiments. Those experiments should, however, always be validated against physical experiments *in vivo* and *in vitro*.

In this paper we focus on cardiac mechanoenergetics. Models of cardiac mechanics and electrical activation have been developed by several groups (reviewed by Hunter et al. (2003)). The primary aim is to combine stress analysis in cardiac muscles with cell energetics. It is shown how to bridge the physiological descriptions to continuum mechanics. In this context special attention is focused on the hierarchy of processes within the cell resulting in active stress. The concept of internal variables is used (Maugin (1990), Maugin and Muschik (1994)). Due to the complicated hierarchical (step-by-step) processes in cells and microstructured tissues, the basic concept of internal variables is generalized into the *concept of hierarchical internal variables*. This concept is demonstrated for the cardiac contraction based on the Huxley model. That means a sequence of internal variables: Ca^{2+} signal, the number of activated cross-bridges, and the number of force-producing cross-bridges. Such a successive modelling permits the build up of a mathematical model for cardiac contraction that can be tested against various physiological experiments (Vendelin et al. (2000)). Numerical calculations using the finite-element method for the left ventricle (LV) demonstrate the effectiveness of such an approach (Vendelin et al. (2002)). The geometry of the LV is taken as a spheroid.

The paper is organized as follows. Section 2 gives a brief overview of the concept of internal variables with the generalization to model hierarchies. In Section 3, the basic features of cardiac modelling are presented and formulated within the framework of hierarchical internal variables. Section 4 involves the discussion, including numerical results and conclusions.

2 The Concept of Internal Variables

The concept of internal variables has its origin in thermodynamics and chemical systems. Contemporary understanding has been reviewed by Maugin and Muschik (1994). It rests upon the assumption that the thermodynamic state is determined not only by observable variables χ (like strain) but also by internal variables α hidden to the external observers. Observable variables are internally governed by a balance law with a kinetic energy. Internal variables, however, do not possess inertia and are governed by kinetic equations. A typical case of an internal parameter in the mechanics of solids is the damage parameter.

The formalism of internal variables in a nutshell is the following (for more detailed description, see Maugin (1990), Maugin and Muschik (1994)). The dependent variables, for example stress σ, must be simultaneously a function of both observable and internal variables:

$$\sigma = \sigma(\chi, \alpha). \tag{1}$$

This must be complemented by an evolution law, such as

$$\dot{\alpha} = f(\chi, \alpha) + g(\chi, \alpha)\dot{\chi}, \tag{2}$$

describing the temporal evolution of the variable α. As usual, stress (i.e. an inertial variable) is derived from a free energy function ψ. In addition to that, a dissipation potential $\mathcal{D} > 0$ is postulated. Then it is possible to show (see Maugin (1990)) that the governing eq. (2) for α is derived as

$$\frac{\delta\ \psi}{\delta\ \alpha} + \frac{\partial\ \mathcal{D}}{\partial\ \dot{\alpha}} = 0, \tag{3}$$

where $\delta/\delta\alpha$ denotes the Euler-Lagrange derivative. This concept has also been used by Maugin and Engelbrecht (1994) for description of nerve pulse dynamics where the ion current is dependent on internal variables.

Biological processes, however, are complex and beside the structural hierarchy are often characterized by several embedded microprocesses, including also the cellular level. In this case we have proposed (Engelbrecht et al. (2000)) the concept of hierarchical internal variables. In general terms, the idea of building up the mathematical model is the following.

(i) a constitutive equation for a dependent variable σ depends on the observable variable χ and the *first-level* internal variable α:

$$\sigma = \sigma(\chi, \alpha); \tag{4}$$

(ii) the evolution law for α is

$$\dot{\alpha} = f_1(\chi, \alpha, \beta), \tag{5}$$

where β is the next, *second-level*, internal variable influencing σ only through dynamics of the first-level internal variable α;

(iii) the evolution law for β is

$$\dot{\beta} = f_2(\chi, \alpha, \beta, \gamma), \tag{6}$$

where γ is again the next, now the *third-level*, internal variable that influences σ only through dynamics of the second-level internal variable β;

(iv) the evolution law for γ is

$$\dot{\gamma} = f_3(\chi, \alpha, \beta, \gamma, ...), \tag{7}$$

etc.

Internal variables $\alpha, \beta, \gamma, ...$ form a hierarchy reflecting the hierarchical processes in the medium (tissue). Note that here we have dropped the gradients and did not discuss the entropy fluxes.

3 Cardiac Contraction

3.1 Physiological Background

Based on fundamental treatises on cardiac performance (Glass et al. (1991), Zipes and Jalife (1995)) we focus our attention on the mechanical behaviour

of the heart. In terms of continuum mechanics, the ventricles are thick-walled shells with complex geometry made of muscle fibres with essential variation of their orientation. A single fibre is made up by the bunches of myofibrils with a surrounding sarcotubular system. The myofibrils convert metabolic energy into mechanical energy and the sarcotubular system governs the Ca^{2+} ions needed for activation. A myofibril, in its turn, is composed of repeating units of myosin and actin filaments (sarcomeres). The excitation of a muscle is triggered by an action potential from the conducting system. This potential releases Ca^{2+} ions that activate the troponin molecules at the actin filament so that they will be able to attach to the heads of myosin molecules. These heads – the cross-bridges – swivel and cause sliding of filaments against each other, i.e. cause contraction of the muscle.

The transformation of the whole actomyosin complex is driven by the free energy of ATP hydrolysis to ADP and inorganic phosphate Pi.

The early phenomenological models tried to describe the relationships between observed macroscopic data. Starting from the Huxley (1957) models, contemporary modelling has put much more emphasis on mechanoenergetics (Glass et al. (1991), van Campen et al. (1994), Humphrey (2003)). Here we follow the ideas of Vendelin et al. (2000), casting them in the formalism of internal variables.

3.2 Mathematical Modelling of Tissue Properties

We assume that the total (Cauchy) stress in the cardiac muscle can be split into two parts,

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_p + \boldsymbol{\sigma}_a, \tag{8}$$

where $\boldsymbol{\sigma}_p$ and $\boldsymbol{\sigma}_a$ denote passive and active stress, respectively. The passive stress results from the elastic deformation of the tissue and can be calculated as

$$\boldsymbol{\sigma}_p = \partial\psi/\partial\boldsymbol{\varepsilon}^e, \tag{9}$$

where $\boldsymbol{\varepsilon}^e$ is the strain. The strain tensor is taken in its full form corresponding to large deformations. The active stress $\boldsymbol{\sigma}_a$ is generated in myofibrils by activation and is directed parallel to the fibre orientation. Hence

$$\boldsymbol{\sigma}_a = \sigma_a \boldsymbol{\varepsilon}_1 \otimes \boldsymbol{\varepsilon}_1, \tag{10}$$

where $\boldsymbol{\varepsilon}_1$ is the unit vector identifying the orientation. The mechanism for generating σ_a involves internal variables, as demonstrated below.

The force developed by the actinmyosin complex depends on the distance z between an attached cross-bridge and the nearest actin site. Actin and myosin produce the mechanical force through cyclic interaction using the free energy of ATP hydrolysis to ADP and Pi. The kinetic scheme of such an interaction

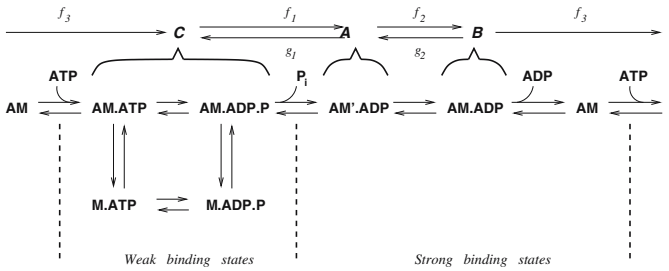

Fig. 1. The kinetic scheme of actin (A) and myosin (M) interaction (lower part) and its simplification as used in the model (upper part). States which include only M in the scheme present the states where myosin head is not attached to actin filament. Adapted from Vendelin et al. (2000).

and the simplified version used in the model are shown in Fig. 1. In the model, there are two states through the cycle producing force. Denoting them by A and B, we may calculate the corresponding forces by

$$F_A = K_A\, z, \quad F_B = K_B\, z, \tag{11}$$

where K_A, K_B are elastic constants. Further we take $K_A = K_B = K$. Assuming the uniform distribution of cross bridges in z over an interval d, we find the active stress

$$\sigma_a = \frac{m l_s K}{2d} \left(\int_{-d/2}^{d/2} z n_A(z) \mathrm{d}z + \int_{-d/2}^{d/2} z n_B(z) \mathrm{d}z \right), \tag{12}$$

where m is the number of cross-bridges per unit volume and $n_A(z), n_B(z)$ are relative numbers of cross-bridges producing force (i.e. being in states A and B). The variables, n_A and n_B, are the *first-level* internal variables. They are governed by the (coupled) kinetic equations (Hill (1974))

$$\frac{\partial n_A}{\partial t} + w \frac{\partial n_A}{\partial z} = f_1 n_C + g_2 n_B - (g_1 + f_2) n_A, \tag{13}$$

$$\frac{\partial n_B}{\partial t} + w \frac{\partial n_B}{\partial z} = f_1 n_A - (g_2 + f_3) n_B, \tag{14}$$

where w is the speed of lengthening, f_1, f_2, f_3, g_1, g_2 are kinetic constants between the states (see Vendelin et al. (2000)) and n_C is the number of cross-bridges that do not produce force. Clearly, the summation of all activated cross-bridges gives

$$A = n_A + n_B + n_C. \tag{15}$$

Now, A is the next in the hierarchy, i.e. the *second-level* internal variable, the change in which affects the observable σ_a only through n_A, n_B. The internal variable A (the activation parameter) has its own kinetic equation, i.e.

$$\frac{\mathrm{d}A}{\mathrm{d}t} = c_1(l_1)[Ca^{2+}](1-A) - c_2(l_s)A, \tag{16}$$

with $c_1(l_s), c_2(l_s)$ as certain parameters. This kinetic equation involves $[Ca^{2+}]$ – the *third-level* internal variable. This variable is governed by its own kinetic equation:

$$\frac{\mathrm{d}[Ca^{2+}]}{\mathrm{d}t} = f\left([Ca^{2+}]\right). \tag{17}$$

As is clear from equations presented, the observable σ_a is influenced by three levels of internal variables. In addition to finding σ_a, it is possible to compute the ATP consumption rate V_{ATP} in the tissue using the kinetic scheme of actomyosin interaction (Fig. 1):

$$V_{\mathrm{ATP}} = \frac{1}{d}\int_{-d/2}^{d/2} f_3(z) n_B(z,t)\mathrm{d}z. \tag{18}$$

Thus, through the model we are able to relate the mechanical function of the muscle (stress and strain) to biochemical energy consumption (ATP consumption).

The model was tested against several experimental results that are described in detail in Vendelin et al. (2000). In short, the following tests were performed: (a) the relationship between ATP consumption and specific area in the stress-strain diagram is linear, with contractile efficiency close to the measured one; (b) the computed isometric active stress during a beat replicates the measured stress in isosarcometric contractions at different sarcomere length values; (c) the contraction duration is smaller in the isotonic case if compared with the isometric case, in agreement with the isotonic contraction experiment results; (d) the end-systolic point in the stress-strain diagram in isotonic contraction lies close to the end-systolic line computed for the isometric case. The model was able to predict the following properties of the muscle: (a) the shortening velocity-afterload relationship at afterloads higher than 2.5 kPa; (b) the drop of ATP consumption by the cross-bridges during a cycle by about 40% if the muscle is released at the time of peak force.

3.3 Mathematical Modelling of the Left Ventricle

Using the material properties described above, we developed a mathematical model of the left ventricle (Vendelin et al. (2002)). The model computes the deformation of the ventricle, local strains, passive and active stress, and ATP

consumption in the ventricular wall. In short, the following assumptions were adopted when constructing the model. First, in the reference state of the model, defined as the state with zero transmural pressure, the endocardial and epicardial surfaces are represented by truncated focal ellipsoids (Streeter and Hanna (1973)), leaving a thick wall between them. The residual stresses in the unloaded state were ignored (Hunter et al. (2003)). Second, the calculations are based on the law of conservation of momentum. We neglected inertial and gravitational effects in our simulations. Third, the hemodynamic coupling of the left ventricle to the aorta is described by a three-element aortic input impedance (Bovendeerd et al. (1992)). Axial displacement of the nodes in the basal surface and circumferential displacement of subepicardial basal ring are suppressed. A uniform left ventricular pressure is applied to the entire endocardial surface. Epicardial pressure is assumed to be zero during a cardiac cycle. Finally, the governing equations were discretized using the finite element method in conjunction with Galerkin's method.

Using this model we studied the influence of fiber orientation in the left ventricular (LV) wall on the ejection fraction, efficiency and heterogeneity of the distributions of developed fiber stress, strain and ATP consumption (Vendelin et al. (2002)). The fiber orientation was quantified by two angles: the helix fiber angle, describing the crossover of fibers between base and apex of the heart, and the transverse angle, describing the crossover of fibers between inner and outer layers of the cardiac wall. For simplicity, the influence of the laminar structure of the myocardium on the distributions of stress and strain in the left ventricular wall was not considered. The computed variances of sarcomere length (VarSL), developed stress (VarDS) and ATP consumption (VarATP) have several minima at different transmural courses of helix fiber angle. Intriguingly, we identified only one region in the design space used with high ejection fraction, high efficiency of the LV and relatively small VarSL, VarDS and VarATP. This region corresponds to the physiological distribution of the helix fiber angle in the LV wall. Transmural fiber angle can be predicted by minimizing VarSL and VarDS, but not VarATP. If VarATP is minimized then the transverse fiber angle is considerably underestimated. The reasons for such differences in estimation are not clear yet. However, our results suggest that the ATP consumption distribution does not regulate the fiber orientation in the heart.

The model was tested against several experiments (Vendelin et al. (2002)). First, the computed increase in the equatorial wall thickness, outer equatorial ventricular radius and outer ventricular length during systole were close to the values measured by Olsen et al. (1981). Second, torsion of the apex during systole was found to be very sensitive to the model parameter values and somewhat different from the measured values (see Vendelin et al. (2002) for results and discussion). Third, the relationship between the pressure developed and the oxygen consumption of the ventricle is reproduced accurately.

An example solution is depicted in Figs 2 and 3. As is shown in the figures, the model can predict mechanical and energetic properties of the left

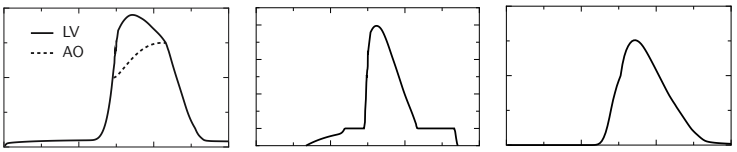

Fig. 2. Developed pressure in left ventricle (LV) and pressure in aorta (AO) (left), blood flow from LV (center), and ATP consumption by LV (right) computed by the model.

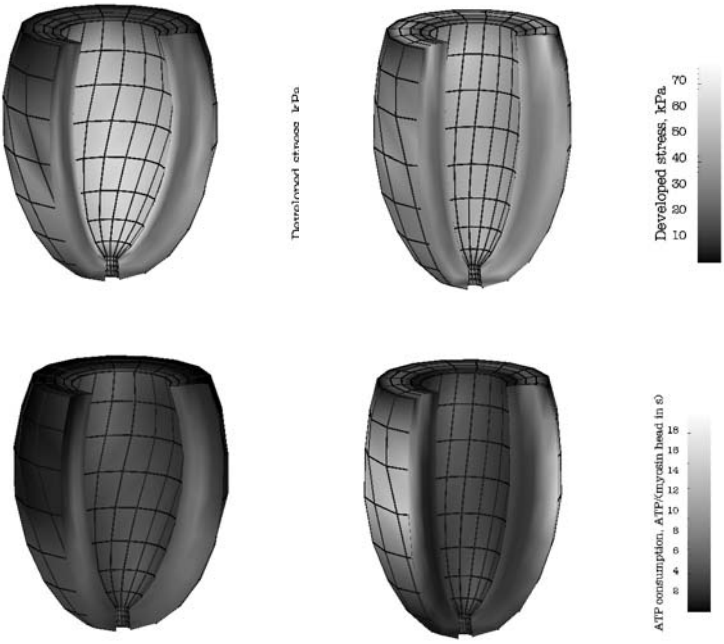

Fig. 3. Developed stress (the top row) and ATP consumption rate (the bottom row) during a systole computed by the model. The time-moments are 0.3 s (the left column) and 0.4 s (the right column).

ventricle. Now the model has to be tested against available experimental data on the distribution of oxygen consumption in the ventricle as well as regional deformation.

4 Discussion

The calculations of contraction for the idealized spheroidal LV are performed using the model described briefly in Section 3 and FEM. Several test problems

were solved and then compared with experimental results (Vendelin et al. (2000)). The tests included isotonic and physiologic contractions, ATP consumption, the quick-release experiment, etc. The model is in good agreement with the classical measurements of the SSA and oxygen consumption dependency.

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