A Cross-Bridge Model Describing the Mechanoenergetics of Actomyosin Interaction

Mari Kalda, Pearu Peterson, Jüri Engelbrecht, Marko Vendelin

Abstract In order to study the mechanical contraction and energy consumption by the cardiomyocytes we further developed an actomyosin model of Vendelin et al. (2000). The model is of a self-consistent Huxley-type and is based on Hill formalism linking the free energy profile of reactions and mechanical force. In several experimental studies it has been shown that the dependency between oxygen consumption and stress-strain area is linear and is the same for isometric and shortening contractions. We analyzed the free energy profiles of actomyosin interaction by changing free energies of intermediate states and activation of different reactions. The model is able to replicate the linear dependence between oxygen consumption and stress-strain area together with other important mechanical properties of a cardiac muscle.

1 Introduction

The intracellular environment of heart muscle cells is extensively compartmentalized with the several diffusion obstacles possibly separating mitochondria, the main source of ATP in mammalian heart, from ATPases (Kaasik et al., 2001; Vendelin and Birkedal, 2008; Sepp et al., 2010; Jepihhina et al., 2011). The compartmentation of the intracellular environment induced by the diffusion obstacles can be changed due to pathological conditions, such as ischemia or ischemia-reperfusion damage (Kay et al., 1997; Boudina et al., 2002). The kinetics of actomyosin ATPase,

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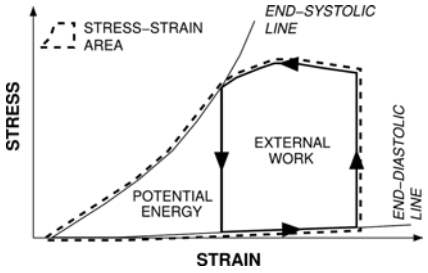

Fig. 1 A schematic representation of regional stress-strain trajectory loop. Stress-strain area (SSA) is the specific area in the stress-strain (SS) diagram surrounded by the end-systolic SS line, the end-diastolic SS line and the systolic segment of the SS trajectory for contraction (Delhaas et al., 1994).

a main consumer of ATP in the cardiomyocytes (Suga, 1990), is also influenced by intracellular compartmentation as evidenced by strong coupling between creatine kinase and actomyosin (Ventura-Clapier et al., 1987). Studies of intracellular compartmentation has benefited from the development of several mathematical models that allowed us to analyze intracellular diffusion using a 2D (Vendelin et al., 2004) or 3D (Ramay and Vendelin, 2009) description of the intracellular environment and suggest the possible intracellular structures that can lead to compartmentalization of the cell (Ramay and Vendelin, 2009). However, this analysis so far has been limited to relaxed cardiomyocytes or fibers with the models taking into account only the endogenous ATPase activity at low calcium concentrations (Saks et al., 2003; Vendelin et al., 2004; Ramay and Vendelin, 2009; Sepp et al., 2010). To study intracellular energy fluxes and how they are changed depending on the contraction of the heart, the development of actomyosin models that are able to link ATPase activity of the muscle and mechanical performance are vital. Using such models, the changes in energy transfer pathways induced by variation in workload as demonstrated by ^{31}P-NMR inversion and saturation transfer experiments (Vendelin et al., 2010) can be analyzed using mechanistic models.

As an important link between mechanical contraction and ATPase activity of actomyosin, a linear relationship between pressure-volume area (PVA) and oxygen consumption of the heart during a single beat has been established experimentally (Suga, 1990). On a fiber level, the linear relationship between an analog of PVA – stress-strain area (SSA, see Fig. 1) – and oxygen consumption has been established (Hisano and Cooper, 1987).

There are several published models that link mechanical contraction and ATPase activity of actomyosin (Cooke and Pate, 1985; Taylor et al., 1993a,b; Landesberg and Sideman, 2000; Vendelin et al., 2000; Månsson, 2010; Tran et al., 2010). Several of these models are based on a Huxley description of the contraction and achieve thermodynamic consistency by applying Hill formalism (Hill, 1974; Eisenberg et al., 1980). That formalism involves describing the spatial dimension of cross-bridge placing and for that partial differential equations (PDE) were used. Solving PDEs is usually considered to be computationally expensive and for that many cross-bridge

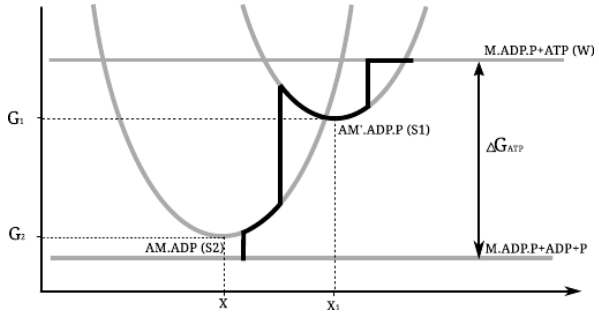

Fig. 2 Scheme of one possible set of free energy profiles and transition trajectory (black solid line) from state where considered cross-bridge is in the weakly bound state with ATP attached to myosin to weakly bound state without ATP attached to myosin. G_1, G_2, x and x_1 are parameters, that are describing the minimum points of free energy profiles for state S_1 and S_2. These parameters were found by optimization.

models have made the simplification and neglected microscopic details of cross-bridge population distribution and instead describe it using average cross-bridge cycling governed by ordinary differential equation (ODE) systems. However, we have demonstrated that it is possible to use a Huxley-type model as a model describing the contraction in the 3D finite element model of the left ventricle (Vendelin et al., 2002). As a basis of actomyosin description in a 3D model, we used a model developed earlier on the basis Hill formalism (Vendelin et al., 2000). In that model, a linear relationship between SSA and ATP consumption during one beat was reproduced together with several other properties of cardiac muscle. Actually, we used a free energy profile of the actomyosin reaction that had two force producing states of the cross-bridge at the same displacement configuration. Namely, the free energy minimum was located at the same position relative to the binding site for the both force producing states. However, the configuration of the cross-bridge is changed during the stroke and to incorporate that into the model, the force producing states should have different free energy minima locations (Eisenberg et al., 1980; Pate and Cooke, 1989).

The aim of this work is to find the set of free energy profiles, with different minimum positions for force producing states of the cross-bridge (Fig. 2) that would allow one to replicate the linear dependence between oxygen consumption and stress-strain area in cardiac muscle. First, we give a short description of the theoretical formalism developed by Hill that allows us to link mechanical contraction and chemical energy consumption. Next, the model description and simulation results are presented.

2 Theoretical Background

According to the sliding filament theory, shortening in sarcomere length during contraction is caused by thick and thin filaments sliding along each other. Thick and thin filaments consist primarily of the protein myosin and actin, respectively. To slide along, the energy from ATP hydrolysis is used in the interaction between myosin heads and actin sites. One possibility to connect the energetic and mechanical behavior for the contraction process is to use a Huxley-type model and the Hill formalism to describe the actin-myosin interaction in a thermodynamically consistent way. Cross-bridges, as defined by Hill, represent the projection from thick filament, despite if it is attached or not to actin site (Hill, 1974).

The initial Huxley model involves two biochemical states for cross-bridges: one state where actin and myosin are not attached (W) and one where they are attached (S). The rate constants to describe the transition from one state to the other are functions of the relative distance between the nearest cross-bridge equilibrium position and actin binding site. In this formalism several assumptions have been made: the cross-bridge is considered to have only one head and this head has ability to bind to only one actin site with significant probability. Cross-bridge behavior is assumed not to depend on other cross-bridge behavior and each cross-bridge can be in different biochemical states. The force F_n produced by an attached cross-bridge in bound state S is assumed to be elastic and depends linearly on the axial distance x along the myosin and actin filaments between the equilibrium position of the myosin head and the nearest actin binding site.

According to Hill (1974), the force produced by the cross-bridge at position x is related to the free energy G in the corresponding state n: $F_n = \partial G_n/\partial x$. Hence the linear dependency of force on x, leads to a parabolic dependence of the free energy on x. Such a relationship between mechanical force and free energy links the chemical reactions with mechanics. Namely, the transition between states is described by forward and reverse rate constants k_{forward} and k_{reverse}, respectively. The ratio between rate constants is determined by the difference in free energies of biochemical states. If we consider a reaction between state W and S then the ratio between the rate constants of the reaction is defined as

$$\frac{k_{\text{forward}}}{k_{\text{reverse}}} = \exp\left[-\frac{G_S(x) - G_W(x)}{RT}\right], \tag{1}$$

where R and T are the universal gas constant and absolute temperature, respectively. It is clear from this relationship that only one of the rate constants can be given at each x with another one determined by the free energy difference. As there is no force associated with state W, the free energy for it is not dependent on x. For values of x, where $G_S < G_W$ the strongly bound state is thermodynamically more stable; otherwise the weakly bounded state is favorable.

To describe muscle contraction, we use a kinetic formalism developed by Hill (1974). In short, it is possible to divide cross-bridges into subensembles according to the distance x between cross-bridge and the closest actin binding site. The cross-

bridges are in the same subensemble, if the distance is between x and $x+\mathrm{d}x$. For the same dx, the number of cross-bridges in subensembles is the same and constant for any x due to the lack of register between myosin and actin. Assuming that the cross-bridge can interact only with the closest actin binding site, the state of the cross-bridges can be described by fractions $n_j(x,t)$ giving the fraction of cross-bridges in state j (j is one of W, or S for two state model) at time t in subensemble at x to $x+\mathrm{d}x$. Taking that the distance between actin binding sites is d, fractions $n_j(x,t)$ are defined for x in the interval $(-d/2, d/2)$. At any time t, all cross-bridges are in one of the two states, $\sum_j n_j(x,t) = 1$. Changes in cross-bridge states are induced by chemical transition from one state to another or sliding of actin and myosin filaments relative to each other with the velocity v of sarcomere lengthening. For example, for state W, this would result in the following governing equation

$$\frac{\partial n_W}{\partial t} + \frac{\partial n_W}{\partial x} v(t) = k_{SW} n_S - k_{WS} n_W, \tag{2}$$

where k_{WS} and k_{SW} are the first order kinetic rate constants for transition from state W to state S.

The integral properties of the muscle, such as developed stress and ATPase rate could be found from integration over subensembles (Hill, 1974). The Cauchy stress σ_a developed by the cross-bridges in a half-sarcomere is, according to Zahalak and Ma (1990)

$$\sigma_\mathrm{a} = \frac{m l_s}{d} \left[\int_{-\frac{d}{2}}^{\frac{d}{2}} n_W(x,t) F_W \mathrm{d}x + \int_{-\frac{d}{2}}^{\frac{d}{2}} n_S(x,t) F_S(x) \mathrm{d}x \right], \tag{3}$$

where m is the number of cross-bridges in the unit volume and l_s is the length of the half-sarcomere. According to our assumptions F_W is zero because only the strong binding state generates force. Assuming that F_S is proportional to x with Hooke constant K, the stress equation will have the following form

$$\sigma_\mathrm{a} = \frac{m l_s K}{d} \int_{-\frac{d}{2}}^{\frac{d}{2}} n_S(x,t) x \mathrm{d}x. \tag{4}$$

The average cross-bridge ATP consumption rate is

$$V_\mathrm{ATP} = \frac{1}{d} \int_{-\frac{d}{2}}^{\frac{d}{2}} \left[k_{SW} n_S(x,t) - k_{WS} n_W(x,t) \right] \mathrm{d}x, \tag{5}$$

leading to the total ATP consumption per cross-bridge during a beat

$$V_\mathrm{ATP}^\mathrm{beat} = \frac{1}{d} \int_0^{T_c} \int_{-\frac{d}{2}}^{\frac{d}{2}} \left[k_{SW} n_S(x,t) - k_{WS} n_W(x,t) \right] \mathrm{d}x \mathrm{d}t, \tag{6}$$

where T_c is the period of a beat.

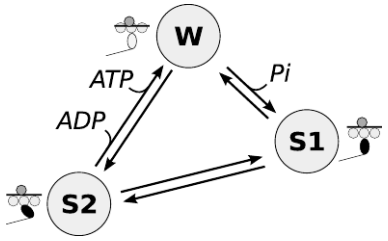

Fig. 3 Kinetic scheme of actin and myosin interaction used in three-state Huxley-type cross-bridge model: W is a weakly bound biochemical state, S_1 and S_2 are strongly bound states, where myosin head is able to generate force.

3 Methods

3.1 Model Description

Our mathematical model of actomyosin interaction is a further development of the cross-bridge model of Vendelin et al. (2000). This model consists of a three state Huxley-type model with two strong binding states (S_1, S_2) and one weak binding state (W) for cross-bridge interaction and a model of Ca^{2+} induced activation (Fig. 3). According to eq. (3), the Cauchy stress σ_a developed by the cross-bridges in a half-sarcomere for the considered three state model is

$$\sigma_a = \frac{ml_sK}{d}\left[\int_{-\frac{d}{2}}^{\frac{d}{2}} n_{S_1}(x,t)(x-x_1)\mathrm{d}x + \int_{-\frac{d}{2}}^{\frac{d}{2}} n_{S_2}(x,t)(x-x_2)\mathrm{d}x\right], \tag{7}$$

where x_1 and x_2 are the minimum positions of free energy profiles for biochemical states S_1 and S_2. The cross-bridge attachment and detachment in the muscle fiber are governed by the following system of equations

$$\frac{\partial n_{S_1}}{\partial t} = k_{WS_1}n_W + k_{S_2S_1}n_{S_2} - (k_{S_1W} + k_{S_1S_2})n_{S_1} - v\frac{\partial n_{S_1}}{\partial x}, \tag{8}$$

$$\frac{\partial n_{S_2}}{\partial t} = k_{s_1S_2}n_{S_1} + k_{WS_1}n_W - (k_{S_2S_1} + k_{S_2W})n_{S_2} - v\frac{\partial n_{S_2}}{\partial x}, \tag{9}$$

$$n_W = A - n_{S_1} - n_{S_2}, \tag{10}$$

where n_W, n_{S_1}, n_{S_2} are the fractions of the cross bridges in states W, S_1, S_2, respectively, A is the relative amount of activated cross bridges and v is the velocity of half sarcomere lengthening

$$v = \frac{\mathrm{d}l_s}{\mathrm{d}t}. \tag{11}$$

The rate constants are constrained as follows:

$$\frac{k_{WS_1}}{k_{S_1W}} = \exp\left[-\frac{G_{S_1}(x) - G_W(x)}{RT}\right], \tag{12}$$

$$\frac{k_{S_1S_2}}{k_{S_2S_1}} = \exp\left[-\frac{G_{S_2}(x) - G_{S_1}(x)}{RT}\right], \tag{13}$$

$$\frac{k_{S_2W}}{k_{WS_2}} = \exp\left[-\frac{G_W(x) - G_{S_2}(x)}{RT}\right]. \tag{14}$$

To describe the activation of the cross-bridges we use a phenomenological model, which is able to reproduce the main properties of heart muscle to generate the stress during the heart beat, which depends on time and the length of the sarcomere (Jewell, 1977). To activate the contraction, the concentration of Ca^{2+} changes. For that we use in the activation model the intermediate state B for reactions between tropomyosin C and Ca^{2+}

$$\frac{dA}{dt} = c_1 B(1-A) - c_2(l_s)\frac{A}{Q+A}, \tag{15}$$

where c_2 is a function of sarcomere length l_s, i.e.

$$c_2 = c_{2MX} + c_{2F}\frac{l_{\max} - l_s}{l_s - l_{\min}}, \tag{16}$$

and normalized concentration B is a function of time, i.e.

$$B = \begin{cases} t \le T_p, & \exp\left[-\left(\frac{t-T_p}{T_a}\right)^2\right], \\ \text{otherwise}, & \exp\left[-\left(\frac{t-T_p}{T_d}\right)^2\right]. \end{cases} \tag{17}$$

The symbols c_2, c_{2MX} and c_{2F} are rate constants for reactions between tropomyosin and Ca^{2+}, Q describes the cooperativity for Ca^{2+} to bind with tropomyosin C (Tobacman and Sawyer, 1990) and $l_{\max}$ and $l_{\min}$ are the maximum and minimum lengths of the half sarcomere, respectively. The constant T_p is the time that is needed to develop maximal contraction. The characteristic time T_D is dependent on the half sarcomere length and is defined as

$$T_D = T_{d0}\left(1 + T_{d1}\frac{l_s - l_{\min}}{l_{\max} - l_{\min}}\right). \tag{18}$$

The ATP consumption rate during one beat is according to eq. (6)

$$V_{ATP}^{beat} = \frac{1}{d}\int_0^{T_c}\int_{-\frac{d}{2}}^{\frac{d}{2}} \left[k_{S_2W} n_{S_2}(x,t) - k_{WS_2} n_W(x,t)\right] dx dt. \tag{19}$$

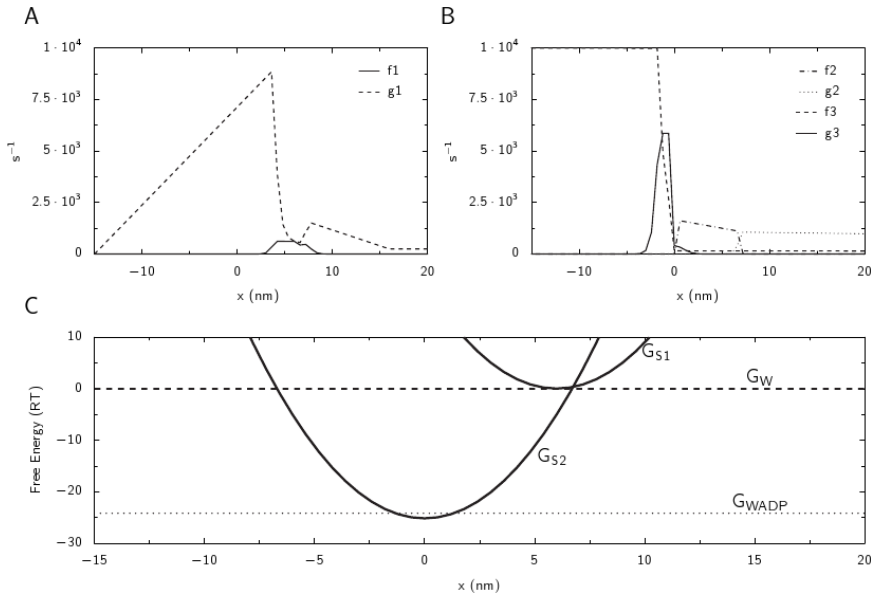

Fig. 4 (A),(B): cross-bridge cycling rates used in the model; (C) free energy profiles found by optimization of the mathematical model.

3.2 Optimization Strategy

The goal of the optimization process is to find the set of model parameters for a cross-bridge model which allows us to replicate the experimentally measured linear dependence of oxygen consumption on SSA. For that we divided the model parameters into two sets: (a) parameters describing free energy profiles (Fig. 2) and (b) parameters describing Ca^{2+} – induced activation of the actomyosin complex and rate constants of the actomyosin complex state transformation reactions.

As a first step in the optimization, (b) parameters were optimized at different sets of parameters (a) by minimization of the different residual functions. After that, the best fit was picked out and all (a) and (b) parameters were optimized again. For finding the parameters for describing the rate constants between biochemical states we predescribed the shape of these functions. The relationship between rate constants pairs (eq. (1)) declare that only one rate constants from the pair is independent. The shapes of the functions are shown at the Figs. 4(A) and (B).

To obtain the optimal model parameters we considered three fitting protocols. Simulation for isometric contraction were fitted against experimental data. The maximal total stress in isometric contraction was used for fitting the end-systolic points for isotonic contraction. And the linear relationship between SSA and ATP consumption was fitted against a pre-described linear line for all considered contraction types.

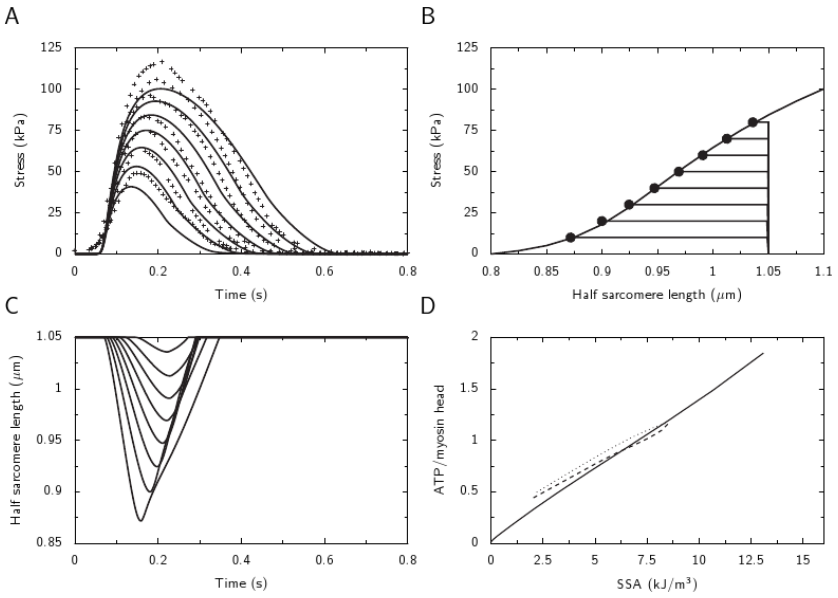

Fig. 5 Simulation results performed by mathematical model: (A) isometric contraction as a function of time at different half sarcomere lengths from 0.95 to 1.1 μm (solid curves) compared with experimental measurements (crosses) (Janssen and Hunter, 1995); (B) end-systolic curve for the isometric contractions and the isotonic contraction traces (end of the trace is marked with the symbol) at different afterloads from 10 to 80 kPa; (C) change in sarcomere length during the isotonic contraction at different afterloads; (D) total amount of consumed ATP molecules per myosin head during a cardiac cycle as a function of SSA for isometric (solid curve), isotonic (dashed curve) and physiologic (dotted curve) contraction.

4 Results and Discussion

We considered three different type of contractions: isometric, isotonic and physiological. Under 'physiologic' contraction we mean the isotonic contraction until the minimal half sarcomere length is reached and isometric contraction after that moment.

In Fig. 5(A) simulation of isometric contraction at different half sarcomere lengths from 0.95 to 1.1 μm (solid curve) is compared with experimental measurements (crosses) (Janssen and Hunter, 1995). Similar to experimental data, simulation results show that an increase in preload increases the maximal developed force and the twitch duration.

End-systolic curve for the isometric contractions and the isotonic contraction traces at different afterloads are compared in Fig. 5(B). End-systolic points for isotonic contraction lie close to the end-systolic curve for isometric contraction, which is in agreement with several experimental studies.

The isotonic contraction showed in Fig. 5(C) are simulated at afterloads from 10 to 80 kPa. To compare the contraction duration at isometric and isotonic contraction the duration is shorter in the isotonic case which is also in agreement with experimental results (Brutsaert et al., 1978).

A linear relationship between ATP consumption and SSA was replicated by our simulations for all considered contraction types (Fig. 5(D)). The linear fit for relationship between ATP and SSA for isometric contraction is

$$V_{\mathrm{ATP}}^{\mathrm{beat}} = 0.103 + 0.140 \left(\frac{SSA}{m \Delta G_{\mathrm{ATP}}} \right). \tag{20}$$

Taking into account the myosin ATPase concentration of $0.18\,\mathrm{mol/m}^3$ (Velden et al., 1998) and free energy change during ATP hydrolysis of 60 kJ/mol (Gibbs and Barclay, 1995), the contraction efficiency calculated from the slope is 66%. This value is in good agreement with experimental data (Suga, 1990), which demonstrates that the chemomechanical efficiency of cross-bridge cycling is in the range of 60-70%.

The set of free energy profiles simulated are shown in Fig. 4(B). This set involves a configuration chance for cross-bridges during the stroke by having different free energy minimal location points for two strong binding biochemical states S_1 and S_2. It is important to note that the set of parameters found by the optimization may not be unique. In our work we tried to find cross-bridge rates with as simple shape as possible to fit the desired data. It is possible to use different functional forms to describe rate constants and still obtain good results.

5 Conclusion

Our mathematical model is able to replicate the classical measurements of SSA and oxygen consumption dependency. As a result of optimization, the model solution is in agreement with the behavior of cardiac muscle in isometric and shortening contractions.

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