Thermodynamical framework for modeling chemo-mechanical coupling in muscle contraction – Formulation and preliminary results

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Résumé :

Nous proposons un modèle multi-échelle de la contraction cardiaque dans lequel les moteurs moléculaires à l'origine du processus contractile sont représentés par des éléments mécaniques multistables paramétrés à la fois par des degrés de liberté géométriques et par des états chimiques. Ce modèle permet de poser les fondements thermodynamiques permettant de décrire l'interaction complexe entre les phénomènes mécaniques et chimiques a l'échelle sub-cellulaire. Ce travail a pour objet de représenter les caractéristiques physiologiques du dispositif contractile observées expérimentalement et en particulier (i) le mécanisme passif de récupération rapide de force, (ii) la relation entre la vitesse de contraction et la charge appliquée et (iii) le cycle dit de Lymn-Taylor décrivant l'activité métabolique.

Abstract :

We propose a multiscale model of cardiac contraction in which the molecular motors at the origin of the contractile process are considered as multistable mechanical entities endowed with internal degrees of freedom of both mechanical and chemical nature. This model provides a thermodynamical basis for modeling the complex interplay of chemical and mechanical phenomena at the sub-cellular level. Important motivations for this work include the ability to represent the experimentally observed physiological characteristics of the contractile apparatus such as (i) the passive quick force recovery mechanism, (ii) the relation between the contraction velocity and the applied force and (iii) the so called Lymn-Taylor cycle describing the metabolism.

Mots clefs : modélisation de la contraction cardiaque, couplage mécano-chimique, mécanique statistique, thermodynamique
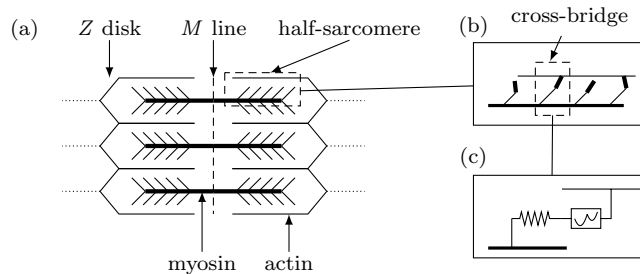
Figure 1: Contractile structure inside a muscle cell. (a) periodic arrangement of sarcomeres; (b) array of attached and detached cross-bridges inside a half-sarcomere; (c) mechanical representation of an attached cross-bridge.

Muscle contraction is an active process taking place at the nanoscale of a hierarchical multi-scale structure characterized by parallel arrangement of fibrillar cells. Each muscle cell exhibits an almost crystalline structure corresponding to the periodic succession of sarcomeres, each of them comprising actin and myosin filaments which are cross-linked by so-called cross-bridges, see Fig. 1.

While attached to the actin filament a cross-bridge undergoes a rapid conformational change named *power-stroke* resulting in stretching an elastic element transmitting the generated force to the myosin backbone. The cooperative action of the sarcomere motors is ultimately responsible for the generation of the macroscopic force.

The traditional approach of the modeling of muscle contraction involves the implementation of a phenomenological rheological law in which the link between the force generated and the underlying physiological process remains rather unclear. A more physiologically relevant description is however necessary for addressing the questions of mechanical efficiency which are linked to the consumption of metabolic fuel at the molecular level and more importantly for using a mechanical model in a clinical context. Therefore we propose a multi-scale model enabling to study the tight coupling between the macroscopic loading conditions and the underlying physiological processes in an adequate thermodynamical framework.

In our model a cross-bridge in itself is seen as a special chemical entity having internal mechanical variables – or degrees of freedom – pertaining to the actual geometric configuration, which implies that the free energy of the cross-bridge – whether in an attached or unattached state – must be made dependent on these internal variables [1]. This provides a thermodynamical basis for modeling the complex interplay of chemical and mechanical phenomena at the sarcomere level.

Our proposed chemo-mechanical model of a cross-bridge is summarized in Fig.2 and explained in details in [2]. The rheological model (a) shows the main ingredients allowing to link – with energy balance properties– the macroscopic equilibrium equations to the underlying active process operating at the micro-scale as introduced in [3]. It consists in a decomposition of the stress into two components. The first component
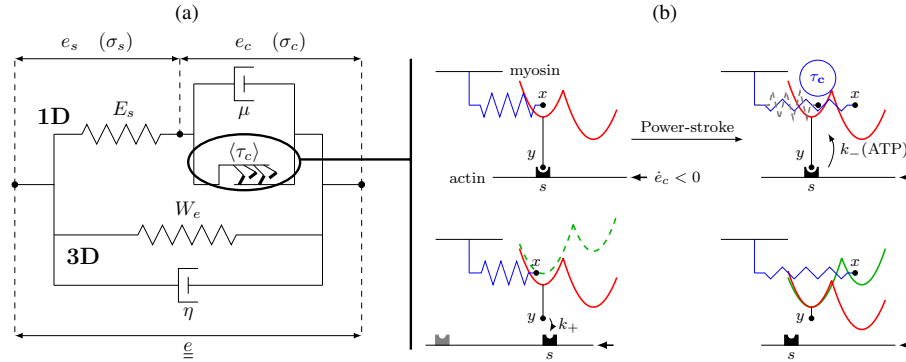
Figure 2: Rheological model of a muscle. (a) rheological model including a description of the contractile apparatus in a 1D branch representing a contractile fiber and a passive 3D component. (b) Chemical-mechanical cross-bridge model in Lymn-Taylor cycle: attached (top) vs. detached (bottom) / pre-power-stroke (left) vs. post-power-stroke (right). The two internal mechanical variables are denoted by x and y, $\dot{e}_c$ is the sarcomere strain rate, and (k_+, k_-) denote the binding and unbinding reaction rates, respectively.

represents the 3D passive visco-elastic behavior of the tissue consisting in an hyperelastic part with energy W_e and a viscous element proportional (with factor η) to the strain rate. The second component allows to incorporate a 1D contribution representing the stress fibers which provide the active tension. In this branch a linear elastic element (E_s) is connected in series to the contractile apparatus whose purpose is to generate an average active stress $\langle \tau_c \rangle$. This average is computed from a stochastic process illustrated in Fig. 2(b) which represents the so-called Lymn-Taylor cycle [4] relating the energy input provided by ATP hydrolysis and the mechanical output τ_c at the level of a single nanometer size molecular motor. During this cycle the myosin motor binds to its companion actin filament and exerts an increment of force through a rapid conformational change – the power-stroke– mediated by thermal fluctuations and represented by a bistable potential (in red). After performing the stroke the myosin motor detaches from the actin filament and gets recocked in its pre-power-stroke conformation. This step requires ATP whose action is modeled by an energy delivery which tilts the bistable energy landscape thereby destabilizing the post-power-stroke conformation, see the transition from the red potential to the green potential. This tilting is then reversed upon the next attachment event.

Here we point out that we consider only two chemical states – namely, attached versus unattached– instead of four in [5], albeit in our case with two internal mechanical variables (x and y) instead of one (s).

Important motivations for this modeling choice include the ability to represent (i) the so-called power-stroke phenomenon playing an important role in short-time responses of a muscle [6], e.g. to load steps and (ii) the force-velocity relation which is determinant for assessing the power output of the tissue. Our approach allows for the systematic

treatment of the model energetics, and in particular one goal of the proposed description is to investigate the potential benefit in mechanical efficiency with systems including – in addition to chemically-induced transformations – thermally-induced conformational changes such as the power-stroke.

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