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Muscle Contraction on the Half-Sarcomere Level: A New Model Approach

***Ivo A. Telley[1], Urs Stöcker[2] and Jachen Denoth[3]**

[1] European Molecular Biology Laboratory (EMBL)
Meyerhofstrasse 1
69117 Heidelberg, Germany
ivo.telley@embl.de
http://www.embl.de

[2] ETH Zurich
Institute for Biomechanics
HCI E 451
8093 Zurich, Switzerland
ustoecker@ethz.ch
http://www.biomech.ethz.ch

[3] ETH Zurich
Institute for Biomechanics
HCI E 357.1
8093 Zurich, Switzerland
jdenoth@ethz.ch
http://www.biomech.ethz.ch

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ABSTRACT

The structure of striated muscle is highly organized from the whole organ down the arrangement of single molecules. Myosin is the molecular motor that drives the muscular force generation. The interaction with actin filaments ('crossbridges') and the internal conformational change ('power stroke') of myosin are responsible for the increase in stiffness and force during activation. However, the structural unit of muscle is the parallel arrangement of many of these filamentous structures, forming the so-called 'sarcomere'. Actin and myosin filaments interdigitate and interact in an overlap zone in each half of the sarcomere; the two zones can change their length while the filaments slide against each other, allowing the muscle to shorten during force generation. In a muscle cell (fiber) many thousands of sarcomeres are serially arranged to a 'myofibril', which is parallely aligned and coupled to other myofibrils in the cell. Thus, a muscle cell resembles a huge 3D network of force-generating motor units, the sarcomeres, presumably with non-identical properties. From an engineering point of view such a construct must exhibit complex internal dynamics and demands for control and stabilizing mechanisms.

Recently, we have demonstrated that not only the sarcomeres but also the two halves of each sarcomere in a myofibril operate non-uniformly and apparently independently although they all produce the same force during contraction [1]. It was the first direct evidence the functional unit of muscle is the *half*-sarcomere. Our highly accurate length measurements of single half-sarcomeres in myofibrils revealed that the dynamics of filament sliding along the half-sarcomeres showed significant variability. The two halves of a sarcomere did not exhibit the same shortening/lengthening behavior, and externally applied stretch induced a slow dynamics that cannot be fully explained by current crossbridge models [2].

We have also shown previously by model considerations that in end-held contractions (constant total length) the dynamics of each half-sarcomere is coupled to all others, and

that tension is a complex convolution of the individual (half-) sarcomeric forces [3,4]. Thus, a lumped model for the *average* interaction of myosin with actin, which is unaffected by the internal dynamics of half-sarcomeres in a fiber, does not fully explain force generation and length changes in all circumstances. To understand the experimental findings and previous findings on sarcomere inhomogeneity from muscle fibers, it is necessary to formulate a multi-segmental model composed of individual half-sarcomere models in series and parallel. The model should incorporate a kinetic formalism of crossbridge formation, and a passive mechanical component in series and parallel to crossbridges. Only with such an approach, it is possible to simulate the transient shortening/lengthening behavior of each individual half-sarcomere and calculate the tension response of a large system such as the myofibril or muscle fiber.

We have established a mathematical framework that facilitates the theoretical analysis of half-sarcomere dynamics in a myofibril during contraction and relaxation for length-clamped and force-clamped conditions. The formalism incorporates the basic ideas of Huxley [5], as well as mechanical components that represent the passive cytoskeletal scaffold ('titin', [6]) and the series elasticity of thin (actin) and thick (myosin) filaments. Mechanical coupling of individual half-sarcomere models is accomplished according to our previous work on modeling sarcomere dynamics [3]. Adopting the idea of the classic Huxley formalism [5], which results in a set of partial differential equations (PDE) for the kinetics of actomyosin binding in a half-sarcomere, the methods of characteristics in space transforms the PDE into parameterized ordinary differential equation (ODE). On a discrete grid of parameters these equations are solved with the condition that the forces in all half-sarcomeres are identical. The response is a set of length changes (velocities) of the half-sarcomeres in the system considered during activation, stretch / shortening and relaxation.

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