Computational modelling identifies impact of subtle anatomical variation on skeletal muscle local calcium dynamics

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Computational modelling identifies impact of subtle anatomical variation on skeletal muscle local calcium dynamics

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ABSTRACT

Calcium is the main regulator of skeletal muscle metabolic activity. The question has been addressed whether the highly structured spatial organization of sites of Ca2+ release, uptake and action in skeletal muscle substantially impacts the dynamics of cytosolic Ca2+ handling and thereby the physiology of the cell. Hereto, the spatiotemporal dynamics of the free calcium distribution in a fast-twitch muscle sarcomere was studied using a reaction-diffusion computational model.

The model was based on the model of Baylor and Hollingworth (J Gen Physiol. 1998 112:297-316), but was adapted to handle local calcium dynamics in mouse EDL fast twitch muscle at 35C. Furthermore, the Ca2+ mass balance was closed by adding a mathematical representation of the sarcoplasmic reticulum. Experimental calcium time courses (high time resolution, but spatially averaged) obtained under physiological conditions (35C, 125 Hz stimulation frequency) were used for model validation.

The model showed that subtle changes in sarcomere microstructure influenced the local calcium concentration. Furthermore, local calcium concentration sensed by mitochondria was higher than average calcium concentration and also above the activation constant of the mitochondria, whereas the local concentration was not. Furthermore, the free Ca2+ concentration was higher at the positions with troponin C than without troponin C.