Multiscale and Modular Analysis of Cardiac Energy Metabolism

Repairing the Broken Interfaces of Isolated System Components

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ABSTRACT: Computational models of large molecular systems can be assembled from modules representing biological function emerging from interactions among a small subset of molecules. Experimental information on isolated molecules can be integrated with the response of the network as a whole to estimate crucial missing parameters. As an example a "skeleton" model is analyzed for the module regulating dynamic adaptation of myocardial oxidative phosphorylation (OxPhos) to fluctuating cardiac energy demand. The module contains adenine nucleotides, creatine and phosphate groups. Enzyme kinetics for two creatine kinase (CK) isoforms was combined with the response time of OxPhos (t_{mito}; generalized time constant) to steps in the cardiac pacing rate to identify module parameters. To obtain t_{mito}, the time course of O_2 uptake was measured for the whole heart. An O_2 transport model was used to deconvolute the whole heart response to the mitochondrial level. By optimizing mitochondrial outer membrane permeability to 21 μm/s the experimental t_{mito}= 3.7 s was reproduced. This *in vivo* value is about 4 times larger, or smaller, than conflicting values obtained from two different *in vitro* studies. This demonstrates an important rule for multiscale analysis: experimental responses and modeling of the system at the larger scale allow estimating essential parameters for the interfaces of components which may have been altered during physical isolation. The model correctly predicts a smaller t_{mito} when CK activity is reduced. The model further predicts substantial pulsatility of myocardial ATP synthesis, a slower response if the muscle CK isoform is overexpressed and a faster response if mitochondrial CK is overexpressed.

KEYWORDS: mitochondria, membrane permeability, systems biology, oxidative phosphorylation, reverse engineering, creatine kinase, modular modeling

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