molecular systems biology

NEWS AND VIEWS

Comment on 'Dynamic analysis of optimality in myocardial energy metabolism under normal and ischemic conditions'

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In a recent paper, Luo *et al* (2006) present an innovative and perhaps useful approach to simulating metabolism, termed M-dynamic flux balance analysis, in which metabolic fluxes are estimated by minimizing an objective function that is computed from a weighted sum of deviations in fluxes and concentrations from baseline conditions. Unfortunately, this study is severely deficient in terms of its presentation, model assumptions, and validation of modeling predictions.

One problem with the presentation is that key variables are not given units. For example, the flow F is varied from 1 to 0.2 to simulate myocardial ischemia. Although the reader is not told about the units by which flow is measured, it is apparent from the equations that F must have units of inverse time. Thus perhaps F represents flow divided by volume. In that case, for the simulated range to be reasonable, we might guess that the units are 1/min. The following analysis of the method and results of Luo *et al* (2006) assumes this guess to be correct.

In addition to the lack of rigor in its presentation, the model and associated simulation of ischemia are based on a wholly inadequate simulation of oxygen transport to the myocardium. Specifically, the model equations assume that the blood and tissue are lumped into one well-mixed compartment, leading to the simplification that oxygen uptake from the arterial blood is equal to the flow times the difference between arterial concentration and tissue concentration times a partition coefficient. As metabolically active tissues such as those of the heart extract a large portion of the oxygen from the blood as it passes through the microcirculation, resulting in significant intracellular gradients and intratissue heterogeneity of oxygen (Beard and Bassingthwaighte, 2001; Beard *et al*, 2003; Schenkman *et al*, 2003; Ejike *et al*, 2005; Beard, 2006), the well-mixed assumption leads to a model that cannot even qualitatively represent reality. This mistake is particularly disastrous for the study of Luo *et al* because ischemia in the heart leads to heterogeneous regional hypoxia, not the homogenous reduction in oxygen concentration that their

model predicts (Beard *et al*, 2003; Schenkman *et al*, 2003; Beard, 2006). This faulty modeling assumption may have contributed to the poor performance of the model in comparison to experimental observations.

Luo *et al* summarize 'three major modeling results that were consistent with previous publications.' The first result is that when oxygen is limited, creatine phosphate decreases and glycogen is consumed. This result is of course immediately apparent from mass balance of energy metabolism in a cell that consumes ATP following a shutdown of oxidative phosphorylation. The third major result is on the trends in glucose uptake with severity of ischemia. Although it would have been ideal to quantitatively compare these results with experimental data to evaluate the validity of the model, the reported second major result is the most troubling. It is reported that the predicted increase in intracellular lactate matches experimental measurements. Specifically, after 10 min of 40% reduction in blood flow, the predicted lactate concentration of $7 \, \mu\text{mol} \, \text{g}^{-1}$ is compared with the value of approximately $5 \, \mu\text{mol} \, \text{g}^{-1}$ reported by Arai *et al* (1991). To make the comparison, we have to make the (unstated) assumption that Luo *et al* averaged data from endocardium, midmyocardium, and epicardium. Although this comparison is reasonable, it ignores a great deal of additional directly relevant data available in the literature in general and even in this particular study by Arai *et al* (1991).

Arai *et al* (1991) report data on ATP, phosphocreatine, and lactate concentrations, lactate and oxygen consumption, and rates of ATP production at three different time points following the onset of ischemia. In total, there are at least 18 data points in the study of Arai *et al* (again averaging endocardium, midmyocardium, and epicardium) that can be directly compared with the predictions of Luo *et al*. Yet Luo *et al* choose to report on only the one out of 18 that compares favorably to their model. For example, at the 5–10 min time point Arai *et al* measure lactate efflux to be more than double that predicted by Luo *et al*. At a later time point, the data show

net lactate uptake, although the model predictions are not reported. The data show a decrease in oxygen uptake of 23% at the 5–10 min time point for 40% of baseline flow, whereas Luo *et al* predict a decrease of approximately 65%. Arai *et al* report that the rate of ATP production is decreased by about 15% at this time point, whereas the model of Luo *et al* predicts that it is less than half of the baseline value. From these results, it is apparent that the model of Luo *et al* does not come close to effectively simulating energy metabolism and oxygen transport in the heart during ischemia.

In summary, the comparison between the simulations of Luo *et al* (2006) and relevant experimental observations is extremely weak and far from adequate for inclusion in the scientific literature. Comparison of model predictions to only a single data point while ignoring the rest of the data set from which that data point is selected is simply not good enough.

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