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NEWS AND VIEWS

In reply: 'Dynamic analysis of optimality in myocardial energy metabolism under normal and ischemic conditions'

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We thank Dr Beard for his thoughtful comments on our recent study (Luo *et al*, 2006). We present the following responses.

Two different aspects of our research are mainly discussed in Dr Beard's comment. One pertains to the parameter of our mathematical model whereas the other relates to the results of the model.

F in our model is a dimensionless parameter and represents the relative blood flow. Given the different levels of relative blood flow, the simulation conditions are defined as normal blood flow conditions ($F=1$) and ischemic conditions ($F<1$), including mild ($F=0.8$), moderate ($F=0.6$, $F=0.4$), and severe ($F=0.2$) ischemia. The format of our model refers to the published work of Salem *et al* (2002). As the objective of our research is to try to understand how cellular metabolic networks can dynamically adjust and adapt to changes in the environment and to predict the trend of the adjustment, we feel that, in this case, it is not absolutely necessary to measure the blood–tissue or tissue–cell partition coefficient and to build a model that simulates metabolites' diffusion between tissue and cell. Based on our objective, we thus simplified the model to concentrate on the adjustment pattern of the cellular metabolic network.

The FBA and DFBA methods are constraint-based and semiquantitative methods (Palsson, 2002), which allow us to get to system's solution by searching for the optimal objective in a large null space. The results of these methods are different from those of the deterministic method such as ordinary differential equation (ODE) in some aspects. There are differences between our results and experimental data; however, those differences should be acceptable. Moreover, the trend of our results is consistent with the experimental results in general.

By selecting objective functions, we found that the M_DFBA model correctly described the phenomenon of the predominant contribution of fatty acids to oxidative ATP production under mild and moderate ischemic conditions, but the DFBA model failed to do so. This finding is the main characteristic of our research. Based on this finding, we suggested that metabolic systems can minimize the fluctuation of the profile of metabolite concentration (its state) under perturbation conditions.

Recently, we studied the robustness of metabolic networks in photosynthetic metabolism of C_3 plants by the M_DFBA method. We found that, in the face of transient perturbation, metabolic systems are inclined to maintain their state by cooperative regulation. This suggests that highly cooperative regulation assures robustness of biological systems by maintaining the system's function under environmental perturbations. This, in turn, results in minimizing fluctuations in the profiles of metabolite concentrations, which is key to maintaining a system's function (Luo *et al*, in preparation).

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