

Supplementary Figure 1. The modeling results of the DFBA model. (A) lactate concentration increased to 10~35 $\mu\text{mol g}^{-1}$ during moderate ischemia and continued to rise during severe ischemia. Lactate concentration, it is severe higher than the experimental data. (B) Fatty acid accumulated. (C, D) The endogenic phosphocreatine and glycogen were consumed to produce ATP under ischemic conditions. (E) During moderate ischemia, the uptake of glucose increased, while during severe ischemia it decreased, but still showed a higher level than normal. (F, H) The uptake of fatty acid and oxygen decreased. But under mild and moderate ischemia, considering the ATP production decreases, the predominant contribution of fatty acid to oxidative ATP synthesis compared to carbohydrates is actually altered. This prediction is not conformable with previous findings. (G) The input flux of lactate converted to an output flux during moderate and severe ischemia, however it is severe higher than the experimental data.

Supplementary Figure 2. The slope of the curve at each point represents the velocity of ATP production at particular time. (A) In DFBA model, under normal condition ($F=1$), the velocity of ATP production approximately equals to $34.9 \mu\text{mol g wet wt}^{-1} \text{min}^{-1}$, the value of the normal velocity of ATP consumption; while under ischemic conditions ($F<1$), it decreases. (B) In M-DFBA model, the velocity of ATP production approximately equals to that in DFBA model under normal condition; while under ischemic conditions, it is always lower than those in DFBA model.

Supplementary Figure 3. The explanation of how calculating the Euclidean distance described in objective function. The upper figure shows the process of dividing time period into a finite number of intervals (finite elements). In this example, the number of intervals is 4. Then each variable was parameterized at the roots of an orthogonal polynomial within each finite element. In this example, the number of orthogonal points in each finite element is 2. The lower figure shows the Euclidean distance of the vector of metabolite concentrations between two adjacent orthogonal roots (j and $j+1$).

Supplementary Figure 4. Modeling results of lactate uptake and lactate concentration in DFBA and M-DFBA model respectively. The experimental data at the original time point are measured under normal condition ($F=1$); while the data marked on the time point of 10 minutes in the figures are experimentally measured under the condition of $F=0.4$ in 10 minutes or longer time. (A,C) The modeling results in DFBA model show that the velocity of lactate uptake decreases approximately to $-4 \mu\text{mol g}^{-1} \text{min}^{-1}$ under the conditions of $F=0.4$, which is much lower than the experimental data of $-0.2 \sim -0.7 \mu\text{mol g}^{-1} \text{min}^{-1}$ (Stanley et al., 1994); while the value of myocardial lactate concentration increases approximately to $20 \mu\text{mol g}^{-1}$ under the conditions of $F=0.4$, which is much higher than the average experimental data of $5 \mu\text{mol g}^{-1}$ (Arai et al., 1991). (B,D) The M-DFBA modeling curves of lactate uptake and myocardial lactate concentration under the condition of $F=0.4$ are more consistent with experimental data compared with those in DFBA model.

Supplementary Table 1. Original substrate concentration in myocardia.

Supplementary Table 2. Substrate concentration in arteria.

Supplementary Table 3. Partition coefficients between blood and myocardia.

Supplementary Table 4. Maximum velocity of fluxes.

Supplementary Table 5. Fluxes.

Supplementary Information 1. Matlab Code.

Supplementary Information 2. The Table of variable.

Supplementary Information 3. A step by step example.