A simple dynamic model for mitochondrial metabolism

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Abstract: A simple dynamical model is proposed in this paper to describe the main time-varying quantities in mitochondrial metabolism. The model is given in the form of kinetic ordinary differential equations containing 11 state equations. The parameters of the model were determined from the literature or from the authors' own laboratory measurements. The obtained simulation result is in good agreement with actual observation for simulating an ischemic process.

Keywords: biomedical systems, dynamical modeling, simulation, differential equations

1. INTRODUCTION

In the Neurobiochemistry working group (Institute of Medical Biochemistry, Semmelweis University), we have taken enzyme kinetic measurements of several mitochondrial enzymes, and we have determined and analyzed interactions between enzymes and substrates. Therefore, a suitable quantitative (mathematical) model is constructed which describes the temporal changes in the quantities of citric acid cycle's (CAC) molecules. The modeling goal in this research phase is to describe qualitatively the increased/decreased operation of the catalyzing enzymes as well as the modified operation of the intermediate molecules.

In previous studies similar models were constructed, it belongs to our goals is to promote further development compared to the known models and to expand them in other aspects. In Wu et al. (2007) the model can predict the individual factors effects (NADH, ATP, metabolic fluxes) in the regulation of CAC function and projects the effect of pH and membrane potential changes on ATP synthesis. In Korla and Mitra (2014) examination of the process of the CAC, electron transport chain and ATP synthesis is described. Reactions of the CAC are described with eight differential equations with Michaelis-Menten reaction kinetic. Korla et al. (2015) extends the earlier model with two transporter systems.

2. BIOLOGICAL BACKGROUND

2.1 Process description

Mitochondria are cell organelles with prokaryotic origin that established endosymbiosis with ancient eukaryotic cells during evolution. CAC is a complex enzyme system in mitochondria, and a key step of metabolism. Mitochondria produce energy during the catabolic degradation of carbohydrates, fats, proteins and nucleic acids. Additionally, molecules of the CAC take part as precursors in the construction of the anabolic procedures (Nelson and Cox (2012)).

2.2 The modeled reactions

In this work we modeled the reactions of CAC, and 3 mitochondrial transporters. The following list contains the reactions and their catalyzing enzymes/transporters involved in our model (Number of reaction, name of enzyme, Enzyme Commission (EC) number of enzyme).

R1: Citrate synthase (CS, 4.1.3.7):
$Acetyl\text{-}CoA + oxaloacetate \rightarrow citrate$
R2: Aconitase (ACON, 4.2.1.3):
$Citrate \rightleftharpoons isocitrate$
R3: Isocitrate dehydrogenase (IDH, 1.1.1.41):
$Isocitrate + NAD^+ \rightarrow oxoglutarate + CO_2 + NADH$
R4: Oxoglutarate dehydrogenase (OGDH, 1.2.4.2):
$Oxoglutarate + CoA\text{-}SH + NAD^+ \rightarrow succinyl\text{-}CoA + CO_2 + NADH$
R5: Succinyl-Coenzyme A ligase (SUCLA, 6.2.1.4):
$Succinyl\text{-}CoA + GDP + P \rightarrow succinate + CoA\text{-}SH + GTP$
R6: Succinate dehydrogenase (SDH, 1.3.5.1):
$Succinate + FAD \rightarrow fumarate + FADH_2$
R7: Fumarase (FH, 4.2.1.2):
$Fumarate + H_2O \rightleftharpoons malate$
R8: Malate dehydrogenase (MDH, 1.1.1.37):
$Malate + NAD^+ \rightleftharpoons oxaloacetate + NADH$
R9: Citrate transporter (CTP):
$Citrate + H^+ \rightleftarrows malate$
R10: Dicarboxylate carrier (DIC):
$HPO_4^{2-} \rightleftarrows malate$
R11: Oxoglutarate carrier (OGC):
$Oxoglutarate \rightleftarrows malate$

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3. KINETIC MODEL OF CITRIC-ACID CYCLE

3.1 Modeling goals

The modeling goals are the following:

(1) To determine the concentrations of substrates which participate in these reactions between physiological conditions.
(2) To predict the new equilibrium status after we modified initial conditions.
(3) To model the changed dynamic of the system in case of specific diseases via using pathological parameters of enzymes and/or pathological initial conditions.

3.2 Parameters

Table 1 contains the kinetic parameters. Source of parameters is the literature and some of them were measured in Institute of Medical Biochemistry, Semmelweis University, namely the values corresponding to OGDH, SDH and MDH.

E or T	substrate	V_{max} (μmol/min)	K_M (μM)
CS	oxaloacetate	1.88	4
ACON	citrate	3.4	470
	isocitrate		120
IDH	isocitrate	0.1	140
OGDH	oxoglutarate	0.0086	71
SUCLA	succinil-CoA	0.39	40
SDH	succinate	0.299	251
FH	fumarate	0.721	13
	malate		140
MDH	malate	1.616	580
	oxaloacetate		52
CTP (T)	citrate	10.5	32/27
	malate	11.5	250/60
DIC (T)	malate	6	490/920
	HPO_4^{2-}	6	1410/930
OGC (T)	oxoglutarate	9.5	310/170
	malate	10	1360/710

Table 1. Parameters and values of enzymes and transporters

3.3 The applied kinetics

Differential equations were described by parameters of enzymes and transporters using the Michaelis-Menten kinetic model. The general form of the reaction rates is

$$V([S]) = \frac{V_{max} \cdot [S]}{K_M + [S]}$$

Rates of reversible reactions and transports are described with two opposite reactions. We assume constant cell concentrations, because the volume of cell is much larger than that of the mitochondrium.

4. COMPUTATIONAL RESULTS FOR SIMULATING REGENERATION AFTER ISCHEMY

The simulations were implemented in MATLAB. We examine a pathological metabolic status after acute ischemy. In this state there is a significant change in substrate concentrations. Based on literature data, the altered initial conditions were the following: citrate decreases to 370 μM, oxoglutarate to 26 μM, fumarate to 180 μM, malate to 795 μM, and succinate to 1355 μM.

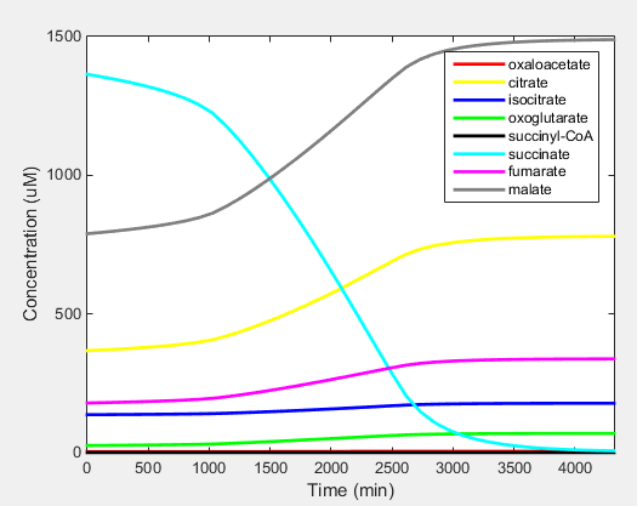

Fig. 1. Changes of concentrations after acute ischemia

The simulation shows that after ischemic status concentrations of substrates are going to physiological concentrations, as the system tries to recover physiological status (Figure 1). Moreover, we can observe that approximately three days are needed to restore normal concentrations of mitochondrial intermediates. These results show us that this model gives good results qualitatively, but further improvements are needed by parameter calibration and by the extension with other transporters.

5. CONCLUSION

A simple dynamic model for describing the dynamics of key quantities in mitochondrial metabolism was proposed in this paper. The model is written in the form of 12 nonlinear ODEs using Michaelis-Menten kinetics. The model was used successfully to simulate recovery from ischemy.

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