Integrative Modeling of Mitochondrial Metabolism

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1 Introduction

We are in the process of constructing a kinetic model of mitochondrial metabolism including the electron transport (respiratory chain), the TCA cycle, the fatty acid metabolism (β oxidation), the inner-membrane metabolite carriers, the protein carriers, and the mitochondrial gene expression system. In this work, we report a model of these metabolic pathways that has been recently completed using the E-CELL system [2], a generic simulation environment for cellular simulation based on multiple ordinary differential equations.

2 Methods and Results

The model consists of the following number of enzymatic reactions: six (6) for the respiratory chain, eight (8) along with some ancillary reactions for the TCA cycle, seven (7) for the β oxidation, seven (7) for the metabolite carrier system, one (1) for the protein carrier system, and five (5) enzymatic reactions and several accompanying reactions for the mitochondrial gene expression system (Table 1). All of the enzymatic reactions are modeled based on kinetic parameters found in the literature or estimated by various parameter-tuning methods [1].

Figure 1 presents an example run of E-CELL from an *in silico* experiment conducted using this model. The figure shows the temporal transition of the concentration of ubiquinone and ubiquinol, a pair of electron transporters; the former is transformed into the latter by accepting two electrons. At the point of 70 seconds, the TCA cycle and the β oxidation pathway were disrupted in order for us to observe their influence on the respiratory chain. Consequently, a sudden change of the ubiquinone/ubiquinol ratio took place (Figure 1).

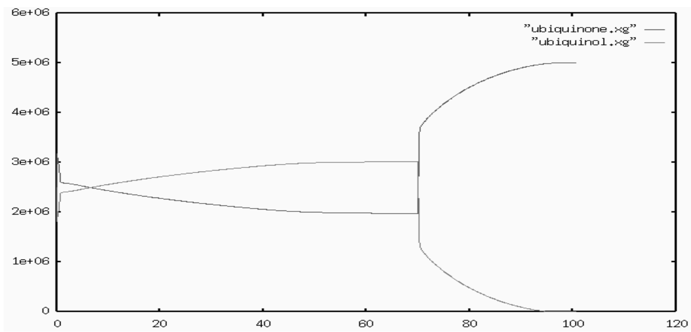

Figure 1: Temporal transition of ubiquinone and ubiquinol

This transition occurs because ETF-Q oxidoreductase in the β oxidation pathway and Succinate dehydrogenase in the TCA cycle had the ability to reduce ubiquinone into ubiquinol. Hence, the example run shows that the TCA cycle and the β oxidation including those enzymes play an important role in maintaining the rate of electron transport.

We will continue to work on this mitochondrial model, with the eventual goal of applying it to pathological analyses of mitochondrial diseases such as Leigh syndrome and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Table 1: The reactions in the model

Group	Enzyme	Group	Enzyme
respiratory chain	NADH dehydrogenase	β oxidation	Acyl-CoA dehydrogenase
	Ubiquinol:Cytochrome *c* oxidoreductase		Enoyl-CoA hydratase
	Cytochrome *c* oxidase		3-hydroxyacyl-CoA dehydrogenase
	ATP synthase		3-ketoacyl-CoA thiolase
TCA cycle	Pyruvate dehydrogenase complex		ETF:Q oxidoreductase
	Malic enzyme		CPT I
	Pyryvate carboxylase		CPT II
	Citrate synthase	Metabolite carriers	Pyruvate carrier
	Citrate hydratase		Citrate carrier
	Isocitrate dehydrogenase		Dicarboxylate carrier
	2-oxoglutare dehydrogenase complex		Oxoglutarate carrier
	Succinyl-CoA synthetase		Adenine nucleotide carrier
	Succinate dehydrogenase		Phosphate carrier
	Fumarase		Carnitine carrier
	Malate dehydrogenase	Protein carrier	Protein carrier
		mitochondrial gene expression system	RNA polymerase
			mtRNase P
			Aminoacyl-tRNA synthetase
			Peptidyl transferase
			MPP

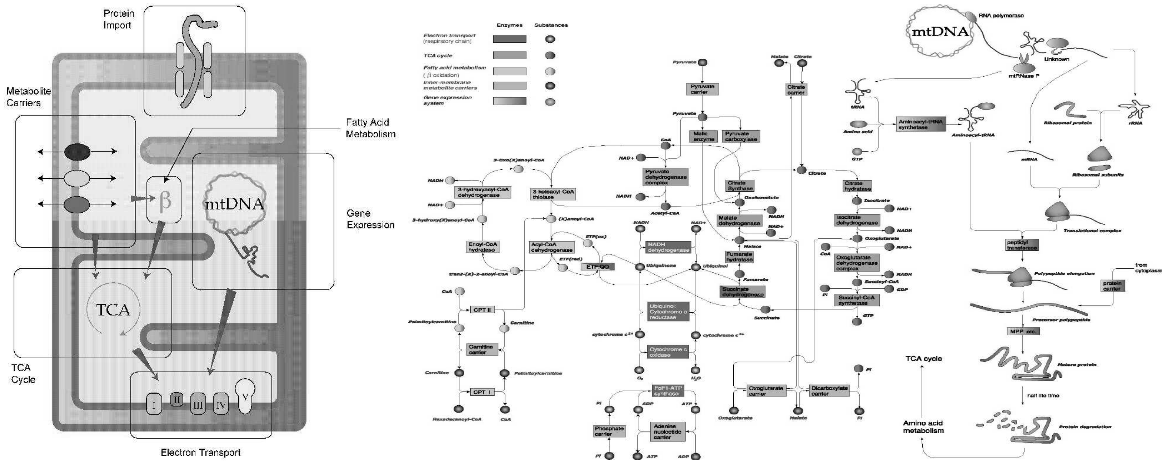

Figure 2: a) An overview of the model and b) the modeled reactions

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