# Integrative Modeling of Mitochondrial Energy Metabolism

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## 1 Introduction

We are in the process of constructing a kinetic model of mitochondrial energy metabolism including the electron transport (respiratory chain), the TCA cycle, the fatty acid metabolism ($\beta$ oxidation), and the inner-membrane metabolite carriers. 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 we have developed for cellular simulation.

## 2 Material and Method

### 2.1 Model

The model consists of the following enzymatic reactions: four (4) for the respiratory chain, twelve (12) along with some ancillary reactions for the TCA cycle, seven (7) for the $\beta$ oxidation, and eight (8) for the metabolite carrier system. All of the enzymatic reactions are modeled based on rate equations and kinetic parameters found in the literature or estimated by genetic algorithm (GA) and various parameter estimating methods [1].

Table 1: The reactions in the model

| Group | Enzyme | Group | Enzyme |
|---|---|---|---|
| respiratory chain | NADH dehydrogenase | $\beta$ 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 |
| | Aconitase | | Dicarboxylate carrier |
| | Isocitrate dehydrogenase (× 2) | | Tricarboxylate carrier |
| | 2-oxoglutare dehydrogenase complex | | Oxoglutarate carrier |
| | Succinyl-CoA synthetase | | Adenine nucleotide carrier |
| | Succinate dehydrogenase | | Phosphate carrier |
| | Fumarase | | Carnitine carrier |
| | Malate dehydrogenase | | Asp/Glu carrier |

## 2.2 Parameter Estimation

Here, we show 2 examples of kinetic parameter estimation. Each graph shows fitness of experimental values in the literature and computer-simulated values.

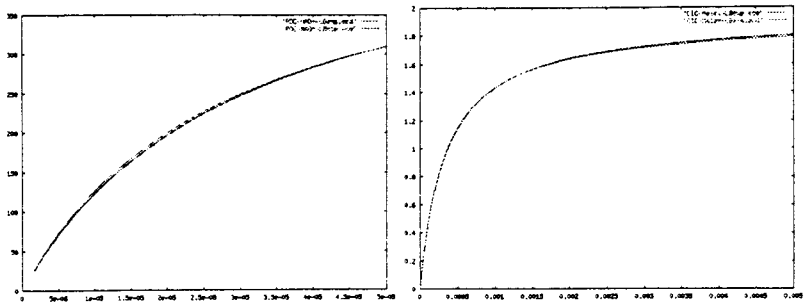

Figure 1. Pyruvate Dehydrogenase Complex (left), Tricalboxylate Carrier (right)
vertical axis: turnover (1/sec), horizontal axis: metabolite concentration (M)

# 3 Future Works

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).

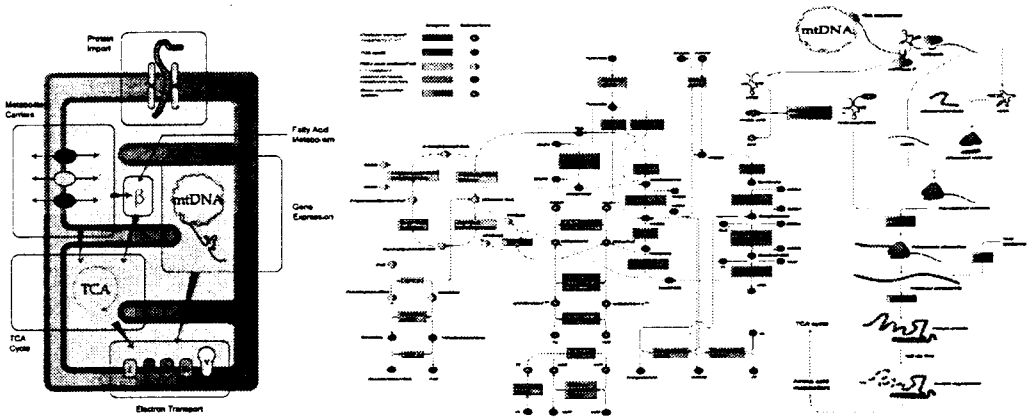


Figure 2: a) An overview of the model and b) the modeled reactions


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# References


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