Kinetic Modelling of Energy Metabolism in Mitochondria

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1 Introduction

We are constructing kinetic models of various mitochondrial metabolisms including gene expression, electron transport (respiratory chain), TCA cycle, fatty acid metabolism (β oxidation), inner-membrane metabolite carriers, and protein carriers. In this work, we report the model of pathways for energy metabolism which is recently completed using the E-Cell system [2].

2 Result

A mitochondrion includes three major energy metabolic pathways: electron transport, TCA cycle, and β oxidation. The basic steps of the energy metabolism are listed below.

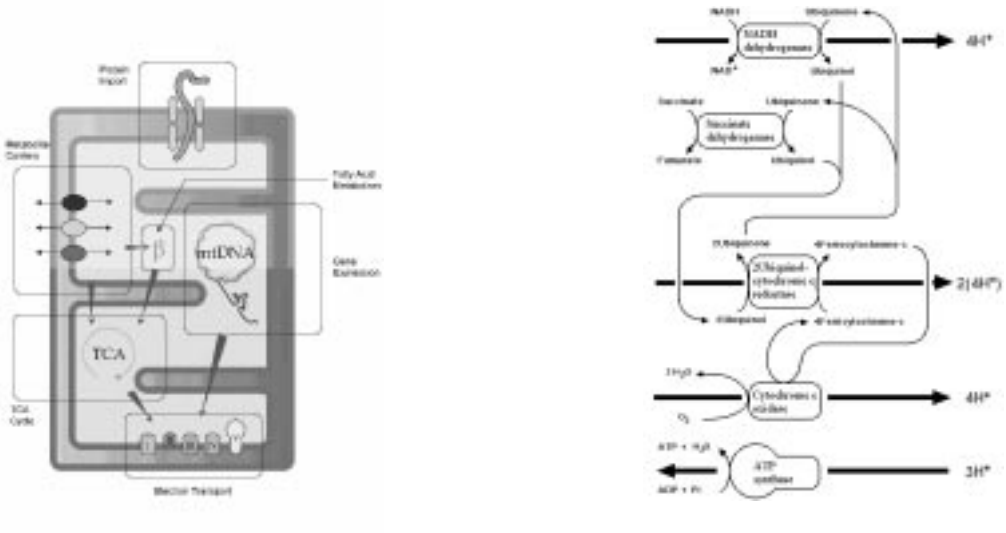

Figure 1: (a) Overview of the mitochondrial model. (b) Pathway map of electron transport.

1. Inner membrane metabolite carriers transport pyruvate, fatty acid, ADP, and P_i.
2. Acetyl-CoA is produced from pyruvate by pyruvate dehydrogenase.
3. From fatty acid, acetyl-CoA is made by β oxidation.
4. TCA cycle oxidizes acetyl-CoA to produce NADH, the substrate of electron transport.
5. The four enzymes of electron transport oxidize NADH.

Table 1: Examples of the reactions and their types in the model

	Enzyme	Reaction type
Electron transport	NADH dehydrogenase	Ping Pong Bi Bi
	Succinate dehydrogenase	Ping Pong Bi Bi
	Ubiquinol:Cytochrome *c* oxidoreductase	Hexa Uni Ping Pong
	Cytochrome *c* oxidase	Michaelis-Menten (Uni Uni)
	ATP synthase	see [1]
TCA cycle	Glutamate dehydrogenase	Rapid Equilibrium Ordered Bi Bi
	2-ketoglutare dehydrogenase complex	Multisite Ping Pong with [P] = 0
	Succinate dehydrogenase	Uni Uni
	Fumarase	Uni Uni
	Malate dehydrogenase	Iso Ordered Bi Bi
	Malic enzyme	Allosteric Michaelis-Menten
	Alanine $\longrightarrow$ Pyruvate	Unimolecular Mass Action
	Pyruvate dehydrogenase complex	Multisite Ping Pong with [P] = 0
	Oxaloacetate 1 $\longrightarrow$ Aspartate	Unimolecular Mass Action
	Aspartate $\longrightarrow$ Oxaloacetate 1	Unimolecular Mass Action
	Citrate synthase	Rapid Equilibrium Ordered Bi Bi
	Citrate 1 $\longrightarrow$ Isocitrate	Unimolecular Mass Action
	Isocitrate dehydrogenase	Rapid Equilibrium Ordered Bi Bi
	Glutamate $\longrightarrow$ Succinate	Unimolecular Mass Action
	Aspartate transaminase	Ping Pong Bi Bi
	Alanine transaminase	Ping Pong Bi Bi
	Oxaloacetate 1 $\longrightarrow$ Oxaloacetate 2	Unimolecular Mass Action
	Aspartate $\longrightarrow$ Oxaloaetate 2	Unimolecular Mass Action
	Succinate $\longrightarrow$ Glutamate	Unimolecular Mass Action
	Oxaloacetate 2 $\longrightarrow$ Aspartate	Unimolecular Mass Action

6. At the end of electron transport, ATP synthase generates ATP.

There are 5 enzymatic reactions for electron transport, 11 enzymatic reactions and 9 other reactions for TCA cycle, 5 enzymatic reactions for β oxidation, and 8 enzymatic reactions for metabolite carrier system. All the enzymatic reactions are modeled based on kinetic parameters found in the literature.

We will continue to enhance this mitochondrial model, adding other major metabolism including gene expression, fatty acid metabolism, and DNA replication. Our eventual goal is to apply this model to pathological analyses of mitochondorial diseases such as Leigh syndrome and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Acknowledgement

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References

[1] Pérez, J.A. and Ferguson, S.J., Kinetics of oxidative phosphorylation in *Paracoccus denitrificans*. 1. Mechanism of ATP synthesis at the active site(s) of F_OF_1-ATPase, *Biochemistry*, 29:10503–10518, 1990.

[2] Tomita, M., Hashimoto, K., Takahashi, K.,Shimizu, T., Matsuzaki, Y., Miyoshi, F., Saito, K., Tanida, S., Yugi, K., Venter, J. C., and Hutchison, C., E-Cell: software environment for whole cell simulation, *Bioinformatics*, 15(1):72–84, 1999.