Multi-objective Optimization for the Mitochondrial Bioenergetics

Costanza J (1), Zammataro L (2), Liò P (3), Nicosia G (1)

(1) Department of Mathematics and Computer Science, University of Catania, Italy
(2) Department of Translational Medicine, University of Milan, Italy
(3) Computer Laboratory University of Cambridge, UK

Motivation
Mitochondrial oxidative phosphorylation is the major ATP synthetic pathway in eu-
karyotes. In addition to ATP synthesis, mitochondria are the site of other important
metabolic reactions. They also play central roles in cellular Ca2+ homeostasis which
affects numerous other cell signaling pathways. In this work, we used a multi-objective
optimization algorithm that computes Pareto Optimal Tradeoff for maximizing the mi-
tochondrial bioenergetic in different matrix Ca2+ concentration. It appears that Ca2+ is
a global positive effector of mitochondrial function, and thus any perturbation in Ca2+
homeostasis will have profound implications at the level of ATP synthesis and NADH
generation.

Methods
The mitochondrial model is a 73 state system of DAEs, each of which represents the
metabolites involved in bioenergetic reactions of mitochondria. The state variables was
initialized to achieve the fully oxidized state. We calculated the metabolites concentra-
tion that leads to maximize the matrix ATP and NADH, maintaining constant oxidized
cytochrome c, reduced cytochrome c, ubiquinone, ubiquinol, NADmtx, NADHmtx, GTP-
mtx, GDPmtx (mtx= matrix), the mitochondrial membrane potential (1 mV), the ma-
trix O2 (0.0652 nmol/mg), the total CO2 (21.4762 nmol/mg) and Ca2+. We initialized
Ca2+ with 5 different value to evaluate the behavior of mitochondria. First we used
Ca2+= 10e-6, then 10e-5, 10e-7, 10e-61.5 and 10e-6/1.5 nmol/mg.

Results
In initial condition, we obtained NADH= 1.5987e-010 nmol/mg (formation) and
ATP= -0.0014 nmol/mg (consumption). After optimization with Ca2+= 10e-6 nmol/mg,
we analyzed three non-dominated solutions: the point with maximum ATP synthesis
(and lower NADH formation), the point with maximum NADH formation (and lower ATP
synthesis), and, finally, the tradeoff point. The first solution provides ATP= 2027.34 nmol/
mg and NADH= 6.17e-015 nmol/mg, with over-production of SUCmtx, PYRmtx, CoASH-
mtx, H+mtx, ATPims ADPims (ims= intermembrane space) and Mg2+ cyt (cyt= cyto-
solic space), and under-production of ISOCmtx, aGmtx, MALmtx, AcCoAmtx, CITims,
ISOCims, aGims, SUCims, MALims and GLU cyt, ASP cyt. The second solution provides
ATP= -3734.6 nmol/mg and NADH= 6.07e-006 nmol/mg, overproducing the following metabolites: H+mtx, ISOC mtx, SUC mtx, FUM mtx, CoASH mtx, ATPims, MAL ims whereas CIT mtx, SCoA mtx, MAL ims, ADP ims, AMP ims, Pi ims, PYR ims, GLU ims; cyt and aKG ims, cyt are totally consumed. The tradeoff point is equal to the first analyzed point. Increasing the matrix calcium concentration from 10e-6 to 10e-5 nmol/mg, ATP synthesis and NADH formation are stopped and both molecules are consumed by mitochondria metabolism. This achievement demonstrates that a perturbation in mitochondrial Ca2+ homeostasis will have profound implications for cell function at the level of ATP synthesis and NADH generation. Data from literature demonstrate that mitochondria are implied to play a crucial role in neuronal cell survival since they are regulators of ATP metabolism, Ca2+ homeostasis, NAD+, NADH, and of endogenous reactive oxygen species production. All these metabolites are key protagonists in cellular mechanisms leading to degenerative process such as Parkinson's disease, Alzheimer disease and Amyotrophic Lateral Sclerosis. If calcium increases by 10e-61.5 nmol/mg we obtain an increase in NADH formation, while ATP is invariant. In case of drastically matrix calcium depletion, 10e-7 nmol/mg, there is a lower ATP synthesis, but with Ca2+ = 10e-6/1.5 nmol/mg both objectives are maximized. By means of the computational quantitative framework here proposed, we are able to mathematically infer dynamics of mitochondrial bioenergetic metabolism, changing the spic behavior pathways. The results demonstrate that at different levels of mitochondrial Ca2+ the organelle changes its bioenergetic activity, and this is bounded by specifics lower and upper matrix Ca2+, beyond which NADH and ATP production are knocked out.

Contact email
costanza@dmi.unict.it