

## Supplemental data S1: Reactions in the mitochondrial metabolic network

Conf: confidence level

Prot: proteomic data

[c]: cytosolic compartment; [m]: mitochondrial compartment; [e]: extracellular compartment

[c] or [m] at the beginning of each equation denotes the compartment where the reaction takes place

[c], [e] or [m] following a metabolite localizes that metabolite to one of the three compartment.

References refer to biochemical evidence for a reaction in addition to, or in place of, proteomic data

Abbreviation	Official Name	Equation	Conf	Subsystem	EC	Prot	References
1 HEX1	hexokinase (D-glucose:AT	[c] : atp + glc-D --> adp + g6p + h	4	Glycolysis	2.7.1.1	yes	(Voet, Voet et al. 1999)
2 G6PI	Glucose-6-phosphate isom	[c] : g6p <==> g6p-B	4	Glycolysis	5.3.1.9	yes	(Voet, Voet et al. 1999)
3 G6PI2	Glucose-6-phosphate isom	[c] : g6p-B <==> f6p-B	4	Glycolysis	5.3.1.9	yes	(Voet, Voet et al. 1999)
4 PGI	glucose-6-phosphate isom	[c] : g6p <==> f6p	4	Glycolysis	5.3.1.9	yes	(Voet, Voet et al. 1999)
5 PFK	phosphofructokinase	[c] : atp + f6p --> adp + fdp + h	4	Glycolysis	2.7.1.11	yes	(Voet, Voet et al. 1999)
6 FBA	fructose-bisphosphate ald	[c] : fdp <==> dhap + g3p	4	Glycolysis	4.1.2.13	yes	(Voet, Voet et al. 1999)
7 TPI	triose-phosphate isomeras	[c] : dhap <==> g3p	4	Glycolysis	5.3.1.1	yes	(Voet, Voet et al. 1999)
8 GAPD	glyceraldehyde-3-phospha	[c] : g3p + nad + pi <==> 13dpg + h + nadh	4	Glycolysis	1.2.1.12	yes	(Voet, Voet et al. 1999)
9 PGK	phosphoglycerate kinase	[c] : 3pg + atp <==> 13dpg + adp	4	Glycolysis	2.7.2.3	yes	(Voet, Voet et al. 1999)
10 PGM	phosphoglycerate mutase	[c] : 2pg <==> 3pg	4	Glycolysis	5.4.2.1		(Voet, Voet et al. 1999)
11 ENO	enolase	[c] : 2pg <==> h2o + pep	4	Glycolysis	4.2.1.11		(Voet, Voet et al. 1999)
12 PYK	pyruvate kinase	[c] : adp + h + pep --> atp + pyr	4	Glycolysis	2.7.1.40	yes	(Voet, Voet et al. 1999)
13 PDHm	pyruvate dehydrogenase	[m] : coa + nad + pyr --> accoa + co2 + nadh	3	TCA cycle	1.2.4.1	yes	(Voet, Voet et al. 1999)
14 CSm	citrate synthase	[m] : accoa + h2o + oaa --> cit + coa + h	4	TCA cycle	4.1.3.7	yes	(Voet, Voet et al. 1999)
15 ACONTM	Aconitate hydratase	[m] : cit <==> icit	4	TCA cycle	4.2.1.3	yes	(Voet, Voet et al. 1999)
16 ICDHxm	Isocitrate dehydrogenase (	[m] : icit + nad --> akc + co2 + nadh	4	TCA cycle	1.1.1.41	yes	(Voet, Voet et al. 1999)
17 ICDHym	Isocitrate dehydrogenase (	[m] : icit + nadp --> akc + co2 + nadph	4	TCA cycle	1.1.1.42	yes	(Voet, Voet et al. 1999)
18 AKGDm	2-oxoglutarate dehydroger	[m] : akc + coa + nad --> co2 + nadh + succoa	4	TCA cycle	1.2.4.2	yes	(Voet, Voet et al. 1999)
19 SUCOASm	succinyl-CoA synthetase (	[m] : coa + gtp + succ <==> gdp + pi + succoa	4	TCA cycle	6.2.1.4	yes	(Voet, Voet et al. 1999)
20 SUCD1m	succinate dehydrogenase	[m] : fad + succ <==> fadh2 + fum	4	TCA cycle	1.3.99.1	yes	(Voet, Voet et al. 1999)
21 FUMm	fumarase, mitochondrial	[m] : fum + h2o <==> mal-L	4	TCA cycle	4.2.1.2	yes	(Voet, Voet et al. 1999)
22 MDHm	malate dehydrogenase, mi	[m] : mal-L + nad <==> h + nadh + oaa (5) h[m] + nadh[m] + q10[m] --> (4) h[c] + nad[m] + q10h2[m]	4	TCA cycle	1.1.1.37	yes	(Voet, Voet et al. 1999)
23 NADH2-u10m	NADH dehydrogenase, mit		4	OxPhos	1.6.99.3	yes	
24 SUCD3-u10m	succinate dehydrogenase	[m] : fadh2 + q10 <==> fad + q10h2 (2) ficytC[m] + (2) h[m] + q10h2[m] --> (2) ficytC[m] + (4) h[c] + q10[m]	4	OxPhos	1.3.5.1	yes	(Voet, Voet et al. 1999)
25 CYOR-u10m	ubiquinol-6 cytochrome c r	(4) ficytC[m] + (7.92) h[m] + o2[m] --> (4) ficytC[m] + (4) h[c] + (1.96) h2o[m] + (0.02) o2-[m]	4	OxPhos	1.10.2.2	yes	(Voet, Voet et al. 1999)
26 CYOom3	cytochrome c oxidase, mit		3	OxPhos	1.9.3.1	yes	(Voet, Voet et al. 1999)
27 ATPS4m	ATP synthase (four proton	adp[m] + (4) h[c] + pi[m] --> atp[m] + (3) h[m] + h2o[m]	4	OxPhos	3.6.3.14	yes	
28 GLUCYS	gamma-glutamylcysteine s	[c] : atp + cys-L + glu-L --> adp + glucys + h + pi	4	ROS detoxification	6.3.2.2		(Meister 1995)
29 GTHDHm	Glutathione dehydrogenas	[m] : dhdascb + (2) gthrd --> ascb-L + gthox	2	ROS detoxification	1.8.5.1		(Meister 1995)



67	C181CRN1	carnitine octadecenoyl trar	[c] : crn + odecoa --> coa + odecrn	4	Fatty acid transport	2.3.1.21	yes	
68	C181CRN2	C181 transport into the mit	odecrn[c] --> odecrn[m]	4	Fatty acid transport			
69	C181CRN3	carnitine octadecenoyl trar	[m] : coa + odecrn --> crn + odecoa	4	Fatty acid transport			
70	C182	C182 fatty acid activation	[c] : atp + coa + ocdcyca --> amp + ocdycacoa + ppi	4	Fatty acid transport	6.2.1.3	yes	
71	C182CRN1	carnitine octadecynoyl tran	[c] : crn + ocdycacoa --> coa + ocdycrn	4	Fatty acid transport	2.3.1.21	yes	
72	C182CRN2	C182 transport into the mit	ocdycrn[c] --> ocdycrn[m]	4	Fatty acid transport			
73	C182CRN3	carnitine octadecynol trans	[m] : coa + ocdycrn --> crn + ocdycacoa	4	Fatty acid transport			
74	C204	C204 fatty acid activation	[c] : atp + c204 + coa --> amp + c204coa + ppi	4	Fatty acid transport	6.2.1.3	yes	
75	C204CRN1	carnitine C20:4 transferase	[c] : c204coa + crn --> c204crn + coa	4	Fatty acid transport	2.3.1.21	yes	
76	C204CRN2	C204 transport into the mit	c204crn[c] --> c204crn[m]	4	Fatty acid transport			
77	C204CRN3	C204 transport into the mit	[m] : c204crn + coa --> c204coa + crn	4	Fatty acid transport			
78	C226	C226 fatty acid activation	[c] : atp + c226 + coa --> amp + c226coa + ppi	4	Fatty acid transport	6.2.1.3	yes	
79	C226CRN1	carnitine C22:6 transferase	[c] : c226coa + crn --> c226crn + coa	4	Fatty acid transport	2.3.1.21	yes	
80	C226CRN2	C226 transport into the mit	c226crn[c] --> c226crn[m]	4	Fatty acid transport			
81	C226CRN3	C226 transport into the mit	[m] : c226crn + coa --> c226coa + crn	4	Fatty acid transport			
82	CRNtim	L-carnitine transport out of	crn[m] --> crn[c]	4	Fatty acid transport			(Murthy and Pande 1984; Indiveri, Tonazzi et al. 1991; Indiveri, Tonazzi et al. 1991; Indiveri, Tonazzi et al. 1994)
83	CHLPCTD	choline phosphate cytididy	[c] : cholp + ctp + h --> cdpchol + ppi	2	Lipid	2.7.7.15		(Zelinski, Savard et al. 1980; Choy, Tran et al. 1997)
84	DAGCPTm	diacylglycerol cholinephosj	[c] : 12dgr_m + cdpchol --> cmp + h + pc_m	4	Lipid	2.7.8.2		(Henneberry, Wright et al. 2002; Wright and McMaster 2002)
85	PCtm	Phosphatidylcholine transp	pc_m[c] --> pc_m[m]	2	Lipid			
86	PSDm	Phosphatidylserine decarb	[m] : h + ps_m --> co2 + pe_m	4	Lipid	4.1.1.65		(Shiao and Vance 1995)
87	PStm	Phosphatidylserine transpc	ps_m[c] --> ps_m[m]	2	Lipid			(Shiao, Lupo et al. 1995)
88	G3PDm	glycerol-3-phosphate dehy	[m] : fad + gly3p --> dhap + fadh2	3	Lipid	1.1.99.5	yes	
89	CLPNSm	Cardiolipin Synthase, mito	[m] : (2) pg_m <==> clpn_m + glyc	4	Lipid			(Daum 1985)
90	PAPAm	Phosphatidate phosphatas	[m] : h2o + pa_m --> 12dgr_m + pi	2	Lipid	3.1.3.4		(Sumikawa, Saeki et al. 1987)
91	DAGKm	Diacylglycerol kinase, mito	[m] : 12dgr_m + atp --> adp + h + pa_m	2	Lipid	2.7.1.107		(Hart, Zhou et al. 1994)
92	ETHAPTm	Ethanolaminophosphotran:	[m] : 12dgr_m + cdpea <==> cmp + h + pe_m	2	Lipid	2.7.8.1		(Wright and McMaster 2002)
93	HMGm	hydroxymethylglutaryl-CoA	[m] : hmgcoa --> acac + accoa	3	Lipid	4.1.3.4	yes	
94	OCOAT1m	3-oxoacid CoA-transferase	[m] : acac + succoa <==> aacoa + succ	3	Lipid	2.8.3.5	yes	
95	ACACT1m	acetyl-CoA C-acetyltransfe	[m] : (2) accoa --> aacoa + coa	2	Lipid	2.3.1.9		(Schwerdt and Huth 1993)
96	MMSAD1m	methylmalonate-semialdeh	[m] : 2mop + coa + nad --> co2 + nadh + ppcoa	3	Lipid	1.2.1.27	yes	
97	PPCOACm	Propionyl-CoA carboxylase	[m] : atp + hco3 + ppcoa --> adp + h + mmcoa-S + pi	3	Lipid	6.4.1.3	yes	
98	HACDm	3-hydroxyacyl-CoA dehydr	[m] : 3hacoa + nad <==> 3oacoa + h + nadh	3	Lipid	1.1.1.35	yes	
99	GLYKm	glycerol kinase	[m] : atp + glyc --> adp + gly3p + h [m] : (0.25) c204coa + (0.05) c226coa + (0.2) ocdycacoa + (0.1) odecoa + (0.2) pmtcoa + (0.2) stcoa	3	Lipid	2.7.1.30	yes	
100	FASYNm	Average fatty acid of heart	--> facoa_m	1	Lipid			Modeling purpose
101	G3PATm	glycerol 3-phosphate acylti	[m] : facoa_m + gly3p --> aglyc3p_m + coa	3	Lipid	2.3.1.15	yes	(Lewin, Schwerbrock et al. 2004)
102	AGATm	1-Acyl-glycerol-3-phosphat	[m] : aglyc3p_m + facoa_m --> coa + pa_m	2	Lipid	2.3.1.51		(Haldar, Kelker et al. 1983)
103	DASYNm	CDP-Diacylglycerol synthe	[m] : ctp + h + pa_m <==> cdpdag_m + ppi	2	Lipid	2.7.7.41		(Monaco and Feldman 1997)
104	PCHOLPm	choline phosphatase	[m] : h2o + pc_m --> chol + h + pa_m	2	Lipid	3.1.4.4		(Monaco and Feldman 1997)
105	PGSAM	Phosphatidylglycerol synth	[m] : cdpdag_m + gly3p <==> cmp + h + pgp_m	2	Lipid	2.7.8.5		(Ohtsuka, Nishijima et al. 1993)
106	PGPPm	Phosphatidylglycerol phosj	[m] : h2o + pgp_m --> pg_m + pi	2	Lipid	3.1.3.27		(MacDonald and McMurray 1980)

107	NH4tm	NH3 mitochondrial transpo	nh4[c] <==> nh4[m]	2	Urea cycle			Physiological data
108	UREAt	Urea transport via facilitate	urea[e] <==> urea[c]	1	Urea cycle			Physiological data
109	CBMKm	Carbamate kinase	[m] : atp + co2 + nh4 --> adp + cbp + (2) h	2	Urea cycle	2.7.2.2		(Voet, Voet et al. 1999)
110	OCBTm	ornithine carbamoyltransfe	[m] : cbp + orn --> citr-L + h + pi	3	Urea cycle	2.1.3.3	yes	(Indiveri, Tonazzi et al. 1999)
111	ARGSS	argininosuccinate synthase	[c] : asp-L + atp + citr-L --> amp + argsuc + h + ppi	2	Urea cycle	6.3.4.5		(Voet, Voet et al. 1999)
112	ARGSL	argininosuccinate lyase	[c] : argsuc <==> arg-L + fum	2	Urea cycle	4.3.2.1		(Voet, Voet et al. 1999)
113	ARGN	arginase	[c] : arg-L + h2o --> orn + urea	3	Urea cycle	3.5.3.1	yes	(Voet, Voet et al. 1999)
114	ORNt4m	ornithine mitochondrial trar	citr-L[c] + h[c] + orn[m] <==> citr-L[m] + h[m] + orn[c]	4	Urea cycle			(Indiveri, Tonazzi et al. 1997; Fiermonte, Dolce et al. 2003; Palmieri 2004)
115	GLYAMDTR	glycine amidinotransferase	[m] : arg-L + gly <==> gudac + orn	3	Urea cycle	2.1.4.1	yes	(Voet, Voet et al. 1999)
116	GACMTR	guanidinoacetate N-methyl	[m] : amet + gudac <==> ahcys + creat + h	2	Urea cycle	2.1.1.2		(Voet, Voet et al. 1999)
117	CK	ATP Creatine kinase	[m] : atp + creat <==> adp + pcreat	3	Urea cycle	2.7.3.2	yes	
118	ADK1	adenylate kinase	[c] : amp + atp <==> (2) adp	3	Nucleotide	2.7.4.3	yes	
119	ADK1m	adenylate kinase, mitochor	[m] : amp + atp <==> (2) adp	3	Nucleotide	2.7.4.3	yes	(Salway 1999)
120	ADK4m	adentylate kinase (ITP), mi	[m] : amp + itp <==> adp + idp	3	Nucleotide	2.7.4.3	yes	
121	DGNSK	deoxyguanosine kinase	[m] : atp + dgsn --> adp + dgmp + h	3	Nucleotide	2.7.1.113	yes	
122	DHORDm	dihydroorotic acid dehydroc	[m] : dhor-S + o2 <==> h2o2 + orot	3	Nucleotide	1.3.3.1	yes	
123	DUTPDPm	dUTP diphosphatase	[m] : dutp + h2o --> dump + h + ppi	3	Nucleotide	3.6.1.23	yes	
124	NDPK1	nucleoside-diphosphate kir	[c] : atp + gdp <==> adp + gtp	2	Nucleotide	2.7.4.6		(Salway 1999)
125	TMDK1m	thymidine kinase (ATP:thi)	[m] : atp + thymd --> adp + dtmp + h	3	Nucleotide	2.7.1.21	yes	
126	GLUDx	glutamate dehydrogenase	[c] : glu-L + h2o + nad <==> akp + h + nadh + nh4	3	Others	1.4.1.2	yes	
127	GLUDy	glutamate dehydrogenase	[c] : glu-L + h2o + nadp <==> akp + h + nadph + nh4	2	Others	1.4.1.4		(Delabar, Martin et al. 1982)
128	TYRTAm	tyrosine transaminase, mit	[m] : akp + tyr-L <==> 34hpp + glu-L	3	Others	2.6.1.5	yes	
129	LDH_L	L-lactate dehydrogenase	[c] : lac-L + nad <==> h + nadh + pyr	3	Others	1.1.1.27	yes	(Kline, Brandt et al. 1986; Brandt, Laux et al. 1987)
130	ME2m	malic enzyme (NADP), mit	[m] : mal-L + nadp --> co2 + nadph + pyr	3	Others	1.1.1.40	yes	
131	PCm	pyruvate carboxylase	[m] : atp + hco3 + pyr --> adp + h + oaa + pi	3	Others	6.4.1.1	yes	
132	PEPCKm	Phosphoenolpyruvate carb	[m] : gtp + oaa --> co2 + gdp + pep	3	Others	4.1.1.32	yes	
133	FTHFLm	formate-tetrahydrofolate li	[m] : atp + for + thf <==> 10thf + adp + pi	2	Others	6.3.4.3		(Prasannan, Pike et al. 2003)
134	GHMT2rm	glycine hydroxymethyltran	[m] : ser-L + thf <==> gly + h2o + mlthf	4	Others	2.1.2.1	yes	(Lin, Huang et al. 1993)
135	HMGCOASm	Hydroxymethylglutaryl CoA	[m] : coa + h + hmgcoa <==> aacoa + accoa + h2o	3	Others	4.1.3.5	yes	
136	THFATm	tetrahydrofolate aminomet	[m] : h2o + methf --> 5thf + h	3	Others	2.1.2.10	yes	
137	H2CO3Dm	carboxylic acid dissociati	[m] : co2 + h2o <==> h2co3	3	Others	4.2.1.1	yes	
138	H2OD	Water dissociation	[c] : h2o <==> h + oh1	2	Others			Physiological data
139	HCO3Em	HCO3 equilibration reactio	[m] : co2 + h2o <==> h + hco3	1	Others			Physiological data
140	PPA	inorganic diphosphatase	[c] : h2o + ppi --> h + (2) pi	3	Others	3.6.1.1	yes	
141	PPAm	inorganic diphosphatase	[m] : h2o + ppi --> h + (2) pi	3	Others	3.6.1.1	yes	
142	ARGtm	arginine mitochondrial tran	arg-L[c] + h[m] <==> arg-L[m] + h[c]	4	Transport			(Fiermonte, Dolce et al. 2003)
143	ATPtm	ADP/ATP transporter, mito	adp[c] + atp[m] --> adp[m] + atp[c]	4	Transport			(De Marcos Lousa, Trezeguet et al. 2002)
144	CITRtm	citruiline mitochondrial tran	citr-L[m] <==> citr-L[c]	4	Transport			(Fiermonte, Dolce et al. 2003)
145	CITtam	citrate transport, mitochon	cit[c] + mal-L[m] <==> cit[m] + mal-L[c]	4	Transport			(Bisaccia, De Palma et al. 1990; Kaplan 2001; De Palma, Scalera et al. 2003; Palmieri 2004)
146	CITtbm	citrate transport, mitochon	cit[c] + pep[m] <==> cit[m] + pep[c]	4	Transport			(Bisaccia, De Palma et al. 1990; Kaplan 2001; De Palma, Scalera et al. 2003; Palmieri 2004)
147	CO2tm	CO2 transport (diffusion), r	co2[c] <==> co2[m]	1	Transport			Modeling purpose

148	COA <sub>tm</sub>	CoA transporter	coa[c] <==> coa[m]	1	Transport			Modeling purpose
149	DNC1C	Deoxynucleotide carrier	atp[m] + cdp[c] <==> atp[c] + cdp[m]	4	Transport			(Dolce, Fiermonte et al. 2001; Palmieri 2004)
150	DNC1G	Deoxynucleotide carrier	atp[m] + gdp[c] <==> atp[c] + gdp[m]	4	Transport			(Dolce, Fiermonte et al. 2001; Palmieri 2004)
151	DNC1U	Deoxynucleotide carrier	atp[m] + udp[c] <==> atp[c] + udp[m]	4	Transport			(Dolce, Fiermonte et al. 2001; Palmieri 2004)
152	FE2 <sub>tm</sub>	iron (II) transport	fe2[c] + h[c] --> fe2[m] + h[m]	2	Transport			(Lange, Kispal et al. 1999)
153	FRD <sub>cm</sub>	fumarate reductase, cytosol	fadh2[m] + fum[c] --> fad[m] + succ[c]	3	Transport	1.3.99.1	yes	
154	GLU <sub>t2m</sub>	L-glutamate reversible transporter	glu-L[c] + h[c] <==> glu-L[m] + h[m]	4	Transport			(Fiermonte, Palmieri et al. 2002)
155	GLYC3P <sub>tm</sub>	glycerol-3-phosphate shuttle	glyc3p[c] --> glyc3p[m]	2	Transport			(Xu and Hatch 1997)
156	GLYC <sub>tm</sub>	glycerol transport	glyc[c] <==> glyc[m]	1	Transport			Modeling purpose
157	GLY <sub>tm</sub>	glycine passive transport transporter	gly[c] <==> gly[m]	4	Transport			(Benavides, Garcia et al. 1980)
158	GTP <sub>tm</sub>	GTP/GDP translocase, mitochondrial	gdp[c] + gtp[m] --> gdp[m] + gtp[c]	2	Transport			(Salway 1999)
159	H2O <sub>tm</sub>	H2O transport, mitochondrial	h2o[c] <==> h2o[m]	1	Transport			Modeling purpose
160	H <sub>tm</sub>	Uncoupling proteins	h[c] --> h[e]	4	Transport			(Kaplan 2001; Palmieri 2004)
161	LYS <sub>tm</sub>	Lysine mitochondrial transporter	h[m] + lys-L[c] <==> h[c] + lys-L[m]	4	Transport			(Fiermonte, Dolce et al. 2003; Palmieri 2004)
162	MAL <sub>tm</sub>	malate transport, mitochondrial	mal-L[c] + pi[m] <==> mal-L[m] + pi[c]	4	Transport			(Palmieri 2004)
163	O2 <sub>tm</sub>	O2 transport (diffusion)	o2[c] <==> o2[m]	1	Transport			Modeling purpose
164	ORN <sub>t3m</sub>	ornithine mitochondrial transporter	h[c] + orn[m] <==> h[m] + orn[c]	4	Transport			(Indiveri, Tonazzi et al. 1997; Indiveri, Tonazzi et al. 1999; Fiermonte, Dolce et al. 2003; Palmieri 2004)
165	PI <sub>t2m</sub>	phosphate transporter, mitochondrial	h[c] + pi[c] <==> h[m] + pi[m]	4	Transport			(Dolce, Fiermonte et al. 1996)
166	PYR <sub>t2m</sub>	pyruvate mitochondrial transporter	h[c] + pyr[c] <==> h[m] + pyr[m]	2	Transport			(Palmieri 2004)
167	SUC <sub>c2m</sub>	succinate transport, mitochondrial	pi[m] + succ[c] <==> pi[c] + succ[m]	4	Transport			(Palmieri 2004)
168	12DGR <sub>t1</sub>	1,2 diacylglycerol transporter	12dgr_m[e] --> 12dgr_m[c]	1	Transport to cytosol			Modeling purpose
169	C20 <sub>4t</sub>	(n-C20:4) transport in via uniporter	c204[e] --> c204[c]	1	Transport to cytosol			Modeling purpose
170	C22 <sub>6t</sub>	(n-C22:6) transport in via uniporter	c226[e] --> c226[c]	1	Transport to cytosol			Modeling purpose
171	CO <sub>2t</sub>	CO2 transporter via diffusion	co2[e] <==> co2[c]	1	Transport to cytosol			Modeling purpose
172	COA <sub>t</sub>	CoA transporter	coa[e] <==> coa[c]	1	Transport to cytosol			Modeling purpose
173	CYS <sub>t2r</sub>	L-cysteine reversible transporter	cys-L[e] + h[e] <==> cys-L[c] + h[c]	1	Transport to cytosol			Modeling purpose
174	FE <sub>2t1</sub>	iron (II) transport	fe2[e] --> fe2[c]	1	Transport to cytosol			Modeling purpose
175	GLC <sub>t1</sub>	glucose transport (uniporter)	glc-D[e] --> glc-D[c]	1	Transport to cytosol			Modeling purpose
176	GLU <sub>t2r</sub>	L-glutamate transport via uniporter	glu-L[e] + h[e] <==> glu-L[c] + h[c]	1	Transport to cytosol			Modeling purpose
177	GLYC3P <sub>t1</sub>	glycerol-3-phosphate transporter	glyc3p[e] --> glyc3p[c]	1	Transport to cytosol			Modeling purpose
178	GLY <sub>c1</sub>	glycerol transport via uniporter	glyc[e] --> glyc[c]	1	Transport to cytosol			Modeling purpose
179	GLY <sub>t2r</sub>	glycine reversible transporter	gly[e] + h[e] <==> gly[c] + h[c]	1	Transport to cytosol			Modeling purpose
180	H2O <sub>t</sub>	H2O transport via diffusion	h2o[e] <==> h2o[c]	1	Transport to cytosol			Modeling purpose
181	HDCA <sub>t</sub>	Hexadecanoate (n-C16:0) transporter	hdca[e] --> hdca[c]	1	Transport to cytosol			Modeling purpose
182	H <sub>t</sub>	proton diffusion	h[c] <==> h[e]	1	Transport to cytosol			Modeling purpose
183	L-LAC <sub>t2r</sub>	L-lactate reversible transporter	h[e] + lac-L[e] <==> h[c] + lac-L[c]	1	Transport to cytosol			Modeling purpose
184	O <sub>2t</sub>	o2 transport (diffusion)	o2[e] <==> o2[c]	1	Transport to cytosol			Modeling purpose
185	OCDCA <sub>t</sub>	Octadecanoate (n-C18:0) transporter	ocdca[e] --> ocdca[c]	1	Transport to cytosol			Modeling purpose
186	OCDC <sub>EA</sub> <sub>t</sub>	Octadecenoate (n-C18:1) transporter	ocdcea[e] --> ocdcea[c]	1	Transport to cytosol			Modeling purpose
187	OCDCY <sub>A</sub> <sub>t</sub>	Octadecynoate (n-C18:2) transporter	ocdcya[e] --> ocdcya[c]	1	Transport to cytosol			Modeling purpose
188	PI <sub>t2r</sub>	phosphate reversible transporter	h[e] + pi[e] <==> h[c] + pi[c]	1	Transport to cytosol			Modeling purpose
189	P <sub>St</sub>	phosphatidylserine transporter	ps_m[e] <==> ps_m[c]	1	Transport to cytosol			Modeling purpose

## Supplemental data S1 (cont.)

### Names and abbreviations of metabolites in the mitochondrial network

Abbreviation	Full name	Formula
10fthf	10-Formyltetrahydrofolate	C20H22N7O7
12dgr_m	1,2-Diacylglycerol	C39H70O5
13dpg	3-Phospho-D-glyceroyl phosphate	C3H4O10P2
2mop	2-Methyl-3-oxopropanoate	C4H5O3
2pg	D-Glycerate 2-phosphate	C3H4O7P
34hpp	3-(4-Hydroxyphenyl)pyruvate	C9H7O4
3hacoa	(S)-3-Hydroxyacyl-CoA	C24H35N7O18P3RS
3oacoa	3-Oxoacyl-CoA	C24H33N7O18P3RS
3pg	3-Phospho-D-glycerate	C3H4O7P
5aop	5-Amino-4-oxopentanoate	C5H9NO3
5fthf	5-Formyltetrahydrofolate	C20H21N7O7
aacoa	Acetoacetyl-CoA	C25H36N7O18P3S
acac	Acetoacetate	C4H5O3
accoa	Acetyl-CoA	C23H34N7O17P3S
adp	ADP	C10H12N5O10P2
aglyc3p_m	1-acyl-sn-glycerol 3-phosphate, mitochondria	C21H38O7P
ahcys	S-Adenosyl-L-homocysteine	C14H20N6O5S
akg	2-Oxoglutarate	C5H4O5
amet	S-Adenosyl-L-methionine	C15H23N6O5S
amp	AMP	C10H12N5O7P
arg-L	L-Arginine	C6H15N4O2
argsuc	N(omega)-(L-Arginino)succinate	C10H17N4O6
ascb-L	L-Ascorbate	C6H8O6
asp-L	L-Aspartate	C4H6NO4
atp	ATP	C10H12N5O13P3
c204	nC20:4	C20H31O2
c204coa	C20:4-CoA	C41H62N7O17P3S
c204crn	C20:4 carnitine	C27H45NO4
c226	nC22:6	C22H31O2
c226coa	C226-CoA	C43H62N7O17P3S
c226crn	C22:6 CoA	C29H45NO4
cbp	Carbamoyl phosphate	CH2NO5P
cdp	CDP	C9H12N3O11P2
cdpchol	CDPcholine	C14H25N4O11P2
cdpdag_m	CDP-Diacylglycerol, mitochondria	C48H81N3O15P2
cdpea	CDPethanolamine	C11H19N4O11P2
chol	Choline	C5H14NO
cholp	Choline phosphate	C5H13NO4P
cit	Citrate	C6H5O7
citr-L	L-Citrulline	C6H13N3O3
clpn_m	cardiolipin, mitochondria	C81H144O17P2
cmp	CMP	C9H12N3O8P
co2	CO2	CO2
coa	Coenzyme A	C21H32N7O16P3S
cpppg3	Coproporphyrinogen III	C36H40N4O8
creat	Creatine	C4H9N3O2
crn	L-Carnitine	C7H15NO3
ctp	CTP	C9H12N3O14P3
cys-L	L-Cysteine	C3H7NO2S
dgmp	dGMP	C10H12N5O7P
dgsn	Deoxyguanosine	C10H13N5O4

dhap	Dihydroxyacetone phosphate	C3H5O6P
dhdascb	Dehydroascorbate	C6H6O6
dhor-S	(S)-Dihydroorotate	C5H5N2O4
dtmp	dTMP	C10H13N2O8P
dump	dUMP	C9H11N2O8P
dutp	dUTP	C9H11N2O14P3
f6p	D-Fructose 6-phosphate	C6H11O9P
f6p-B	beta-D-Fructose 6-phosphate	C6H11O9P
facoa_m	Average fatty acid of human heart mitochondria	C39H63N7O17P3S
fad	FAD	C27H31N9O15P2
fadh2	FADH2	C27H33N9O15P2
fdp	D-Fructose 1,6-bisphosphate	C6H10O12P2
fe2	Fe2+	Fe
ficytC	Ferricytochrome c	C42H54FeN8O6S2
focytC	Ferrocyclochrome C	C42H54FeN8O6S2
for	Formate	CH1O2
fum	Fumarate	C4H2O4
g3p	Glyceraldehyde 3-phosphate	C3H5O6P
g6p	D-Glucose 6-phosphate	C6H11O9P
g6p-B	beta-D-glucose 6-phosphate	C6H11O9P
gdp	GDP	C10H12N5O11P2
glc-D	D-Glucose	C6H12O6
glucy	gamma-L-Glutamyl-L-cysteine	C8H13N2O5S
glu-L	L-Glutamate	C5H8NO4
gly	Glycine	C2H5NO2
glyc	Glycerol	C3H8O3
glyc3p	Glycerol 3-phosphate	C3H7O6P
gthox	Oxidized glutathione	C20H30N6O12S2
gthrd	Reduced glutathione	C10H16N3O6S
gtp	GTP	C10H12N5O14P3
gudac	Guanidinoacetate	C3H7N3O2
h	H+	H
h2co3	carbonic acid	H2CO3
h2o	H2O	H2O
h2o2	Hydrogen peroxide	H2O2
hco3	Bicarbonate	CHO3
hdca	Hexadecanoate (n-C16:0)	C16H31O2
hmbil	Hydroxymethylbilane	C40H38N4O17
hmgcoa	Hydroxymethylglutaryl-CoA	C27H39N7O20P3S
icit	Isocitrate	C6H5O7
idp	IDP	C10H11N4O11P2
itp	ITP	C10H11N4O14P3
lac-L	L-Lactate	C3H5O3
lys-L	L-Lysine	C6H15N2O2
mal-L	L-Malate	C4H4O5
methf	5,10-Methenyltetrahydrofolate	C20H20N7O6
mlthf	5,10-Methylenetetrahydrofolate	C20H22N7O6
mmcoa-S	(S)-Methylmalonyl-CoA	C25H35N7O19P3S
nad	Nicotinamide adenine dinucleotide	C21H26N7O14P2
nadh	Nicotinamide adenine dinucleotide - reduced	C21H27N7O14P2
nadp	Nicotinamide adenine dinucleotide phosphate	C21H25N7O17P3
nadph	Nicotinamide adenine dinucleotide phosphate - reduced	C21H26N7O17P3
nh4	Ammonium	H4N
o2	O2	O2
o2-	Superoxide anion	O2
oaa	Oxaloacetate	C4H2O5
ocdca	octadecanoate (n-C18:0)	C18H35O2

ocdcea	octadecenoate (n-C18:1)	C18H33O2
ocdcya	octadecynoate (n-C18:2)	C18H31O2
ocdycacoa	Octadecynoyl-CoA (n-C18:2CoA)	C39H62N7O17P3S
ocdycrn	octadecynoyl carnitine	C25H45NO4
odecoa	Octadecenoyl-CoA (n-C18:1CoA)	C39H64N7O17P3S
odecrn	octadecenoyl carnitine	C25H47NO4
oh1	hydroxide ion	HO
orn	Ornithine	C5H13N2O2
orot	Orotate	C5H3N2O4
pa_m	phosphatidate, mitochondria	C39H69O8P1
pc_m	phosphatidylcholine, mitochondria	C5H3N2O4
pcreat	Phosphocreatine	C4H9N3O5P
pe_m	phosphatidylethanolamine, mitochondria	C41H76N1O8P1
pep	Phosphoenolpyruvate	C3H2O6P
pg_m	phosphatidylglycerol	C42H76O10P
pgp_m	phosphatidylglycerolphosphate, mitochondria	C42H75O13P2
pHEME	Protoheme	C34H30FeN4O4
pi	Phosphate	HO4P
pmitcoa	Palmitoyl-CoA (n-C16:0CoA)	C37H62N7O17P3S
pmitcrn	L-Palmitoylcarnitine	C23H45NO4
ppbng	Porphobilinogen	C10H13N2O4
ppcoa	Propanoyl-CoA	C24H36N7O17P3S
ppi	Diphosphate	HO7P2
ppp9	Protoporphyrin	C34H32N4O4
pppg9	Protoporphyrinogen IX	C34H38N4O4
ps_m	phosphatidylserine	C42H75N1O10P1
pyr	Pyruvate	C3H3O3
q10	Ubiquinone-10	C59H90O4
q10h2	Ubiquinol-10	C59H92O4
ser-L	L-Serine	C3H7NO3
stcoa	Stearoyl-CoA (n-C18:0CoA)	C39H66N7O17P3S
stcrn	stearoylcarnitine	C25H49NO4
succ	Succinate	C4H4O4
succoa	Succinyl-CoA	C25H35N7O19P3S
thf	5,6,7,8-Tetrahydrofolate	C19H22N7O6
thymd	Thymidine	C10H14N2O5
tyr-L	L-Tyrosine	C9H11NO3
udp	UDP	C9H11N2O12P2
uppg3	Uroporphyrinogen III	C40H36N4O16
urea	Urea	CH4N2O



## Supplemental data S2: Constraints on enzymatic capacities and transport reactions

**LB** Lower bound  
**UB** Upper bound  
**unit**  $\mu\text{mol}/\text{min}/\text{g}$  protein

### Three objective functions and exchange reactions with the extracellular space

Abbreviation	Equation	LB	UB	
DM_atp(c)	atp + h2o --> adp + h + pi			objective function
DM_heme(m)	pheme -->			objective function
DM_phoslipid(m)	(0.18) clpn_m + (0.43) pc_m + (0.34) pe_m -->			objective function
EX_co2(e)	co2 <==>	-1.00E+30	1.00E+30	
EX_h2o(e)	h2o <==>	-1.00E+30	1.00E+30	
EX_urea(e)	urea <==>	0	1.00E+30	
EX_12dgr_m(e)	12dgr_m <==>	-1.00E+30	1.00E+30	
EX_c204(e)	c204 <==>	-1	0	
EX_c226(e)	c226 <==>	-1	0	
EX_glu-L(e)	glu-L <==>	-1.00E+30	1.00E+30	
EX_glyc(e)	glyc <==>	-1	0	
EX_glyc3p(e)	glyc3p <==>	-1	0	
EX_h(e)	h <==>	-1.00E+30	1.00E+30	
EX_hdca(e)	hdca <==>	-1	0	
EX_o2(e)	o2 <==>	-31.25	0	
EX_ocdca(e)	ocdca <==>	-1	0	
EX_ocdcea(e)	ocdcea <==>	-1	0	
EX_ocdcya(e)	ocdcya <==>	-1	0	
EX_pi(e)	pi <==>	-1.00E+30	1.00E+30	
EX_ps_m(e)	ps_m <==>	-1.00E+30	1.00E+30	
EX_coa(e)	coa <==>	-1.00E+30	1.00E+30	
EX_cys-L(e)	cys-L <==>	-1.00E+30	1.00E+30	
EX_fe2(e)	fe2 <==>	-1.00E+30	1.00E+30	
EX_glc(e)	glc-D <==>	-1.00E+30	1.00E+30	
EX_gly(e)	gly <==>	-1	0	
EX_lac-L(e)	lac-L <==>	0	1.00E+30	
sink_atpctp	[m] : amp + ctp <==> atp + cmp	-1.00E+30	0.00E+00	
sink_cdpchol(c)	cdpchol <==>	-1.00E+30	0.00E+00	
sink_cmp(c)	cmp <==>	-1.00E+30	0.00E+00	

Abbreviation	Equation	LB	UB	Tissue	References
CRNtim	crn[m] --> crn[c]	0	200	rat liver	Indiveri, C., 1991
C160CPT2	[m] : coa + pmtcrn --> crn + pmtcoa	0	475	rat heart mitochondria	Murthy, M.S., 1984
C160CPT1	[c] : crn + pmtcoa --> coa + pmtcrn	0	468	rat heart mitochondria	Murthy, M.S., 1984
ASPGLUm	asp-L[m] + glu-L[c] + h[c] <==> asp-L[c] + glu-L[m] + h[m]	-40	93.33	rat liver	Williamson, J.R., 1980
PDHm	[m] : coa + nad + pyr --> accoa + co2 + nadh	0	32	physiologically working pig heart	Bunger, R., 1993
MALtm	mal-L[c] + pi[m] <==> mal-L[m] + pi[c]	-20.4	18.7	human gene (Citrin), reconstitution	Palmieri, L., 2001
CITtbm	cit[c] + pep[m] <==> cit[m] + pep[c]	-104.17	104.17	bovine liver, reconstitution	Claeys, D., 1989
PYRt2m	h[c] + pyr[c] <==> h[m] + pyr[m]	-110	110	physiologically working pig heart	Bunger, R., 1993
CITtam	cit[c] + mal-L[m] <==> cit[m] + mal-L[c]	-91.67	113.33	bovine liver, reconstitution	Claeys, D., 1989
SUCct2m	pi[m] + succ[c] <==> pi[c] + succ[m]	-13.3	13.3	rat homolog in proteoliposomes	Fiermonte, G., 1999
LYStm	h[m] + lys-L[c] <==> h[c] + lys-L[m]	-120	120	human gene, reconstitution	Fiermonte, G., 2003
ARGtm	arg-L[c] + h[m] <==> arg-L[m] + h[c]	-105	105	human gene, reconstitution	Fiermonte, G., 2003

CITRtm	citr-L[m] <==> citr-L[c]	-60	60	human gene, reconstitution	Fiermonte, G., 2003
ATPtm	adp[c] + atp[m] --> adp[m] + atp[c]	-32.6	32.6	human gene, intact yeast	De Marcos Lousa, C., 2002
ORNt4m	citr-L[c] + h[c] + orn[m] <==> citr-L[m] + h[m] + orn[c]	-145	145	mitochondria	
				rat liver gene, reconstitution	Indiveri, G., 1997

## Supplemental data S3: Results of flux variability analysis

Reactions marked with (\*) are reversible reactions that can not have negative fluxes based on flux balancing

Reactions	Reversible	ATP		Heme		Phospholipids		No obj function		Notes
		MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	
12DGR1	R	0	0	0	0	1.59	1.59	1.59	0	
5AOPtm	R	0	0	-1.00	-1.00	0	0	0	-1.00	*
ACACT1m	I	0	0	0	0	0	0	0	0	
ACONTm	R	10.68	10.68	12.36	0	12.01	0	12.36	0	
ADK1	R	0.08	0.08	10.89	0	13.24	2.67	13.55	0	
ADK1m	R	0	0	0	0	1.33	1.33	1.33	0	
ADK4m	R	0	0	0	0	0	0	0	0	*
AGATm	I	0	0	0	0	1.33	1.33	1.33	0	
AKGDm	I	10.68	10.68	21.27	1.00	21.15	0	21.27	0	
AKGMALtm	R	9.80	9.80	9.80	-20.27	9.80	-21.15	9.80	-21.15	
ALASm	I	0	0	1.00	1.00	0	0	1.00	0	
ARGN	I	0	0	10.89	0	10.58	0	10.89	0	
ARGSL	R	0	0	10.89	0	10.58	0	10.89	0	
ARGSS	I	0	0	10.89	0	10.58	0	10.89	0	
ARGtm	R	0	0	0	0	0	0	0	0	*
ASPLUm	R	9.80	9.80	11.02	1.00	10.32	0	11.02	0	
ASPTA	R	9.80	9.80	10.16	-9.89	10.06	-10.58	10.16	-10.58	
ASPTAm	R	-9.80	-9.80	-1.00	-11.02	0	-10.32	0	-11.02	*
ATPS4m	I	144.70	32.60	143.52	0	145.42	0	145.42	0	
ATPtm	I	32.60	32.60	4.37	-19.01	8.21	-15.11	32.60	-20.32	
C160	I	0	0	1.00	0	1.00	0	1.00	0	
C160CPT1	I	0	0	1.00	0	1.00	0	1.00	0	
C160CPT2	I	0	0	1.00	0	1.00	0	1.00	0	
C160CRN	I	0	0	1.00	0	1.00	0	1.00	0	
C180	I	0	0	1.00	0	1.00	0.53	1.00	0	
C180CPT1	I	0	0	1.00	0	1.00	0.53	1.00	0	
C180CPT2	I	0	0	1.00	0	1.00	0.53	1.00	0	
C180CRN	I	0	0	1.00	0	1.00	0.53	1.00	0	
C181	I	0	0	1.00	0	1.00	0.27	1.00	0	
C181CRN1	I	0	0	1.00	0	1.00	0.27	1.00	0	
C181CRN2	I	0	0	1.00	0	1.00	0.27	1.00	0	
C181CRN3	I	0	0	1.00	0	1.00	0.27	1.00	0	
C182	I	0	0	1.00	0	1.00	0.53	1.00	0	
C182CRN1	I	0	0	1.00	0	1.00	0.53	1.00	0	
C182CRN2	I	0	0	1.00	0	1.00	0.53	1.00	0	
C182CRN3	I	0	0	1.00	0	1.00	0.53	1.00	0	
C204	I	0	0	1.00	0	1.00	0.67	1.00	0	
C204CRN1	I	0	0	1.00	0	1.00	0.67	1.00	0	
C204CRN2	I	0	0	1.00	0	1.00	0.67	1.00	0	
C204CRN3	I	0	0	1.00	0	1.00	0.67	1.00	0	
C204t	I	0	0	1.00	0	1.00	0.67	1.00	0	
C226	I	0.08	0.08	1.00	0	1.00	0.13	1.00	0	
C226CRN1	I	0.08	0.08	1.00	0	1.00	0.13	1.00	0	
C226CRN2	I	0.08	0.08	1.00	0	1.00	0.13	1.00	0	
C226CRN3	I	0.08	0.08	1.00	0	1.00	0.13	1.00	0	
C226t	I	0.08	0.08	1.00	0	1.00	0.13	1.00	0	
CATm	I	0.16	0.15	0.16	0	0.16	0	0.16	0	
CBMKm	I	0	0	10.89	0	10.58	0	10.89	0	
CHLPCTD	I	0	0	0	0	0	0	0	0	
CITRtm	R	0	0	0	0	0	0	0	0	*
CITtam	R	0	-10.68	0	-20.27	0	-21.15	0	-21.15	*
CITtbn	R	10.68	0	20.27	0	21.15	0	21.15	0	

CK	R	0	0	0	0	0	0	0	0	*
CLPNSm	R	0	0	0	0	0.67	0.67	0.67	0	
CO2t	R	-31.16	-31.16	-2.00	-32.41	-1.26	-32.99	0	-33.67	*
CO2tm	R	-31.16	-31.16	-1.25	-31.66	-1.26	-32.99	0	-32.99	*
COAt	R	0	0	0	0	0	0	0	0	*
COAtm	R	0	0	0	0	0	0	0	0	*
CPPPGO	I	0	0	0.13	0.13	0	0	0.13	0	
CRNtim	I	0.08	0.08	1.39	0	3.97	2.67	4.00	0	
CSm	I	10.68	10.68	12.36	0	12.01	0	12.36	0	
CYOOm3	I	31.73	31.72	31.41	1.00	31.73	0	31.73	0	
CYOR_u10m	I	63.45	63.44	62.82	1.99	63.45	0	63.45	0	
CYSt2r	R	0	0	0	0	0	0	0	0	*
DAGCPTm	I	0	0	0	0	1.59	1.59	1.59	0	
DAGKm	I	112.10	0	161.18	0	156.20	0	165.02	0	
DASYNm	R	0	0	0	0	1.33	1.33	1.33	0	
DGNSKm	I	0	0	0	0	0	0	0	0	
DHORDm	R	0	0	0	0	0	0	0	0	*
DNC1C	R	0	0	0	0	0	0	0	0	*
DNC1G	R	0	0	0	0	0	0	0	0	*
DNC1U	R	0	0	0	0	0	0	0	0	*
DUTPDPm	I	0	0	0	0	0	0	0	0	
ENO	R	9.80	9.80	9.80	0	9.80	0	9.80	0	
ETHAPTm	R	0	0	0	0	0	0	0	0	*
FAOXC160	I	0	0	1.38	0	1.29	0	1.38	0	
FAOXC180	I	0	0	1.00	0	0.47	0	1.00	0	
FAOXC181	I	0	0	1.00	0	0.73	0	1.00	0	
FAOXC182	I	0	0	1.00	0	0.47	0	1.00	0	
FAOXC204	I	0	0	1.00	0	0.33	0	1.00	0	
FAOXC226	I	0.08	0.08	1.00	0	0.87	0	1.00	0	
FASYNm	I	0	0	0	0	2.67	2.67	2.67	0	
FBA	R	4.90	4.90	4.90	0	4.90	0	4.90	0	
FCLTm	I	0	0	0.13	0.13	0	0	0.13	0	
FE2t1	I	0	0	0.13	0.13	0	0	0.13	0	
FE2tm	I	0	0	0.13	0.13	0	0	0.13	0	
FRDcm	I	0	0	10.89	0	10.58	0	10.89	0	
FTHFLm	R	0	0	0	0	0	0	0	0	*
FUMm	R	10.68	10.68	31.16	0	31.73	0	31.73	0	
G3PATm	I	0	0	0	0	1.33	1.33	1.33	0	
G3PDm	I	0	0	0	0	0	0	0	0	
G6PI	R	0	0	0	0	0	0	0	0	*
G6PI2	R	0	0	0	0	0	0	0	0	*
GACMTR	R	0	0	0	0	0	0	0	0	*
GAPD	R	9.80	9.80	9.80	0	9.80	0	9.80	0	
GHMT2rm	R	0	0	0	0	0	0	0	0	*
GLCt1	I	4.90	4.90	4.90	0	4.90	0	4.90	0	
GLUCYS	I	0	0	0	0	0	0	0	0	
GLUDx	R	0	0	10.39	-0.50	10.58	0	10.58	-0.50	
GLUDy	R	0	0	0	0	0	0	0	0	*
GLUt2m	R	0	0	0	0	0	0	0	0	*
GLUt2r	R	0	0	21.27	-0.50	21.15	0	21.27	-0.50	
GLYAMDTR	R	0	0	0	0	0	0	0	0	*
GLYC3Pt1	I	0	0	0	0	1.00	1.00	1.00	0	
GLYC3Ptm	I	0	0	0	0	1.00	1.00	1.00	0	
GLYct1	I	0	0	0	0	1.00	1.00	1.00	0	
GLYctm	R	0	0	0	0	1.00	1.00	1.00	0	
GLYKm	I	0	0	0	0	1.67	1.67	1.67	0	
GLYt2r	R	0	0	1.00	1.00	0	0	1.00	0	

GLYtm	R	0	0	1.00	1.00	0	0	1.00	0	
GTHDHm	I	0	0	0	0	0	0	0	0	
GTHOm	I	0.01	0	0.31	0	0.32	0	0.32	0	
GTHPm	R	0.01	0	0.31	0	0.32	0	0.32	0	
GTHRDt	R	0	0	0	0	0	0	0	0	*
GTHS	I	0	0	0	0	0	0	0	0	
GTPtm	I	10.68	0	11.66	0	12.15	0	12.15	0	
H2CO3Dm	R	0	0	0	0	0	0	0	0	*
H2OD	R	0	0	0	0	0	0	0	0	*
H2Ot	R	-29.73	-29.73	-3.35	-32.62	-4.33	-34.59	0	-36.95	*
H2Otm	R	-72.93	-72.93	6.69	-43.48	2.80	-48.35	9.80	-76.25	
HACDm	R	0	0	0	0	0	0	0	0	*
HCO3Em	R	10.69	0	12.67	0	12.33	0	12.67	0	
HDCAt	I	0	0	1.00	0	1.00	0	1.00	0	
HEX1	I	4.90	4.90	4.90	0	4.90	0	4.90	0	
HMBS	I	0	0	0.13	0.13	0	0	0.13	0	
HMGCOASm	R	0	0	0	-11.66	0	-12.15	0	-12.15	*
HMGLm	I	0	0	11.66	0	12.15	0	12.15	0	
Ht	R	1.82	1.82	3.38	1.50	-1.43	-3.33	3.38	-3.33	
Htm	I	448.40	0	574.08	0	581.69	0	581.69	0	
ICDHxm	I	10.68	10.67	12.36	0	12.01	0	12.36	0	
ICDHym	I	0.01	0	0.31	0	0.32	0	0.32	0	
L_LACT2r	R	0	0	0	-30.07	0	-30.95	0	-30.95	*
LDH_L	R	0	0	0	-30.07	0	-30.95	0	-30.95	*
LYStm	R	0	0	0	0	0	0	0	0	*
MALtm	R	0	-10.68	0.41	-11.36	0.16	-12.01	0.41	-12.01	
MDH	R	-9.80	-9.80	9.89	-10.16	10.58	-10.06	10.58	-10.16	
MDHm	R	20.48	20.47	21.27	0.97	21.15	0	21.27	0	
ME2m	I	0.01	0	0.31	0	0.32	0	0.32	0	
MMSAD1m	I	0	0	0	0	0	0	0	0	
NADH2_u10m	I	52.45	52.44	52.57	1.99	52.68	0	52.68	0	
NDPK1	R	0	-10.68	0	-11.66	0	-12.15	0	-12.15	*
NH4tm	R	0	0	10.89	0	10.58	0	10.89	0	
O2t	R	31.25	31.25	31.25	1.30	31.25	0	31.25	0	
O2tm	R	31.25	31.25	31.13	1.17	31.25	0	31.25	0	
OCBTm	I	0	0	10.89	0	10.58	0	10.89	0	
OCDCAt	I	0	0	1.00	0	1.00	0.53	1.00	0	
OCDCAt	I	0	0	1.00	0	1.00	0.27	1.00	0	
OCDCYAt	I	0	0	1.00	0	1.00	0.53	1.00	0	
OCOAT1m	R	0	0	11.66	0	12.15	0	12.15	0	
ORnt3m	R	0	0	0	0	0	0	0	0	*
ORnt4m	R	0	0	0	-10.89	0	-10.58	0	-10.89	*
PAPAm	I	112.10	0	161.18	0	156.20	0	165.02	0	
PCHOLPm	I	0	0	0	0	0	0	0	0	
PCm	I	10.69	0	12.67	0	12.33	0	12.67	0	
PCtm	I	0	0	0	0	1.59	1.59	1.59	0	
PDHm	I	9.80	9.80	10.02	0	10.32	0	10.32	0	
PEPCKm	I	10.68	0	20.27	0	21.15	0	21.15	0	
PFK	I	4.90	4.90	4.90	0	4.90	0	4.90	0	
PGI	R	4.90	4.90	4.90	0	4.90	0	4.90	0	
PGK	R	-9.80	-9.80	0	-9.80	0	-9.80	0	-9.80	*
PGM	R	-9.80	-9.80	0	-9.80	0	-9.80	0	-9.80	*
PGPPm	I	0	0	0	0	1.33	1.33	1.33	0	
PGSAm	R	0	0	0	0	1.33	1.33	1.33	0	
Plt2m	R	43.28	32.60	23.08	-19.51	27.13	-14.77	54.85	-20.32	
Plt2r	R	0	0	0	0	0.33	0.33	0.67	-0.33	
PPA	I	0.08	0.08	10.89	0	13.24	2.67	13.55	0	

PPAm	I	0	0	0	0	1.33	1.33	1.33	0	
PPBNGS	I	0	0	0.50	0.50	0	0	0.50	0	
PPCOACm	I	0	0	0	0	0	0	0	0	
PPPG9tm	R	0	0	0.13	0.13	0	0	0.13	0	
PPPGOm	I	0	0	0.06	0.06	0	0	0.06	0	
PSDm	I	0	0	0	0	1.26	1.26	1.26	0	
PSt	R	0	0	0	0	1.26	1.26	1.26	0	
PStm	I	0	0	0	0	1.26	1.26	1.26	0	
PYK	I	20.48	9.80	30.07	0	30.95	0	30.95	0	
PYRt2m	R	20.48	9.80	20.05	-0.31	20.63	-0.32	20.63	-0.32	
SPODMm	I	0.32	0.32	0.31	0.01	0.32	0	0.32	0	
SUCct2m	R	0	0	10.89	0	10.58	0	10.89	0	
SUCD1m	R	10.68	10.68	31.16	0	31.73	0	31.73	0	
SUCD3_u10m	R	11.00	11.00	20.27	0	21.15	0	21.15	0	
SUCOASm	R	-10.68	-10.68	0	-20.27	0	-21.15	0	-21.15	*
THD1m	R	0.01	0	0.31	0	0.32	0	0.32	0	
THFATm	I	0	0	0	0	0	0	0	0	
TMDK1m	I	0	0	0	0	0	0	0	0	
TPI	R	4.90	4.90	4.90	0	4.90	0	4.90	0	
TYRTAm	R	0	0	0	0	0	0	0	0	*
UPP3S	I	0	0	0.13	0.13	0	0	0.13	0	
UPPDC1	I	0	0	0.13	0.13	0	0	0.13	0	
UREAt	R	0	0	0	-10.89	0	-10.58	0	-10.89	*

## Supplemental data S4: Correlated reaction sets

Correlated reaction sets with respect to the three objective functions and among highly correlated flux distributions  
 These correlated sets are ordered based on the frequency they appear among the set of alternate optima

<b>Obj func = ATP</b>		<b>Obj func = Heme</b>		<b>Obj func = Phospholipid</b>		<b>Among correlated fluxes</b>	
<b>Reactions always used</b>		<b>Reactions always used</b>		<b>Reactions always used</b>		<b>Phospholipid biosynthesis</b>	
FAOXC226	Fatty acid oxidation	ALASm	Heme biosynthesis	C180	Fatty acid transport	DAGCPTm	Lipid
C226	Fatty acid transport	FCLTm	Heme biosynthesis	C180CPT1	Fatty acid transport	PCTm	Lipid
C226CRN1	Fatty acid transport	5AOPtm	Heme biosynthesis	C180CPT2	Fatty acid transport	PSDm	Lipid
C226CRN2	Fatty acid transport	PPBNGS	Heme biosynthesis	C180CRN	Fatty acid transport	PStm	Lipid
C226CRN3	Fatty acid transport	HMBS	Heme biosynthesis	C181	Fatty acid transport	CLPNSm	Lipid
CRNtim	Fatty acid transport	UPP3S	Heme biosynthesis	C181CRN1	Fatty acid transport	GLYKm	Lipid
HEX1	Glycolysis	UPPDC1	Heme biosynthesis	C181CRN2	Fatty acid transport	FASYNm	Lipid
PYK	Glycolysis	CPPPGO	Heme biosynthesis	C181CRN3	Fatty acid transport	G3PATm	Lipid
PGI	Glycolysis	PPP9tm	Heme biosynthesis	C182	Fatty acid transport	AGATm	Lipid
PFK	Glycolysis	PPPGOm	Heme biosynthesis	C182CRN1	Fatty acid transport	DASYNm	Lipid
FBA	Glycolysis	ASPLUm	Mal-Asp Shuttle	C182CRN2	Fatty acid transport	PGSAm	Lipid
TPI	Glycolysis	ASPTA	Mal-Asp Shuttle	C182CRN3	Fatty acid transport	PGPPm	Lipid
GAPD	Glycolysis	MDH	Mal-Asp Shuttle	C204	Fatty acid transport	ADK1m	Nucleotide
PGK	Glycolysis	ASPTAm	Mal-Asp Shuttle	C204CRN1	Fatty acid transport	PPAm	Others
PGM	Glycolysis	GLUDx	Others	C204CRN2	Fatty acid transport	GLYC3Ptm	Transport
ENO	Glycolysis	CYOOm3	OxPhos	C204CRN3	Fatty acid transport	GLYctm	Transport
PAPAm	Lipid	CYORu10m	OxPhos	C226	Fatty acid transport	GLYC3Pt1	Transport to cytosol
DAGKm	Lipid	NADH2u10m	OxPhos	C226CRN1	Fatty acid transport	GLYct1	Transport to cytosol
ASPLUm	Mal-Asp Shuttle	SPODMm	ROS detoxification	C226CRN2	Fatty acid transport	Plt2r	Transport to cytosol
ASPTA	Mal-Asp Shuttle	AKGDm	TCA cycle	C226CRN3	Fatty acid transport	PSSt	Transport to cytosol
MDH	Mal-Asp Shuttle	MDHm	TCA cycle	CRNtim	Fatty acid transport	12DGRt1	Transport to cytosol
AKGMALtm	Mal-Asp Shuttle	ATPtm	Transport	DAGCPTm	Lipid	<b>HEME biosynthesis</b>	
ASPTAm	Mal-Asp Shuttle	CO2tm	Transport	PCTm	Lipid	ALASm	Heme biosynthesis
ADK1	Nucleotide	FE2tm	Transport	PSDm	Lipid	FCLTm	Heme biosynthesis
PPA	Others	GLYtm	Transport	PStm	Lipid	5AOPtm	Heme biosynthesis
ATPS4m	OxPhos	H2Otm	Transport	CLPNSm	Lipid	PPBNGS	Heme biosynthesis
CYOOm3	OxPhos	MALtm	Transport	GLYKm	Lipid	HMBS	Heme biosynthesis
CYORu10m	OxPhos	O2tm	Transport	FASYNm	Lipid	UPP3S	Heme biosynthesis
NADH2u10m	OxPhos	CO2t	Transport to cytosol	G3PATm	Lipid	UPPDC1	Heme biosynthesis
SUCD3u10m	OxPhos	FE2t1	Transport to cytosol	AGATm	Lipid	CPPPGO	Heme biosynthesis
CATm	ROS detoxification	GLUt2r	Transport to cytosol	DASYNm	Lipid	PPP9tm	Heme biosynthesis
SPODMm	ROS detoxification	GLYt2r	Transport to cytosol	PGSAm	Lipid	PPPGOm	Heme biosynthesis
PDHm	TCA cycle	H2Ot	Transport to cytosol	PGPPm	Lipid	FE2tm	Transport
CSm	TCA cycle	Ht	Transport to cytosol	ADK1	Nucleotide	GLYtm	Transport
ACONTm	TCA cycle	O2t	Transport to cytosol	ADK1m	Nucleotide	FE2t1	Transport to cytosol
ICDHxm	TCA cycle	<b>Urea cycle</b>		PPA	Others	GLYt2r	Transport to cytosol
AKGDm	TCA cycle	FRDcm	Transport	PPAm	Others	<b>Aerobic metabolism</b>	
SUCOASm	TCA cycle	SUCct2m	Transport	ATPtm	Transport	ADK1	Nucleotide
SUCD1m	TCA cycle	NH4tm	Urea cycle	CO2tm	Transport	PPA	Others
FUMm	TCA cycle	UREAt	Urea cycle	GLYC3Ptm	Transport	CYOOm3	OxPhos
MDHm	TCA cycle	CBMKm	Urea cycle	GLYctm	Transport	CYORu10m	OxPhos
ATPtm	Transport	OCBTm	Urea cycle	H2Otm	Transport	NADH2u10m	OxPhos
CO2tm	Transport	ARGSS	Urea cycle	Plt2m	Transport	SUCD3u10m	OxPhos
H2Otm	Transport	ARGSL	Urea cycle	12DGRt1	Transport to cytosol	SPODMm	ROS detoxification
O2tm	Transport	ARGN	Urea cycle	C204t	Transport to cytosol	CSm	TCA cycle
Plt2m	Transport	ORNt4m	Urea cycle	C226t	Transport to cytosol	ACONTm	TCA cycle
PYRt2m	Transport	<b>Glycolysis</b>		CO2t	Transport to cytosol	ICDHxm	TCA cycle
C226t	Transport to cytosol	HEX1	Glycolysis	GLYC3Pt1	Transport to cytosol	AKGDm	TCA cycle
CO2t	Transport to cytosol	PGI	Glycolysis	GLYct1	Transport to cytosol	SUCD1m	TCA cycle
GLct1	Transport to cytosol	PFK	Glycolysis	H2Ot	Transport to cytosol	FUMm	TCA cycle
H2Ot	Transport to cytosol	FBA	Glycolysis	Ht	Transport to cytosol	MDHm	TCA cycle

Ht	Transport to cytosol	TPI	Glycolysis	OCDCAt	Transport to cytosol	ATPtm	Transport
O2t	Transport to cytosol	GAPD	Glycolysis	OCDCeAt	Transport to cytosol	CO2tm	Transport
<b>GTP consumption path 1</b>		PGK	Glycolysis	OCDCYAt	Transport to cytosol	H2Otm	Transport
NDPK1	Nucleotide	PGM	Glycolysis	Plt2r	Transport to cytosol	Htm	Transport
GTPtm	Transport	ENO	Glycolysis	PSt	Transport to cytosol	O2tm	Transport
<b>GTP consumption path 2</b>		GLCt1	Transport to cytosol	<b>TCA</b>		Plt2m	Transport
CITtam	Transport	<b>Palmitate</b>		CSm	TCA cycle	CO2t	Transport to cytosol
CITbm	Transport	C160CPT1	Fatty acid transport	ACONTm	TCA cycle	H2Ot	Transport to cytosol
HCO3Em	Others	C160CPT2	Fatty acid transport	<b>Oxygen metabolism</b>		Ht	Transport to cytosol
MALtm	Transport	C160CRN	Fatty acid transport	CYOOm3	OxPhos	O2t	Transport to cytosol
PCm	Others	HDCAt	Transport to cytosol	CYORu10m	OxPhos	<b>Urea cycle</b>	
PEPCKm	Others	C160	Fatty acid transport	NADH2u10m	OxPhos	GLUDx	Others
		<b>Stearate</b>		SUCD3u10m	OxPhos	FRDcm	Transport
		C180CPT1	Fatty acid transport	SPODMm	ROS detoxification	MALtm	Transport
		C180CPT2	Fatty acid transport	AKGDm	TCA cycle	SUCct2m	Transport
		C180CRN	Fatty acid transport	SUCD1m	TCA cycle	GLUt2r	Transport to cytosol
		FAOXC180	Fatty acid oxidation	FUMm	TCA cycle	NH4tm	Urea cycle
		OCDCAt	Transport to cytosol	MDHm	TCA cycle	UREAt	Urea cycle
		C180	Fatty acid transport	O2tm	Transport	CBMKm	Urea cycle
		<b>Oleate</b>		O2t	Transport to cytosol	OCBTm	Urea cycle
		C181CRN1	Fatty acid transport	<b>Urea cycle</b>		ARGSS	Urea cycle
		C181CRN2	Fatty acid transport	GLUDx	Others	ARGSL	Urea cycle
		C181CRN3	Fatty acid transport	FRDcm	Transport	ARGN	Urea cycle
		FAOXC181	Fatty acid oxidation	SUCct2m	Transport	ORNt4m	Urea cycle
		OCDCeAt	Transport to cytosol	GLUt2r	Transport to cytosol	<b>Mal-Asp Shuttle</b>	
		C181	Fatty acid transport	NH4tm	Urea cycle	ASPLUm	Mal-Asp Shuttle
		<b>Octadecynoate</b>		UREAt	Urea cycle	ASPTAm	Mal-Asp Shuttle
		C182CRN1	Fatty acid transport	CBMKm	Urea cycle	<b>Mal-Asp Shuttle</b>	
		C182CRN2	Fatty acid transport	OCBTm	Urea cycle	ASPTA	Mal-Asp Shuttle
		C182CRN3	Fatty acid transport	ARGSS	Urea cycle	MDH	Mal-Asp Shuttle
		FAOXC182	Fatty acid oxidation	ARGSL	Urea cycle	<b>Palmitate</b>	
		OCDCYAt	Transport to cytosol	ARGN	Urea cycle	C160CPT1	Fatty acid transport
		C182	Fatty acid transport	ORNt4m	Urea cycle	C160CPT2	Fatty acid transport
		<b>Arachidonate</b>		<b>Mal-Asp Shuttle</b>		C160CRN	Fatty acid transport
		C204CRN1	Fatty acid transport	ASPLUm	Mal-Asp Shuttle	HDCAt	Transport to cytosol
		C204CRN2	Fatty acid transport	ASPTAm	Mal-Asp Shuttle	C160	Fatty acid transport
		C204CRN3	Fatty acid transport	PDHm	TCA cycle	<b>Stearate</b>	
		C204t	Transport to cytosol	<b>Mal-Asp Shuttle</b>		C180CPT1	Fatty acid transport
		FAOXC204	Fatty acid oxidation	MDH	Mal-Asp Shuttle	C180CPT2	Fatty acid transport
		C204	Fatty acid transport	ASPTA	Mal-Asp Shuttle	C180CRN	Fatty acid transport
		<b>Docosohexaenoate</b>		<b>Palmitate</b>		OCDCAt	Transport to cytosol
		C226CRN1	Fatty acid transport	C160CPT1	Fatty acid transport	C180	Fatty acid transport
		C226CRN2	Fatty acid transport	C160CPT2	Fatty acid transport	<b>Oleate</b>	
		C226CRN3	Fatty acid transport	C160CRN	Fatty acid transport	C181CRN1	Fatty acid transport
		C226t	Transport to cytosol	HDCAt	Transport to cytosol	C181CRN2	Fatty acid transport
		FAOXC226	Fatty acid oxidation	C160	Fatty acid transport	C181CRN3	Fatty acid transport
		C226	Fatty acid transport	<b>Dicarboxylate transport</b>		OCDCeAt	Transport to cytosol
		<b>TCA</b>		CITbm	Transport	C181	Fatty acid transport
		ACONTm	TCA cycle	PEPCKm	Others	<b>Octadecynoate</b>	
		CSm	TCA cycle	CITtam	Transport	C182CRN1	Fatty acid transport
		<b>Nucleotide</b>		<b>Lipid</b>		C182CRN2	Fatty acid transport
		ADK1	Nucleotide	PAPAm	Lipid	C182CRN3	Fatty acid transport
		PPA	Others	DAGKm	Lipid	OCDCYAt	Transport to cytosol
		<b>TCA</b>		<b>Glycolysis</b>		C182	Fatty acid transport
		FUMm	TCA cycle	HEX1	Glycolysis	<b>Arachidonate</b>	
		SUCD1m	TCA cycle	PGI	Glycolysis	C204CRN1	Fatty acid transport
		<b>ROS</b>		PFK	Glycolysis	C204CRN2	Fatty acid transport

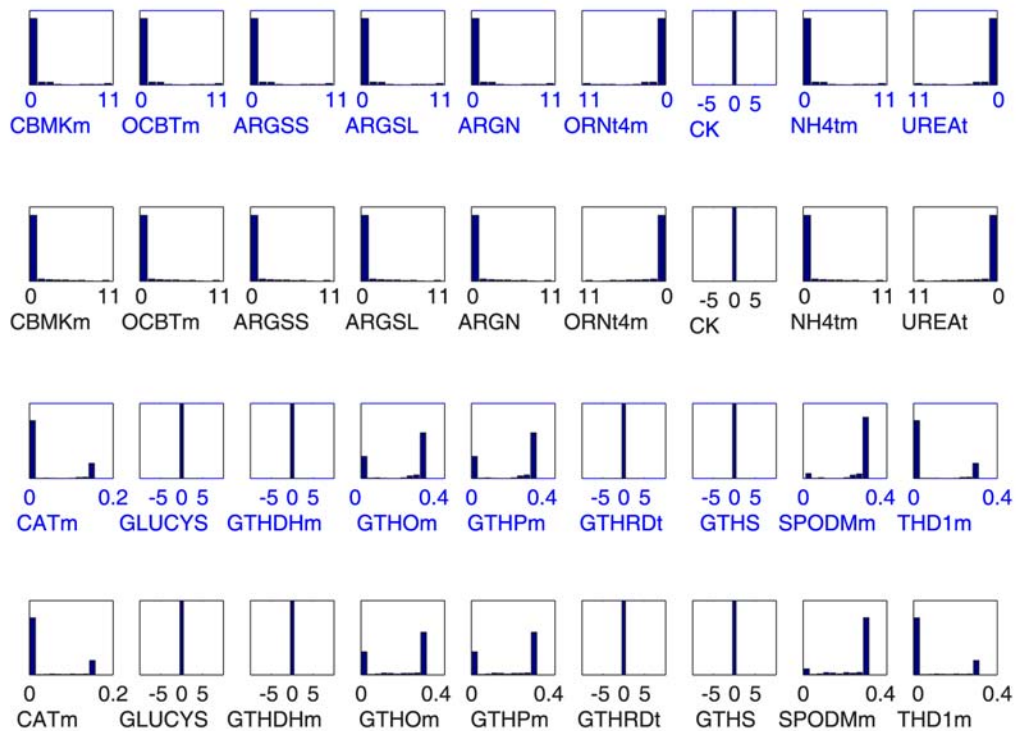


GTHOm	ROS detoxification	FBA	Glycolysis	C204CRN3	Fatty acid transport
GTHPm	ROS detoxification	TPI	Glycolysis	C204t	Transport to cytosol
<b>GTP consumption path 1</b>		GAPD	Glycolysis	C204	Fatty acid transport
GTPtm	Transport	PGK	Glycolysis	<b>Docosohexaenoate</b>	
NDPK1	Nucleotide	PGM	Glycolysis	C226CRN1	Fatty acid transport
<b>Carbonate</b>		ENO	Glycolysis	C226CRN2	Fatty acid transport
HCO3Em	Others	GLCt1	Transport to cytosol	C226CRN3	Fatty acid transport
PCm	Others	<b>ROS</b>		C226t	Transport to cytosol
<b>Ketone bodies</b>		GTHPm	ROS detoxification	C226	Fatty acid transport
HMGCOASm	Others	GTHOm	ROS detoxification	<b>Dicarboxylate transport</b>	
HMGLm	Lipid	<b>Nucleotide</b>		PEPCKm	Others
OCOAT1m	Lipid	NDPK1	Nucleotide	CITtm	Transport
<b>Lactate metabolism</b>		GTPtm	Transport	CITtam	Transport
LDHL	Others	<b>Carbonate</b>		<b>Lipid</b>	
LLACT2r	Transport to cytosol	PCm	Others	PAPAm	Lipid
<b>Lipid</b>		HCO3Em	Others	DAGKm	Lipid
DAGKm	Lipid	<b>Ketone bodies</b>		<b>Glycolysis</b>	
PAPAm	Lipid	HMGLm	Lipid	HEX1	Glycolysis
<b>Dicarboxylate transport</b>		OCOAT1m	Lipid	PGI	Glycolysis
CITtam	Transport	HMGCOASm	Others	PFK	Glycolysis
CITtm	Transport	<b>Lactate metabolism</b>		FBA	Glycolysis
PEPCKm	Others	LDHL	Others	TPI	Glycolysis
		LLACT2r	Transport to cytosol	GAPD	Glycolysis
				PGK	Glycolysis
				PGM	Glycolysis
				ENO	Glycolysis
				GLCt1	Transport to cytosol
				<b>ROS detoxification</b>	
				GTHPm	ROS detoxification
				GTHOm	ROS detoxification
				<b>GTP consumption path 1</b>	
				NDPK1	Nucleotide
				GTPtm	Transport
				<b>GTP consumption path 2</b>	
				PCm	Others
				HCO3Em	Others
				<b>Ketone bodies</b>	
				HMGLm	Lipid
				OCOAT1m	Lipid
				HMGCOASm	Others
				<b>Lactate metabolism</b>	
				LDHL	Others
				LLACT2r	Transport to cytosol

## Supplemental data S5

**Figure A:** See Map.tif file. Map of the reconstructed mitochondrial metabolic network and correlated reaction sets. Reactions in the network are more connected than they are drawn here. Nineteen reaction sets are shown in colored and labeled in italics: glycolysis (10), urea cycle (10), oxygen metabolism (11), fatty acid shuttling and oxidation (six sets of 5-6 reactions each), GTP consumption path 1 (2) and path 2 (6), lactate metabolism (2), ROS detoxification (2), TCA cycle reactions (2), lipid (2), ketone body metabolism (3), Mal/Asp shuttle (2 sets of 2 reaction each), nucleotide metabolism (2), where the numbers in the parentheses correspond to the number of reactions belonging to that reaction set. See supplemental data S4 for a completed list of correlated reaction sets. Figures in files Map2.tif and Map3.tif are higher resolution images of this map.

**Figure B:** Distribution of flux values among alternate optima for reactions in the urea cycle and ROS detoxification. Figures labeled in blue correspond to the case where heme synthesis is the objective function; the rest corresponds to the case where phospholipid synthesis is the objective function. Values on the x-axes denote the minimum and maximum flux values the corresponding reaction can take on. Y-axes have values from 0 to 1, denoting the probability of a particular flux value. See supplemental data S1 for reaction abbreviations.



## Supplemental data S5

**Figure C:** Distribution of flux values among alternate optima for reactions in fatty acid metabolism. Figures labeled in blue correspond to the case where heme synthesis is the objective function; the rest corresponds to the case where phospholipid synthesis is the objective function. Values on the x-axes denote the minimum and maximum flux values the corresponding reaction can take on. Y-axes have values from 0 to 1, denoting the probability of a particular flux value. See supplemental data S1 for reaction abbreviations.



Mitochondria Metabolism

