Supplemental Material

Description

The supplemental materials consist of five parts.

Part A: Tables of parameters in the transport and reaction fluxes.

Part B: Dynamic mass balance equation

Part C: Description of reaction flux and transport fluxes

Part D: Description of transport fluxes

Part A Tables of transport and reaction fluxes at resting, steady state, and corresponding parameters.

A1: Table of parameters in transport fluxes

Species k	$J^0_{bl\leftrightarrow cyt,F,k}$ *(mmol/min/ kg fiber)*	$M_{bl\leftrightarrow cyt}$ *(mmol/kg)*	*Type I fiber (R)*		*Type I fiber (R)*	
			$T_{\max,bl\leftrightarrow cyt,R,k}$ *(mmol/min/kg)*	$\lambda_{bl\leftrightarrow cyt,R,k}$ *(l/min/kg)*	$T_{\max,bl\leftrightarrow cyt,W,k}$ *(mmol/min/kg)*	$\lambda_{bl\leftrightarrow cyt,W,k}$ *(l/min/kg)*
Transport between blood and cytosol						
Glc	0.0488	2.5	0.103	N/A	0.102	N/A
Pyr	0.003	1.0	0.266	N/A	0.224	N/A
Lac	-0.0225	5.0	0.518	N/A	0.595	N/A
Ala	-0.0163	N/A	N/A	0.019	N/A	0.012
Glr	-0.002	N/A	N/A	0.08	N/A	0.092
FFA	0.0183	1.0	0.261	N/A	0.23	
CO_2	-0.471	N/A	N/A	6.454	N/A	6.454
O_2	0.605	N/A	N/A	39.58	N/A	39.582
H^+	-1.81E-6	4.79E-5	1.46E-5	N/A	1.46E-5	N/A

Transport between cytosol and mitochondria

Species k	$J^0_{cyt\leftrightarrow mit,F,k}$ *(mmol/min/ kg fiber)*	$M_{cyt\leftrightarrow mit}$ *(mmol/L)*	$T_{\max,cyt\leftrightarrow mit,R,k}$ *(mmol/min)*	$\lambda_{cyt\leftrightarrow mit,R,k}$ *(l/min/kg)*	$T_{\max,cyt\leftrightarrow mit,W,k}$ *(mmol/min)*	$\lambda_{cyt\leftrightarrow mit,W,k}$ *(l/min/kg)*
O_2	0.605	N/A	N/A	89.57	N/A	89.57
CO_2	-0.471	N/A	N/A	3.863	N/A	3.863
Pyr	0.05975	0.053	0.268	N/A	0.487	N/A
FAC	0.01825	0.002	0.080	N/A	0.154	N/A
Pi	2.895	1.375	12.649	N/A	24.495	N/A
CoA	-0.0183	0.04	0.128	N/A	0.072	N/A
ATP - ADP	-2.895	666.4 0.554	5.251	N/A	4.831	N/A
NADH-NAD	0.071	0.001 15.794	0.096	N/A	0.096	N/A
H^+	6.86E-6	2.64E-5	2.51E-5	N/A	2.64E-5	N/A

A2: Table of parameters in reaction fluxes

Reaction	$V^{f}_{\max,R,S\leftrightarrow P}$	$V^{f}_{\max,W,S\leftrightarrow P}$	$K_{eq,S\leftrightarrow P}$	$K^{f}_{m,S\leftrightarrow P}$	$K^{b}_{m,S\leftrightarrow P}$	K^{Ctrl}_{m}
Hexokinase	4.42E-01	6.7E-1	1.63E+04	3.29E+00	3.93E-07	2.78E+01
Glycogen synthase	6.93E+01	3.55E+01	2.67E+05	1.74E+04	1.58E+02	0
Glycogen phosphorylase	2.54E-01	2.55E-01	6.95E+00	3.06E-03	2.93E+05	1.87E-05
Phosphoglucose isomerase	4.24E-01	2.19E-01	3.67E-01	2.78E-01	4.86E-02	0
Phosphofructokinase	2.00E+00	1.52E+00	1.03E+04	2.88E-01	9.42E-08	9.35E-02
Aldolase +TPI	6.59E-01	6.77E-01	9.60E-01	6.67E-01	7.90E-02	0
GA3P dehydrogenase	2.63E-01	3.21E-01	7.87E-01	3.87E-02	1.96E-09	0
Phosphoglycerate kinase	1.19E-01	1.14E-01	5.88E+02	1.58E-03	3.19E-02	0
Pyruvate kinase	1.23E-01	1.18E-01	1.50E+09	7.61E-09	3.13E-01	2.67E-03
Lactate dehydrogenase	2.44E+44	2.44E+44	1.51E+09	1.17E+23	1.30E-15	0
Lipases	4.48E-03	7.61E-03	8.75E+00	1.67E+01	4.52E-15	0
G3P dehydrogenase	5.80E-03	6.86E-03	3.41E+08	1.96E-09	2.51E-02	0
Acyltransferase	6.69E-03	5.36E-03	3.32E+08	8.42E-09	2.73E-04	0
Acyl-CoA synthetase	2.16E+00	2.61E+00	3.75E+05	3.12E-01	6.21E-14	0
ATPase	1.51E+01	1.51E+01	1.47E+06	5.92E+00	1.04E-05	0
Adenylate kinase	200	200	0.111	1.32E+02	3.18E-05	0
Creatine kinase	200	200	2.37E+05	2.97E-04	2.07E+01	0
Alanine aminotransferase	4.55E-02	5.30E-02	2.94E+03	5.28E-02	1.44E+00	0
Pyruvate dehydrogenase	2.84E-01	1.99E-01	1.28E+07	3.15E-03	3.81E-07	3.61E-01
beta oxidation	5.00E-02	2.77E-02	2.40E+185	4.67E-04	6.00E-06	0
Citrate synthase	9.25E-01	7.43E-01	5.83E+06	4.80E-04	9.55E-07	3.61E-01
Isocitrate dehydrogenase	8.88E-01	8.15E-01	1.71E+00	2.99E+00	9.48E-02	3.61E-01
AKG dehydrogenase	7.39E-01	4.98E-01	7.00E+06	1.58E-02	9.48E-01	0
SCoA synthetase	6.32E-01	6.70E-01	2.44E+00	1.35E+01	3.30E-01	0
Succinate dehydrogenase	7.12E-01	5.46E-01	1.62E+01	2.01E+00	2.28E-01	0
Malate dehydrogenase	6.58E-01	5.76E-01	1.30E-01	2.99E+00	3.00E-07	0
Complex I +III+IV	2.63E+31	2.63E+31	9.88E+40	2.05E-06	3.15E+00	0
Complex II+III+IV	4.25E+18	3.72E+18	1.02E+27	3.94E-02	2.12E+00	0
ATP synthase	4.53E-09	5.05E-09	1.64E-04	2.71E-04	8.68E+00	0

Part B: Dynamic Mass Balances equation

Overall, the model incorporates 50 parameters associated with transport fluxes and 123 parameters associated with reaction fluxes, which can be evaluated and determined at resting and exercise steady state. In addition, 28 unknown activation coefficients are incorporated into specific transport (19) and reaction (9) fluxes.

Note:

1) The volume of blood domain V_{bl} includes the volume of capillary blood and the volume of interstitial fluid. Here we assume they are in equilibrium.

2) The transport and reaction fluxes in each type of muscle fibers are normalized to the volume of each type of muscle fibers [mmol/(min kg fiber)].

Capillary Blood + Tissue ISF Domain

B1. $$V_{bl}\frac{dC_{bl,Glc}}{dt}=Q\left(C_{art,Glc}-C_{bl,Glc}\right)-J^{f}_{bl\leftrightarrow cyt,R,Glc}V_R-J^{f}_{bl\leftrightarrow cyt,W,Glc}V_W$$

B2. $$V_{bl}\frac{dC_{bl,Pyr}}{dt}=Q\left(C_{art,Pyr}-C_{bl,Pyr}\right)-J^{f}_{bl\leftrightarrow cyt,R,Pyr}V_R-J^{f}_{bl\leftrightarrow cyt,W,Pyr}V_W$$

B3. $$V_{bl}\frac{dC_{bl,Lac}}{dt}=Q\left(C_{art,Lac}-C_{bl,Lac}\right)-J^{f}_{bl\leftrightarrow cyt,R,Lac}V_R-J^{f}_{bl\leftrightarrow cyt,W,Lac}V_W$$

B4. $$V_{bl}\frac{dC_{bl,Ala}}{dt}=Q\left(C_{art,Ala}-C_{bl,Ala}\right)-J^{p}_{bl\leftrightarrow cyt,R,Ala}V_R-J^{p}_{bl\leftrightarrow cyt,W,Ala}V_W$$

B5. $$V_{bl}\frac{dC_{bl,Glr}}{dt}=Q\left(C_{art,Glr}-C_{bl,Glr}\right)-J^{p}_{bl\leftrightarrow cyt,R,Glr}V_R-J^{p}_{bl\leftrightarrow cyt,W,Glr}V_W$$

B6. $$V_{bl}\frac{dC_{bl,FFA}}{dt}=Q\left(C_{art,FFA}-C_{bl,FFA}\right)-J^{f}_{bl\leftrightarrow cyt,R,FFA}V_R-J^{f}_{bl\leftrightarrow cyt,W,FFA}V_W$$

B7. $$V_{bl,CO2}\frac{dC^{F}_{bl,CO2}}{dt}=Q\left(C^{T}_{art,CO2}-C^{T}_{bl,CO2}\right)-J^{p}_{bl\leftrightarrow cyt,R,CO2}V_R-J^{p}_{bl\leftrightarrow cyt,W,CO2}V_W$$

B8. $$V_{bl,O2}\frac{dC^{F}_{bl,O2}}{dt}=Q\left(C^{T}_{art,O2}-C^{T}_{bl,O2}\right)-J^{p}_{bl\leftrightarrow cyt,R,O2}V_R-J^{p}_{bl\leftrightarrow cyt,W,O2}V_W$$

B9. $V_{bl}\frac{dC_{bl,H^+}}{dt}=Q\left(C_{art,H^+}-C_{bl,H^+}\right)-J^{f}_{bl\leftrightarrow cyt,R,H^+}V_R-J^{f}_{bl\leftrightarrow cyt,W,H^+}V_W$

Tissue Cells Cytosolic Domain: $F\in(ST,FT)$

C1. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Glc}}{dt}=J^{f}_{bl\leftrightarrow cyt,F,Glc}-\phi_{cyt,F,Glc\leftrightarrow G6P}$

C2. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Pyr}}{dt}=J^{f}_{bl\leftrightarrow cyt,F,Pyr}-J^{f}_{cyt\leftrightarrow mit,F,Pyr}+\phi_{cyt,F,PEP\leftrightarrow Pyr}-\phi_{cyt,F,Pyr\leftrightarrow Lac}-\phi_{cyt,F,Pyr\leftrightarrow Ala}$

C3. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Lac}}{dt}=J^{f}_{bl\leftrightarrow cyt,F,Lac}+\phi_{cyt,F,Pyr\leftrightarrow Lac}$

C4. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Ala}}{dt}=J^{p}_{bl\leftrightarrow cyt,F,Ala}+\phi_{cyt,F,Pyr\leftrightarrow Ala}$

C5. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Glr}}{dt}=J^{p}_{bl\leftrightarrow cyt,F,Glr}+\phi_{cyt,F,Tgl\leftrightarrow Glr}$

C6. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,FFA}}{dt}=J^{f}_{bl\leftrightarrow cyt,F,FFA}+3\phi_{cyt,F,Tgl\leftrightarrow Glr}-\phi_{cyt,F,FFA\leftrightarrow FAC}$

C7. $\frac{V_{cyt,F,CO2}}{V_F}\frac{dC^{F}_{cyt,F,CO2}}{dt}=J^{p}_{bl\leftrightarrow cyt,F,CO2}-J^{p}_{cyt\leftrightarrow mit,F,CO2}$

C8. $\frac{V_{cyt,F,O2}}{V_F}\frac{dC^{F}_{cyt,F,O2}}{dt}=J^{p}_{bl\leftrightarrow cyt,F,O2}-J^{p}_{cyt\leftrightarrow mit,F,O2}$

C9. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Gly}}{dt}=\phi_{cyt,F,G6P\leftrightarrow Gly}-\phi_{cyt,F,Gly\leftrightarrow G6P}$

C10. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,G6P}}{dt}=\phi_{cyt,F,Glc\leftrightarrow G6P}-\phi_{cyt,F,G6P\leftrightarrow Gly}+\phi_{cyt,F,Gly\leftrightarrow G6P}-\phi_{cyt,F,G6P\leftrightarrow F6P}$

C11. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,F6P}}{dt}=\phi_{cyt,F,G6P\leftrightarrow F6P}-\phi_{cyt,F,F6P\leftrightarrow F16BP}$

C12. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,F16BP}}{dt}=\phi_{cyt,F,F6P\leftrightarrow F16BP}-\phi_{cyt,F,F16BP\leftrightarrow GA3P}$

C13. $\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,GA3P}}{dt}=2\phi_{cyt,F,F16BP\leftrightarrow GA3P}-\phi_{cyt,F,GA3P\leftrightarrow Gr3P}-\phi_{cyt,F,GA3P\leftrightarrow 13BPG}$

C14. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,13BPG}}{dt}=\phi_{cyt,F,GA3P\leftrightarrow 13BPG}-\phi_{cyt,F,13BPG\leftrightarrow PEP}$$

C15. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,PEP}}{dt}=\phi_{cyt,F,13BPG\leftrightarrow PEP}-\phi_{cyt,F,PEP\leftrightarrow Pyr}$$

C16. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Tgl}}{dt}=\phi_{cyt,F,Gr3P\leftrightarrow Tgl}-\phi_{cyt,F,Tgl\leftrightarrow Glr}$$

C17. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Gr3P}}{dt}=\phi_{cyt,F,GA3P\leftrightarrow Gr3P}-\phi_{cyt,F,Gr3P\leftrightarrow Tgl}$$

C18. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,FAC}}{dt}=-J^{f}_{cyt\leftrightarrow mit,F,FAC}+\phi_{cyt,F,FFA\leftrightarrow FAC}-3\phi_{cyt,F,Gr3P\leftrightarrow Tgl}$$

C19. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,PCr}}{dt}=-\phi_{cyt,F,PCr\leftrightarrow Cr}=-V_{cyt,F}\frac{dC_{cyt,F,Cr}}{dt}$$

C20.

$$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,ATP}}{dt}=\begin{pmatrix}-J^{f}_{cyt\leftrightarrow mit,F,ATP/ADP}-\phi_{cyt,F,G6P\leftrightarrow Gly}-\phi_{cyt,F,Glc\leftrightarrow G6P}-\\ \phi_{cyt,F,F6P\leftrightarrow F16BP}+\phi_{cyt,F,13BPG\leftrightarrow PEP}+\phi_{cyt,F,PEP\leftrightarrow Pyr}-\\ 2\phi_{cyt,F,FFA\leftrightarrow FAC}-\phi_{cyt,F,ATP\leftrightarrow ADP}+\phi_{cyt,F,PCr\leftrightarrow Cr}-\phi_{cyt,F,AMP\leftrightarrow ADP}\end{pmatrix}=-\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,ADP}}{dt}$$

C21. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,\mathrm{AMP}}}{dt}=-\phi_{cyt,F,\mathrm{AMP}\leftrightarrow\mathrm{ADP}}$$

C22. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,Pi}}{dt}=-J^{f}_{cyt\leftrightarrow mit,F,Pi}-\phi_{cyt,F,Gly\leftrightarrow G6P}+2\phi_{cyt,F,G6P\leftrightarrow Gly}-\phi_{cyt,F,GA3P\leftrightarrow 13BPG}+\phi_{cyt,F,Gr3P\leftrightarrow Tgl}+$$
$$2\phi_{cyt,F,FFA\leftrightarrow FAC}+\phi_{cyt,F,ATP\leftrightarrow ADP}$$

C23. $$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,CoA}}{dt}=-J^{f}_{cyt\leftrightarrow mit,F,CoA}+3\phi_{cyt,F,Gr3P\leftrightarrow Tgl}-\phi_{cyt,F,FFA\leftrightarrow FAC}$$

C24.

$$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,NADH}}{dt}=-J^{f}_{cyt\leftrightarrow mit,F,NADH/NAD^+}+\phi_{cyt,F,GA3P\leftrightarrow 13BPG}-\phi_{cyt,F,Pyr\leftrightarrow Lac}-\phi_{cyt,F,GA3P\leftrightarrow Gr3P}=-V_{cyt,F}\frac{dC_{cyt,F,NAD^+}}{dt}$$

C25.

$$\frac{V_{cyt,F}}{V_F}\frac{dC_{cyt,F,H^+}}{dt}=\begin{pmatrix} J^f_{bl\leftrightarrow cyt,F,H^+} \\ -J^f_{cyt\leftrightarrow mit,F,H^+} \end{pmatrix}+\frac{2.303}{\beta_{cyt}}C_{cyt,F,H^+}\begin{pmatrix} \phi_{cyt,F,Glc\leftrightarrow G6P}+\phi_{cyt,F,F6P\leftrightarrow F16BP}+\phi_{cyt,F,GA3P\leftrightarrow 13BPG} \\ -\phi_{cyt,F,PEP\leftrightarrow Pyr}-\phi_{cyt,F,Pyr\leftrightarrow Lac}+3\phi_{cyt,F,Tgl\leftrightarrow Glr}-\phi_{cyt,F,GA3P\leftrightarrow Gr3P} \\ +2\phi_{cyt,F,FFA\leftrightarrow FAC}+\phi_{cyt,F,ATP\leftrightarrow ADP}-\phi_{cyt,F,PCr\leftrightarrow Cr}-J^{\text{leak}}_{cyt\leftrightarrow mit,F,H^+} \end{pmatrix}$$

where β_{cyt} is buffering capacity of cytosol for protons

Tissue Cells Mitochondrial Domain:

M1. $$\frac{V_{mit,F,O2}}{V_F}\frac{dC^F_{mit,F,O2}}{dt}=J^p_{cyt\leftrightarrow mit,F,O2}-0.5\phi_{mit,F,O2\leftrightarrow H2O,NADH}-0.5\phi_{mit,F,O2\leftrightarrow H2O,FADH2}$$

M2. $$\frac{V_{mit,F,CO2}}{V_F}\frac{dC^F_{mit,F,CO2}}{dt}=J^p_{cyt\leftrightarrow mit,F,CO2}+\left(\phi_{mit,F,Pyr\leftrightarrow ACoA}+\phi_{mit,F,Cit\leftrightarrow AKG}+\phi_{mit,F,AKG\leftrightarrow SCoA}\right)$$

M3. $$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,Pyr}}{dt}=J^f_{cyt\leftrightarrow mit,F,Pyr}-\phi_{mit,F,Pyr\leftrightarrow ACoA}$$

M4. $$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,FAC}}{dt}=J^f_{cyt\leftrightarrow mit,F,FAC}-\phi_{mit,F,FAC\leftrightarrow ACoA}$$

M5.

$$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,NADH}}{dt}=\begin{pmatrix} J^f_{cyt\leftrightarrow mit,F,NADH/NAD^+}+\phi_{mit,F,Pyr\leftrightarrow ACoA}+7\phi_{mit,F,FAC\leftrightarrow ACoA} \\ +\phi_{mit,F,Cit\leftrightarrow AKG}+\phi_{mit,F,AKG\leftrightarrow SCoA}+\phi_{mit,F,Mal\leftrightarrow Oxa}- \\ \phi_{mit,F,O2\leftrightarrow H2O,NADH} \end{pmatrix}=-\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,NAD^+}}{dt}$$

M6. $$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,ATP}}{dt}=-J^f_{cyt\leftrightarrow mit,F,ATP/ADP}+\phi_{mit,F,SCoA\leftrightarrow Suc}+\phi_{mit,F,ADP\leftrightarrow ATP}=-V_{mit,F}\frac{dC_{mit,F,ADP}}{dt}$$

M7. $$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,Pi}}{dt}=J^f_{cit\leftrightarrow mit,F,Pi}-\phi_{mit,F,SCoA\leftrightarrow Suc}-\phi_{mit,F,ADP\leftrightarrow ATP}$$

M8.

$$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,CoA}}{dt}=J^f_{cyt\leftrightarrow mit,F,CoA}-\phi_{mit,F,Pyr\leftrightarrow ACoA}-7\phi_{mit,F,FAC\leftrightarrow ACoA}+\phi_{mit,F,ACoA\leftrightarrow Cit}-\phi_{mit,F,AKG\leftrightarrow SCoA}+\phi_{mit,F,SCoA\leftrightarrow Suc}$$

M9. $$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,ACoA}}{dt}=\phi_{mit,F,Pyr\leftrightarrow ACoA}+8\phi_{mit,F,FAC\leftrightarrow ACoA}-\phi_{mit,F,ACoA\leftrightarrow Cit}$$

M10. $$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,Cit}}{dt}=\phi_{mit,F,ACoA\leftrightarrow Cit}-\phi_{mit,F,Cit\leftrightarrow AKG}$$

M11. $\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,AKG}}{dt}=\phi_{mit,F,Cit\leftrightarrow AKG}-\phi_{mit,F,AKG\leftrightarrow SCoA}$

M12. $\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,SCoA}}{dt}=\phi_{mit,F,AKG\leftrightarrow SCoA}-\phi_{mit,F,SCoA\leftrightarrow Suc}$

M13. $\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,Suc}}{dt}=\phi_{mit,F,SCoA\leftrightarrow Suc}-\phi_{mit,F,Suc\leftrightarrow Mal}$

M14. $\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,Mal}}{dt}=\phi_{mit,F,Suc\leftrightarrow Mal}-\phi_{mit,F,Mal\leftrightarrow Oxa}$

M15.

$$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,OAA}}{dt}=\phi_{mit,Mal\leftrightarrow OAA}-\phi_{mit,ACoA\leftrightarrow Cit}=-\frac{V_{mit,F}}{V_F}\frac{d}{dt}\left[C_{mit,Cit}+C_{mit,AKG}+C_{mit,SCoA}+C_{mit,Suc}+C_{mit,Mal}\right]$$

M16. $\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,FADH2}}{dt}=7\phi_{mit,F,FAC\leftrightarrow ACoA}+\phi_{mit,F,Suc\leftrightarrow Mal}-\phi_{mit,F,O2\to H2O,FADH2}=-\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,FAD}}{dt}$

M17.

$$\frac{V_{mit,F}}{V_F}\frac{dC_{mit,F,H^+}}{dt}=J^{f}_{cyt\leftrightarrow mit,F,H^+}+\frac{2.303}{\beta_{mit}}C_{mit,F,H^+}\begin{pmatrix}J^{\text{leak}}_{cyt\leftrightarrow mit,F,H^+}+\phi_{mit,F,Pyr\leftrightarrow ACoA}+7\phi_{mit,F,FAC\leftrightarrow ACoA}+\phi_{mit,F,ACoA\leftrightarrow Cit}\\+\phi_{mit,F,Mal\leftrightarrow Oxa}-(10+1)\phi_{mit,F,O2\to H2O,NADH}-6\phi_{mit,F,O2\to H2O,FADH2}\\+(3-1)\phi_{mit,F,ADP\leftrightarrow ATP}\end{pmatrix}$$

where β_{mit} is buffering capacity of mitochondria for protons

$$C_{\text{IMM}}\frac{d\Delta\Psi_F}{dt}=10\phi_{mit,F,O2\to H2O,NADH}+6\phi_{mit,F,O2\to H2O,FADH2}-3\phi_{mit,F,ADP\leftrightarrow ATP}-J^{\text{leak}}_{cyt\leftrightarrow mit,F,H^+}$$

M18. where C_{IMM} is the capacitance of the IMM

Part C: Metabolic Reaction Fluxes

Reactions in Cytosol

1. *Glycogen Phosphorylase*

$$\mathrm{Gly}_{n+1} + \mathrm{Pi} \leftrightarrow \mathrm{Gly}_n + \mathrm{G6P}$$

$$\phi_{\mathrm{cyt,F,Gly\leftrightarrow G6P}} = \left[\frac{\dfrac{C_{\mathrm{cyt,F,AMP}}}{C_{\mathrm{cyt,F,ATP}}}}{K^{\mathrm{Ctrl}}_{\mathrm{Gly\leftrightarrow G6P}} + \dfrac{C_{\mathrm{cyt,F,AMP}}}{C_{\mathrm{cyt,F,ATP}}}}\right]\left[\frac{V_{\mathrm{F,Gly\to G6P}}\dfrac{C_{\mathrm{cyt,F,Gly}_{n+1}}C_{\mathrm{cyt,F,Pi}}}{K_{\mathrm{Gly\to G6P}}} - V_{\mathrm{F,Gly\leftarrow G6P}}\dfrac{C_{\mathrm{cyt,F,Gly}_n}C_{\mathrm{cyt,F,G6P}}}{K_{\mathrm{Gly\leftarrow G6P}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Gly}_{n+1}}C_{\mathrm{cyt,F,Pi}}}{K_{\mathrm{Gly\to G6P}}} + \dfrac{C_{\mathrm{cyt,F,Gly}_n}C_{\mathrm{cyt,F,G6P}}}{K_{\mathrm{Gly\leftarrow G6P}}}}\right]$$

2. *Glycogen Synthase*

$$\mathrm{Gly}_n + \mathrm{G6P} + \mathrm{ATP} \leftrightarrow \mathrm{Gly}_{n+1} + \mathrm{ADP} + 2\ \mathrm{Pi}$$

$$\phi_{\mathrm{cyt,F,G6P\leftrightarrow Gly}} = \left[\frac{V_{\mathrm{F,G6P\to Gly}}\dfrac{C_{\mathrm{cyt,F,Gly}_n}C_{\mathrm{cyt,F,G6P}}C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{G6P\to Gly}}} - V_{\mathrm{F,G6P\leftarrow Gly}}\dfrac{C_{\mathrm{cyt,F,Gly}_{n+1}}C^2_{\mathrm{cyt,F,Pi}}C_{\mathrm{cyt,F,ADP}}}{K_{\mathrm{G6P\leftarrow Gly}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Gly}_n}C_{\mathrm{cyt,F,G6P}}C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{G6P\to Gly}}} + \dfrac{C_{\mathrm{cyt,F,Gly}_{n+1}}C^2_{\mathrm{cyt,F,Pi}}C_{\mathrm{cyt,F,ADP}}}{K_{\mathrm{G6P\leftarrow Gly}}}}\right].$$

3. *Hexokinase*

$$\mathrm{Glc} + \mathrm{ATP} \leftrightarrow \mathrm{G6P} + \mathrm{ADP} + \mathrm{H}^+$$

$$\phi_{\mathrm{cyt,F,Glc\leftrightarrow G6P}} = \left[\frac{K^{\mathrm{Ctrl}}_{\mathrm{cyt,F,Glc\leftrightarrow G6P}}}{K^{\mathrm{Ctrl}}_{\mathrm{Glc\leftrightarrow G6P}} + C_{\mathrm{cyt,F,G6P}}}\right]\left[\frac{V_{\mathrm{F,Glc\to G6P}}\dfrac{C_{\mathrm{cyt,F,Glc}}C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{Glc\to G6P}}} - V_{\mathrm{F,Glc\leftarrow G6P}}\dfrac{C_{\mathrm{cyt,F,G6P}}C_{\mathrm{cyt,F,ADP}}C_{\mathrm{cyt,F,H^+}}}{K_{\mathrm{Glc\leftarrow G6P}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Glc}}C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{Glc\to G6P}}} + \dfrac{C_{\mathrm{cyt,F,G6P}}C_{\mathrm{cyt,F,ADP}}C_{\mathrm{cyt,F,H^+}}}{K_{\mathrm{Glc\leftarrow G6P}}}}\right]$$

4. *Phosphoglucose Isomerase*

$$\mathrm{G6P} \leftrightarrow \mathrm{F6P}$$

$$\phi_{\mathrm{cyt,F,G6P\leftrightarrow F6P}} = \left[\frac{V_{\mathrm{F,G6P\to F6P}}\dfrac{C_{\mathrm{cyt,F,G6P}}}{K_{\mathrm{G6P\to F6P}}} - V_{\mathrm{G6P\leftarrow F6P}}\dfrac{C_{\mathrm{cyt,F,F6P}}}{K_{\mathrm{G6P\leftarrow F6P}}}}{1 + \dfrac{C_{\mathrm{cyt,F,G6P}}}{K_{\mathrm{G6P\to F6P}}} + \dfrac{C_{\mathrm{cyt,F,F6P}}}{K_{\mathrm{G6P\leftarrow F6P}}}}\right]$$

5. *Phosphofructokinase*

$$\mathrm{F6P} + \mathrm{ATP} \leftrightarrow \mathrm{F16BP} + \mathrm{ADP} + \mathrm{H}^+$$

$$\phi_{\mathrm{cyt,F,F6P\leftrightarrow F16BP}} = \left[\frac{C_{\mathrm{cyt,F,AMP}}}{K^{\mathrm{Ctrl}}_{\mathrm{F6P\leftrightarrow F16BP}} + C_{\mathrm{cyt,F,AMP}}}\right]\left[\frac{V_{\mathrm{F,F6P\to F16BP}}\dfrac{C_{\mathrm{cyt,F,F6P}}C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{F6P\to F16BP}}} - V_{\mathrm{F,F6P\leftarrow F16BP}}\dfrac{C_{\mathrm{cyt,F,F16BP}}C_{\mathrm{cyt,F,ADP}}C_{\mathrm{cyt,F,H^+}}}{K_{\mathrm{F6P\leftarrow F16BP}}}}{1 + \dfrac{C_{\mathrm{cyt,F,F6P}}C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{F6P\to F16BP}}} + \dfrac{C_{\mathrm{cyt,F,F16BP}}C_{\mathrm{cyt,F,ADP}}C_{\mathrm{cyt,F,H^+}}}{K_{\mathrm{F6P\leftarrow F16BP}}}}\right]$$

6. *Glyceraldehyde 3-Phosphate Formation*

$$\mathrm{F16BP} \leftrightarrow 2\ \mathrm{GA3P}$$

$$\phi_{\mathrm{cyt,F,F16BP\leftrightarrow GA3P}} = \left[\frac{V_{\mathrm{F,F16BP\to GA3P}}\dfrac{C_{\mathrm{cyt,F,F16BP}}}{K_{\mathrm{F16BP\to GA3P}}} - V_{\mathrm{F,F16BP\leftarrow GA3P}}\dfrac{C^2_{\mathrm{cyt,F,GA3P}}}{K_{\mathrm{F16BP\leftarrow GA3P}}}}{1 + \dfrac{C_{\mathrm{cyt,F,F16BP}}}{K_{\mathrm{F16BP\to GA3P}}} + \dfrac{C^2_{\mathrm{cyt,F,GA3P}}}{K_{\mathrm{F16BP\leftarrow GA3P}}}}\right]$$

7. *Glyceraldehyde 3-Phosphate Dehydrogenase* $\mathrm{GA3P + Pi + NAD^{+} \leftrightarrow 13BPG + NADH + H^{+}}$

$$\phi_{\mathrm{cyt,F,GA3P\leftrightarrow 13BPG}} = \left[\frac{V_{\mathrm{F,GA3P\to 13BPG}} \dfrac{C_{\mathrm{cyt,F,GA3P}} C_{\mathrm{cyt,F,Pi}} C_{\mathrm{cyt,F,NAD^{+}}}}{K_{\mathrm{GA3P\to 13BPG}}} - V_{\mathrm{F,GA3P\leftarrow 13BPG}} \dfrac{C_{\mathrm{cyt,F,13BPG}} C_{\mathrm{cyt,F,NADH}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{GA3P\leftarrow 13BPG}}}}{1 + \dfrac{C_{\mathrm{cyt,F,GA3P}} C_{\mathrm{cyt,F,Pi}} C_{\mathrm{cyt,F,NAD^{+}}}}{K_{\mathrm{GA3P\to 13BPG}}} + \dfrac{C_{\mathrm{cyt,F,13BPG}} C_{\mathrm{cyt,F,NADH}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{GA3P\leftarrow 13BPG}}}} \right]$$

8. *Phosphoglycerate Kinase* $\mathrm{13BPG + ADP \leftrightarrow PEP + ATP}$

$$\phi_{\mathrm{cyt,F,13BPG\leftrightarrow PEP}} = \left[\frac{V_{\mathrm{F,13BPG\to PEP}} \dfrac{C_{\mathrm{cyt,F,13BPG}} C_{\mathrm{cyt,F,ADP}}}{K_{\mathrm{13BPG\to PEP}}} - V_{\mathrm{F,13BPG\leftarrow PEP}} \dfrac{C_{\mathrm{cyt,F,PEP}} C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{13BPG\leftarrow PEP}}}}{1 + \dfrac{C_{\mathrm{cyt,F,13BPG}} C_{\mathrm{cyt,F,ADP}}}{K_{\mathrm{13BPG\to PEP}}} + \dfrac{C_{\mathrm{cyt,F,PEP}} C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{13BPG\leftarrow PEP}}}} \right]$$

9. *Pyruvate Kinase* $\mathrm{PEP + ADP + H^{+} \leftrightarrow Pyr + ATP}$

$$\phi_{\mathrm{cyt,F,PEP\leftrightarrow Pyr}} = \left[\frac{C_{\mathrm{cyt,F,F16BP}}}{K^{\mathrm{Ctrl}}_{\mathrm{PEP\leftrightarrow PYR}} + C_{\mathrm{cyt,F,F16BP}}} \right] \left[\frac{V_{\mathrm{F,PEP\to Pyr}} \dfrac{C_{\mathrm{cyt,F,PEP}} C_{\mathrm{cyt,F,ADP}} C_{\mathrm{cyt,F,H+}}}{K_{\mathrm{PEP\to Pyr}}} - V_{\mathrm{F,PEP\leftarrow Pyr}} \dfrac{C_{\mathrm{cyt,F,Pyr}} C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{PEP\leftarrow Pyr}}}}{1 + \dfrac{C_{\mathrm{cyt,F,PEP}} C_{\mathrm{cyt,F,ADP}} C_{\mathrm{cyt,F,H+}}}{K_{\mathrm{PEP\to Pyr}}} + \dfrac{C_{\mathrm{cyt,F,Pyr}} C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{PEP\leftarrow Pyr}}}} \right]$$

10. *Lactate Dehydrogenase* $\mathrm{Pyr + NADH + H^{+} \leftrightarrow Lac + NAD^{+}}$

$$\phi_{\mathrm{cyt,F,Pyr\leftrightarrow Lac}} = \left[\frac{V_{\mathrm{F,Pyr\to Lac}} \dfrac{C_{\mathrm{cyt,F,Pyr}} C_{\mathrm{cyt,F,NADH}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{Pyr\to Lac}}} - V_{\mathrm{F,Pyr\leftarrow Lac}} \dfrac{C_{\mathrm{cyt,F,Lac}} C_{\mathrm{cyt,F,NAD^{+}}}}{K_{\mathrm{Pyr\leftarrow Lac}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Pyr}} C_{\mathrm{cyt,F,NADH}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{Pyr\to Lac}}} + \dfrac{C_{\mathrm{cyt,F,Lac}} C_{\mathrm{cyt,F,NAD^{+}}}}{K_{\mathrm{Pyr\leftarrow Lac}}}} \right]$$

11. *Alanine Formation (Alanine Aminotransferase)* $\mathrm{Pyr \leftrightarrow Ala}$

$$\phi_{\mathrm{cyt,F,Pyr\leftrightarrow Ala}} = \left[\frac{V_{\mathrm{F,Pyr\to Ala}} \dfrac{C_{\mathrm{cyt,F,Pyr}}}{K_{\mathrm{Pyr\to Ala}}} - V_{\mathrm{F,Pyr\leftarrow Ala}} \dfrac{C_{\mathrm{cyt,F,Ala}}}{K_{\mathrm{Pyr\leftarrow Ala}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Pyr}}}{K_{\mathrm{Pyr\to Ala}}} + \dfrac{C_{\mathrm{cyt,F,Ala}}}{K_{\mathrm{Pyr\leftarrow Ala}}}} \right]$$

12. *Lipases (Triglycerides Hydrolysis)*

$$\mathrm{Tgl} \leftrightarrow \mathrm{Glr} + 3\ \mathrm{FFA} + 3\ \mathrm{H}^{+}$$

$$\phi_{\mathrm{cyt,F,Tgl\leftrightarrow Glr}} = \left[\frac{V_{\mathrm{F,Tgl\rightarrow Glr}} \dfrac{C_{\mathrm{cyt,F,Tgl}}}{K_{\mathrm{Tgl\rightarrow Glr}}} - V_{\mathrm{F,Tgl\leftarrow Glr}} \dfrac{C_{\mathrm{cyt,F,Glr}} C^{3}_{\mathrm{cyt,F,FFA}} C^{3}_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{Tgl\leftarrow Glr}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Tgl}}}{K_{\mathrm{Tgl\rightarrow Glr}}} + \dfrac{C_{\mathrm{cyt,F,Glr}} C^{3}_{\mathrm{cyt,F,FFA}} C^{3}_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{Tgl\leftarrow Glr}}}} \right]$$

13. *Glycerol 3-Phosphate Dehydrogenase*

$$\mathrm{GA3P} + \mathrm{NADH} + \mathrm{H}^{+} \leftrightarrow \mathrm{Gr3P} + \mathrm{NAD}^{+}$$

$$\phi_{\mathrm{cyt,F,GA3P\leftrightarrow Gr3P}} = \left[\frac{V_{\mathrm{F,GA3P\rightarrow Gr3P}} \dfrac{C_{\mathrm{cyt,F,GA3P}} C_{\mathrm{cyt,F,NADH}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{GA3P\rightarrow Gr3P}}} - V_{\mathrm{F,GA3P\leftarrow Gr3P}} \dfrac{C_{\mathrm{cyt,F,Gr3P}} C_{\mathrm{cyt,F,NAD^{+}}}}{K_{\mathrm{GA3P\leftarrow Gr3P}}}}{1 + \dfrac{C_{\mathrm{cyt,F,GA3P}} C_{\mathrm{cyt,F,NADH}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{GA3P\rightarrow Gr3P}}} + \dfrac{C_{\mathrm{cyt,F,Gr3P}} C_{\mathrm{cyt,F,NAD^{+}}}}{K_{\mathrm{GA3P\leftarrow Gr3P}}}} \right]$$

14. *Acyltransferase (Triglyceride Synthesis)*

$$\mathrm{Gr3P} + 3\ \mathrm{FAC} \leftrightarrow \mathrm{Tgl} + 3\ \mathrm{CoA} + \mathrm{Pi}$$

$$\phi_{\mathrm{cyt,F,Gr3P\leftrightarrow Tgl}} = \left[\frac{V_{\mathrm{F,Gr3P\rightarrow Tgl}} \dfrac{C_{\mathrm{cyt,F,Gr3P}} C^{3}_{\mathrm{cyt,F,FAC}}}{K_{\mathrm{Gr3P\rightarrow Tgl}}} - V_{\mathrm{F,Gr3P\leftarrow Tgl}} \dfrac{C_{\mathrm{cyt,F,Tgl}} C^{3}_{\mathrm{cyt,F,CoA}} C_{\mathrm{cyt,F,Pi}}}{K_{\mathrm{Gr3P\leftarrow Tgl}}}}{1 + \dfrac{C_{\mathrm{cyt,F,Gr3P}} C^{3}_{\mathrm{cyt,F,FAC}}}{K_{\mathrm{Gr3P\rightarrow Tgl}}} + \dfrac{C_{\mathrm{cyt,F,Tgl}} C^{3}_{\mathrm{cyt,F,CoA}} C_{\mathrm{cyt,F,Pi}}}{K_{\mathrm{Gr3P\leftarrow Tgl}}}} \right]$$

15. *Acyl-CoA Synthetase*

$$\mathrm{FFA} + \mathrm{CoA} + 2\ \mathrm{ATP} \leftrightarrow \mathrm{FAC} + 2\ \mathrm{ADP} + 2\ \mathrm{Pi} + 2\ \mathrm{H}^{+}$$

$$\phi_{\mathrm{cyt,F,FFA\leftrightarrow FAC}} = \left[\frac{V_{\mathrm{F,FFA\rightarrow FAC}} \dfrac{C_{\mathrm{cyt,F,FFA}} C_{\mathrm{cyt,F,CoA}} C^{2}_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{FFA\rightarrow FAC}}} - V_{\mathrm{F,FFA\leftarrow FAC}} \dfrac{C_{\mathrm{cyt,F,FAC}} C^{2}_{\mathrm{cyt,F,ADP}} C^{2}_{\mathrm{cyt,F,Pi}} C^{2}_{\mathrm{cyt,F,H+}}}{K_{\mathrm{FFA\leftarrow FAC}}}}{1 + \dfrac{C_{\mathrm{cyt,F,FFA}} C_{\mathrm{cyt,F,CoA}} C^{2}_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{FFA\rightarrow FAC}}} + \dfrac{C_{\mathrm{cyt,F,FAC}} C^{2}_{\mathrm{cyt,F,ADP}} C^{2}_{\mathrm{cyt,F,Pi}} C^{2}_{\mathrm{cyt,F,H+}}}{K_{\mathrm{FFA\leftarrow FAC}}}} \right]$$

16. *ATPase (ATP Hydrolysis)*

$$\mathrm{ATP} \leftrightarrow \mathrm{ADP} + \mathrm{Pi} + \mathrm{H}^{+}$$

$$\phi_{\mathrm{cyt,F,ATP\leftrightarrow ADP}} = \left[\frac{V_{\mathrm{F,ATP\rightarrow ADP}} \dfrac{C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{ATP\rightarrow ADP}}} - V_{\mathrm{F,ATP\leftarrow ADP}} \dfrac{C_{\mathrm{cyt,F,ADP}} C_{\mathrm{cyt,F,Pi}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{ATP\leftarrow ADP}}}}{1 + \dfrac{C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{ATP\rightarrow ADP}}} + \dfrac{C_{\mathrm{cyt,F,ADP}} C_{\mathrm{cyt,F,Pi}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{ATP\leftarrow ADP}}}} \right]$$

17. *Creatine Kinase*

$$\mathrm{PCr} + \mathrm{ADP} + \mathrm{H}^{+} \leftrightarrow \mathrm{Cr} + \mathrm{ATP}$$

$$\phi_{\mathrm{cyt,F,PCr\leftrightarrow Cr}} = \left[\frac{V_{\mathrm{F,PCr\rightarrow Cr}} \dfrac{C_{\mathrm{cyt,F,PCr}} C_{\mathrm{cyt,F,ADP}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{PCr\rightarrow Cr}}} - V_{\mathrm{F,PCr\leftarrow Cr}} \dfrac{C_{\mathrm{cyt,F,Cr}} C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{PCr\leftarrow Cr}}}}{1 + \dfrac{C_{\mathrm{cyt,F,PCr}} C_{\mathrm{cyt,F,ADP}} C_{\mathrm{cyt,F,H^{+}}}}{K_{\mathrm{PCr\rightarrow Cr}}} + \dfrac{C_{\mathrm{cyt,F,Cr}} C_{\mathrm{cyt,F,ATP}}}{K_{\mathrm{PCr\leftarrow Cr}}}} \right]$$

18. *Adenylate Kinase* $\mathrm{ATP + AMP \leftrightarrow 2\ ADP}$

$$\phi_{\mathrm{cyt,F,AMP\leftrightarrow ADP}} = \left[\frac{V_{\mathrm{F,AMP\to ADP}} \dfrac{C_{\mathrm{cyt,F,ATP}} C_{\mathrm{cyt,F,AMP}}}{K_{\mathrm{AMP\to ADP}}} - V_{\mathrm{F,AMP\leftarrow ADP}} \dfrac{C^2_{\mathrm{cyt,F,ADP}}}{K_{\mathrm{AMP\leftarrow ADP}}}}{1 + \dfrac{C_{\mathrm{cyt,F,ATP}} C_{\mathrm{cyt,F,AMP}}}{K_{\mathrm{AMP\to ADP}}} + \dfrac{C^2_{\mathrm{cyt,F,ADP}}}{K_{\mathrm{AMP\leftarrow ADP}}}} \right]$$

Reactions in Mitochondria

19. *Pyruvate Dehydrogenase* $\mathrm{Pyr + CoA + NAD^+ \leftrightarrow ACoA + CO_2 + NADH + H^+}$

$$\phi_{\mathrm{mit,F,Pyr\leftrightarrow ACoA}} = \left[\frac{\dfrac{C_{\mathrm{mit,F,ADP}}}{C_{\mathrm{mit,F,ATP}}}}{K^{\mathrm{Ctrl}}_{\mathrm{Pyr\leftrightarrow ACoA}} + \dfrac{C_{\mathrm{mit,F,ADP}}}{C_{\mathrm{mit,F,ATP}}}} \right] \times \left[\frac{V_{\mathrm{F,Pyr\to ACoA}} \dfrac{C_{\mathrm{mit,F,Pyr}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,NAD^+}}}{K_{\mathrm{Pyr\to ACoA}}} - V_{\mathrm{F,Pyr\leftarrow ACoA}} \dfrac{C_{\mathrm{mit,F,ACoA}} C_{\mathrm{mit,F,CO_2}} C_{\mathrm{mit,F,NADH}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{Pyr\leftarrow ACoA}}}}{1 + \dfrac{C_{\mathrm{mit,F,Pyr}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,NAD^+}}}{K_{\mathrm{Pyr\to ACoA}}} + \dfrac{C_{\mathrm{mit,F,ACoA}} C_{\mathrm{mit,F,CO_2}} C_{\mathrm{mit,F,NADH}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{Pyr\leftarrow ACoA}}}} \right]$$

20. *Fatty Acyl-CoA Oxidation*
(β-Oxidation)

$\mathrm{FAC + 7\ CoA + 7\ NAD^+ + 7\ FAD \leftrightarrow}$
$\mathrm{8\ ACoA + 7\ NADH + 7\ FADH_2 + 7\ H^+}$

$$\phi_{\mathrm{mit,F,FAC\leftrightarrow ACoA}} = \left[\frac{V_{\mathrm{F,FAC\to ACoA}} \dfrac{C_{\mathrm{mit,F,FAC}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,NAD^+}} C_{\mathrm{mit,F,FAD}}}{K_{\mathrm{FAC\to ACoA}}} - V_{\mathrm{F,FAC\leftarrow ACoA}} \dfrac{C_{\mathrm{mit,F,ACoA}} C_{\mathrm{mit,F,NADH}} C_{\mathrm{mit,F,FADH_2}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{FAC\leftarrow ACoA}}}}{1 + \dfrac{C_{\mathrm{mit,F,FAC}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,NAD^+}} C_{\mathrm{mit,F,FAD}}}{K_{\mathrm{FAC\to ACoA}}} + \dfrac{C_{\mathrm{mit,F,ACoA}} C_{\mathrm{mit,F,NADH}} C_{\mathrm{mit,F,FADH_2}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{FAC\leftarrow ACoA}}}} \right]$$

21. *Citrate Synthase* $\mathrm{ACoA + Oxa \leftrightarrow Cit + CoA + H^+}$

$$\phi_{\mathrm{mit,F,ACoA\leftrightarrow Cit}} = \left[\frac{\dfrac{C_{\mathrm{mit,F,ADP}}}{C_{\mathrm{mit,F,ATP}}}}{K^{\mathrm{Ctrl}}_{\mathrm{ACoA\leftrightarrow Cit}} + \dfrac{C_{\mathrm{mit,F,ADP}}}{C_{\mathrm{mit,F,ATP}}}} \right] \left[\frac{V_{\mathrm{F,ACoA\to Cit}} \dfrac{C_{\mathrm{mit,F,ACoA}} C_{\mathrm{mit,F,Oxa}}}{K_{\mathrm{ACoA\to Cit}}} - V_{\mathrm{F,ACoA\leftarrow Cit}} \dfrac{C_{\mathrm{mit,F,Cit}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{ACoA\leftarrow Cit}}}}{1 + \dfrac{C_{\mathrm{mit,F,ACoA}} C_{\mathrm{mit,F,Oxa}}}{K_{\mathrm{ACoA\to Cit}}} + \dfrac{C_{\mathrm{mit,F,Cit}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{ACoA\leftarrow Cit}}}} \right]$$

22. *Aconitase + Isocitrate Dehydrogenase* $\mathrm{Cit + NAD^+ \leftrightarrow AKG + CO_2 + NADH}$

$$\phi_{\mathrm{mit,F,Cit\leftrightarrow AKG}} = \left[\frac{\dfrac{C_{\mathrm{mit,F,ADP}}}{C_{\mathrm{mit,F,ATP}}}}{K^{\mathrm{Ctrl}}_{\mathrm{Cit\leftrightarrow AKG}} + \dfrac{C_{\mathrm{mit,F,ADP}}}{C_{\mathrm{mit,F,ATP}}}} \right] \left[\frac{V_{\mathrm{F,Cit\to AKG}} \dfrac{C_{\mathrm{mit,F,Cit}} C_{\mathrm{mit,F,NAD^+}}}{K_{\mathrm{Cit\to AKG}}} - V_{\mathrm{F,Cit\leftarrow AKG}} \dfrac{C_{\mathrm{mit,F,AKG}} C_{\mathrm{mit,F,CO_2}} C_{\mathrm{mit,F,NADH}}}{K_{\mathrm{Cit\leftarrow AKG}}}}{1 + \dfrac{C_{\mathrm{mit,F,Cit}} C_{\mathrm{mit,F,NAD^+}}}{K_{\mathrm{Cit\to AKG}}} + \dfrac{C_{\mathrm{mit,F,AKG}} C_{\mathrm{mit,F,CO_2}} C_{\mathrm{mit,F,NADH}}}{K_{\mathrm{Cit\leftarrow AKG}}}} \right]$$

23. *α-Ketoglutarate Dehydrogenase* $\mathrm{AKG + CoA + NAD^{+} \leftrightarrow SCoA + CO_2 + NADH}$

$$\phi_{\mathrm{mit,F,AKG\leftrightarrow SCoA}} = \left[\frac{V_{\mathrm{F,AKG\to SCoA}} \dfrac{C_{\mathrm{mit,F,AKG}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,NAD^{+}}}}{K_{\mathrm{AKG\to SCoA}}} - V_{\mathrm{F,AKG\leftarrow SCoA}} \dfrac{C_{\mathrm{mit,F,SCoA}} C_{\mathrm{mit,F,CO_2}} C_{\mathrm{mit,F,NADH}}}{K_{\mathrm{AKG\leftarrow SCoA}}}}{1 + \dfrac{C_{\mathrm{mit,F,AKG}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,NAD^{+}}}}{K_{\mathrm{AKG\to SCoA}}} + \dfrac{C_{\mathrm{mit,F,SCoA}} C_{\mathrm{mit,F,CO_2}} C_{\mathrm{mit,F,NADH}}}{K_{\mathrm{AKG\leftarrow SCoA}}}} \right]$$

24. *Succinyl-CoA Synthetase* $\mathrm{SCoA + GDP + Pi \leftrightarrow Suc + CoA + GTP}$

$$\phi_{\mathrm{mit,F,SCoA\leftrightarrow Suc}} = \left[\frac{V_{\mathrm{F,SCoA\to Suc}} \dfrac{C_{\mathrm{mit,F,SCoA}} C_{\mathrm{mit,F,ADP}} C_{\mathrm{mit,F,Pi}}}{K_{\mathrm{SCoA\to Suc}}} - V_{\mathrm{F,SCoA\leftarrow Suc}} \dfrac{C_{\mathrm{mit,F,Suc}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,ATP}}}{K_{\mathrm{SCoA\leftarrow Suc}}}}{1 + \dfrac{C_{\mathrm{mit,F,SCoA}} C_{\mathrm{mit,F,ADP}} C_{\mathrm{mit,F,Pi}}}{K_{\mathrm{SCoA\to Suc}}} + \dfrac{C_{\mathrm{mit,F,Suc}} C_{\mathrm{mit,F,CoA}} C_{\mathrm{mit,F,ATP}}}{K_{\mathrm{SCoA\leftarrow Suc}}}} \right]$$

25. *Succinate Dehydrogenase* $\mathrm{Suc + FAD \leftrightarrow Mal + FADH_2}$

$$\phi_{\mathrm{mit,F,Suc\leftrightarrow Mal}} = \left[\frac{V_{\mathrm{F,Suc\to Mal}} \dfrac{C_{\mathrm{mit,F,Suc}} C_{\mathrm{mit,F,FAD}}}{K_{\mathrm{Suc\to Mal}}} - V_{\mathrm{F,Suc\leftarrow Mal}} \dfrac{C_{\mathrm{mit,F,Mal}} C_{\mathrm{mit,F,FADH_2}}}{K_{\mathrm{Suc\leftarrow Mal}}}}{1 + \dfrac{C_{\mathrm{mit,F,Suc}} C_{\mathrm{mit,F,FAD}}}{K_{\mathrm{Suc\to Mal}}} + \dfrac{C_{\mathrm{mit,F,Mal}} C_{\mathrm{mit,F,FADH_2}}}{K_{\mathrm{Suc\leftarrow Mal}}}} \right]$$

26. *Malate Dehydrogenase* $\mathrm{Mal + NAD^{+} \leftrightarrow Oxa + NADH + H^{+}}$

$$\phi_{\mathrm{mit,F,Mal\leftrightarrow Oxa}} = \left[\frac{V_{\mathrm{F,Mal\to Oxa}} \dfrac{C_{\mathrm{mit,F,Mal}} C_{\mathrm{mit,F,NAD^{+}}}}{K_{\mathrm{Mal\to Oxa}}} - V_{\mathrm{Mal\leftarrow Oxa}} \dfrac{C_{\mathrm{mit,F,Oxa}} C_{\mathrm{mit,F,NADH}} C_{\mathrm{mit,F,H^{+}}}}{K_{\mathrm{Mal\leftarrow Oxa}}}}{1 + \dfrac{C_{\mathrm{mit,F,Mal}} C_{\mathrm{mit,F,NAD^{+}}}}{K_{\mathrm{Mal\to Oxa}}} + \dfrac{C_{\mathrm{mit,F,Oxa}} C_{\mathrm{mit,F,NADH}} C_{\mathrm{mit,F,H^{+}}}}{K_{\mathrm{Mal\leftarrow Oxa}}}} \right]$$

27. *Complex I+III+IV* $\mathrm{NADH + H^{+} + 0.5\ O_2 \leftrightarrow NAD^{+} + H_2O + 10\ \Delta H^{+}}$

$$\phi_{\mathrm{mit,F},O_2\leftrightarrow H_2O,NADH} = \left[\frac{\exp\left(-\dfrac{10\Delta G_{\mathrm{H+}}}{RT}\right) V_{F,O_2\to H_2O,NADH} \dfrac{C_{\mathrm{mit,F,NADH}} C^{0.5}_{\mathrm{mit,F,O_2}} C_{\mathrm{mit,F,H^{+}}}}{K_{O_2\to H_2O,NADH}} - V_{F,O_2\leftarrow H_2O,NADH} \dfrac{C_{\mathrm{mit,F,NAD^{+}}}}{K_{O_2\leftarrow H_2O,NADH}}}{1 + \dfrac{C_{\mathrm{mit,F,NADH}} C^{0.5}_{\mathrm{mit,F,O_2}} C_{\mathrm{mit,F,H^{+}}}}{K_{O_2\to H_2O,NADH}} + \dfrac{C_{\mathrm{mit,F,NAD^{+}}}}{K_{O_2\leftarrow H_2O,NADH}}} \right]$$

28. *Complex II+III+IV* $\mathrm{FADH_2} + 0.5\ \mathrm{O_2} \leftrightarrow \mathrm{FAD} + \mathrm{H_2O} + 6\ \Delta\mathrm{H^+}$

$$\phi_{\mathrm{mit,F},O_2 \leftrightarrow H_2O,FADH2} = \left[\frac{\exp\left(-\frac{6\Delta G_{\mathrm{H+}}}{RT}\right) V_{F,O_2 \rightarrow H_2O,FADH2} \frac{C_{\mathrm{mit,F,FADH_2}} C^{0.5}_{\mathrm{mit,F,O_2}}}{K_{O_2 \rightarrow H_2O,FADH2}} - V_{F,O_2 \leftarrow H_2O,FADH2} \frac{C_{\mathrm{mit,F,FAD}}}{K_{O_2 \leftarrow H_2O,FADH2}}}{1 + \frac{C_{\mathrm{FADH_2}} C^{0.5}_{\mathrm{O_2}}}{K_{O_2 \rightarrow H_2O,FADH2}} + \frac{C_{\mathrm{FAD}}}{K_{O_2 \leftarrow H_2O,FADH2}}} \right]$$

29. *ATP Synthesis (F_1F_0-ATPase or Complex V)* $\mathrm{ADP} + \mathrm{Pi} + \mathrm{H^+} + 3\Delta\mathrm{H^+} \leftrightarrow \mathrm{ATP}$

$$\phi_{\mathrm{mit,F,ADP \leftrightarrow ATP}} = \left[\frac{\exp\left(+\frac{3\Delta G_{\mathrm{H+}}}{RT}\right) V_{\mathrm{F,ADP \rightarrow ATP}} \frac{C_{\mathrm{mit,F,ADP}} C_{\mathrm{mit,F,Pi}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{ADP \rightarrow ATP}}} - V_{\mathrm{F,ADP \leftarrow ATP}} \frac{C_{\mathrm{mit,F,ATP}}}{K_{\mathrm{ADP \leftarrow ATP}}}}{1 + \frac{C_{\mathrm{mit,F,ADP}} C_{\mathrm{mit,F,Pi}} C_{\mathrm{mit,F,H^+}}}{K_{\mathrm{ADP \rightarrow ATP}}} + \frac{C_{\mathrm{mit,F,ATP}}}{K_{\mathrm{ADP \leftarrow ATP}}}} \right]$$

Appendix D: Transport Fluxes

Species transport between blood and tissue

Passive transport ($J \in (Glr, Ala, CO_2, O_2)$ $\quad F \in (R,W)$

$$J^{p}_{bl\leftrightarrow cyt,F,j} = \lambda_{F,j}(C_{bl,j} - C_{cyt,F,j}) \tag{D1}$$

Carrier-mediated transport $J \in (Glc, Pyr, Lac, FFA, H^{+})$ $F \in (R,W)$

$$J^{f}_{bl\leftrightarrow cyt,F,j} = T_{bl\leftrightarrow cyt,F,j}\left(\frac{C_{bl,j}}{M_{bl\leftrightarrow cyt,j} + C_{bl,F,j}} - \frac{C_{cyt,F,j}}{M_{bl\leftrightarrow cyt,j} + C_{cyt,F,j}}\right) \tag{D2}$$

Species transport between cytosol and mitochondria

Passive transport ($J \in (CO_2, O_2)$ $\quad F \in (R,W)$

$$J^{p}_{cyt\leftrightarrow mit,F,j} = \lambda_{F,j}(C_{cyt,F,j} - C_{mit,F,j}) \tag{D3}$$

Carrier-mediated transport $J \in (Pyr, FAC, Pi, CoA, H)$ $\quad F \in (R,W)$

$$J^{f}_{cyt\leftrightarrow mit,F,j} = T_{cyt\leftrightarrow mit,F,j}\left(\frac{C_{cyt,F,j}}{M_{cyt\leftrightarrow mit,j} + C_{cyt,F,j}} - \frac{C_{mit,F,j}}{M_{cyt\leftrightarrow mit,j} + C_{mit,F,j}}\right) \tag{D4}$$

For ATP-ADP and NADH –NAD, special transport equations are defined as

$$J^{f}_{cyt\leftrightarrow mit,NADH} = T_{cyt\leftrightarrow mit,RS}\left(\frac{RS_{cyt}}{M^{cyt}_{cyt\leftrightarrow mit,RS} + RS_{cyt}} - \frac{RS_{mit}}{M^{mit}_{cyt\leftrightarrow mit,RS} + RS_{mit}}\right) = -J^{f}_{cyt\leftrightarrow mit,NAD^{+}} \tag{D5}$$

$$J^{f}_{cyt\leftrightarrow mit,ATP} = T_{cyt\leftrightarrow mit,PS}\left(\frac{PS_{cyt}}{M^{cyt}_{cyt\leftrightarrow mit,PS} + PS_{cyt}} - \frac{PS_{mit}}{M^{mit}_{cyt\leftrightarrow mit,PS} + PS_{mit}}\right) = -J^{f}_{cyt\leftrightarrow mit,ADP} \tag{D6}$$

Here RS is redox state in each domain $RS_X = NADH_X / NAD^{+}$, PS is phosphorylation state $RS_X = ATP_X \,/\, ADP_X \quad X \in (cyt,\ mit)$.