

## **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	$J_{bl \leftrightarrow cyt, F, k}^0$ (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 <sub>2</sub>	-0.471	N/A	N/A	6.454	N/A	6.454
O <sub>2</sub>	0.605	N/A	N/A	39.58	N/A	39.582
H <sup>+</sup>	-1.81E-6	4.79E-5	1.46E-5	N/A	1.46E-5	N/A
Transport between cytosol and mitochondria						
Species k	$J_{cyt \leftrightarrow mit, F, k}^0$ (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 <sub>2</sub>	0.605	N/A	N/A	89.57	N/A	89.57
CO <sub>2</sub>	-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 <sup>+</sup>	6.86E-6	2.64E-5	2.51E-5	N/A	2.64E-5	N/A

A2: Table of parameters in reaction fluxes

Reaction	$V_{\max,R,S \leftrightarrow P}^f$	$V_{\max,W,S \leftrightarrow P}^f$	$K_{eq,S \leftrightarrow P}$	$K_{m,S \leftrightarrow P}^f$	$K_{m,S \leftrightarrow P}^b$	$K_m^{Ctrl}$
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***

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

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

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

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

$$B5. \quad V_{bl} \frac{dC_{bl,Glucose}}{dt} = Q(C_{art,Glucose} - C_{bl,Glucose}) - J_{bl \leftrightarrow cyt,R,Glucose}^p V_R - J_{bl \leftrightarrow cyt,W,Glucose}^p V_W$$

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

$$B7. \quad V_{bl,CO2} \frac{dC_{bl,CO2}^F}{dt} = Q(C_{art,CO2}^T - C_{bl,CO2}^T) - J_{bl \leftrightarrow cyt,R,CO2}^p V_R - J_{bl \leftrightarrow cyt,W,CO2}^p V_W$$

$$B8. \quad V_{bl,O2} \frac{dC_{bl,O2}^F}{dt} = Q(C_{art,O2}^T - C_{bl,O2}^T) - J_{bl \leftrightarrow cyt,R,O2}^p V_R - J_{bl \leftrightarrow cyt,W,O2}^p V_W$$

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

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

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

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

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

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

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

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

$$C7. \quad \frac{V_{cyt,F,CO_2}}{V_F} \frac{dC_{cyt,F,CO_2}^F}{dt} = J_{bl \leftrightarrow cyt,F,CO_2}^p - J_{cyt \leftrightarrow mit,F,CO_2}^p$$

$$C8. \quad \frac{V_{cyt,F,O_2}}{V_F} \frac{dC_{cyt,F,O_2}^F}{dt} = J_{bl \leftrightarrow cyt,F,O_2}^p - J_{cyt \leftrightarrow mit,F,O_2}^p$$

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

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

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

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

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

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

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

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

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

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

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

C20.

$$\frac{V_{\text{cyt},F}}{V_F} \frac{dC_{\text{cyt},F,ATP}}{dt} = \left( \begin{array}{l} -J_{\text{cyt} \leftrightarrow \text{mit},F,ATP/ADP}^f - \phi_{\text{cyt},F,G6P \leftrightarrow Gly} - \phi_{\text{cyt},F,Glc \leftrightarrow G6P} - \\ \phi_{\text{cyt},F,F6P \leftrightarrow F16BP} + \phi_{\text{cyt},F,13BPG \leftrightarrow PEP} + \phi_{\text{cyt},F,PEP \leftrightarrow Pyr} - \\ 2\phi_{\text{cyt},F,FFA \leftrightarrow FAC} - \phi_{\text{cyt},F,ATP \leftrightarrow ADP} + \phi_{\text{cyt},F,PCr \leftrightarrow Cr} - \phi_{\text{cyt},F,AMP \leftrightarrow ADP} \end{array} \right) = -\frac{V_{\text{cyt},F}}{V_F} \frac{dC_{\text{cyt},F,ADP}}{dt}$$

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

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

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

C24.

$$\frac{V_{\text{cyt},F}}{V_F} \frac{dC_{\text{cyt},F,NADH}}{dt} = -J_{\text{cyt} \leftrightarrow \text{mit},F,NADH/NAD}^f + \phi_{\text{cyt},F,GA3P \leftrightarrow 13BPG} - \phi_{\text{cyt},F,Pyr \leftrightarrow Lac} - \phi_{\text{cyt},F,GAB \leftrightarrow G6P} = -V_{\text{cyt},F} \frac{dC_{\text{cyt},F,NAD}}{dt}$$

C25.

$$\frac{V_{\text{cyt},F}}{V_F} \frac{dC_{\text{cyt},F,H^+}}{dt} = \begin{pmatrix} J_{\text{bl} \leftrightarrow \text{cyt},F,H^+}^f \\ -J_{\text{cyt} \leftrightarrow \text{mit},F,H^+}^f \end{pmatrix} + \frac{2.303}{\beta_{\text{cyt}}} C_{\text{cyt},F,H^+} \begin{pmatrix} \phi_{\text{cyt},F,Glc \leftrightarrow G6P} + \phi_{\text{cyt},F,F6P \leftrightarrow F16BP} + \phi_{\text{cyt},F,GA3P \leftrightarrow I3BPG} \\ -\phi_{\text{cyt},F,PEP \leftrightarrow Pyr} - \phi_{\text{cyt},F,Pyr \leftrightarrow Lac} + 3\phi_{\text{cyt},F,Tgl \leftrightarrow Glr} - \phi_{\text{cyt},F,GA3P \leftrightarrow Gr3P} \\ + 2\phi_{\text{cyt},F,FFA \leftrightarrow FAC} + \phi_{\text{cyt},F,ATP \leftrightarrow ADP} - \phi_{\text{cyt},F,PCr \leftrightarrow Cr} - J_{\text{cyt} \leftrightarrow \text{mit},F,H^+}^{\text{leak}} \end{pmatrix}$$

where  $\beta_{\text{cyt}}$  is buffering capacity of cytosol for protons

### ***Tissue Cells Mitochondrial Domain:***

$$\text{M1. } \frac{V_{\text{mit},F,O_2}}{V_F} \frac{dC_{\text{mit},F,O_2}^F}{dt} = J_{\text{cyt} \leftrightarrow \text{mit},F,O_2}^p - 0.5\phi_{\text{mit},F,O_2 \leftrightarrow H_2O,NADH} - 0.5\phi_{\text{mit},F,O_2 \leftrightarrow H_2O,FADH_2}$$

$$\text{M2. } \frac{V_{\text{mit},F,CO_2}}{V_F} \frac{dC_{\text{mit},F,CO_2}^F}{dt} = J_{\text{cyt} \leftrightarrow \text{mit},F,CO_2}^p + (\phi_{\text{mit},F,Pyr \leftrightarrow ACoA} + \phi_{\text{mit},F,Cit \leftrightarrow AKG} + \phi_{\text{mit},F,AKG \leftrightarrow SCoA})$$

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

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

M5.

$$\frac{V_{\text{mit},F}}{V_F} \frac{dC_{\text{mit},F,NADH}}{dt} = \begin{pmatrix} J_{\text{cyt} \leftrightarrow \text{mit},F,NADH/NAD^+}^f + \phi_{\text{mit},F,Pyr \leftrightarrow ACoA} + 7\phi_{\text{mit},F,FAC \leftrightarrow ACoA} \\ + \phi_{\text{mit},F,Cit \leftrightarrow AKG} + \phi_{\text{mit},F,AKG \leftrightarrow SCoA} + \phi_{\text{mit},F,Mal \leftrightarrow Oxa} - \\ \phi_{\text{mit},F,O_2 \leftrightarrow H_2O,NADH} \end{pmatrix} = -\frac{V_{\text{mit},F}}{V_F} \frac{dC_{\text{mit},F,NAD^+}}{dt}$$

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

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

M8.

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

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

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

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

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

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

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

M15.

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

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

M17.

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

where  $\beta_{mit}$  is buffering capacity of mitochondria for protons

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

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



## Part C: Metabolic Reaction Fluxes

### Reactions in Cytosol

#### 1. Glycogen Phosphorylase



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

#### 2. Glycogen Synthase



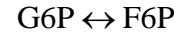
$$\phi_{\text{cyt,F,G6P} \leftrightarrow \text{Gly}} = \left[ \frac{V_{\text{F,G6P} \rightarrow \text{Gly}} \frac{C_{\text{cyt,F,Gly}_n} C_{\text{cyt,F,G6P}} C_{\text{cyt,F,ATP}}}{K_{\text{G6P} \rightarrow \text{Gly}}} - V_{\text{F,G6P} \leftarrow \text{Gly}} \frac{C_{\text{cyt,F,Gly}_{n+1}} C_{\text{cyt,F,Pi}}^2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

#### 3. Hexokinase



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

#### 4. Phosphoglucose Isomerase



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

#### 5. Phosphofructokinase



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

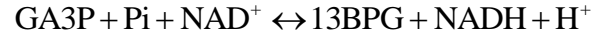
#### 6. Glyceraldehyde 3-Phosphate Formation



$$\phi_{\text{cyt,F,F16BP} \leftrightarrow \text{GA3P}} = \left[ \frac{V_{\text{F,F16BP} \rightarrow \text{GA3P}} \frac{C_{\text{cyt,F,F16BP}}}{K_{\text{F16BP} \rightarrow \text{GA3P}}} - V_{\text{F,F16BP} \leftarrow \text{GA3P}} \frac{C_{\text{cyt,F,GA3P}}^2}{K_{\text{F16BP} \leftarrow \text{GA3P}}}}{1 + \frac{C_{\text{cyt,F,F16BP}}}{K_{\text{F16BP} \rightarrow \text{GA3P}}} + \frac{C_{\text{cyt,F,GA3P}}^2}{K_{\text{F16BP} \leftarrow \text{GA3P}}}} \right]$$

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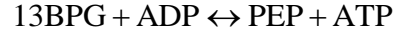
7. *Glyceraldehyde 3-Phosphate Dehydrogenase*



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

---

8. *Phosphoglycerate Kinase*



$$\phi_{\text{cyt,F,13BPG} \leftrightarrow \text{PEP}} = \left[ \frac{V_{\text{F,13BPG} \rightarrow \text{PEP}} \frac{C_{\text{cyt,F,13BPG}} C_{\text{cyt,F,ADP}}}{K_{\text{13BPG} \rightarrow \text{PEP}}} - V_{\text{F,13BPG} \leftarrow \text{PEP}} \frac{C_{\text{cyt,F,PEP}} C_{\text{cyt,F,ATP}}}{K_{\text{13BPG} \leftarrow \text{PEP}}}}{1 + \frac{C_{\text{cyt,F,13BPG}} C_{\text{cyt,F,ADP}}}{K_{\text{13BPG} \rightarrow \text{PEP}}} + \frac{C_{\text{cyt,F,PEP}} C_{\text{cyt,F,ATP}}}{K_{\text{13BPG} \leftarrow \text{PEP}}}}$$

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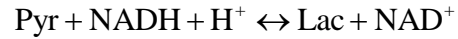
9. *Pyruvate Kinase*



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

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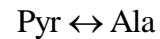
10. *Lactate Dehydrogenase*



$$\phi_{\text{cyt,F,Pyr} \leftrightarrow \text{Lac}} = \left[ \frac{V_{\text{F,Pyr} \rightarrow \text{Lac}} \frac{C_{\text{cyt,F,Pyr}} C_{\text{cyt,F,NADH}} C_{\text{cyt,F,H}^+}}{K_{\text{Pyr} \rightarrow \text{Lac}}} - V_{\text{F,Pyr} \leftarrow \text{Lac}} \frac{C_{\text{cyt,F,Lac}} C_{\text{cyt,F,NAD}^+}}{K_{\text{Pyr} \leftarrow \text{Lac}}}}{1 + \frac{C_{\text{cyt,F,Pyr}} C_{\text{cyt,F,NADH}} C_{\text{cyt,F,H}^+}}{K_{\text{Pyr} \rightarrow \text{Lac}}} + \frac{C_{\text{cyt,F,Lac}} C_{\text{cyt,F,NAD}^+}}{K_{\text{Pyr} \leftarrow \text{Lac}}}}$$

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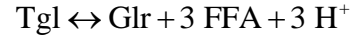
11. *Alanine Formation (Alanine Aminotransferase)*



$$\phi_{\text{cyt,F,Pyr} \leftrightarrow \text{Ala}} = \left[ \frac{V_{\text{F,Pyr} \rightarrow \text{Ala}} \frac{C_{\text{cyt,F,Pyr}}}{K_{\text{Pyr} \rightarrow \text{Ala}}} - V_{\text{F,Pyr} \leftarrow \text{Ala}} \frac{C_{\text{cyt,F,Ala}}}{K_{\text{Pyr} \leftarrow \text{Ala}}}}{1 + \frac{C_{\text{cyt,F,Pyr}}}{K_{\text{Pyr} \rightarrow \text{Ala}}} + \frac{C_{\text{cyt,F,Ala}}}{K_{\text{Pyr} \leftarrow \text{Ala}}}}

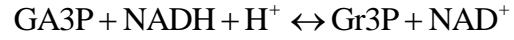
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12. *Lipases (Triglycerides Hydrolysis)*



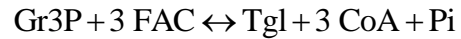
$$\phi_{\text{cyt,F,Tgl} \leftrightarrow \text{Glr}} = \left[ \frac{V_{\text{F,Tgl} \rightarrow \text{Glr}} \frac{C_{\text{cyt,F,Tgl}}}{K_{\text{Tgl} \rightarrow \text{Glr}}} - V_{\text{F,Tgl} \leftarrow \text{Glr}} \frac{C_{\text{cyt,F,Glr}} C_{\text{cyt,F,FFA}}^3 C_{\text{cyt,F,H}^+}^3}{K_{\text{Tgl}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

13. *Glycerol 3-Phosphate Dehydrogenase*



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

14. *Acyltransferase (Triglyceride Synthesis)*



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

15. *Acyl-CoA Synthetase*



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

16. *ATPase (ATP Hydrolysis)*



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

17. *Creatine Kinase*



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

18. *Adenylate Kinase*



$$\phi_{\text{cyt,F,AMP} \leftrightarrow \text{ADP}} = \left[ \frac{V_{\text{F,AMP} \rightarrow \text{ADP}} \frac{C_{\text{cyt,F,ATP}} C_{\text{cyt,F,AMP}}}{K_{\text{AMP} \rightarrow \text{ADP}}} - V_{\text{F,AMP} \leftarrow \text{ADP}} \frac{C_{\text{cyt,F,ADP}}^2}{K_{\text{AMP} \leftarrow \text{ADP}}}}{1 + \frac{C_{\text{cyt,F,ATP}} C_{\text{cyt,F,AMP}}}{K_{\text{AMP} \rightarrow \text{ADP}}} + \frac{C_{\text{cyt,F,ADP}}^2}{K_{\text{AMP} \leftarrow \text{ADP}}}} \right]$$

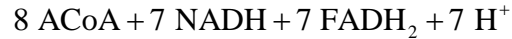
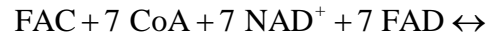
**Reactions in Mitochondria**

19. *Pyruvate Dehydrogenase*



$$\phi_{\text{mit,F,Pyr} \leftrightarrow \text{ACoA}} = \left[ \frac{\frac{C_{\text{mit,F,ADP}}}{C_{\text{mit,F,ATP}}}}{K_{\text{Pyr} \leftrightarrow \text{ACoA}}^{\text{Ctrl}} + \frac{C_{\text{mit,F,ADP}}}{C_{\text{mit,F,ATP}}}} \right] \times \left[ \frac{V_{\text{F,Pyr} \rightarrow \text{ACoA}} \frac{C_{\text{mit,F,Pyr}} C_{\text{mit,F,CoA}} C_{\text{mit,F,NAD}^+}}{K_{\text{Pyr} \rightarrow \text{ACoA}}} - V_{\text{F,Pyr} \leftarrow \text{ACoA}} \frac{C_{\text{mit,F,ACoA}} C_{\text{mit,F,CO}_2} C_{\text{mit,F,NADH}} C_{\text{mit,F,H}^+}}{K_{\text{Pyr} \leftarrow \text{ACoA}}}}{1 + \frac{C_{\text{mit,F,Pyr}} C_{\text{mit,F,CoA}} C_{\text{mit,F,NAD}^+}}{K_{\text{Pyr} \rightarrow \text{ACoA}}} + \frac{C_{\text{mit,F,ACoA}} C_{\text{mit,F,CO}_2} C_{\text{mit,F,NADH}} C_{\text{mit,F,H}^+}}{K_{\text{Pyr} \leftarrow \text{ACoA}}}} \right]$$

20. *Fatty Acyl-CoA Oxidation*  
( $\beta$ -Oxidation)



$$\phi_{\text{mit,F,FAC} \leftrightarrow \text{ACoA}} = \left[ \frac{V_{\text{F,FAC} \rightarrow \text{ACoA}} \frac{C_{\text{mit,F,FAC}} C_{\text{mit,F,CoA}} C_{\text{mit,F,NAD}^+} C_{\text{mit,F,FAD}}}{K_{\text{FAC} \rightarrow \text{ACoA}}} - V_{\text{F,FAC} \leftarrow \text{ACoA}} \frac{C_{\text{mit,F,ACoA}} C_{\text{mit,F,NADH}} C_{\text{mit,F,FADH}_2} C_{\text{mit,F,H}^+}}{K_{\text{FAC} \leftarrow \text{ACoA}}}}{1 + \frac{C_{\text{mit,F,FAC}} C_{\text{mit,F,CoA}} C_{\text{mit,F,NAD}^+} C_{\text{mit,F,FAD}}}{K_{\text{FAC} \rightarrow \text{ACoA}}} + \frac{C_{\text{mit,F,ACoA}} C_{\text{mit,F,NADH}} C_{\text{mit,F,FADH}_2} C_{\text{mit,F,H}^+}}{K_{\text{FAC} \leftarrow \text{ACoA}}}} \right]$$

21. *Citrate Synthase*



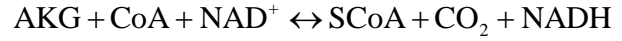
$$\phi_{\text{mit,F,ACoA} \leftrightarrow \text{Cit}} = \left[ \frac{\frac{C_{\text{mit,F,ADP}}}{C_{\text{mit,F,ATP}}}}{K_{\text{ACoA} \leftrightarrow \text{Cit}}^{\text{Ctrl}} + \frac{C_{\text{mit,F,ADP}}}{C_{\text{mit,F,ATP}}}} \right] \left[ \frac{V_{\text{F,ACoA} \rightarrow \text{Cit}} \frac{C_{\text{mit,F,ACoA}}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

22. *Aconitase + Isocitrate Dehydrogenase*



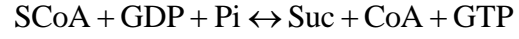
$$\phi_{\text{mit,F,Cit} \leftrightarrow \text{AKG}} = \left[ \frac{\frac{C_{\text{mit,F,ADP}}}{C_{\text{mit,F,ATP}}}}{K_{\text{Cit} \leftrightarrow \text{AKG}}^{\text{Ctrl}} + \frac{C_{\text{mit,F,ADP}}}{C_{\text{mit,F,ATP}}}} \right] \left[ \frac{V_{\text{F,Cit} \rightarrow \text{AKG}} \frac{C_{\text{mit,F,Cit}} C_{\text{mit,F,NAD}^+}}{K_{\text{Cit} \rightarrow \text{AKG}}} - V_{\text{F,Cit} \leftarrow \text{AKG}} \frac{C_{\text{mit,F,AKG}} C_{\text{mit,F,CO}_2} C_{\text{mit,F,NADH}}}{K_{\text{Cit} \leftarrow \text{AKG}}}}{1 + \frac{C_{\text{mit,F,Cit}} C_{\text{mit,F,NAD}^+}}{K_{\text{Cit} \rightarrow \text{AKG}}} + \frac{C_{\text{mit,F,AKG}} C_{\text{mit,F,CO}_2} C_{\text{mit,F,NADH}}}{K_{\text{Cit} \leftarrow \text{AKG}}}} \right]$$

23.  $\alpha$ -Ketoglutarate Dehydrogenase



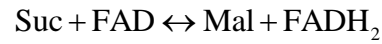
$$\phi_{\text{mit,F,AKG} \leftrightarrow \text{SCoA}} = \left[ \frac{V_{\text{F,AKG} \rightarrow \text{SCoA}} \frac{C_{\text{mit,F,AKG}} C_{\text{mit,F,CoA}} C_{\text{mit,F,NAD}^+}}{K_{\text{AKG} \rightarrow \text{SCoA}}} - V_{\text{F,AKG} \leftarrow \text{SCoA}} \frac{C_{\text{mit,F,SCoA}} C_{\text{mit,F,CO}_2} C_{\text{mit,F,NADH}}}{K_{\text{AKG} \leftarrow \text{SCoA}}}}{1 + \frac{C_{\text{mit,F,AKG}} C_{\text{mit,F,CoA}} C_{\text{mit,F,NAD}^+}}{K_{\text{AKG} \rightarrow \text{SCoA}}} + \frac{C_{\text{mit,F,SCoA}} C_{\text{mit,F,CO}_2} C_{\text{mit,F,NADH}}}{K_{\text{AKG} \leftarrow \text{SCoA}}}} \right]$$

24. Succinyl-CoA Synthetase



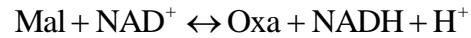
$$\phi_{\text{mit,F,SCoA} \leftrightarrow \text{Suc}} = \left[ \frac{V_{\text{F,SCoA} \rightarrow \text{Suc}} \frac{C_{\text{mit,F,SCoA}} C_{\text{mit,F,ADP}} C_{\text{mit,F,Pi}}}{K_{\text{SCoA} \rightarrow \text{Suc}}} - V_{\text{F,SCoA} \leftarrow \text{Suc}} \frac{C_{\text{mit,F,Suc}} C_{\text{mit,F,CoA}}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

25. Succinate Dehydrogenase



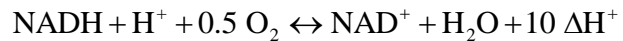
$$\phi_{\text{mit,F,Suc} \leftrightarrow \text{Mal}} = \left[ \frac{V_{\text{F,Suc} \rightarrow \text{Mal}} \frac{C_{\text{mit,F,Suc}} C_{\text{mit,F,FAD}}}{K_{\text{Suc} \rightarrow \text{Mal}}} - V_{\text{F,Suc} \leftarrow \text{Mal}} \frac{C_{\text{mit,F,Mal}} C_{\text{mit,F,FADH}_2}}{K_{\text{Suc} \leftarrow \text{Mal}}}}{1 + \frac{C_{\text{mit,F,Suc}} C_{\text{mit,F,FAD}}}{K_{\text{Suc} \rightarrow \text{Mal}}} + \frac{C_{\text{mit,F,Mal}} C_{\text{mit,F,FADH}_2}}{K_{\text{Suc} \leftarrow \text{Mal}}}} \right]$$

26. Malate Dehydrogenase



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

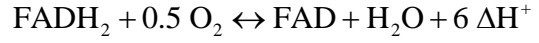
27. Complex I+III+IV



$$\phi_{\text{mit,F,O}_2 \leftrightarrow \text{H}_2\text{O}, \text{NADH}} = \left[ \frac{\exp\left(-\frac{10\Delta G_{\text{H}^+}}{RT}\right) V_{\text{F,O}_2 \rightarrow \text{H}_2\text{O}, \text{NADH}} \frac{C_{\text{mit,F,NADH}} C_{\text{mit,F,O}_2}^{0.5} C_{\text{mit,F,H}^+}}{K_{\text{O}_2 \rightarrow \text{H}_2\text{O}, \text{NADH}}} - V_{\text{F,O}_2 \leftarrow \text{H}_2\text{O}, \text{NADH}} \frac{C_{\text{mit,F,NAD}^+}}{K_{\text{O}_2 \leftarrow \text{H}_2\text{O}, \text{NADH}}}}{1 + \frac{C_{\text{mit,F,NADH}} C_{\text{mit,F,O}_2}^{0.5} C_{\text{mit,F,H}^+}}{K_{\text{O}_2 \rightarrow \text{H}_2\text{O}, \text{NADH}}} + \frac{C_{\text{mit,F,NAD}^+}}{K_{\text{O}_2 \leftarrow \text{H}_2\text{O}, \text{NADH}}}} \right]$$

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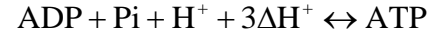
28. *Complex II+III+IV*



$$\phi_{\text{mit,F,O}_2 \leftrightarrow \text{H}_2\text{O,FADH}_2} = \left[ \frac{\exp\left(-\frac{6\Delta G_{\text{H}^+}}{RT}\right) V_{\text{F,O}_2 \rightarrow \text{H}_2\text{O,FADH}_2} \frac{C_{\text{mit,F,FADH}_2} C_{\text{mit,F,O}_2}^{0.5}}{K_{\text{O}_2 \rightarrow \text{H}_2\text{O,FADH}_2}} - V_{\text{F,O}_2 \leftarrow \text{H}_2\text{O,FADH}_2} \frac{C_{\text{mit,F,FAD}}}{K_{\text{O}_2 \leftarrow \text{H}_2\text{O,FADH}_2}}}{1 + \frac{C_{\text{FADH}_2} C_{\text{O}_2}^{0.5}}{K_{\text{O}_2 \rightarrow \text{H}_2\text{O,FADH}_2}} + \frac{C_{\text{FAD}}}{K_{\text{O}_2 \leftarrow \text{H}_2\text{O,FADH}_2}}} \right]$$

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29. *ATP Synthesis (F<sub>1</sub>F<sub>0</sub>-ATPase or Complex V)*



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


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## Appendix D: Transport Fluxes

### Species transport between blood and tissue

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

$$J_{bl \leftrightarrow cyt, F, j}^P = \lambda_{F, j} (C_{bl, j} - C_{cyt, F, j}) \quad (D1)$$

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

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

### Species transport between cytosol and mitochondria

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

$$J_{cyt \leftrightarrow mit, F, j}^P = \lambda_{F, j} (C_{cyt, F, j} - C_{mit, F, j}) \quad (D3)$$

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

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

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

$$J_{cyt \leftrightarrow mit, NADH}^f = T_{cyt \leftrightarrow mit, RS} \left( \frac{RS_{cyt}}{M_{cyt \leftrightarrow mit, RS}^{cyt} + RS_{cyt}} - \frac{RS_{mit}}{M_{cyt \leftrightarrow mit, RS}^{mit} + RS_{mit}} \right) = -J_{cyt \leftrightarrow mit, NAD^+}^f \quad (D5)$$

$$J_{cyt \leftrightarrow mit, ATP}^f = T_{cyt \leftrightarrow mit, PS} \left( \frac{PS_{cyt}}{M_{cyt \leftrightarrow mit, PS}^{cyt} + PS_{cyt}} - \frac{PS_{mit}}{M_{cyt \leftrightarrow mit, PS}^{mit} + PS_{mit}} \right) = -J_{cyt \leftrightarrow mit, ADP}^f \quad (D6)$$

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