Table S1. Mitochondrial energetics and ROS-induced-ROS-release model equations.

S1.1. Mitochondrial membrane potential ($\Delta\Psi_m$)

$$\frac{d\Delta\Psi_m}{dt} = \frac{V_{He} + V_{He(F)} - V_{Hu} - V_{ANT} - V_{HLeak} - V_{NaCa} - 2V_{uni} - V_{IMAC}}{C_{mito}} \qquad \text{E1}$$

S1.2. Energy metabolites mass balance equations

$\dfrac{d\,[\text{ADP}]_m}{dt} = V_{\text{ANT}} - V_{\text{ATPase}} - V_{\text{SL}}$	E2
$[\text{ATP}]_m = C_A - [\text{ADP}]_m$	E3
$\dfrac{d[\text{NADH}]}{dt} = -V_{O2} + V_{\text{IDH}} + V_{\text{KGDH}} + V_{\text{MDH}}$	E4
$\dfrac{d[\text{ISOC}]}{dt} = V_{\text{ACO}} - V_{\text{IDH}}$	E5
$\dfrac{d[\alpha\text{KG}]}{dt} = V_{\text{IDH}} - V_{\text{KGDH}} + V_{\text{AAT}}$	E6
$\dfrac{d[\text{SCoA}]}{dt} = V_{\text{KGDH}} - V_{\text{SL}}$	E7
$\dfrac{d[\text{Suc}]}{dt} = V_{\text{SL}} - V_{\text{SDH}}$	E8
$\dfrac{d[\text{FUM}]}{dt} = V_{\text{SDH}} - V_{\text{FH}}$	E9
$\dfrac{d[\text{MAL}]}{dt} = V_{\text{FH}} - V_{\text{MDH}}$	E10
$\dfrac{d[\text{OAA}]}{dt} = V_{\text{MDH}} - V_{\text{CS}} - V_{\text{AAT}}$	E11
$[\text{CIT}] = C_{\text{Kint}} - \left(\begin{array}{l} [\text{ISOC}] + [\alpha\text{KG}] + [\text{SCoA}] + [\text{Suc}] \\ \qquad\qquad + [\text{FUM}] + [\text{MAL}] + [\text{OAA}] \end{array} \right)$	E12
$\dfrac{d[O2^-]_m}{dt} = \text{shunt} \cdot V_{O_2} - V_{\text{ROS}}^{\text{Tr}}$	E13
$\dfrac{d[O2^-]_i}{dt} = V_{\text{ROS}}^{\text{Tr}} - V_{\text{SOD}}$	E14
$\dfrac{d[H_2O_2]}{dt} = V_{\text{SOD}} - V_{\text{CAT}} - V_{\text{GPX}}$	E15
$\dfrac{d[GSH]}{dt} = V_{\text{GR}} - V_{\text{GPX}}$	E16
$\dfrac{d[Ca^{2+}]_m}{dt} = \delta(V_{uni} - V_{NaCa})$	E51

S1.3. Tricarboxylic acid cycle reaction rates

$$V_{CS} = k_{cat}^{CS}\, E_T^{CS}\left(1 + \frac{K_M^{AcCoA}}{[AcCoA]} + \frac{K_M^{OAA}}{[OAA]} + \frac{K_M^{AcCoA}}{[AcCoA]}\,\frac{K_M^{OAA}}{[OAA]}\right)^{-1}$$
E17

$$V_{ACO} = k_f^{ACO}\left([CIT] - \frac{[ISOC]}{K_E^{ACO}}\right)$$
E18

$$f_a^{IDH} = \left[\left(1 + \frac{[ADP]_m}{K_{ADP}^a}\right)\left(1 + \frac{[Ca^{2+}]_m}{K_{Ca}^a}\right)\right]^{-1}$$
E19

$$f_i^{IDH} = \left(1 + \frac{[NADH]}{K_{i,NADH}}\right)$$
E20

$$V_{IDH} = k_{cat}^{IDH}\, E_T^{IDH}\left[\left(1 + \frac{[H^+]}{k_{h,1}} + \frac{k_{h,2}}{[H^+]}\right) + f_i^{IDH}\left(\frac{K_M^{NAD}}{[NAD]}\right) + f_a^{IDH}\left(\frac{K_M^{ISOC}}{[ISOC]}\right)^{ni} + f_a^{IDH}\, f_i^{IDH}\left(\frac{K_M^{ISOC}}{[ISOC]}\right)^{ni}\left(\frac{K_M^{NAD}}{[NAD]}\right)\right]^{-1}$$
E21

$$f_a^{KGDH} = \left[\left(1 + \frac{[Mg^{2+}]}{K_D^{Mg^{2+}}}\right)\left(1 + \frac{[Ca^{2+}]_m}{K_D^{Ca^{2+}}}\right)\right]^{-1}$$
E22

$$V_{KGDH} = \frac{k_{cat}^{KGDH}\, E_T^{KGDH}}{1 + f_a^{KGDH}\,\frac{K_M^{\alpha KG}}{[\alpha KG]} + f_a^{KGDH}\left(\frac{K_M^{NAD}}{[NAD]}\right)^{n_{aKG}}}$$
E23

$$V_{SL} = k_f^{SL}\left([SCoA][ADP]_m - \frac{[Suc][ATP]_m[CoA]}{K_E^{SL}}\right)$$
E24

$$V_{SDH} = \frac{k_{cat}^{SDH}\, E_T^{SDH}}{1 + \left(\frac{K_M^{Suc}}{[Suc]}\right)\left(1 + \frac{[OAA]}{K_{i,sdh}^{OAA}}\right)\left(1 + \frac{[FUM]}{K_i^{FUM}}\right)}$$
E25

$$V_{FH} = k_f^{FH}\left([FUM] - \frac{[MAL]}{K_E^{FH}}\right)$$
E26

$$f_{h,a} = \left(1 + \frac{[H^+]}{k_{h1}} + \frac{[H^+]^2}{k_{h1}\,k_{h2}}\right)^{-1} + k_{offset}$$
E27

$$f_{h,i} = \left(1 + \frac{k_{h3}}{[H^+]} + \frac{k_{h3}\,k_{h4}}{[H^+]^2}\right)^{-2}$$

E28

$$V_{MDH} = \frac{k_{cat}^{MDH}\,E_T^{MDH}\,f_{h,a}\,f_{h,i}}{1 + \dfrac{K_M^{MAL}}{[MAL]}\left(1 + \dfrac{[OAA]}{K_i^{OAA}}\right) + \dfrac{K_M^{NAD}}{[NAD]} + \dfrac{K_M^{MAL}}{[MAL]}\left(1 + \dfrac{[OAA]}{K_i^{OAA}}\right)\dfrac{K_M^{NAD}}{[NAD]}}$$

E29

$$V_{AAT} = k_f^{AAT}[OAA][GLU]\,\frac{k_{ASP}\,K_E^{AAT}}{\left(k_{ASP}\,K_E^{AAT} + [\alpha KG]\,k_f^{AAT}\right)}$$

E30

S1.4. Oxidative phosphorylation reaction rates

$$V_{O_2} = 0.5\,\rho^{res}\frac{\left(r_a + r_{c1}\,e^{\left(\frac{6F\,\Delta\Psi_B}{R\,T}\right)}\right)e^{\left(\frac{A_{res}\,F}{R\,T}\right)} - r_a\,e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)} + r_{c2}\,e^{\left(\frac{A_{res}\,F}{R\,T}\right)}\,e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}}{\left(1 + r_1\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{6\,F\Delta\Psi_B}{R\,T}\right)} + \left(r_2 + r_3\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}}$$ <div style="text-align:right">E31</div>

$$V_{He} = 6\,\rho^{res}\frac{\left(r_a\,e^{\left(\frac{A_{res}\,F}{R\,T}\right)} - (r_a + r_b)\,e^{\left(\frac{g\,6F\,\Delta\mu_H}{R\,T}\right)}\right)}{\left(1 + r_1\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{6\,F\Delta\Psi_B}{R\,T}\right)} + \left(r_2 + r_3\,e^{\left(\frac{F\,A_{res}}{R\,T}\right)}\right)e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}}$$ <div style="text-align:right">E32</div>

$$A_{res} = \frac{R\,T}{F}\ln\left(K_{res}\sqrt{\frac{[NADH]}{[NAD^+]}}\right)$$ <div style="text-align:right">E33</div>

$$[NAD^+] = C_{PN} - [NADH]$$ <div style="text-align:right">E34</div>

$$V_{He(F)} = \frac{4\,\rho^{res(F)} \times \left(r_a\,e^{\left(\frac{A_{res(F)}\,F}{R\,T}\right)} - (r_a + r_b)\,e^{\left(\frac{g\,6F\,\Delta\mu_H}{R\,T}\right)}\right)}{\left(1 + r_1\,e^{\left(\frac{F\,A_{res(F)}}{R\,T}\right)}\right)e^{\left(\frac{6\,F\Delta\Psi_B}{R\,T}\right)} + \left(r_2 + r_3\,e^{\left(\frac{F\,A_{res(F)}}{R\,T}\right)}\right)e^{\left(\frac{g\,6\,F\,\Delta\mu_H}{R\,T}\right)}}$$ <div style="text-align:right">E35</div>

$$A_{res(F)} = \frac{R\,T}{F}\ln\left(K_{res(F)}\sqrt{\frac{[FADH_2]}{[FAD]}}\right)$$ <div style="text-align:right">E36</div>

$$V_{ATPase} = -\rho^{F1}\frac{\left(10^2\,p_a + p_{c1}\,e^{\left(\frac{3\,F\Delta\Psi_B}{R\,T}\right)}\right)e^{\left(\frac{A_{F1}\,F}{R\,T}\right)} - \left(p_a\,e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)} + p_{c2}\,e^{\left(\frac{A_{F1}\,F}{R\,T}\right)}\,e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)}\right)}{\left(1 + p_1\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\Psi_B}{R\,T}\right)} + \left(p_2 + p_3\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)}}$$ <div style="text-align:right">E37</div>

$$V_{Hu} = -3\,\rho^{F1}\frac{10^2\,p_a\left(1 + e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right) - (p_a + p_b)\,e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)}}{\left(1 + p_1\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\Psi_B}{R\,T}\right)} + \left(p_2 + p_3\,e^{\left(\frac{F\,A_{F1}}{R\,T}\right)}\right)e^{\left(\frac{3\,F\Delta\mu_H}{R\,T}\right)}}$$ <div style="text-align:right">E38</div>

$A_{F1} = \dfrac{R\,T}{F} \ln\left(K_{F1}\, \dfrac{[\text{ATP}]_m}{[ADP]_m\, \text{Pi}} \right)$	E39
$V_{\text{Hleak}} = g_H\, \Delta\mu_H$	E40
$\Delta\mu_H = -2.303 \dfrac{R\,T}{F} \Delta\text{pH} + \Delta\Psi_m$	E41

S1.5. Mitochondrial Ca^{2+} uniporter and and Ca^{2+}-Na^{+} exchanger rates

$$V_{uni} = V_{max}^{uni} \frac{\dfrac{[Ca^{2+}]_i}{K_{trans}}\left(1 + \dfrac{[Ca^{2+}]_i}{K_{trans}}\right)^3 \dfrac{2\,F\left(\Delta\Psi_m - \Delta\Psi^o\right)}{R\,T}}{\left(\left(1 + \dfrac{[Ca^{2+}]_i}{K_{trans}}\right)^4 + \dfrac{L}{\left(1 + \dfrac{[Ca^{2+}]_i}{K_{act}}\right)^{n_a}}\right)\left(1 - e^{\left\{\dfrac{-2\,F\left(\Delta\Psi_m - \Delta\Psi^o\right)}{R\,T}\right\}}\right)}$$

E42

$$V_{NaCa} = V_{max}^{NaCa} \frac{e^{\left(\dfrac{b\,F\left(\Delta\Psi_m - \Delta\Psi^o\right)}{R\,T}\right)} e^{\left(\ln\dfrac{[Ca^{2+}]_m}{[Ca^{2+}]_i}\right)}}{\left(1 + \dfrac{K_{Na}}{[Na^{+}]_i}\right)^n \left(1 + \dfrac{K_{Ca}}{[Ca^{2+}]_m}\right)}$$

E43

S1.6. ROS-induced-ROS-release rates

$$V_{SOD} = \frac{2\,k_{SOD}^1\,k_{SOD}^5\left(k_{SOD}^1 + k_{SOD}^3\left(1 + \frac{[H_2O_2]}{K_i^{H2O2}}\right)\right) E_{SOD}^T\,[O_2^{\cdot-}]}{k_{SOD}^5\left(2\,k_{SOD}^1 + k_{SOD}^3\left(1 + \frac{[H_2O_2]}{K_i^{H2O2}}\right)\right) + [O_2^{\cdot-}]\,k_{SOD}^1\,k_{SOD}^3\left(1 + \frac{[H_2O_2]}{K_i^{H2O2}}\right)}$$

E44

$$V_{CAT} = 2\,k_{CAT}^1\,E_{CAT}^T\,[H_2O_2]\,e^{-fr\,[H_2O_2]}$$

E45

$$V_{GPX} = \frac{E_{GPX}^T\,[H_2O_2][GSH]}{\Phi_1\,[GSH] + \Phi_2\,[H_2O_2]}$$

E46

$$V_{GR} = \frac{k_{GR}^1\,E_{GR}^T}{1 + \frac{K_M^{GSSG}}{[GSSG]} + \frac{K_M^{NADPH}}{[NADPH]} + \frac{K_M^{GSSG}}{[GSSG]}\frac{K_M^{NADPH}}{[NADPH]}}$$

E47

$$V_{ROS}^{Tr} = j \cdot \frac{V_{IMAC}}{\Delta\Psi_m}\left(\Delta\Psi_m - \tfrac{RT}{F}\log\left(\frac{[O_2^{\cdot-}]_m}{[O_2^{\cdot-}]_i}\right)\right)$$

E48

$$V_{IMAC} = \left(a + \frac{b}{1 + \frac{K_{cc}}{[O_2^{\cdot-}]_i}}\right)\left(G_L + \frac{G_{max}}{1 + e^{\left(\kappa\left(\Delta\Psi_m^b - \Delta\Psi_m\right)\right)}}\right)\Delta\Psi_m$$

E49

$$G_T = [GSH] + 2 \times [GSSG]$$

E50