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| **Table S2. Parameter values used in the simulations: ROS production and scavenging** | | | | | |
| **Symbol** | **Value** | **Units** | **Description** | **Eq** | **Reference** |
|  | 1.2×103 | mM-1ms-1 | Second order rate constant of SOD | S29,S30 |  |
|  | 24 | mM-1ms-1 | Second-order rate constant of SOD | S29,S30 |  |
|  | 2.4×10-4 | ms-1 | First-order rate constant of SOD | S29,S30 |  |
|  | 0.5 | mM | Inhibition constant for H2O2 | S29,S30 | f |
|  | T. 1 | mM | Mitochondrial matrix concentration of MnSOD | S29 | Adjusted |
|  | T. 1 | mM | Concentration of Cu,ZnSOD | S30 | Adjusted |
|  | 2×10-4 | ms-1 | Diffusion constant for H2O2 | S31 | Adjusted |
|  | 5.0×10-3 | mM ms | Constant for GPX activity | S32,S33 | a |
|  | 0.75 | mM ms | Constant for GPX activity | S32,S33 | a |
|  | 0.5 | mM | Mitochondrial matrix concentration of GPX | S32 | Adjusted |
|  | 0.5 | mM | Extra-matrix concentration of GPX | S33 | Adjusted |
|  | 2.5×10-3 | ms- | Catalytic constant of GR | S34,S35 | a |
|  | 0.5 | mM | Mitochondrial matrix concentration of GR | S34 | Adjusted |
|  | 0.5 | mM | Extra-matrix concentration of GR | S35 | Adjusted |
|  | 0.015 | mM | Michaelis constant for NADPH of GR | S34, S35 | a |
|  | 0.06 | mM | Michaelis constant for GSSG of GR | S34, S35 | a |
|  | 7.5×10-2 | mM | Extra-matrix NADPH concentration | S34, S35 |  |
|  | 6 | mM | Total pool of glutathione | S40, S41 | a |
|  | 3.6×10-4 | mM s-1 | Rate constant of mitochondrial matrix  glutaredoxin reaction | S36 | Adjusted |
|  | 3.6×10-4 | mM s-1 | Rate constant of extra-matrix glutaredoxin reaction | S37 |  |
|  | 1.37×10-3 | mM-1 | Equilibrium constant of glutaredoxin | S36,S37 |  |
|  | 0.01 | mM | Michaelis constant for GSH of GRX | S36,S37 |  |
|  | 0.0005 | mM | Michaelis constant for glutathionylated protein of glutaredoxin | S36,S37 |  |
|  | 0.64 | ms-1 | Rate constant of protein glutathionylation | S38,S39 |  |
|  | 8×10-4 | mM | Concentration of proteins that can become glutathionylated | S38,S39 |  |
|  | 0.75 | mM | Michaelis constant of GSH for glutathionylation | S38,S39 |  |
|  | 0.002 | mM | Glutaredoxin concentration | S38,S39 |  |
|  | 1.5×10-8 | ms-1 | Rate constant of glutathione transporter | S42 |  |
|  | 2.6 | mM | transport association constant of GSH | S42 |  |
|  | T. 1 | mM | Mitochondrial matrix concentration of Trx peroxidase (Prx) | S43 | Adjusted |
|  | T. 1 | mM | Extra-matrix concentration Prx | S44 | Adjusted |
|  | 3.83 | mM ms | Constant for TxPX activity | S43,S44 | b |
|  | 1.85 | mM ms | Constant for TxPX activity | S43,S44 | b |
|  | T. 1 | mM | Mitochondrial matrix concentration of  TrxR2 | S45 |  |
|  | T. 1 | mM | Extra-matrix concentration of TrxR | S46 |  |
|  | 0.035 | mM | Michaelis constant for oxidized Trx  [Trx(SS)] of TrxR | S45,S46 | d,e |
|  | 0.012 | mM | Michaelis constant for NADPH of Trx | S45,S46 | d,e |
|  | 22.7×10-3 | ms-1 | Rate constant of TrxR | S45,S46 | d,e |
|  | 0.025 | mM | Total pool of mitochondrial matrix  thioredoxin | S47 | c |
|  | 0.05 | mM | Total pool of extra-matrix thioredoxin | S48 |  |
|  | 17 | mM-1ms-1 | Rate constant of catalase (CAT) | S49 |  |
|  | 1.0×10-6 | mM | Extra-matrix concentration of CAT | S49 |  |
|  | 5.0×10-2 | mM-1 | Hydrogen peroxide inhibition factor of CAT | S49 |  |
| *(a)* (3); *(b)* (10); *(c)* (9); *(d)* (11); *(e)* (12); *(f)* (13). | | | | | |

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| **Table S3. Parameter values used in the simulations: Mitochondrial NADPH handling** | | | | | |
| **Symbol** | **Value** | **Units** | **Description** | **Eq** | **Reference** |
|  | 0.1 | mM | Sum of NADPH plus NADP+ | S50 |  |
|  | 0.5 | mM | Dissociation constant for H+ of IDH2 | S51 |  |
|  | 3.9×10-3 | mM | Michaelis constant for ISOC in IDH2 | S51,S52 |  |
|  | 6.7×10-3 | mM | Michaelis constant for NADP in IDH2 | S51,S52 |  |
|  | 2×10-6 | mM | Inhibition constant for NADP in IDH2 | S51,S52 |  |
|  | 1.2×10-2 | mM | Michaelis constant for NADPH in IDH2 | S51,S52 |  |
|  | 0.51 | mM | Michaelis constant for αKG in IDH2 | S51,S52 |  |
|  | 8.7×10-5 | mM-1ms-1 | Maximal rate of IDH2 in the forward direction | S52 |  |
|  | 5.45×10-6 | mM-1ms-1 | Maximal rate of IDH2 in the reverse direction | S52 |  |
|  | 0.02 | mM | Michaelis constant for NADPH in transhydrogenase (THD) | S53,S54 |  |
|  | 0.01 | mM | Michaelis constantfor NADH in THD | S53,S54 |  |
|  | 0.125 | mM | Michaelis constant for NAD in THD | S53,S54 |  |
|  | 0.017 | mM | Michaelis constant for NADP in THD | S53,S54 |  |
|  | 1.187×10-5 | mM | Concentration of THD enzyme | S54 |  |
|  | 1.17474 | ms-1 | Forward catalytic constant of THD | S54 |  |
|  | 10 | ms-1 | Reverse catalytic constant of THD | S54 |  |

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| **Table S4. Parameter values for the mitochondrial Na+/H+ proton exchanger and phosphate carrier** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | 0.0252 | ms-1 | NHE forward rate constant |
|  | 0.0429 | ms-1 | NHE backward rate constant |
|  | 0.16 | ms-1 | NHE forward rate constant |
|  | 0.0939 | ms-1 | NHE backward rate constant |
|  | 24 | mM | Na+Dissociation constant |
|  | 1.585×10-4 | mM | H+Dissociation constant |
|  | 8.52 |  | Proton inhibitory constant |
|  | 3 |  | Hill coefficient for H+ binding |
|  | 0.00785  (mitochondria) | mM | NHE concentration |
|  | 11.06 | mM | Extra-matrix Pi binding constant |
|  | 11.06 | mM | Mitochondrial matrix Pi binding constant |
|  | 4.08×10-5 | mM | Extra-matrix OH- binding constant |
|  | 4.08×10-5 | mM | Mitochondrial matrix OH- binding constant |
|  | 90 | μmol min-1 mg protein-1 | Forward Vmax of phosphate carrier |
|  | 90 | μmol min-1 mg protein-1 | Backward Vmax of phosphate carrier |
|  | 1.6915  (mitochondria) | mg protein ml-1 | PiC concentration |

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| **Table S5. Parameter values used in the simulations: Tricarboxylic acid cycle** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | 1×10-6-1 | mM | Acetyl CoA concentration |
|  | 7.841×10-6 | ms-1 | Catalytic constant of CS |
|  | 0.4 | mM | Concentration of CS |
|  | 0.0126 | mM | Michaelis constant for AcCoA |
|  | 6.4×10-4 | mM | Michaelis constant for OAA |
|  | 1.3 | mM | Sum of TCA cycle intermediates |
|  | 3.896×10-6 | ms-1 | Forward rate constant of ACO |
|  | 2.22 |  | Equilibrium constant of ACO |
|  | 0.19 | mM | Inhibition constant by NADH |
|  | 0.264 | ms-1 | Rate constant of IDH |
|  | 0.109 | mM | Concentration of IDH |
|  | 1×10-5 | mM | Inoization constant of IDH |
|  | 9×10-4 | mM | Inoization constant of IDH |
|  | 1.52 | mM | Michaelis constant for isocitrate 2.0 |
|  | 2.0 |  | Cooperativity for isocitrate |
|  | 0.923 | mM | Michaelis constant for NAD+ |
|  | 0.62 | mM | Activation constant by ADP |
|  | 5×10-4 | mM | IDH activation constant for Ca2+ |
|  | 0.5 | mM | Concentration of KGDH |
|  | 8..83×10-4 | ms-1 | Rate constant of KGDH |
|  | 30 | mM | Michaelis constant for αKG |
|  | 38.7 | mM | Michaelis constant for NAD+ of KGDH |
|  | 4×10-5 | mM | Ionization constant of KGDH |
|  | 7×10-5 | mM | Ionization constant of KGDH |
|  | 0.0308 | mM | Activation constant for Mg2+ |
|  | 1.5×10-4 | mM | Activation constant for Ca2+ |
|  | 1.2 |  | Hill coefficient of KGDH for αKG |
|  | 0.4 | mM | Mg2+ concentration in mitochondria |
|  | 1.0 | mM | Mg2+ concentration in cytosol/buffer |
|  | 1.4×10-3 | mM-1 ms-1 | Forward rate constant of SL |
|  | 3.115 |  | Equilibrium constant of the SL reaction |
|  | 0.02 | mM | Coenzyme A concentrations. |
|  | 4.15×10-4 | ms-1 | Forward rate constant for FH. |
|  | 1.0 |  | Equilibrium constant of FH |
|  | 1.131×10-5 | mM | Ionization constant of MDH |
|  | 26.7 | mM | Ionization constant of MDH |
|  | 6.68×10-9 | mM | Ionization constant of MDH |
|  | 5.62×10-6 | mM | Ionization constant of MDH |
|  | 3.99×10-2 |  | Offset of MDH pH activation factor |
|  | 6.21×10-3 | ms-1 | Rate constant of MDH |
|  | 0.154 | mM | Total MDH enzyme concentration |
|  | 1.493 | mM | Michaelis constant for malate |
|  | 0.031 | mM | Inhibition constant for oxalacetate |
|  | 0.2244 | mM | Michaelis constant for NAD+ |
|  | 1×10-4 ~ 30 | mM | Glutamate concentration. |
|  | 1.07×10-3 | ms-1 | Forward rate constant of AAT |
|  | 6.6 |  | Equilibrium constant of AAT |
|  | 1.5×10-6 | ms-1 | Rate constant of aspartate consumption |

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| **Table S6. Parameter values used in the simulations: Oxidative phosphorylation** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | 6.394×10-13 | ms-1 | Sum of products of rate constants |
|  | 1.762×10-16 | ms-1 | Sum of products of rate constants |
|  | 2.656×10-22 | ms-1 | Sum of products of rate constants |
|  | 8.632×10-30 | ms-1 | Sum of products of rate constants |
|  | 2.077×10-18 |  | Sum of products of rate constants |
|  | 1.728×10-9 |  | Sum of products of rate constants |
|  | 1.059×10-26 |  | Sum of products of rate constants |
|  | T.1 | mM | Concentration of electron carriers  (respiratory complexes I-III-IV) |
|  | 1.35×1018 |  | Equilibrium constant of respiration |
|  | T.1 | mM | Concentration of electron carriers  (respiratory complexes II-III-IV) |
|  | 50 | mV | Phase boundary potential |
|  | 0.85 |  | Correction factor for voltage |
|  | 0.15 |  | Inhibition constant for OAA |
|  | 5.765×1013 |  | Equilibrium constant of SDH |
|  | 1.656×10-8 | ms-1 | Sum of products of rate constants |
|  | 3.373 ×10-10 | ms-1 | Sum of products of rate constants |
|  | 9.651×10-17 | ms-1 | Sum of products of rate constants |
|  | 4.585×10-17 | ms-1 | Sum of products of rate constants |
|  | 1.346×10-4 |  | Sum of products of rate constants |
|  | 7.739×10-7 |  | Sum of products of rate constants |
|  | 6.65×10-15 |  | Sum of products of rate constants |
|  | T.1 | mM | Concentration of F1F0-ATPase |
|  | 1.71×10-6 |  | Equilibrium constant of ATP synthesis |
|  | T.1 | mM | Inorganic phosphate concentration |
|  | 1.5 | mM | Total sum of adenine nucleotides |
|  | T.1 | mM ms-1 | Maximal rate of the ANT |
|  | 0.5 |  | Fraction of |
|  | T.1 | mM ms-1 | Ionic conductance of the inner |
|  |  | mV-1 | membrane |
|  | 1.0 | mM | Total sum of pyridine nucleotides |
|  | 1.812×10-3 | mM mV-1 | Inner membrane capacitance |

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| **Table S7. Parameter values used in the simulations: Mitochondrial Ca2+ handling** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | T.1 | mM ms-1 | Vmaxuniporter Ca2+ transport |
|  | 91 | mV | Offset membrane potential |
|  | 3.8×10-4 | Mm | Activation constant |
|  | 0.019 | mM | Kd for translocated Ca2+ |
|  | 110.0 |  | Keq for conformational transitions in uniporter |
|  | 2.8 |  | Uniporter activation cooperativity |
|  | T.1 | mM ms-1 | Vmax of Na+/Ca2+ exchanger |
|  | 0.5 |  | dependence on Na+/Ca2+ exchanger |
|  | 9.4 | mM | Exchanger Na2+ constant |
|  | 3.75×10-4 | mM | Exchanger Ca2+ constant |
|  | 3.0 |  | Na+/Ca2+ exchanger cooperativity |
|  | 3×10-4 |  | Fraction of free [Ca2+]m |

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| **Table S8. Parameter values used in the simulations: Mitochondrial H+ and Na+ handling** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | 1×10-5\* | dimensionless | mitochondria H+ buffering capacity |
|  | 4.17×10-7 |  | ADP dissociation constant |
|  | 3.31×10-7 |  | ATP dissociation constant |
|  | 1.78×10-7 |  | Pi dissociation constant |
|  | 6.46×10-5 |  | Mg2+ATP dissociation constant |
|  | 5.62×10-4 |  | Mg2+ADP dissociation constant |
|  | 6.3×10-6 |  | Ka of succinate dissociation constant |
|  | 1×10-14 | M | dissociation constant for water |
|  | 1×10-4 | mM | cytosolic H+ concentration |
|  | T.1 | mM | cytosolic Na+ concentration |
|  | 1×10-4 | mM | cytosolic Ca2+ concentration |
|  | 0.01~1.0 | mM | cytosolic ADP concentration |
| \*from Nyguyen (18) and Vaughan-Jones (19) | | | |

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| **Table S9. Parameter values used in the simulations: ROS transport** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | 1×10-3 | dimensionless | Basal IMAC conductance |
|  | 1×104 | dimensionless | Activation factor by cytoplasmic O2.- |
|  | 1×10-2 | mM | Activation constant by cytoplasmic O2.- |
|  | 3.5×10-8 |  | Integral conductance for IMAC |
|  | 3.9085×10-6 |  | Leak conductance of IMAC at saturation |
|  | 7.0×10-2 | mV-1 | Steepness factor |
|  | 4 | mV | Potential at half saturation |
|  | 0.1 | dimensionless | Fraction of IMAC conductance |
|  | 26.730818 |  |  |

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| **Section 11. State variables initial conditions** | | | |
| **Symbol** | **Value** | **Units** | **Description** |
|  | 2.738×10-5 | mM | Mitochondrial matrix Ca2+ |
| [ADP]m | 0.0158 | mM | Mitochondrial matrix ADP |
|  | 193.0 | mV | Mitochondrial membrane potential |
| [NADH] | 0.965 | mM | Mitochondrial matrix NADH |
|  | 6.97×10-5 | mM | Mitochondrial matrix H+ |
|  | 8.28 | mM | Mitochondrial matrix Pi |
| [ISOC] | 0.121 | mM | Isocitrate |
| [αKG] | 0.13 | mM | α-ketoglutarate |
| [SCoA] | 0.0161 | mM | Succinyl CoA |
| [Suc] | 0.037 | mM | Succinate |
| [FUM] | 0.235 | mM | Fumarate |
| [MAL] | 0.228 | mM | Malate |
| [OAA] | 0.00128 | mM | Oxalacetate |
|  | 0.0985 | mM | Mitochondrialmatrix Na+ |
|  | 6.39×10-6 | mM | Mitochondrial matrix Superoxide |
|  | 4.83×10-8 | mM | Extra-matrix Superoxide |
|  | 8.23×10-5 | mM | Mitochondrial matrix Hydrogen peroxide |
|  | 2.83×10-7 | mM | Extra-matrix Hydrogen peroxide |
| [GSH]m | 1.65 | mM | Mitochondrial matrix GSH |
| [GSH]i | 1.65 | mM | Extra-matrix GSH |
| [GSSG]m | 1.32 | mM | Mitochondrial matrix GSSG |
|  | 0.0243 | mM | Mitochondrial matrix TrxSH2 |
|  | 0.0499 | mM | Extra-matrix TrxSH2 |
| [PSSG]m | 6.76×10-4 | mM | Mitochondrial matrix PSSG |
| [PSSG]i | 2.64×10-5 | mM | Extra-matrix PSSG |