## Luczak et al., Mitochondrial CaMKII causes metabolic reprogramming, energetic insufficiency, and dilated cardiomyopathy

### Simulation conditions

| Parameters | WT | CKmito | mtCaMKII | mtCaMKII x CKmito | Source |
| --- | --- | --- | --- | --- | --- |
| Complex I expression/activity | 100% | 100% | 45% | 70% | Fig. 5E and 5H |
| CKmito expression/activity | 100% | 120% | 80% | 120% | Fig. 4E and 4F |
| cytosolic ATP hydrolysis | 100% | 100% | 100% | 100% |  |
| TCA cycle enzyme activity (IDH, αKGDH, FH, MDH) | 100% | 100% | 120% | 120% | Fig. 6B |
| Complex II expression/activity | 100% | 100% | 130% | 130% | Fig. 5E |
| diastolic cytosolic calcium | 100% | 100% | 120% | 100% | Fig. 3E |
| peak cytosolic calcium | 100% | 100% | 105% | 100% | Fig. 3E |

### Model validation

The model is constructed by integrating two computational models: van Beek 2007 creatine kinase model[[1]](#footnote-21) and Gauthier 2013 cardiac bioenergetic model[[2]](#footnote-22). The model parameters were directly taken from these two model unless stated otherwise. The metabolite steady state levels in the control group were matched to the original model as a model validation.

## Ordinary Differential Equations[[3]](#footnote-25)

## Simulation protocol

### The ATP hydrolysis pulse[[4]](#footnote-27)

$$

$$

### Cytosolic calcium pulse

Cytosolic calcium is set around 1E-4 to 3E-4mM, and the heart rate is set at 120ms/beat ().

## Creatine kinase system[^van Beek 2007]

| Parameter | Value | Units | Desc. |
| --- | --- | --- | --- |
| MiCK |  |  | mitochondrial creatine kinase enzyme |
|  | 2.658E-3 | mM/ms | maximum velocity in the forward direction (PCr production) |
|  | calculated | mM/ms | maximum velocity in the backward direction (ATP production); Vb/Vf = 4.199 |
|  | 7.1532E-1 | mM | binary dissociation constant ATP |
|  | 2.8733E1 | mM | binary dissociation constant Cr |
|  | 2.017E-1 | mM | binary dissociation constant ADP |
|  | 1.5977 | mM | binary dissociation constant PCr |
|  | 5.209 | mM | ternary dissociation constant Cr |
|  | 4.99E-1 | mM | ternary dissociation constant PCr |
|  | / | mM | ternary dissociation constant ADP |
|  |  | mM | ternary dissociation constant Cr from dead end complex |
|  | 1 |  | mitochondrial creatine kinase activity |
|  |  |  |  |
| MMCK |  |  | cytosol creatine kinase enzyme (MiCK activity is about 15% of the total CK activity in heart) |
|  | 6.996E-3 | mM/ms | maximum velocity in the forward direction (PCr production) |
|  | calculated | mM/ms | maximum velocity in the backward direction (ATP production) |
|  | 9E-1 | mM | binary dissociation constant ATP |
|  | 1.55E1 | mM | binary dissociation constant Cr |
|  | 2.224E-1 | mM | binary dissociation constant ADP |
|  | 1.670 | mM | binary dissociation constant PCr |
|  | 3.49E1 | mM | ternary dissociation constant Cr |
|  | 4.73 | mM | ternary dissociation constant PCr |
|  | / | mM | ternary dissociation constant ADP |
|  |  | mM | ternary dissociation constant Cr from dead end complex |
|  | 1 |  | cytosol creatine kinase activity |
|  |  |  |  |
| Permeability |  |  |  |
|  | 8.16 | Hz | diffusional conductance ATP |
|  | 65.2227 | Hz | diffusional conductance ADP |
|  | 24615 | Hz | diffusional conductance PCr |
|  | 1166.7 | Hz | diffusional conductance Cr |
|  | 6.0318 | Hz | diffusional conductance Pi |
|  | 3 |  | Fractional volume of cytosol. Total volume 1 corresponds to =0.153mL/gww. |
|  | 1/4 |  | Fractional volume of intermembrane space. |

## Common parameters

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
| F | 96485 | C/mol | Faraday constant |
| T | 310 | K | Absolute temperature |
| R | 8.314 | J/molK | Universal gas constant |
|  | 26.71 | mV | Thermal voltage (=) |
|  | 1.0 | μF/cm^2 | Plasma membrane capacitance |
|  | 1.812 | mM/V | Mitochondrial inner membrane capacitance |
|  | 7 |  | Cytosolic pH |
|  | 7.3-7.8 |  | Mitochondrial pH |
|  | 6 | μM | Tissue oxygen concentration |
|  | 1.0 | mM | Cytosolic magnesium concentration |
|  | 0.4 | mM | Mitochondrial magnesium concentration |
|  |  | mM | Sum of mitochondrial inorganic phosphate |
|  | 1 | mM | Sum of mitochondrial NAD and NADH |
|  |  | mM | Sum of mitochondrial ATP and ADP (Cm) |
|  |  | mM | Sum of cytosolic ATP and ADP (Catp) |
|  | 0.1 | mM | Sum of mitochondrial NADPH plus NADP (VNADPHm) |

## TCA cycle rates[[5]](#footnote-33)

### Citrate synthase (CS)

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 0.23523 | Hz | Catalytic constant |
|  | 400 | μM | Enzyme concentration of CS |
|  | 12.6 | μM | Michaelis constant for AcCoA |
|  | 0.64 | μM | Michaelis constant for OAA |
|  | 1000 | μM | Acetyl CoA concentration |
| (cell) | 0.15891 | Hz | Catalytic constant (cellular model) |

### Aconitase (ACO)

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 0.11688 | Hz | Forward rate constant of ACO |
|  | 2.22 | - | Equilibrium constant of ACO |
|  | 1300 | μM | Sum of TCA cycle intermediates |
| (cell) | 0.078959 | Hz | Forward rate constant (cellular model) |

### Isocitrate dehydrogenase, NADH-producing (IDH3)

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 11.88 | kHz | Rate constant of IDH3 |
|  | 109 | μM | Concentration of IDH3 |
|  | 1E-9 | M | Ionization constant of IDH3 |
|  | 9E-7 | M | Ionization constant of IDH3 |
|  | 923 | μM | Michaelis constant for NAD |
|  | 1520 | μM | Michaelis constant for isocitrate |
|  | 2 | - | Cooperativity for isocitrate |
|  | 620 | μM | Activation constant by ADP |
|  | 0.5 | μM | Activation constant for calcium |
|  | 190 | μM | Inhibition constant by NADH |
| (cell) | 535 | Hz | Rate constant (cellular model) |

### Alpha-ketoglutarate dehydrogenase (KGDH)

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 13.2 | Hz | Rate constant of KGDH |
|  | 500 | μM | Concentration of KGDH |
|  | 4E-8 | M | Ionization constant of KGDH |
|  | 7E-8 | M | Ionization constant of KGDH |
|  | 38700 | μM | Michaelis constant for NAD |
|  | 30000 | μM | Michaelis constant for αKG |
|  | 1.2 | - | Hill coefficient for αKG |
|  | 30.8 | μM | Activation constant for Mg |
|  | 0.15 | μM | Activation constant for Ca |
| (cell) | 17.9 | Hz | Rate constant (cellular model) |

### Succinate-CoA ligase (SL)

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 0.028 | μM \* Hz | Forward rate constant of SL |
|  | 3.115 | - | Equilibrium constant of SL |
| [CoA] | 20 | μM | Coenzyme A concentration |
| (cell) | 0.0284 | μM \* Hz | Forward rate constant (cellular model) |

### Succinate dehydrogenase (SDH)

See electron transport chain.

### Fumarate hydratase (FH)

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 8.3 | Hz | Forward rate constant |
|  | 1.0 | - | Equilibrium constant |
| (cell) | 8.4 | Hz | Forward rate constant (cellular model) |

### Malate dehydrogenase (MDH)

| Parameter | Value | Units | Description |
| --- | --- | --- | --- |
|  | 124.2 | Hz | Rate constant |
|  | 154 | μM |  |
|  | 1.131E-8 | M | Ionization constant |
|  | 2.67E-2 | M | Ionization constant |
|  | 6.68E-12 | M | Ionization constant |
|  | 5.62E-9 | M | Ionization constant |
|  | 0.0399 |  | Offset of MDH pH activation factor |
|  | 224.4 | μM | Michaelis constant for NAD |
|  | 1493 | μM | Michaelis constant for malate |
|  | 31 | μM | Inhibition constant for oxaloacetate |
| (cell) | 125.9 | Hz | Rate constant for cellular model |

### Aspartate aminotransferase (AAT)

| Parameter | Value | Units | Description |
| --- | --- | --- | --- |
|  | 21.4 | Hz | Forward rate constant |
|  | 0.0015 | Hz | Rate constant of aspartate consumption |
|  | 6.6 |  | Equilibrium constant |
| [GLU] | 30000 | μM | Glutamate concentration |
| (cell) | 21.7 | Hz | Forward rate constant (cellular model) |

## Acid-base equilibria and binding polynomials[[6]](#footnote-45)

For both cytoplasmic and mitochondrial compartments.

| Parameter | Value | Unit | Description |
| --- | --- | --- | --- |
|  | 1E-5 | - | mitochondria [H^+] buffering capacity |
|  | 6.48 | - | pK of ATP acid dissociation constant |
|  | 6.38 | - | pK of ADP acid dissociation constant |
|  | 6.75 | - | pKa of phosphate acid dissociation constant |
|  | 4.19 | - | pK of ATP magnesium dissociation constant |
|  | 3.25 | - | pK of ADP magnesium dissociation constant |
|  | 5.2 | - | pK of succinic acid dissociation constant |
|  | 14 |  | pK of water acid dissociation constant |

## Phosphate carrier[[7]](#footnote-47)

Follows equilibrium random Bi:Bi reaction kinetics

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 11.06 | mM | Extra-matrix Pi binding constant |
|  | 11.06 | mM | Mitochondrial matrix Pi binding constant |
|  | 4.08E-5 | mM | Extra-matrix OH- binding constant |
|  | 4.08E-5 | mM | Mitochondrial matrix OH- binding constant |
|  | 1.5 | Hz | Forward rate |
|  | 4.9 | mM | PiC activity |
|  | 1 | - | Equilibrium constant of PiC |

## Mitochondrial Sodium-hydrogen exchanger (mNHE)[[8]](#footnote-49)

Following Smith and Crampin’s model of counterpart on the plasma membrane

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 0.00785 | mM | NHE concentration |
|  | 24 | mM | Na Dissociation constant |
|  | 158.5 | nM | H Dissociation constant |
|  | 3.02 | nM | Proton binding constant |
|  | 3 | - | Hill coefficient for H+ binding |
|  | 25.2 | Hz | NHE forward rate constant |
|  | 42.9 | Hz | NHE backward rate constant |
|  | 160 | Hz | NHE forward rate constant |
|  | 1 | - | Equilibrium constant of NHE |

## Adenine Nucleotide translocator (ANT) [[9]](#footnote-51)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 3.15 | mM \* kHz | Maximal rate |
|  | 0.5 | - | Fraction of dpsi |

## Mitochondrial calcium uniporter (MCU)[[10]](#footnote-53)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 4.46 | mM\*Hz | Maximal rate |
|  | 91 | mV | Offset potential |
|  | 0.38 | μM | Activation constant for calcium |
|  | 19 | μM | Dissociation constant for calcium |
| n | -2.8 | - | Activation cooperativity |
| L | 110 | - | Keq for conformational transitions |

## Mitochondrial sodium-calcium exchanger (NCLX)[[11]](#footnote-55)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 0.183 | mM\*Hz |  |
| b | 0.5 | - |  |
|  | 9.4 | mM |  |
|  | 0.375 | μM |  |
|  | 3 |  |  |

## Mitochondrial proton leak

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 2 | mM\*Hz/V | Ionic conductance of the inner membrane |

## Mitochondrial hydrogen flux balance[[12]](#footnote-58)

: Proton influx to mitochondrial matrix by pumps / transporters : Proton flux due to enzyme stoichiometry : Proton flux due to ligand binding / unbinding

## Complex I model[[13]](#footnote-60)

Assuming single electron transfer for each cycle.

#### Parameters

| Parameter | Value | Units | Desc. |
| --- | --- | --- | --- |
|  | 8849 | μ | Concentration of complex I(Adjustable) |
|  | 50 | mV | Phase boundary potential |
|  | 6.3396E11 | Hz/mM^2 |  |
|  | 5 | Hz |  |
|  | 100 | Hz |  |
|  | 2.5119E13 | Hz/mM^2 |  |
|  | 1E7 | Hz |  |
|  | 130 | Hz |  |
|  | 3886.7 | Hz/mM^{1/2} |  |
|  | 9.1295E6 | Hz |  |
|  | 639.1364 | Hz |  |
|  | 3.2882 | Hz/mM^{1/2} |  |
|  | 1.5962E7 | Hz/mM |  |
|  | 65.2227 | Hz |  |
|  | 24615 | Hz |  |
|  | 1166.7 | Hz/mM^{1/2} |  |
|  | 6.0318 | Hz/mM |  |
|  | -0.375 | V | Midpoint potential of flavin mononucleotide |
|  | -0.15 | V | Midpoint potential of superoxide |

## Complex II (Succinate dehydrogenase)[[14]](#footnote-63)

| Parameter | Value | Units | Desc. |
| --- | --- | --- | --- |
|  | 4.167 | mMHz | Maximum rate of SDH |
|  | 0.150 | mM | Inhibition constant for oxaloacetate |
|  | 0.6 | - | Michaelis constant for CoQ |

## Complex III[[15]](#footnote-65)

ODE System in the Q cycle:

#### Parameters

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 1,666.63 | Hz/mM | Reverse rate constant for reaction 3 |
|  | 0.6877 | - | Equilibrium constant for reaction 3 |
|  | 60.67 | Hz/mM | Reverse rate constant for reaction 4 |
|  | 129.9853 | - | Equilibrium constant for reaction 4 (bH oxidized) |
|  | 13.7484 | - | Equilibrium constant for reaction 4 (bH reduced) |
|  | 0.5 | - |  |
|  | 0.2497 | - |  |
|  | 22000 | Hz | Rate of diffusion across the membrane for Q and QH2 |
|  | 166.67 | Hz/mM | Reverse rate constant for reaction 6 |
|  | 9.4596 | - | Equilibrium constant for reaction 6 |
|  | 0.5 | - |  |
|  | 0.5006 | - |  |
|  | 13.33 | Hz/mM | Reverse rate constant for reaction 7 (bL oxidized) |
|  | 3.0748 | - | Equilibrium constant for reaction 7 (bL oxidized) |
|  | 1.667 | Hz/mM | Reverse rate constant for reaction 7 (bL reduced) |
|  | 29.0714 | - | Equilibrium constant for reaction 7 (bL reduced) |
|  | 0.5 | - |  |
|  | 0.2497 | - |  |
|  | 83.33 | Hz/mM | Reverse rate constant for reaction 8 (bL oxidized) |
|  | 129.9853 | - | Equilibrium constant for reaction 8 (bL oxidized) |
|  | 8.333 | Hz/mM | Reverse rate constant for reaction 8 (bL reduced) |
|  | 9.4596 | - | Equilibrium constant for reaction 8 (bL reduced) |
|  | 833 | Hz/mM | Reverse rate constant for reaction 9 |
|  | 0.2697 | - | Equilibrium constant for reaction 9 |
|  | 0.8333 | Hz/mM | Reverse rate constant for reaction 10 |
|  | 1.4541 | - | Equilibrium constant for reaction 10 |
|  | 2469.13 | Hz/mM | Reverse rate constant for reaction 33 |
|  | 2.1145 | - | Equilibrium constant for reaction 33 |
|  | 0.325 | mM | Total complex III protein |

## Complex IV[[16]](#footnote-68)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 0.325 | mM | Cytochrome c pool |
|  | 0.325 | mM | Complex IV concentration |
|  | 2.9445E10 | Hz/mM^3 | @ pH = 7 |
|  | 290.03 | Hz/mM^3 | @ pH = 7 |
|  | 45000 | Hz/mM |  |
|  | 4.826E11 | Hz/mM | @ pH = 7 |
|  | 4.826 | Hz/mM | @ pH = 7 |
|  | 1.7245E8 | Hz | @ pH = 7 |
|  | 17.542 | Hz | @ pH = 7 |

## Complex V (ATP synthase) rates[[17]](#footnote-70)

$$
\begin{aligned}
J\_{F1Fo} &= -\rho^{F1} ((100 p\_a + p\_{c1} v\_B) v\_a - (p\_a + p\_{c2} v\_a) v\_h) / \Delta \\
J\_H^{F1Fo} &= -3\rho^{F1} (100p\_a(1 + v\_a) - (p\_a + p\_b)v\_h) / \Delta \\
\Delta &= (1 + p\_1 v\_a)v\_B + (p\_2 + p\_3 v\_a)v\_h \\
v\_B &= \text{exp}(3\Delta\Psi\_B / V\_T) \\
v\_h &= \text{exp}(3\Delta p / V\_T) \\
v\_a &= {K\_{eq}^{'} [ATP^{4-}]\_m \over \Sigma [Pi]\_m([ADP^{3-}]\_m + [HADP^{2-}]\_m)}
\end{aligned}
$$

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 5 | mM | Concentration of F1-Fo ATPase |
|  | 4.1175E6 | M | Apparent equilibrium constant for ATP hydrolysis |
|  | 50 | mV | Phase boundary potential |
|  | 1.656E-5 | Hz |  |
|  | 3.373E-7 | Hz |  |
|  | 9.651E-14 | Hz |  |
|  | 4.585E-14 | Hz |  |
|  | 1.346E-4 | - |  |
|  | 7.739E-7 | - |  |
|  | 6.65E-15 | - |  |

## Reactive oxygen species (ROS) scavenging and transport

## Catalase (CAT)[[18]](#footnote-73)

Includes inhibition by high levels of hydrogen peroxide

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 17000 | mM\*Hz | Rate constant |
|  | 1 | nM | Extra-matrix concentration of catalase |
|  | 0.05 | 1/mM | Hydrogen peroxide inhibition factor |

## Superoxide dismutase (SOD) [[19]](#footnote-76)

Based on McADAM, 1976 model, for both cytosolic and mitochondrial compartments.

$$
\begin{aligned}
J\_{SOD} &= {2k\_5E\_Tf\_{sox}(k\_1 + k\_3^\prime) \over k\_5(2 k\_1 + k\_3^\prime) + k\_3^\prime f\_{sox}} \\
k\_3^\prime &= k\_3 (1 + \frac{[H\_2O\_2]}{K\_{H\_2O\_2}}) \\
f\_{sox} &= k\_1^{SOD} [O\_2^-]
\end{aligned}
$$

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 1200000 | Hz/mM | Rate constant for EA -> EB |
|  | 24000 | Hz/mM | Rate constant for EB -> EC |
|  | 0.24 | Hz | Rate constant for EC -> EA |
|  | 0.5 | mM | Inhibition constant for H2O2 |
|  | 0.0003 | mM | Concentration of Cu,ZnSOD (cytosolic) |
|  | 0.00024 | mM | Concentration of MnSOD (mitochondrial) |

## Glutathione (GSH) systems[[20]](#footnote-78)

### Glutathione peroxidase (GPX)

Dalziel type Ping-pong mechanism, for both cytosolic and mitochondrial compartments.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 50 | nM | GPX content (cytosolic) |
|  | 50 | nM | GPX content (mitochondrial) |
|  | 5E-6 | mM\*s | Dalziel coefficient |
|  | 7.5-E4 | mM\*s | Dalziel coefficient |

### Glutathione reductase (GR)

Michaelis-Menten kinetics, for both cytosolic and mitochondrial compartments.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 9E-4 | mM | GR content (cytosolic) |
|  | 9E-4 | mM | GR content (mitochondrial) |
|  | 2.5 | Hz | Catalytic constant of GR |
|  | 0.06 | mM | Michaelis constant for GSSG |
|  | 0.015 | mM | Michaelis constant for NADPH |

### Glutaredoxin system[[21]](#footnote-81)

Disabled in the cellular model.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 3.6E-4 | mM\*Hz | Extra-matrix glutaredoxin reaction rate |
|  | 3.6E-4 | mM\*Hz | Mitochondrial glutaredoxin reaction rate |
|  | 1.37E-3 | 1/mM | Equilibrium constant of glutaredoxin |
|  | 0.01 | mM | Michaelis constant for GSH of GRX |
|  | 0.0005 | mM | Michaelis constant for glutathionylated protein of glutaredoxin |
|  | 0.002 | mM | Glutaredoxin concentration |
|  | 0 |  | Cellular model |
|  | 0 |  | Cellular model |

### Glutathionylated protein[[22]](#footnote-84)

Disabled in the cellular model.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 640 | Hz | Rate constant of protein glutathionylation |
|  | 8E-4 |  | Concentration of proteins that can become glutathionylated |
|  | 1E-3 | mM | Total PSSG |
|  | 0.75 | mM | Michaelis constant of GSH |
|  | 1E-3 | mM | Activation constant of H2O2 |
|  | 0 |  | Cellular model |

### Glutathione transport[[23]](#footnote-86)

Disabled in the cellular model.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 1.5E-5 | mM \* Hz | Rate constant of glutathione transporter |
|  | 2.6 | mM | Transport association constant of GSH |
|  | 0 |  | Cellular model |

### Conservation relationship of glutathione

for both cytosolic and mitochondrial compartments.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  |  | mM | Cytosolic GSH pool |
|  |  | mM | Mitochondrial GSH pool |

## Thioredoxin system[[24]](#footnote-90)

### Peroxiredoxin (TPX)

Dalziel type Ping-pong mechanism, for both cytosolic and mitochondrial compartments.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 100 | μM | GPX content (cytosolic) |
|  | 3 | μM | GPX content (mitochondrial) |
|  | 3.83 | mM \* s | Dalziel coefficient |
|  | 1.85 | mM \* s | Dalziel coefficient |

### Thioredoxin reductase (TR)

Michaelis-Menten kinetics, for both cytosolic and mitochondrial compartments.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 0.35 | μM | TR content (cytosolic) |
|  | 0.35 | μM | TR content (mitochondrial) |
|  | 22.75 | Hz | Catalytic constant of GR |
|  | 35 | μM | Michaelis constant for GSSG |
|  | 65 | μM | Michaelis constant for NADPH |

### Conservation relationship of thioredoxin

For both cytosolic and mitochondrial compartments.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 25 | μM | Sum of cytosolic thioreoxin |
|  | 50 | μM | Sum of mitochondrial thioreoxin |

## Inner mitochondrial anion channel[[25]](#footnote-95)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
| a | 0.001 | - | Basal IMAC conductance |
| b | 10000 | - | Activation factor by |
|  | 10 | μM | Activation constant by |
|  | 0.035 | μM \* Hz / mV | Integral conductance for IMAC |
|  | 3.9085 | μM \* Hz / mV | Leak conductance of IMAC |
|  | 0.07 | 1/mV | Steepness factor |
|  | 4 | mV | Potential at half saturation |
| j | 0.1 | - | Fraction of IMAC conductance |

## Hydrogen peroxide transfer[[26]](#footnote-97)

Simple diffusion.

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 0.2 | Hz | Diffusion rate across IMM |

## Conservation of NADPH

## NADPH-producing isocitrate dehydrogenase (IDH2)[[27]](#footnote-100)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 500 | μM | Dissociation constant for H |
|  | 3.9 | μM | Michaelis constant for isocitrate |
|  | 6.7 | μM | Michaelis constant for NADP |
|  | 0.002 | μM | Inhibition constant for NADP |
|  | 12 | μM | Michaelis constant for NADPH |
|  | 510 | μM | Michaelis constant for αKG |
|  | 87 | μM\*Hz | Maximal forward rate of IDH2 |
|  | 5.45 | μM\*Hz | Maximal backward rate of IDH2 |

## Transhydrogenase (THD)[[28]](#footnote-102)

| Parameter | Value | Unit | Desc. |
| --- | --- | --- | --- |
|  | 20 | μM | Michaelis constant for NADPH |
|  | 10 | μM | Michaelis constant for NADH |
|  | 125 | μM | Michaelis constant for NAD |
|  | 17 | μM | Michaelis constant for NADP |
|  | 0.01187 | μM | Concentration of THD |
|  | 1174.74 | Hz | Forward catalytic constant |
|  | 1 | - | Apparent equilibrium constant |

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