FIGURES

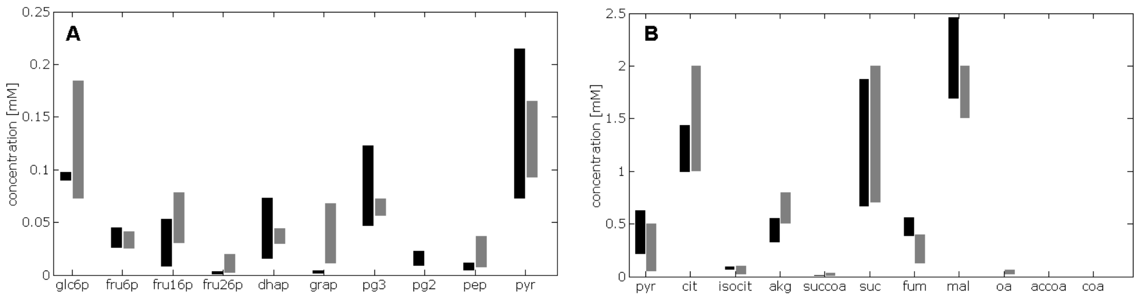

Figure S1 Calculated and measured concentrations of glycolytic metabolites (A) and intermediates of the TCA cycle (B).

Grey bars indicate experimentally determined concentration ranges taken from the literature (for glycolytic intermediates[1-13] and TCA-cycle intermediates[5, 14-20]). Black bars indicate calculated metabolite concentration ranges for a normal energetic load (non-excited but spontaneously firing neuron) and in a highly activated state of the neuron (e.g. interneurons involved in gamma oscillations in hippocampal slices) where the activation is about 4-fold of the normal.[21]

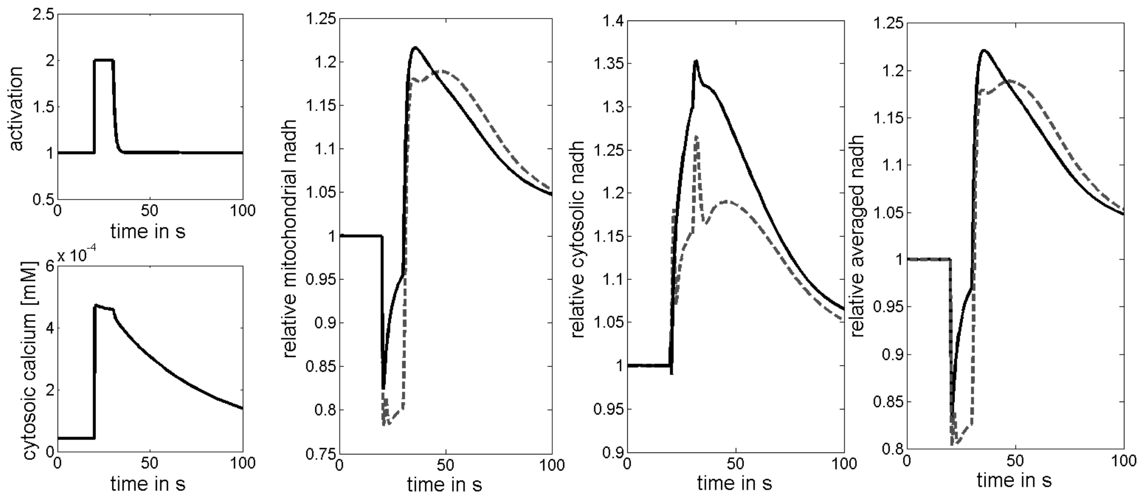

Figure S2 Comparison of the response of a more glycolytic cell (astrocyte) to a neuron with identical activation and cytosolic calcium transients

Dashed lines show astrocytic NADH transients, while solid lines show the NADH transients for the neuron. The relative glycolytic response is lower in the astrocyte due to the higher baseline level (not shown). However the abrupt changes in the energy demand are very pronounce in the astrocytic cytosolic NADH transients as the absolute contribution of the glycolytic pathway is higher and the buffering through the shuttle systems and the mitochondrial NADH pool is lower. Mitochondrial traces are similar, but the activation is lower in the astrocyte since the respiratory and citric acid cycle are closer to their maximal capacity in the basal state. The averaged transients (as measured by fluorescence) are very similar.

MODEL EQUATIONS

Kinetic rate equations for the individual enzymes were constructed on the basis of kinetic data gathered from the literature. Guiding principle was the construction of a comprehensive rate law that captures the regulatory features of the enzyme relevant to the chosen network and the intended purpose of the model. The example of the α-ketoglutarate dehydrogenase reaction below illustrates the strategy applied to select the relevant experimental information form the literature to establish a rate law that can be used as a module of the network model. First, the enzyme name and the literature used for the retrieval of kinetic parameters are given. Second, the stoichiometry of the reaction catalyzed by the enzyme is depicted. Third, the implemented rate equation and the numerical values of the kinetic parameters are given. Binding constants (K values) are given in mM, enzyme activity is given in mM/s.

The α-ketoglutarate dehydrogenase complex (KGDHC) catalyzes the irreversible reaction: akg + NAD + CoA → SucCoA + NADH. The rate equation is of the Michaelis-Menten type with respect to reactants akg, NAD, and CoA. The K_m values are dynamic functions of metabolite concentrations. Activity of the enzyme is affected by the substrates akg, NAD and CoA while other metabolites as SucCoA, NADH, Ca, Mg, pH, ATP, ADP, P, NH4, various keto-acyl CoA esters act as allosteric regulators. Included in the rate equation were only effectors that occur as variables of the network model. Effectors that are not part of the network model like Mg, NH_4^+ or keto-acyl CoA esters were omitted. Further reduction of the set of included effectors was achieved by taking into account the known metabolic alterations in the physiological regime considered. Under physiological conditions, the metabolites ATP, ADP, P as well as the proton concentration (pH value) do not exert regulatory control and were omitted as well. K_m values were either taken directly from the literature or obtained by fitting the rate law to published data. It was checked that used K_m values were consistent with values found in various publications. V_{max} values for all enzymes are free parameters. They are adjusted to reproduce the correct systems behavior under the various conditions considered. They do not directly represent catalytic activity of the enzymes but absorb all activity influencing regulations considered to be constant within the model. For the KGDH, the V_{max} value takes into account the effect of Mg, acyl esters, pH and otherwise unknown or neglected effectors.

Example:

α-ketogluterate dehydrogenase complex[16, 22-26]

(akg + NAD + CoA → SucCoA + NADH)

$$v_{akdhc} = V_{\max}^{akdhc} \left(\frac{akg_{mito}}{akg_{mito} + K_m^{akdhc}} \right) \left(\frac{NAD_{mito}}{NAD_{mito} + K_m^{NAD} \cdot \left(1 + \frac{NADH_{mito}}{K_i^{NADH}} \right)} \right) \left(\frac{CoA}{CoA + K_m^{CoA} \cdot \left(1 + \frac{SucCoA}{K_i^{SucCoA}} \right)} \right)$$

$$V_{\max}^{akdhc} = 268.8$$

$$K_m^{akdhc} = \left(\frac{K_{m1}^{akdhc}}{\left(1 + \frac{Ca_{mito}}{K_{i-akg}^{Ca}} \right)} + K_{m2}^{akgh} \right) \left(1 + \frac{NADH_{mito}}{K_{i-akg}^{NADH}} \right)$$

$$K_{m1}^{akdhc} = 2.5$$

$K_{m2}^{akdhc} = 0.13$

$K_m^{NAD} = 0.021$

$K_i^{NADH} = 0.0045$

$K_m^{CoA} = 0.0013$

$K_i^{SucCoA} = 0.0045$

Glycolysis

Glucose transporter[27]

(glc_ex ↔ glc_cyt)

$$v_{glct} = V_{\max-glct}\left(\frac{glc_{ext} - glc}{1 + \frac{glc}{K_m^{glc}} + \frac{glc_{ext}}{K_m^{glc_{ext}}}}\right)$$

$V_{\max-glc} = 0.72$

$K_m^{glc} = 2.87$

$K_m^{glc_{ext}} = 2.87$

Hexokinase[28-31]

(Glc + ATP → Glc6P + ADP)

$$v_{hexk} = V_{\max-hexk}\left(\frac{glc}{glc + K_m^{glc}}\right)\left(\frac{atp}{atp + K_m^{atp}\left(1 + \frac{glc6p}{K_{i-atp}^{glc6p}}\right)}\right)\left(1 - \frac{glc6p}{K_i^{glc6p}}\right)$$

$V_{\max-hexk} = 9.36$

$K_m^{glc} = 0.043$

$K_m^{atp} = 0.37$

$K_{i-atp}^{glc6p} = 0.074$

$K_i^{glc6p} = 0.1$

Glucose-6-phosphate isomerase[32, 33]

(Glc6P ↔ Fru6P)

$$v_{g6piso} = V_{\max-g6piso}\left(\frac{glc6p - \dfrac{fru6p}{K_{eq-g6piso}}}{1 + \dfrac{glc6p}{K_m^{glc6p}} + \dfrac{fru6p}{K_m^{fru6p}}}\right)$$

$V_{\max-g6piso} = 24.4$

$K_{eq-g6piso} = 0.5157$

$K_m^{glc6p} = 0.593$

$K_m^{fru6p} = 0.095$

Phosphofructokinase I[7, 11, 34]

(Fru6P + ATP → Fru16P + ADP)

$$v_{pfkI} = V_{\max-pfkI}\left(\frac{fru6p}{fru6p + K_m^{fru6p}\cdot\left(1 - K_0\dfrac{fru26p^{n_{fru26p}}}{fru26p^{n_{fru26p}} + \left(K_a^{fru26}\right)^{n_{fru26p}}}\right)}\right)\left(\frac{atp}{atp + K_m^{atp}}\right)\left(1 - \frac{atp^n}{atp^n + \left(K_i^{atp}\right)^n}\right)\left(\frac{fru26p}{fru26p + K_a^{fru26p}}\right)$$

$$V_{\max-pfkI} = 49.6$$

$$K_m^{fru6p} = 0.111$$

$$K_m^{atp} = 0.04$$

$$n = 1.8$$

$$K_i^{atp} = 1.2$$

$$K_0 = 0.55$$

$$K_a^{fru26p} = 0.0042$$

$$n_{fru26p} = 5.5$$

$$K_a^{fru26p} = 0.005$$

Fructose-1,6-bisphosphatase[35]

(fru16bp ⟶ fru6p + Pi)

$$v_{fbpI} = V_{\max-fbpI}\left(\frac{fru6p}{fru6p + K_m^{fru6p}}\right)$$

$$V_{\max-fbpI} = 0.455$$

$$K_m^{fru6p} = 0.132$$

Phosphofructokinase II[36-41]

(Fru6P + ATP → Fru26P + ADP)

$$v_{pfkII} = V_{\max-pfkII}\left(\frac{fru6p}{fru6p + K_m^{fru6p}}\right)\left(\frac{atp}{atp + K_m^{atp}}\right)\left(\frac{amp}{amp + K_a^{amp}}\right)\left(\frac{adp}{adp + K_a^{adp}}\right)$$

$V_{\max - pfkII} = 0.0026$

$K_m^{fru6p} = 0.027$

$K_m^{atp} = 0.055$

$K_a^{amp} = 0.073$

$K_a^{adp} = 0.056$

Fructose-2,6-bisphosphatase[36, 37]

(Fru26P → Fru6P + Pi)

$$v_{fru26pp} = V_{\max - fru26pp}\left(\frac{fru26p}{fru26p + K_m^{fru26p}\left(1 + \frac{fru6p}{K_i^{fru6p}}\right)}\right)$$

$V_{\max - fru26pp} = 0.052$

$K_m^{fru26p} = 0.07$

$K_i^{fru6p} = 0.02$

Aldolase[42]

(Fru16P ↔ Grap + Dhap)

$$v_{aldo} = V_{\max - aldo}\left(\frac{fru16p - \frac{grap \cdot dhap}{K_{eq}^{aldo}}}{\left(1 + \frac{fru16p}{K_m^{fru16p}}\right) + \left(1 + \frac{grap}{K_m^{grap}}\right)\left(1 + \frac{dhap}{K_m^{dhap}}\right) - 1}\right)$$

$V_{\max - aldo} = 46.8$

$K_{eq}^{aldo} = 0.0976$

$K_{m}^{fru16p} = 0.003$

$K_{m}^{grap} = 0.08$

$K_{m}^{dhap} = 0.03$

Triosephosphate isomerase[43]

(Dhap ↔ Grap)

$$v_{tpi} = V_{\max-tpi}\left(\frac{dhap - \frac{grap}{K_{eq}^{tpi}}}{1 + \frac{dhap}{K_{m}^{dhap}} + \frac{grap}{K_{m}^{grap}}}\right)$$

$V_{\max-tpi=}10^{6}$

$K_{eq}^{tpi} = 0.0545$

$K_{m}^{dhap} = 0.84$

$K_{m}^{grap} = 1.65$

Glyceraldehyde 3-phosphate dehydrogenase[44-46]

(Grap + Pi + NAD → Bpg13 + NADH)

$$v_{gapdh} = V_{\max-gapdh}\left(\frac{nad \cdot grap \cdot pi - \frac{bpg13 \cdot nadh}{K_{eq}^{gapdg}}}{\left(1 + \frac{nad}{K_{m}^{nad}}\right)\left(1 + \frac{grap}{K_{m}^{grap}}\right)\left(1 + \frac{pi}{K_{m}^{pi}}\right) + \left(1 + \frac{nadh}{K_{m}^{nadh}}\right)\left(1 + \frac{bpg13}{K_{m}^{bpg13}}\right) - 1}\right)$$

$V_{\max-gapdh} = 72000$

$K_{eq}^{gapdh} = 0.0868$

$K_m^{nad} = 0.01$

$K_m^{nad} = 0.027$

$K_m^{grap} = 0.101$

$K_m^{pi} = 3.9$

$K_m^{nadh} = 0.008$

$K_m^{bpg13} = 0.0035$

Phophoglycerate kinase[47]

(Bgp13 + ADP ↔ Pg3 + ATP)

$$v_{pgk} = V_{\max - pgk} \left(\frac{bpg13 \cdot adp - \frac{pg3 \cdot atp}{K_{eq}^{pgk}}}{\left(1 + \frac{bpg13}{K_m^{bpg13}}\right)\left(1 + \frac{adp}{K_m^{adp}}\right) + \left(1 + \frac{pg3}{K_m^{pg3}}\right)\left(1 + \frac{atp}{K_m^{atp}}\right) - 1} \right)$$

$V_{\max - pg} = 396$

$K_{eq}^{pgk} = 1310$

$K_m^{bpg13} = 0.063$

$K_m^{adp} = 0.42$

$K_m^{pg3} = 0.67$

$K_m^{atp} = 0.25$

Phosphoglycerate mutase[48, 49]

(Pg3 ↔ Pg2)

$$v_{pgm} = V_{\max-pgm}\left(\frac{pg3-\dfrac{pg2}{K_{eq}^{pgm}}}{\left(1+\dfrac{pg3}{K_m^{pg3}}\right)+\left(1+\dfrac{pg2}{K_m^{pg2}}\right)-1}\right)$$

$$V_{\max-pgm} = 14400$$

$$K_{eq}^{pgm} = 0.1814$$

$$K_m^{pg3} = 0.22$$

$$K_m^{pg2} = 0.28$$

Enolase[50]

(Pg2 ↔ Pep)

$$v_{eno} = V_{\max-eno}\left(\frac{pg2-\dfrac{pep}{K_{eq}^{eno}}}{\left(1+\dfrac{pg2}{K_m^{pg2}}\right)+\left(1+\dfrac{pep}{K_m^{pep}}\right)-1}\right)$$

$$V_{\max-eno} = 216000$$

$$K_{eq}^{eno} = 0.5$$

$$K_m^{pg2} = 0.05$$

$$K_m^{pep} = 0.15$$

Pyruvate kinase[51, 52]

(Pep + ADP → Pyr +ATP)

$$v_{pk} = V_{\max-pk}\left(\frac{pep}{pep + K_m^{pep}}\right)\left(\frac{adp}{adp + K_m^{adp}\left(1 + \frac{atp}{K_i^{atp}}\right)}\right)$$

$$V_{\max-pk} = 23.76$$

$$K_m^{pep} = 0.074$$

$$K_m^{adp} = 0.42$$

$$K_i^{atp} = 4.4$$

Lactate dehydrogenase[53-55]

(Pyr + NADH ↔ Lac +NAD)

$$v_{ldh} = V_{\max-ldh}\left(\frac{pyr \cdot nadh - \frac{lac \cdot nad}{K_{eq}^{ldh}}}{\left(1 + \frac{pyr}{K_m^{pyr}}\right)\left(1 + \frac{nadh}{K_m^{nadh}}\right) + \left(1 + \frac{lac}{K_m^{lac}}\right)\left(1 + \frac{nad}{K_m^{nad}}\right) - 1}\right)$$

$$V_{\max-ldh} = 100000$$

$$K_{eq}^{ldh} = 8400$$

$$K_m^{pyr} = 0.36$$

$$K_m^{nadh} = 0.043$$

$$K_m^{lac} = 4.2$$

$$K_m^{nad} = 0.088$$

Monocarboxylate transporter (MCT)[56, 57]

(Lac_cyt ↔ Lac_ex)

$$v_{mct} = V_{\max-mct}\left(\frac{lac - \frac{lac_{ex}}{K_{eq}^{mct}}}{\left(1+\frac{lac}{K_m^{lac}}\right)+\left(1+\frac{lac_{ex}}{K_m^{lac_{ex}}}\right)-1}\right)$$

$$V_{\max-mct} = 5$$

$$K_{eq}^{mct} = \frac{h_{cyt}}{h_{ext}} = 1.737$$

$$K_m^{lac} = 1.1$$

$$K_m^{lac_{ex}} = 1.1$$

Creatine kinase[4]

(ATP + Cr ↔ ADP + CrP)

$$v_{ck} = V_{\max-ck}\left(adp \cdot crp - \frac{atp \cdot cr}{K_{eq-app}^{ck}}\right)$$

$$V_{\max-ck} = 0.0135$$

$$K_{eq-app}^{ck} = 7$$

The apparent equilibrium constant is lower than the thermodynamic equilibrium constant[58] as is known for muscle cells.[59]

<u>Malate-Aspartate Shuttle</u>

Cytosolic malate dehydrogenase[60-62]

(Mal_in + NAD_in ↔ Oa_in + NADH_in)

$$v_{mdh}^{cyt} = V_{\max-mdh}^{cyt} \left(\frac{mal \cdot nad - \frac{oa \cdot nadh}{K_{eq}^{mdh}}}{\left(1+\frac{mal}{K_m^{mal}}\right)\left(1+\frac{nad}{K_m^{nad}}\right)+\left(1+\frac{oa}{K_m^{oa}}\right)\left(1+\frac{nadh}{K_m^{nadh}}\right)-1} \right)$$

$V_{\max-mdh}^{cyt} = 10^4$

$K_{eq}^{mdh} = 10^{-4}$

$K_m^{nad} = 0.05$

$K_m^{mal} = 0.77$

$K_m^{oa} = 0.04$

$K_m^{nadh} = 0.05$

Mitochondrial malate dehydrogenase

(Mal_ mito + NAD_ mito ↔ Oa_ mito + NADH_ mito)

→ see section CAC

Cytosolic aspartate aminotransferase[63]

(Asp_cyt + akg_cyt ↔ oa_cyt + glu_cyt)

$$v_{aat}^{cyt} = V_{\max-aat}^{cyt} \left(asp \cdot akg - \frac{oa \cdot glu}{K_{eq}^{aat}} \right)$$

$V_{\max-aat}^{cyt} = 32$

$K_{eq}^{aat} = 0.147$

Mitochondrial aspartate aminotransferase[63]

(Asp_mito + akg_mito ↔ oa_ mito + glu_ mito)

$$v_{aat}^{mito} = V_{\max-aat}^{mito}\left(asp \cdot akg - \frac{oa \cdot glu}{K_{eq}^{aat}}\right)$$

$$V_{\max-aat}^{mito} = 32$$

$$K_{eq}^{aat} = 0.147$$

Aspartate/glutamate carrier[64]

(Asp_mito + glu_cyt + h_cyt ↔ Asp_cyt + glu_mito + h_mito)

$$v_{asp-glu-c.} = V_{\max-asp-glu-c.}\left(\frac{asp_{mito} \cdot glu_{cyt} - \dfrac{asp_{cyt} \cdot glu_{mito}}{K_{eq}^{asp-glu-c.}}}{\left(asp_{mito} + K_m^{asp_{mito}}\right)\left(glu_{cyt} + K_m^{glu_{cyt}}\right) + \left(asp_{cyt} + K_m^{asp_{cyt}}\right)\left(glu_{mito} + K_m^{glu_{mito}}\right)}\right)$$

$$V_{\max-asp-glu-c.} = 3.2 \cdot 10^3$$

$$dG_{asp-glu-c} = -V_{mm} + \frac{1000 \cdot R \cdot T}{F}\log\left(\frac{h_{cyt}}{h_{mito}}\right)$$

$$K_{eq}^{asp-glu-c.} = \exp\left(\frac{F \cdot dGp}{1000 \cdot R \cdot T}\right)$$

$$K_m^{asp_{mito}} = 0.05$$

$$K_m^{glu_{cyt}} = 2.8$$

$$K_m^{asp_{cyt}} = 0.05$$

$$K_m^{glu_{mito}} = 2.8$$

Malate/α-ketoglutarate carrier[65, 66]

(Mal_cyt + akg_mito ↔ Mal_mito + akg_cyt)

$$v_{mal-akg-c.} = V_{\max-mal-akg-c.}\left(\frac{mal_{cyt}\cdot akg_{mito} - mal_{mito}\cdot akg_{cyt}}{\left(mal_{cyt}+K_m^{mal_{cyt}}\right)\left(akg_{mito}+K_m^{akg_{mito}}\right)+\left(mal_{mito}+K_m^{mal_{mito}}\right)\left(akg_{cyt}+K_m^{akg_{cyt}}\right)}\right)$$

$$V_{\max-mal-akg-c.} = 32$$

$$K_m^{mal_{cyt}} = 1.36$$

$$K_m^{akg_{cyt}} = 0.1$$

$$K_m^{mal_{mito}} = 0.71$$

$$K_m^{akg_{mito}} = 0.2$$

Glycerol-3-Phosphate Shuttle

Cytosolic glycerol-3-phosphate dehydrogenase[67, 68]

(dhap_cyt + nadh_cyt ↔ g3p_cyt + nad_cyt)

$$v_{g3pdh}^{cyt} = V_{\max-g3pdh}^{cyt}\left(\frac{dhap_{cyt}\cdot nadh_{cyt} - \dfrac{g3p_{cyt}\cdot nad_{cyt}}{K_{eq-g3pdh}^{cyt}}}{\left(1+\dfrac{\mathrm{dhap}_{\mathrm{cyt}}}{K_m^{dhap}}\right)\cdot\left(1+\dfrac{nadh_{\mathrm{cyt}}}{K_m^{nadh}}\right)+\left(1+\dfrac{g3p_{\mathrm{cyt}}}{K_m^{g3p}}\right)\cdot\left(1+\dfrac{nad_{\mathrm{cyt}}}{K_m^{nad}}\right)-1}\right)$$

$$V_{\max-g3pdh}^{cyt} = 3.2\cdot 10^4$$

$$K_{eq-g3pdh}^{cyt} = 3257.3$$

$$K_m^{dhap} = 0.17$$

$$K_m^{nadh} = 0.01$$

$$K_m^{g3p} = 0.3$$

$K_m^{nad} = 0.03$

Mitochondrial glycerol-3-phosphate dehydrogenase[19, 67, 68]

(dhap_cyt + FAD_g3p ↔ g3p_cyt + FADH2_g3p)

(FADH2_g3p + Q ↔ FAD_g3p + QH2)

$$v_{g3pdh}^{mito} = V_{\max-g3pdh}^{mito}\left(\frac{dhap_{cyt}\cdot FAD_{g3pdh} - \dfrac{g3p_{cyt}\cdot FADH_{2_{gpdh}}}{K_{eq-g3pdh}^{mito}}}{\left(1+\dfrac{\mathrm{dhap_{cyt}}}{K_m^{dhap}}\right)+\left(1+\dfrac{\mathrm{g3}p_{\mathrm{cyt}}}{K_m^{g3p}}\right)}\right)$$

$$v_{g3pdh\_Q} = V_{\max}^{g3pdh\_Q}\cdot\left(FADH_{2\_pdhc}\cdot Q_{mito} - \frac{1}{K_{eq\_g3p\_fad\_Q}} FAD_{pdhc}\cdot QH_{2mito}\right)$$

$V_{\max-g3pdh}^{cyt} = 6.4\cdot 10^4$

$V_{\max}^{g3pdh\_Q} = 3.2\cdot 10^6$

$$K_{eq-g3pdh}^{mito} = \exp\left(\frac{\left(2\cdot Em_{dhap/g3p} - 2\cdot Em_{FAD_{g3p}}\right)\cdot F}{1000\cdot R\cdot T}\right)$$

$$K_{eq-g3\_fad\_Q}^{mito} = \exp\left(\frac{\left(2\cdot Em_{FAD_{g3p}} + 2\cdot Em_{Q}\right)\cdot F}{1000\cdot R\cdot T}\right)$$

$Em_{dhap/g3p} = 190mV$

$Em_{FAD_{g3p}} = 210mV$

<u>Oxidative Phosphorylation</u>

ATP synthetase[33]

(ATP ↔ ADP + Pi)

$$v_{syn} = V_{\max}^{syn} \cdot \left(ADP_{mito} \cdot P_{mito} - \frac{ATP_{mito}}{K_{eq-syn}} \right)$$

$$V_{\max}^{syn} = 1.8 \cdot 10^{-16} \left(dG^{n} \right)$$

$$dG = -V_{mm} + \frac{R \cdot T}{1000 \cdot F} \ln\left(\frac{h_{cyt}}{h_{mito}} \right)$$

$$n = 3$$

$$K_{eq-syn} = \exp\left(\frac{dG_0^{syn}}{R \cdot T} - k \cdot U \right) \cdot \left(\frac{h_{cyt}}{h_{mito}} \right)^{k}$$

$$dG_0^{syn} = 30500$$

$$k = 3$$

The *dG* containing term describes activation by the proton motive force.

ADP/ATP exchanger[69]

(ATP_mito + ADP_cyt ↔ ADP_mito + ATP_cyt)

$$v_{ATP-exchanger} = V_{\max}^{ATP-exchanger} \left(\frac{1 - \frac{ATP_{in} \cdot ADP_{mito}}{ADP_{in} \cdot ATP_{mito}} \exp(U)}{\left(\left(1 + \frac{ATP_{in}}{ADP_{in}} \exp\left(S_{V_{mm}} \cdot U\right)\right) \left(1 + \frac{ADP_{mito}}{ATP_{mito}}\right) \right)} \right)$$

$$V_{\max}^{ATP-exchanger} = 5.4 \cdot 10^{-5}$$

$$S_{V_{mm}} = 0.3$$

ATP Consumption

ATP consumption is modeled as a Michaelis-Menten equation with low K_m value.

$$v_{ATP-use} = V_{\max-ATP-use} \frac{ATP_{in}}{ATP_{in} + K_m^{ATP}} (1 + activation)$$

$$K_m^{ATP} = 1$$

The activation describes the additional ATP consumption upon excitation. The value for the activation is 1 in undisturbed state.

Electrophysiology

$$U = \frac{V_{mm} \cdot F}{1000 \cdot R \cdot T}$$

$$F = 96490.0 \frac{C}{mol}$$

$$R = 8.314 \frac{J}{K \cdot mol}$$

$$T = 310 \; K$$

Electro diffusion

The passive efflux of sodium ions, potassium ions, chloride ions and protons is modeled by the Goldman-Hodgkin equation.

Potassium[70]

$$I_{K_{mito}}^{ed} = A_m \cdot P_{K_{mito}} \cdot U \cdot F \cdot \left(\frac{K_{in} - K_{mito} \cdot \exp(U)}{1 - \exp(U)} \right)$$

$$P_{Pot_{mito}} = 2 \cdot 10^{-10} \frac{m}{s}$$

Sodium

$$I_{Na_{mito}}^{ed} = A_m \cdot P_{Na_{mito}} \cdot U \cdot F \cdot \left(\frac{Na_{in} - Na_{mito} \cdot \exp(U)}{1 - \exp(U)} \right)$$

$$P_{Na_{mito}} = 1 \cdot 10^{-10} \frac{m}{s}$$

Protons[71, 72]

$$I_{H_{mito}}^{ed} = -A_m \cdot P_{H_{mito}} \cdot U \cdot F \cdot \left(\frac{H_{in} - H_{mito} \cdot \exp(U)}{1 - \exp(U)} \right)$$

$$P_{H_{mito}} = 2 \cdot 10^{-4} \frac{m}{s}$$

Pumps[73]

The pumping of sodium, potassium and phosphate is modeled as electro-neutral proton driven antiport.

$$v_{Phos-exchanger} = V_{\max}^{Phos-exchanger} \left(P_{in} \cdot H_{in} - P_{mito} \cdot H_{mito} \right)$$

$$V_{\max}^{Phos-exchanger} = 43.3485$$

$$I_{Na_{mito}}^{pump} = V_{\max}^{Na-pump} \left(Na_{in} \cdot H_{mito} - Na_{mito} \cdot H_{in} \right)$$

$$V_{\max}^{Na-pup} = 5 \cdot 10^{-3}$$

$$I_{Pot_{mito}}^{pump} = V_{\max}^{Pot-pump} \left(K_{in} \cdot H_{mito} - K_{mito} \cdot H_{in} \right)$$

$$V_{\max}^{K-pump} = 7.5 \cdot 10^{-4}$$

Protons are pumped by the corresponding processes in complex I, complex III and complex IV.

$$I_{H_{mito}}^{pump} = -\left(4v_{cx1} + 2v_{cx2} + 2v_{cx4} \right)$$

Calcium[73-79]

$$I_{Ca_{mito}}^{ed} = A_m \cdot 2 \cdot U \cdot F \cdot \left(\frac{Ca_{in} - Ca_{mito} \cdot \exp(2 \cdot U)}{1 - \exp(2 \cdot U)} \right) \left(P_{ca}^{RMC} \left(1 - \frac{ca_{cyt}}{ca_{cyt} + K_i^{ca_{cyt}}} \right) + P_{Ca}^{Mcu} \left(\frac{{Ca_{in}}^{n}}{{Ca_{in}}^{n} + \left(K_{m-Ca}^{Mcu}\right)^{n}} \right) \cdot \left(\frac{{Ca_{in}}^{n_a}}{{Ca_{in}}^{n_a} + \left(K_a^{Ca}\right)^{n_a}} \right) \right)$$

$$P_{ca}^{RMC} = 2 \cdot 10^{-6} \frac{m}{s}$$

$$K_i^{ca_{cyt}} = 0.0001$$

$$P_{Ca}^{Mcu} = 2 \cdot 10^{-2} \frac{m}{s}$$

$$K_{m-Ca}^{Mcu} = 19.2$$

$$n = 0.6$$

$$K_a^{Ca} = 0.0003$$

$$n_a = 5$$

$$I_{Ca-Na}^{pump} = \left(\frac{Ca_{mito}}{Ca_{mito} + K_m^{Ca_{mito}}} \right) \left(\frac{(Na_{in})^n}{(Na_{in})^n + \left(K_m^{Na_{in}}\right)^n} \right) \left(Ca_{mito} \cdot {Na_{in}}^{n^{Na}} - \frac{1}{K_{eq}^{Ca-Na}} Ca_{in} \cdot {Na_{mito}}^{n^{Na}} \right)$$

$$K_{eq}^{Ca-Na} = \exp\left(- \frac{V_{mm} \cdot F}{1000 \cdot R \cdot T} \right)$$

$$K_m^{Na_{in}} = 8$$

$$K_m^{Ca_{mito}} = 0.0096$$

$$n^{Na} = 3$$

$$n = 2.8$$

$$I_{Ca-H}^{pump} = \left(\frac{Ca_{mito}}{Ca_{mito} + K_m^{Ca_{mito}}} \right) \left(Ca_{mito} \cdot (H_{in})^n - \frac{1}{K_{eq}^{Ca-H}} Ca_{in} \cdot (H_{mito})^n \right)$$

$$K_{eq}^{Ca-H} = \exp\left(- \frac{V_{mm} \cdot F}{1000 \cdot R \cdot T} \right)$$

$$K_m^{Ca_{mito}} = 0.01$$

$$n^H = 3$$

Currents

$$I_{Na_{mito}} = I_{Na_{mito}}^{pump} + I_{Na_{mito}}^{ed} - n^{Na} \cdot I_{Ca-Na}^{pump}$$

$$I_{Pot_{mito}} = I_{Pot_{mito}}^{pump} + I_{Pot_{mito}}^{ed}$$

$$I_{H_{mito}} = I_{H_{mito}}^{ed} + I_{H_{mito}}^{pump} + I_{Na_{mito}}^{pump} + I_{Pot_{mito}}^{pump} - n^H \cdot I_{Ca-H}^{pump} + v_{Phos-exchanger} + 3 \cdot v_{syn}$$

$$I_{Ca_{mito}} = I_{Ca-Na}^{pump} + I_{Ca-H}^{pump} + I_{Ca_{mito}}^{ed}$$

Membrane potential

The mitochondrial membrane is modeled by the capacitor equation.

$$v_{V_{mm}} = \frac{1}{c_m \cdot A_m} \left(- I_C + I_K + I_H + I_{Na} + 2 \cdot I_{Ca} - v_{Phos-exchanger} + v_{ATP-exchanger} \right)$$

$$c_m = 0.9 \cdot 10^{-6}\ farad / cm^2$$

$$A_m = 3.7 \cdot 10^{-5} cm^2$$

Complex I[19]

(NADH + Q + 4 H_mito <-> NAD + QH2 + 4 H_in)

$$v_{cxI} = V_{\max}^{cxI} \cdot \left(nadh_{mito} \cdot Q - \frac{1}{K_{eq}^{cxI}} nad_{mito} \cdot QH_2 \right)$$

$$V_{\max}^{cxI} = 2.25$$

$$K_{eq}^{cxI} = \exp\left(2 \cdot Em_N + 2 \cdot Em_Q + \frac{4 \cdot V_{mm} \cdot F}{1000 \cdot R \cdot T}\right)\left(\frac{h_{mito}}{h_{in}}\right)^4$$

Complex III[19]

$$v_{cxIII} = V_{\max}^{cxIII} \cdot \left(QH_2 \cdot cytc_{ox}{}^n - \frac{1}{K_{eq}^{cxIII}} Q \cdot cytc_{red}{}^n\right)$$

$$V_{\max}^{cxIII} = 2.25 \cdot 10^4$$

$$K_{eq}^{cxIII} = \exp\left(-2 \cdot Em_Q + 2 \cdot Em_{cytc} + \frac{2 \cdot V_{mm} \cdot F}{1000 \cdot R \cdot T}\right)\left(\frac{h_{mito}}{h_{in}}\right)^4$$

Complex IV[80-82]

(2 cyt_red + O2 + 4 H_mito → H2O + 2 cyt_ox + 2 H_ in)

$$v_{C_4} = V_{\max}^{Cx4} \cdot \frac{cytC_{red}{}^n}{cytC_{red}{}^n + \left(K_m^{cytC_{red}}\right)^n} \frac{O_{2mito}}{O_{2mito} + K_m^{O_2}} \exp\left(-\frac{dG_H \cdot F}{1000 \cdot R \cdot T}\right)^2$$

$$V_{\max}^{Cx4} = 32.5$$

$$K_m^{O_2} = 0.001$$

$$K_m^{cytC_{red}} = 0.001$$

$$n = 2$$

The factor $\exp\left(-\frac{dG_H \cdot F}{1000 \cdot R \cdot T}\right)^2$ was included to ensure proper activation of complex IV with increased demand, but complex IV activity might actually be regulated by the intra- and/or extramitochondrial ATP/ADP ratio and/or calcium, but exact kinetics are unknown.

CAC

Pyruvate exchanger[83]

(Pyr_in + H_mito <-> Pyr_mito + H_in)

$$v_{pyr-exchanger} = V_{\max}^{Pyr-exchanger} \cdot \frac{(Pyr_{in} \cdot H_{in} - Pyr_{mito} \cdot H_{mito})}{\left(1 + \frac{Pyr_{in}}{K_m^{Pyr_{in}}}\right)\left(1 + \frac{Pyr_{mito}}{K_m^{Pyr_{mito}}}\right)}$$

$$V_{\max}^{Pyr-exchanger} = 128$$

$$K_m^{Pyr_{in}} = 0.15$$

$$K_m^{Pyr_{mito}} = 0.15$$

Pyruvate dehydrogenase complex[26, 84, 85]

(Pyr_mito + CoA + FAD_pdhc -> AcCoA + CO_2 + $FADH_2$_pdhc)

($FADH_2$_pdhc + NAD_mito <-> FAD_pdhc + NADH_mito)

$$v_{pdhc\_fad} = V_{\max}^{pdhc\_fad}\left(1 + A_{\max}^{Ca_{mito}} \frac{Ca_{mito}}{Ca_{mito} + K_a^{Ca_{mito}}}\right)\left(\frac{Pyr_{mito}}{Pyr_{mtio} + K_m^{Pyr}}\right)\left(\frac{FAD_{pdhc}}{FAD_{pdhc} + K_m^{FAD_{pdhc}}}\right)\left(\frac{CoA_{mito}}{CoA_{mito} + K_m^{CoA_{mito}} \cdot \left(1 + \frac{ACoA_{mito}}{K_i^{ACoA}}\right)}\right)$$

$$v_{pdhc\_nad} = V_{\max}^{pdhc\_nad} \cdot \frac{\left(FADH_{2\_pdhc} \cdot NAD_{mito} - \frac{1}{K_{eq\_pdhc\_fad\_nad}} FAD_{pdhc} \cdot NADH_{mito}\right)}{\left(NAD_{mito} + K_m^{NAD_{mito}}\right)}$$

$$V_{\max}^{pdhc\_fad} = 13.1$$

$$V_{\max}^{pdhc\_nad} = 1e4$$

$$A_{\max}^{Ca_{mito}} = 1.7$$

$$K_a^{Ca_{mito}} = 10^{-3}$$

$$K_m^{Pyr} = 0.068$$

$$K_m^{NAD_{mito}} = 0.041$$

$$K_m^{CoA_{mito}} = 0.0047$$

$$K_i^{ACoA_{mito}} = 0.0004$$

$$K_m^{FAD_{pdhc}} = 0.00001$$

$$K_{eq-pdhc\_fad\_nad} = \exp\left(\frac{\left(2 \cdot Em_{FAD} + 2 \cdot Em_{NAD}\right) \cdot F}{1000 \cdot R \cdot T}\right)$$

$$Em_m^{FAD} = 297mV$$

Citrate synthetase[86]

(Oxa + AcCoA → Cit)

$$v_{cs} = V_{\max}^{cs}\left(\frac{Oxa_{mtio}}{Oxa_{mito} + K_m^{Oxa}\left(1 + \frac{Cit_{mito}}{K_i^{cit}}\right)}\right)\left(\frac{AcCoA_{mito}}{AcCoA_{mito} + K_m^{AcCoA} \cdot \left(1 + \frac{CoA_{mito}}{K_i^{CoA}}\right)}\right)$$

$$V_{\max}^{cs} = 1.28 \cdot 10^3$$

$$K_m^{Oxa} = 0.0045$$

$$K_i^{Cit} = 3.7$$

$$K_m^{accoa} = 0.005$$

$$K_i^{CoA} = 0.025$$

$$K_{eq}^{Aco} =$$

Aconitase[87]

(Cit ↔ IsoCit)

$$v_{Aco} = V_{\max}^{Aco} \frac{Cit_{mito} - \frac{IsoCit_{mito}}{K_{eq}^{Aco}}}{1 + \frac{Cit_{mito}}{K_m^{Cit}} + \frac{IsoCit_{mito}}{K_m^{IsoCit}}}$$

$$V_{\max}^{Aco} = 1.6 \cdot 10^6$$

$$K_{eq}^{Aco} = 0.067$$

$$K_m^{Cit} = 0.48$$

$$K_m^{IsoCit} = 0.12$$

NAD-dependent isocitrate dehydrogenase[88-92]

(IsoCit + NAD → akg + NADH)

$$v_{icdh} = V_{\max}^{icdh} \left(\frac{IsoCit_{mito}^{n^{IsoCit}}}{IsoCit_{mito}^{n^{IsoCit}} + \left(K_m^{IsoCit}\right)^{n^{IsoCit}}} \right) \left(\frac{NAD_{mito}}{NAD_{mito} + K_m^{NAD} \cdot \left(1 + \frac{NADH_{mito}}{K_i^{NADH}}\right)} \right)$$

$$V_{\max}^{icdh} = 64$$

$$n^{IsoCit} = 1.9$$

$$K_m^{IsoCit} = \frac{K_{m1}^{IsoCit}}{\left(1 + \left(\frac{Ca_{mito}}{K_a^{Ca}}\right)^{n^{Ca}}\right)} + K_{m2}^{IsoCit}$$

$$K_{m1}^{IsoCit} = 0.11$$

$$K_{m2}^{IsoCit} = 0.06$$

$$K_a^{Ca} = 0.0074$$

$$n^{Ca} = 2$$

$$K_m^{NAD} = 0.091$$

$$K_i^{NADH} = 0.041$$

α-ketogluterate dehydrogenase complex[16, 22-26]

(akg + NAD + CoA → SucCoA + NADH)

$$v_{akdhc\_fad} = V_{\max}^{akdhc\_fad}\left(\frac{akg_{mito}}{akg_{mito} + K_m^{akdhc}}\right)\left(\frac{FAD_{kgdhc}}{FAD_{mito} + K_m^{FAD_{kgdhc}}}\right)\left(\frac{CoA}{CoA + K_m^{CoA}\cdot\left(1+\frac{SucCoA}{K_i^{SucCoA}}\right)}\right)$$

$$v_{pdhc\_nad} = V_{\max}^{pdhc\_nad}\cdot\frac{\left(FADH_{2\_kgdhc}\cdot NAD_{mito} - \frac{1}{K_{eq\_kgdhc\_fad\_nad}}FAD_{kgdhc}\cdot NADH_{mito}\right)}{\left(NAD_{mito} + K_m^{NAD}\cdot\left(1+\frac{NADH_{mito}}{K_i^{NADH}}\right)\right)}$$

$$V_{\max}^{akdhc\_nad} = 134.4$$

$$V_{\max}^{akdhc\_fad} = 1e4$$

$$K_m^{akdhc} = \left(\frac{K_{m1}^{akdhc}}{\left(1+\frac{Ca_{mito}}{K_{i-akg}^{Ca}}\right)} + K_{m2}^{akgh}\right)\left(1+\frac{NADH_{mito}}{K_{i-akg}^{NADH}}\right)$$

$$K_{m1}^{akdhc} = 2.5$$

$$K_m^{NAD} = 0.021$$

$$K_i^{NADH} = 0.0045$$

$$K_m^{CoA} = 0.0013$$

$$K_i^{SucCoA} = 0.0045$$

$$K_m^{FAD_{kgdhc}} = 0.00001$$

$$K_{eq-kgdhc\_fad\_nad} = \exp\left(\frac{(2 \cdot Em_{FAD} + 2 \cdot Em_{NAD}) \cdot F}{1000 \cdot R \cdot T}\right)$$

$$Em_m^{FAD} = 297 mV$$

Succinyl-CoA synthetase[93-96]

(SucCoA + ADP/GDP + P ↔ Succ + CoA + ATP/GTP)

$$v_{succoa-atp} = V_{\max}^{succoa-atp}\left(1 + A_{\max}^{P} \cdot \left(\frac{P_{mito}^{n^P}}{P_{mito}^{n^P} + \left(K_m^P\right)^{n^P}}\right)\right)\left(\frac{SucCoA_{mito} \cdot ADP_{mito} \cdot P_{mito} - \frac{Succ_{mito} \cdot CoA_{mito} \cdot ATP_{mito}}{K_{eq-succoas}}}{\left(1+\frac{SucCoA_{mito}}{K_m^{SucCoA}}\right)\left(1+\frac{ADP_{mito}}{K_m^{ADP}}\right)\left(1+\frac{P_{mito}}{K_m^{P}}\right)+\left(1+\frac{Succ_{mito}}{K_m^{Succ}}\right)\left(1+\frac{CoA_{mito}}{K_m^{CoA}}\right)\left(1+\frac{ATP_{mito}}{K_m^{ATP}}\right)-1}\right)$$

$$V_{\max-succoas-atp} = 1.92 \cdot 10^4$$

$$K_{eq-succoas} = 3.8$$

$$A_{\max}^{P} = 1.2$$

$$K_m^P = 2.5$$

$$n^P = 3$$

$$K_m^{SucCoA} = 0.041$$

$$K_m^{ADP} = 0.25$$

$$K_m^P = 0.72$$

$$K_m^{Succ} = 1.6$$

$$K_m^{CoA} = 0.056$$

$$K_m^{ATP} = 0.017$$

$$v_{succoa-gtp} = V_{\max}^{succoa-gtp}\left(1 + A_{\max}^{P}\cdot\left(\frac{P_{mito}^{n^P}}{P_{mito}^{n^P} + \left(K_m^P\right)^{n^P}}\right)\right)\left(\frac{SucCoA_{mito}\cdot GDP_{mito}\cdot P_{mito} - \frac{Succ_{mito}\cdot CoA_{mito}\cdot GTP_{mito}}{K_{eq-succoas}}}{\left(1+\frac{SucCoA_{mito}}{K_m^{SucCoA}}\right)\left(1+\frac{GDP_{mito}}{K_m^{GDP}}\right)\left(1+\frac{P_{mito}}{K_m^P}\right) + \left(1+\frac{Succ_{mito}}{K_m^{Succ}}\right)\left(1+\frac{CoA_{mito}}{K_m^{CoA}}\right)\left(1+\frac{GTP_{mito}}{K_m^{GTP}}\right) - 1}\right)$$

$$K_{eq-succoas} = 3.8$$

$$A_{\max}^{P} = 1.2$$

$$K_m^P = 2.5$$

$$n^P = 3$$

$$K_m^{SucCoA} = 0.086$$

$$K_m^{GDP} = 0.007$$

$$K_m^P = 2.26$$

$$K_m^{Succ} = 0.49$$

$$K_m^{CoA} = 0.036$$

$$K_m^{GTP} = 0.036$$

Succinate dehydrogenase[97-99]

(Succ + FAD_succdh ↔ Fum + FADH2_succdh)

(Succ + Q ↔ Fum + QH_2)

$$v_{succdh\_fad} = V_{\max-succdh\_fad}\left(\frac{Succ_{mito}\cdot Q_n - \frac{Fum_{mito}\cdot (QH_2)_n}{K_{eq-succdh}}}{Succ_{mito} + K_m^{Succ}\left(1+\frac{Mal_{mito}}{K_i^{Mal}}\right)}\right)$$

$$v_{succdhc\_nad} = V_{\max}^{succdh\_nad} \cdot \frac{\left(FADH_{2\_pdhc} \cdot NAD_{mito} - \frac{1}{K_{eq\_pdhc\_fad\_nad}} FAD_{pdhc} \cdot NADH_{mito} \right)}{\left(NAD_{mito} + K_m^{NAD_{mito}} \right)}$$

$$V_{\max-succdh} = 1.6 \cdot 10^5$$

$$V_{\max}^{succdh\_nad} = 10^{12}$$

$$K_{eq-succdh\_fad} = \exp\left(\frac{25 \cdot F}{R \cdot T} \right) \cdot \exp\left(\frac{-Em_{FAD-succdh} \cdot F}{R \cdot T} \right)$$

$$K_{eq-succdh\_nad} = \exp\left(\frac{Em_{FAD-succdh} \cdot F}{R \cdot T} \right)$$

$$K_m^{Succ} = 1.6$$

$$K_i^{Mal} = 2.2$$

$$Em_{FAD-succdh} = 100mV$$

Fumarase[100, 101]

(Fum ↔ Mal)

$$v_{fum} = V_{\max-fum} \left(\frac{Fum_{mito} - \frac{Mal_{mito}}{K_{eq-fum}}}{1 + \frac{Fum_{mito}}{K_m^{Fum}} + \frac{Mal_{mito}}{K_m^{Mal}}} \right)$$

$$V_{\max-fum} = 6.4 \cdot 10^7$$

$$K_{eq-fum} = 4.4$$

$$K_m^{Fum} = 0.14$$

$$K_m^{Mal} = 0.3$$

Malate dehydrogenase[61, 88, 102]

(Mal + NAD ↔ Oxa + NADH)

$$v_{mdh} = V_{\max-mdh}\left(\frac{Mal_{mito}\cdot NAD_{mito} - \dfrac{Oxa_{mito}\cdot NADH_{mito}}{K_{eq-mdh}}}{\left(1+\dfrac{Mal_{mito}}{K_m^{Mal}}\right)\left(1+\dfrac{NAD_{mito}}{K_m^{NAD}}\right)+\left(1+\dfrac{Oxa_{mito}}{K_m^{Oxa}}\right)\left(1+\dfrac{NADH_{mito}}{K_m^{NADH}}\right)-1}\right)$$

$$V_{\max-mdh} = 3.2\cdot 10^{4}$$

$$K_{eq-mdh} = 1\cdot 10^{-4}$$

$$K_m^{Mal} = 0.145$$

$$K_m^{NAD} = 0.06$$

$$K_m^{Oxa} = 0.017$$

$$K_m^{NADH} = 0.044$$

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