SUPPLEMENTAL MATERIAL

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SUPPLEMENTAL METHODS AND RESULTS

Supplement S1: Information to Kinetic rate laws

Important note: Due to reference restrictions, we do not cite the references for the kinetic parameters in this version of the Supplemental Material. You can find a version of this document with complete references on our homepage at:

https://icm.charite.de/en/research/metabolic_and_biophysical_simulations_in_systems_medicine/publications/cardiokin1/

Fatty acid uptake

Carrier mediated FATP

$$v_{CD36} = V_{max}^{CD36} \cdot \frac{(ffa_{ext} - c16_{cyt})}{1 + \frac{ffa_{ext}}{K_m^{ffa_{ext}}} + \frac{c16_{cyt}}{K_m^{c16_{cyt}}}}$$

V_{max}^{CD36} for numerical value see Supplemental Table II

$K_m^{ffa_{ext}} = 0.000085$

$K_m^{c16_{cyt}} = 0.004$

(Long-chain) acyl-coa synthetase

$$v_{ACS1} = V_{max}^{ACS1} \cdot \frac{c16_{cyt}}{c16_{cyt} + K_m^{c16_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \cdot \frac{coa_{cyt}}{coa_{cyt} + K_m^{coa_{cyt}}}$$

V_{max}^{ACS1} for numerical value see Supplemental Table II

$K_m^{c16_{cyt}} = 0.033$

$K_m^{atp_{cyt}} = 0.320$

$K_m^{coa_{cyt}} = 0.0064$

$$v_{FATP1} = V_{max}^{FATP1} \cdot \frac{c16_{cyt}}{c16_{cyt}+K_m^{c16_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt}+K_m^{atp_{cyt}}} \cdot \frac{coa_{cyt}}{coa_{cyt}+K_m^{coa_{cyt}}}$$

$$V_{max}^{FATP1} = \frac{V_{max}^{ACS1}}{27}$$

$K_m^{c16_{cyt}}$ =0.021

$K_m^{atp_{cyt}}$ =0.850

$K_m^{coa_{cyt}}$ =0.0083

$$v_{FATP4} = V_{max}^{FATP4} \cdot \frac{c16_{cyt}}{c16_{cyt}+K_m^{c16_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt}+K_m^{atp_{cyt}}} \cdot \frac{coa_{cyt}}{coa_{cyt}+K_m^{coa_{cyt}}}$$

$V_{max}^{FATP4} = 1.3 \cdot V_{max}^{ACS1}$

$K_m^{c16_{cyt}}$ =0.013

$K_m^{atp_{cyt}}$ =1.4

$K_m^{coa_{cyt}}$ =0.047

Beta-oxidation

Carnitine palmitoyltransferase I (muscle isoform)

$$v_{CPT1} = V_{max}^{CPT1} \cdot \frac{c16coa_{cyt} \cdot car_{cyt}}{\left(c16coa_{cyt} + K_m^{c16coa_{cyt}}\right) \cdot \left(car_{cyt} + K_m^{car_{cyt}}\right)}$$

V_{max}^{CPT1} for numerical value see Supplemental Table II

$$K_m^{c16coa_{cyt}} = K_0^{c16coa_{cyt}} \cdot \left(1 + \frac{malcoa2_{imm}}{K_i^{malcoa2_{imm}}}\right)$$

$K_0^{c16coa_{cyt}}$ =0.073

$K_i^{malcoa2_{imm}} =$ 0.0001

$K_m^{car_{cyt}}$ =0.19

Carnitine acylcarnitine translocase

$$v_{CACT} = V_{max}^{CACT} \cdot \left(\frac{car_{mito} \cdot c16car_{cyt} - {}^{1}\!/\!_{K_{eq}^{CACT}} \cdot car_{cyt} \cdot c16car_{mito}}{\left(1 + \frac{car_{mito}}{K_m^{car_{mito}}}\right)\left(1 + \frac{c16car_{cyt}}{K_m^{c16coa_{cyt}}}\right) + \left(1 + \frac{car_{cyt}}{K_m^{car_{cyt}}}\right)\left(1 + \frac{c16car_{mito}}{K_m^{c16car_{mito}}}\right) - 1}\right)$$

V_{max}^{CACT} for numerical value see Supplemental Table II

$K_{eq}^{CACT} = 1.6$

$K_m^{car_{mito}} = 5.8$

$K_m^{c16car_{cyt}}$ =0.001

$K_m^{car_{cyt}} = 1.3$

$K_m^{c16car_{mito}} = 0.0051$

Carnitine palmitoyltransferase 2

$$v_{CPT2} = V_{max}^{CPT2} \cdot \left(\frac{c16car_{mito} \cdot coa_{mito} - 1/K_{eq}^{CPT2} \cdot c16coa_{mito} \cdot car_{mito}}{\left(1 + \frac{c16car_{mito}}{K_m^{c16car_{mito}}}\right)\left(1 + \frac{coa_{mito}}{K_m^{coa_{mito}}}\right) + \left(1 + \frac{c16coa_{mito}}{K_m^{c16coa_{mito}}}\right)\left(1 + \frac{car_{mito}}{K_m^{car_{mito}}}\right) - 1} \right)$$

V_{max}^{CPT2} for numerical value see Supplemental Table II

$K_{eq}^{CPT2} = 2$

$K_m^{c16car_{mito}}$ =0.12

$K_m^{coa_{mito}} = 0.0055$

$K_m^{c16coa_{mito}}$ =0.191

$K_m^{car_{mito}}$ =0.46

Short chain acyl-coa dehydrogenase (c4) (identical to liver enzyme)

$$v_{c4coa-scdh} = V_{max}^{c4coa-dh} \cdot \left(\frac{c4coa_{mito}}{c4coa_{mito} + K_m^{c4coa_{mito}}} \right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}} \right)$$

$V_{max}^{c4coa-dh}$ for numerical value see Supplemental Table II

$K_m^{c4coa_{mito}} = 0.0107$

$K_m^{etffad_{mito}} = 0.0038$

Short chain acyl-coa dehydrogenase (c5) (identical to liver enzyme)

$$v_{c5coa-scdh} = V_{max}^{c5coa-dh} \cdot \left(\frac{c5coa_{mito}}{c5coa_{mito} + K_m^{c5coa_{mito}}} \right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}} \right)$$

$V_{max}^{c5coa-dh}$ for numerical value see Supplemental Table II

$K_m^{c5coa_{mito}} = 0.01$

$K_m^{etffad_{mito}} = 0.0038$

Medium chain acyl-coa dehydrogenase (c6) (identical to liver enzyme)

$$v_{c6coa-mcdh} = V_{max}^{c6coa-dh} \cdot \left(\frac{c6coa_{mito}}{c6coa_{mito} + K_m^{c6coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c6coa-dh}$ for numerical value see Supplemental Table II

$K_m^{c6coa_{mito}} = 0.0094$

$K_m^{etffad_{mito}} = 0.0045$

Medium chain acyl-coa dehydrogenase (c8) (identical to liver enzyme)

$$v_{c8coa-mcdh} = V_{max}^{c8coa-dh} \cdot \left(\frac{c8coa_{mito}}{c8coa_{mito} + K_m^{c8coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c8coa-dh}$ for numerical value see Supplemental Table II

$K_m^{c8coa_{mito}} = 0.004$

$K_m^{etffad_{mito}} = 0.0045$

Medium chain acyl-coa dehydrogenase (c10) (identical to liver enzyme)

$$v_{c10coa-mcdh} = V_{max}^{c10coa-dh} \cdot \left(\frac{c10coa_{mito}}{c10coa_{mito} + K_m^{c10coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c10coa-dh}$ for numerical value see Supplemental Table II

$K_m^{c10coa_{mito}} = 0.0054$

$K_m^{etffad_{mito}} = 0.0045$

Medium chain acyl-coa dehydrogenase (c12) (identical to liver enzyme)

$$v_{c12coa-mcdh} = V_{max}^{c12coa-dh} \cdot \left(\frac{c12coa_{mito}}{c12coa_{mito} + K_m^{c12coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c12coa-dh}$ for numerical value see Supplemental Table II

$K_m^{c12coa_{mito}} =0.0057$

$K_m^{etffad_{mito}} = 0.0045$

Long chain acyl-coa dehydrogenase (c10) (identical to liver enzyme)

$$v_{c10coa-lcdh} = V_{max}^{c10coa-dh} \cdot \left(\frac{c10coa_{mito}}{c10coa_{mito} + K_m^{c10coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c10coa-dh}$ for numerical value see Supplemental Table II

$$K_m^{c10coa_{mito}} = K_0^{c10coa_{mito}} \cdot \left(1 + \frac{kc16coa_{mito}}{K_i^{kc16coa_{mito}}}\right)$$

$K_i^{kc16coa_{mito}} = 0.00047$

$K_0^{c10coa_{mito}} = 0.0243$

$K_m^{etffad_{mito}} = 0.0083$

Long chain acyl-coa dehydrogenase (c12) (identical to liver enzyme)

$$v_{c12coa-lcdh} = V_{max}^{c12coa-dh} \cdot \left(\frac{c12coa_{mito}}{c12coa_{mito} + K_m^{c12coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c12coa-dh}$ for numerical value see Supplemental Table II

$$K_m^{c12coa_{mito}} = K_0^{c12coa_{mito}} \cdot \left(1 + \frac{kc16coa_{mito}}{K_i^{kc16coa_{mito}}}\right)$$

$K_i^{kc16coa_{mito}} = 0.00047$

$K_0^{c12coa_{mito}} = 0.009$

$K_m^{etffad_{mito}} = 0.0083$

Long chain acyl-coa dehydrogenase (c14) (identical to liver enzyme)

$$v_{c14coa-lcdh} = V_{max}^{c14coa-dh} \cdot \left(\frac{c14coa_{mito}}{c14coa_{mito} + K_m^{c14coa_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{c14coa-dh}$ for numerical value see Supplemental Table II

$$K_m^{c14coa_{mito}} = K_0^{c14coa_{mito}} \cdot \left(1 + \frac{kc16coa_{mito}}{K_i^{kc16coa_{mito}}}\right)$$

$K_i^{kc16coa_{mito}} = 0.00047$

$K_0^{c14coa_{mito}} = 0.0074$

$K_m^{etffad_{mito}} = 0.0083$

Long chain acyl-coa dehydrogenase (c16) (identical to liver enzyme)

$$v_{c16coa-lcdh} = V_{max}^{c16coa-dh} \cdot \left(\frac{c16coa_{mito}}{c16coa_{mito} + K_m^{c16coa_{mito}}} \right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}} \right)$$

$V_{max}^{c16coa-dh}$ for numerical value see Supplemental Table II

$$K_m^{c16coa_{mito}} = K_0^{c16coa_{mito}} \cdot \left(1 + \frac{kc16coa_{mito}}{K_i^{kc16coa_{mito}}} \right)$$

$K_i^{kc16coa_{mito}} = 0.00047$

$K_0^{c16coa_{mito}} = 0.0025$ [62]

$K_m^{etffad_{mito}} = 0.0083$ [62]

Enoyl-coa hydratase (Crontonase) (ec4)

$$v_{ehyd-ec4} = V_{max}^{ehyd-ec4} \cdot \left(\frac{ec4coa_{mito} - {}^{1}\!/\!_{K_{eq}^{ehyd-ec4}} \cdot lc4coa_{mito}}{ec4coa_{mito} + K_m^{ec4coa_{mito}}} \right)$$

$V_{max}^{ehyd-ec4}$ for numerical value see Supplemental Table II

$K_{eq}^{ehyd-ec4} = 0.25$

$$K_m^{ec4coa_{mito}} = K_0^{ec4coa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}} \right)$$

$K_0^{ec4coa_{mito}} = 0.013$

$K_i^{kc4coa_{mito}} = 0.025$

Enoyl-coa hydratase (Crontonase) (ec6)

$$v_{ehyd-ec6} = V_{max}^{ehyd-ec6} \cdot \left(\frac{ec6coa_{mito} - {}^{1}\!/\!_{K_{eq}^{ehyd-ec6}} \cdot lc6coa_{mito}}{ec6coa_{mito} + K_m^{ec6coa_{mito}}} \right)$$

$V_{max}^{ehyd-ec6} = V_{max}^{ehyd-ec4} \cdot \frac{1280}{1670}$

$K_{eq}^{ehyd-ec6} = 2$

$$K_m^{ec6coa_{mito}} = K_0^{ec6_{coa_{mito}}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}} \right)$$

$K_0^{ec6coa_{mito}} = 0.029$

$K_i^{kc4coa_{mito}}$ =0.025

Enoyl-coa hydratase (Crontonase) (ec8)

$$v_{ehyd-ec8} = V_{max}^{ehyd-ec8} \cdot \left(\frac{ec8coa_{mito} - {}^{1}\!/_{K_{eq}^{ehyd-ec8}} \cdot lc8coa_{mito}}{ec8coa_{mito} + K_m^{ec8coa_{mito}}} \right)$$

$V_{max}^{ehyd-ec8} = V_{max}^{ehyd-ec4} \cdot \frac{910}{1670}$

$K_{eq}^{ehyd-ec8} = 2$

$K_m^{ec8coa_{mito}} = K_0^{ec8coa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$

$K_0^{ec8coa_{mito}} = 0.029$

$K_i^{kc4coa_{mito}}$ =0.025

Enoyl-coa hydratase (Crontonase) (ec10)

$$v_{ehyd-ec10} = V_{max}^{ehyd-ec10} \cdot \left(\frac{ec10coa_{mito} - {}^{1}\!/_{K_{eq}^{ehyd-ec10}} \cdot lc10coa_{mito}}{ec10coa_{mito} + K_m^{ec10coa_{mito}}} \right)$$

$V_{max}^{ehyd-ec10} = V_{max}^{ehyd-ec4} \cdot \frac{540}{1670}$

$K_{eq}^{ehyd-ec10} = 2$

$K_m^{ec10coa_{mito}} = K_0^{ec10coa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$

$K_0^{ec10coa_{mito}} = 0.029$

$K_i^{kc4coa_{mito}}$ =0.025

Enoyl-coa hydratase (Crontonase) (ec12)

$$v_{ehyd-ec12} = V_{max}^{ehyd-ec12} \cdot \left(\frac{ec12coa_{mito} - {}^{1}\!/_{K_{eq}^{ehyd-ec12}} \cdot lc12coa_{mito}}{ec12coa_{mito} + K_m^{ec12coa_{mito}}} \right)$$

$$V_{max}^{ehyd-ec12} = V_{max}^{ehyd-ec4} \cdot \frac{160}{1670}$$

$$K_{eq}^{ehyd-ec12} = 2$$

$$K_m^{ec12coa_{mito}} = K_0^{ec12coa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$$

$$K_0^{ec12coa_{mito}} = 0.030$$

$$K_i^{kc4coa_{mito}} = 0.025$$

Enoyl-coa hydratase (Crontonase) (ec14)

$$v_{ehyd-ec14} = V_{max}^{ehyd-ec14} \cdot \left(\frac{ec14coa_{mito} - {}^{1}/_{K_{eq}^{ehyd-ec14}} \cdot lc14coa_{mito}}{ec14coa_{mito} + K_m^{ec14coa_{mito}}}\right)$$

$$V_{max}^{ehyd-ec14} = V_{max}^{ehyd-ec16} \cdot \frac{5}{2.3}$$

$$K_{eq}^{ehyd-ec14} = 2$$

$$K_m^{ec14coa_{mito}} = K_0^{ec14coa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$$

$$K_0^{ec14coa_{mito}} = 0.025$$

$$K_i^{kc4coa_{mito}} = 0.025$$

Enoyl-coa hydratase (Crontonase) (ec16)

$$v_{ehyd-ec16} = V_{max}^{ehyd-ec16} \cdot \left(\frac{ec16coa_{mito} \ {}^{1}/_{K_{eq}^{ehyd-ec16}} \cdot lc16coa_{mito}}{ec16coa_{mito} + K_m^{ec16coa_{mito}}}\right)$$

$$V_{max}^{ehyd-ec16} = V_{max}^{ehyd-ec4} \cdot \frac{40}{1670}$$

$$K_{eq}^{ehyd-ec16} = 2$$

$$K_m^{ec16coa_{mito}} = K_0^{ec16coa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$$

$$K_0^{ec16coa_{mito}} = 0.030$$

$$K_i^{kc4coa_{mito}} = 0.025$$

3-hydroxyacyl-coa dehydrogenase (lc4) (identic with liver enzyme)

$$v_{3hdh-lc4} = V_{max}^{3hdh-lc4} \cdot \left(\frac{lc4coa_{mito} \cdot nad_{mito} - 1/K_{eq}^{3hdh-lc4} \cdot kc4coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc4coa_{mito}}{K_m^{lc4coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc4coa_{mito}}{K_m^{kc4coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc4}$ for numerical value see Supplemental Table II

$K_{eq}^{3hdh-lc4} = \frac{1}{0.012}$

$K_m^{lc4coa_{mito}} = 0.0072$

$K_m^{nad_{mito}} = 0.0154$

$K_m^{kc4coa_{mito}} = 0.0169$

$K_m^{nadh_{mito}} = 0.0118$

3-hydroxyacyl-coa dehydrogenase (lc6) (identic with liver enzyme)

$$v_{3hdh-lc6} = V_{max}^{3hdh-lc6} \cdot \left(\frac{lc6coa_{mito} \cdot nad_{mito} - 1/K_{eq}^{3hdh-lc6} \cdot kc6coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc6coa_{mito}}{K_m^{lc6coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc6coa_{mito}}{K_m^{kc6coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc6}$ for numerical value see Supplemental Table II

$K_{eq}^{3hdh-lc6} = \frac{1}{8 \cdot 10^{-4}}$

$K_m^{lc6coa_{mito}} = 0.0286$

$K_m^{nad_{mito}} = 0.015$

$K_m^{kc6coa_{mito}} = 0.0057$

$K_m^{nadh_{mito}} = 0.011$

3-hydroxyacyl-coa dehydrogenase (lc8) (identic with liver enzyme)

$$v_{3hdh-lc8} = V_{max}^{3hdh-lc8} \cdot \left(\frac{lc8coa_{mito} \cdot nad_{mito} - 1/K_{eq}^{3hdh-lc8} \cdot kc8coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc8coa_{mito}}{K_m^{lc8coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc8coa_{mito}}{K_m^{kc8coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc8}$ for numerical value see Supplemental Table II

$K_{eq}^{3hdh-lc8} = \frac{1}{10^{-3}}$

$K_m^{lc8coa_{mito}} = 0.0163$

$K_m^{nad_{mito}} = 0.015$

$K_m^{kc8coa_{mito}} = 0.0031$

$K_m^{nadh_{mito}} = 0.011$

3-hydroxyacyl-coa dehydrogenase (lc10) (identic with liver enzyme)

$$v_{3hdh-lc10} = V_{max}^{3hdh-lc10} \cdot \left(\frac{lc10coa_{mito} \cdot nad_{mito} - 1/K_{eq}^{3hdh-lc10} \cdot kc10coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc10coa_{mito}}{K_m^{lc10coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc10coa_{mito}}{K_m^{kc10coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc10}$ for numerical value see Supplemental Table II

$K_{eq}^{3hdh-lc10} = \frac{1}{10^{-3}}$

$K_m^{lc10coa_{mito}} = 0.0029$

$K_m^{nad_{mito}} = 0.0104$

$K_m^{kc10_{coa_{mito}}} = 0.0018$

$K_m^{nadh_{mito}} = 0.0011$

3-hydroxyacyl-coa dehydrogenase (lc12) (identic with liver enzyme)

$$v_{3hdh-lc12} = V_{max}^{3hdh-lc12} \cdot \left(\frac{lc12coa_{mito} \cdot nad_{mito} - {}^{1}\!/\!{}_{K_{eq}^{3hdh-lc12}} \cdot kc12coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc12coa_{mito}}{K_m^{lc12coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc12coa_{mito}}{K_m^{kc12coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc12}$ for numerical value see Supplemental Table II

$K_{eq}^{3hdh-lc12} = \frac{1}{10^{-3}}$

$K_m^{lc12coa_{mito}} = 0.0018$

$K_m^{nad_{mito}} = 0.015$

$K_m^{kc12coa_{mito}} = 0.0018$

$K_m^{nadh_{mito}} = 0.011$

3-hydroxyacyl-coa dehydrogenase (lc14) (identic with liver enzyme)

$$v_{3hdh-lc14} = V_{max}^{3hdh-lc14} \cdot \left(\frac{lc14coa_{mito} \cdot nad_{mito} - {}^{1}\!/\!{}_{K_{eq}^{3hdh-lc14}} \cdot kc14coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc14coa_{mito}}{K_m^{lc14coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc14coa_{mito}}{K_m^{kc14coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc14}$ for numerical value see Supplemental Table II

$K_{eq}^{3hdh-lc14} = \frac{1}{10^{-3}}$

$K_m^{lc14coa_{mito}}$ =0.0015

$K_m^{nad_{mito}} = 0.015$

$K_m^{kc14coa_{mito}} = 0.0013$

$K_m^{nadh_{mito}} = 0.011$

3-hydroxyacyl-coa dehydrogenase (lc16) (identic with liver enzyme)

$$v_{3hdh-lc16} = V_{max}^{3hdh-lc16} \cdot \left(\frac{lc16coa_{mito} \cdot nad_{mito} - {}^{1}\!/\!{}_{K_{eq}^{3hdh-lc16}} \cdot kc16coa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{lc16coa_{mito}}{K_m^{lc16coa_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{kc16coa_{mito}}{K_m^{kc16coa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{3hdh-lc16}$ for numerical value see Supplemental Table II

$$K_{eq}^{3hdh-lc16} = \frac{1}{10^{-3}}$$

$$K_m^{lc16_{coa_{mito}}} = 0.003$$

$$K_m^{nad_{mito}} = 0.0145$$

$$K_m^{kc16_{coa_{mito}}} = 0.0013$$

$$K_m^{nadh_{mito}} = 0.011$$

3-ketoacyl-coa thiolase I (kc4)

$$v_{3kt}^{kc4coa} = V_{max}^{3kt-kc4_{coa}} \cdot \left(\frac{coa_{mito} \cdot kc4coa_{mito} - {}^{1}\!/\!{}_{K_{eq}^{3kt}} \cdot acoa_{mito}^2}{\left(1 + \frac{coa_{mito}}{K_m^{coa_{mito}}}\right) \cdot \left(1 + \frac{kc4coa_{mito}}{K_m^{kc4coa_{mito}}}\right) + \left(1 + \frac{acoa_{mito}}{K_m^{acoa_{mito}}}\right) \quad - 1} \right)$$

$V_{max}^{3kt-kc4}$ for numerical value see Supplemental Table II

$$K_{eq}^{3kt} = 2500$$

$$K_m^{coa_{mito}} = \ 0.0087$$

$$K_m^{kc4coa_{mito}} = K_0^{kc4coa_{mito}} \cdot \left(1 + \frac{acoa_{mito}}{K_i^{acao_{mito}}}\right)$$

$$K_i^{acoa_{mito}} = 0.125$$

$$K_0^{kc4coa_{mito}} = 0.017$$

$$K_m^{acoa_{mito}} = K_0^{acoa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$$

$$K_0^{acoa_{mito}} = 0.3$$

$$K_i^{kc4coa_{mito}} = 0.0022$$

3-ketoacyl-coa thiolase II (kc4)

$$v_{3ktII}^{kc4coa} = V_{max}^{3ktII-kc4_{coa}} \cdot \left(\frac{coa_{mito} \cdot kc4coa_{mito} - {}^{1}\!/_{K_{eq}^{3kt}} \cdot acoa_{mito}^{2}}{\left(1 + \frac{coa_{mito}}{K_m^{coa_{mito}}}\right) \cdot \left(1 + \frac{kc4coa_{mito}}{K_m^{kc4coa_{mito}}}\right) + \left(1 + \frac{acoa_{mito}}{K_m^{acoa_{mito}}}\right)^2 - 1} \right)$$

$V_{max}^{3ktII-kc4}$ for numerical value see Supplemental Table II

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = \ 0.0513$

$K_m^{kc4coa_{mito}} = K_0^{kc4coa_{mito}} \cdot \left(1 + \frac{acoa_{mito}}{K_i^{acao_{mito}}}\right)$

$K_i^{acoa_{mito}} = 0.125$

$K_0^{kc4coa_{mito}} = 0.0135$

$K_m^{acoa_{mito}} = K_0^{acoa_{mito}} \cdot \left(1 + \frac{kc4coa_{mito}}{K_i^{kc4coa_{mito}}}\right)$

$K_0^{acoa_{mito}} = 0.3$

$K_i^{kc4coa_{mito}} = 0.0022$

3-ketoacyl-coa thiolase I (kc6)

$$v_{3kt}^{kc6coa} = V_{max}^{3kt-c6_{coa}} \cdot \left(\frac{kc6coa_{mito} \cdot coa_{mito} \ - {}^{1}\!/_{K_{eq}^{3kt}} \cdot acoa_{mito} \cdot c4coa_{mito}}{\left(coa_{mito} + K_m^{coa_{mito}}\right) \cdot \left(kc6coa_{mito} + K_m^{kc6coa_{mito}}\right)} \right)$$

$V_{max}^{3kt-kc6} = 2.4 \cdot V_{max}^{3kt-kc4}$

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = 0.0087$

$K_m^{kc6coa_{mito}} = 0.0083$

3-ketoacyl-coa thiolase I (kc8)

$$v_{3kt}^{kc8coa} = V_{max}^{3kt-kc8} \cdot \left(\frac{kc8coa_{mito} \cdot coa_{mito} \ - {}^{1}\!/_{K_{eq}^{3kt}} \cdot acoa_{mito} \cdot c6coa_{mito}}{\left(coa_{mito} + K_m^{coa_{mito}}\right) \cdot \left(kc8coa_{mito} + K_m^{kc8coa_{mito}}\right)} \right)$$

$V_{max}^{3kt-kc8} = 2.2 \cdot V_{max}^{3kt-kc4}$

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = 0.0024$

$K_m^{kc8coa_{mito}} = 0.025$

3-ketoacyl-coa thiolase I (kc10)

$$v_{3kt}^{kc10coa} = V_{max}^{3kt-kc10} \cdot \left(\frac{kc10coa_{mito} \cdot coa_{mito} - {}^{1}\!/_{K_{eq}^{3kt}} \cdot acoa_{mito} \cdot c8coa_{mito}}{\left(coa_{mito} + K_m^{coa_{mito}}\right) \cdot \left(kc10coa_{mito} + K_m^{kc10coa_{mito}}\right)} \right)$$

$V_{max}^{3kt-kc10} = 2.3 \cdot V_{max}^{3kt-kc4}$

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = 0.0087$

$K_m^{kc10coa_{mito}} = 0.0018$

3-ketoacyl-coa thiolase I (kc12)

$$v_{3kt}^{kc12coa} = V_{max}^{3kt-kc12} \cdot \left(\frac{kc12coa_{mito} \cdot coa_{mito} - {}^{1}\!/_{K_{eq}^{3kt}} \cdot acoa_{mito} \cdot c10coa_{mito}}{\left(coa_{mito} + K_m^{coa_{mito}}\right) \cdot \left(kc12coa_{mito} + K_m^{kc12coa_{mito}}\right)} \right)$$

$V_{max}^{3kt-kc12} = 2.1 \cdot V_{max}^{3kt-kc4}$

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = 0.0087$

$K_m^{kc12coa_{mito}} = 0.006$

3-ketoacyl-coa thiolase I (kc14)

$$v_{3kt}^{kc14coa} = V_{max}^{3kt-kc14} \cdot \left(\frac{kc14coa_{mito} \cdot coa_{mito} - {}^{1}\!/_{K_{eq}^{3kt}} \cdot acoa_{mito} \cdot c12coa_{mito}}{\left(coa_{mito} + K_m^{coa_{mito}}\right) \cdot \left(kc14coa_{mito} + K_m^{kc14coa_{mito}}\right)} \right)$$

$V_{max}^{3kt-kc14} = 1.7 \cdot V_{max}^{3kt-kc4}$

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = 0.0087$

$K_m^{kc14coa_{mito}} = 0.0065$

3-ketoacyl-coa thiolase I (kc16)

$$v_{3kt}^{kc16coa} = V_{max}^{3kt-kc16} \cdot \left(\frac{kc16coa_{mito} \cdot coa_{mito} - {}^{1}\!/\!_{K_{eq}^{3kt}} \cdot acoa_{mito} \cdot c14coa_{mito}}{\left(coa_{mito} + K_m^{coa_{mito}}\right) \cdot \left(kc16coa_{mito} + K_m^{kc16coa_{mito}}\right)} \right)$$

$V_{max}^{3kt-kc16}$ for numerical value see Supplemental Table II

$K_{eq}^{3kt} = 2500$

$K_m^{coa_{mito}} = 0.0087$

$K_m^{kc16coa_{mito}} = 0.0011$

ETF-FAD

$$v_{ETF-FAD} = V_{max}^{ETF-FAD} \cdot \left(etffadh2_{mito} \cdot etfq_{mito} - {}^{1}\!/\!_{K_{eq}^{ETF-FAD}} \cdot etfqh2_{mito} \cdot etffad_{mito} \right)$$

$V_{max}^{ETF-FAD}$ for numerical value see Supplemental Table II

$$K_{eq}^{ETF-FAD} = \exp\left(\frac{\left(-n \cdot E_0^{etffad_{mito}/etffadh2_{mito}} - n \cdot E_0^{etfqh2_{mito}/etfq_{mito}}\right) \cdot F}{R \cdot T} \right)$$

$E_0^{etfqh2_{mito}/etfq_{mito}} = -25\ mV$

$E_0^{etffad_{mito}/etffadh2_{mito}} = -23\ mV$

$n = 2$

ETF-QO

$$v_{ETF-QO} = V_{max}^{ETF-QO} \cdot \left(etfqh2_{mito} \cdot q_{mm} - {}^{1}\!/\!_{K_{eq}^{ETF-QO}} \cdot etfq_{mito} \cdot qh_{2_{mm}} \right)$$

V_{max}^{ETF-QO} for numerical value see Supplemental Table II

$$K_{eq}^{ETF-QO} = \exp\left(\frac{\left(n \cdot E_0^{q_{mm}/qh2_{mm}} + n \cdot E_0^{etfqh2_{mito}/etfq_{mito}}\right) \cdot F}{R \cdot T} \right)$$

$E_0^{q_{mm}/qh2_{mm}} = 87$ mV

$E_0^{etfqh2_{mito}/etfq_{mito}} = -25\ mV$

$n = 2$

Citric acid cycle

Pyruvate dehydrogenase complex

$$v_{pdhc} = \gamma_{pdhc} \cdot v_{pdhc-np}$$

$$v_{pdhc-np} = V_{max}^{pdhc-np} \cdot \left(\frac{pyr_{mito}}{pyr_{mito} + K_{m-pyr}^{pdhc-np}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_{m-nad}^{pdhc-np}}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_{m-coa}^{pdhc-np}}\right) \cdot \left(1 + k_{ca}\frac{ca_{mito}}{ca_{mito} + K_a^{ca}}\right)$$

$V_{max}^{pdhc-np}$ for numerical value see Supplemental Table II

$K_{m-pyr}^{pdhc-np} = 0.077$

$K_{m-nad}^{pdhc-np} = K_0^{nad} \cdot \left(1 + \frac{nadh_{mito}}{K_i^{nadh_{mito}}}\right)$

$K_0^{nad} = 0.07$

$K_i^{nadh_{mito}} = 0.3$

$K_{m-coa}^{pdhc-np} = K_0^{coa} \cdot \left(1 + \frac{acoa_{mito}}{K_i^{acoa_{mito}}}\right)$

$K_0^{coa} = 0.0122$

$K_i^{acoa_{mito}} = 0.029$

$k_{ca} = 1.7$

$K_a^{ca} = 0.001$

$\gamma_{pdhc} = \gamma_{pdhc}^{acoa} \cdot \gamma_{pdhc}^{nadh}$

$$\gamma_{pdhc}^{acoa} = 1 - f_1 \cdot \frac{\frac{acoa_{mito}}{coa_{mito}}}{\frac{acoa_{mito}}{coa_{mito}} + K_i^{\left(\frac{acoa_{mito}}{coa_{mito}}\right)}}$$

$K_i^{\left(\frac{acoa_{mito}}{coa_{mito}}\right)} = 0.4$

$f_1 = 0.71$

$$\gamma_{pdhc}^{nadh} = 1 - f_2 \cdot \frac{\frac{nadh_{mito}}{nad_{mito}}}{\frac{nadh_{mito}}{nad_{mito}} + K_i^{\left(\frac{nadh_{mito}}{nad_{mito}}\right)}}$$

$f_2 = 0.75$

$K_i^{\left(\frac{nadh_{mito}}{nad_{mito}}\right)} = 0.5$

Citrate synthase

$$v_{cs} = V_{max}^{cs} \cdot \left(\frac{oaa_{mito}}{oaa_{mito} + K_m^{oaa_{mito}}}\right) \cdot \left(\frac{acoa_{mito}}{acoa_{mito} + K_m^{acoa_{mito}}}\right)$$

$$V_{max}^{cs} = \frac{V_0^{cs}}{\left(1 + \frac{c16coa_{mito}}{K_i^{c16coa_{mito}}}\right) \cdot \left(1 + \frac{atp_{mito}}{K_i^{atp_{mito}}}\right)}$$

V_0^{cs} for numerical value see Supplemental Table II

$K_i^{c16coa_{mito}} = 0.0042$

$K_i^{atp_{mito}} = 0.7$

$$K_m^{oaa_{mito}} = K_0^{oaa_{mito}} \cdot \left(1 + \frac{cit_{mito}}{K_i^{cit_{mito}}}\right)$$

$K_i^{cit_{mito}} = 1.6$

$K_0^{oaa_{mito}}$ =0.0036

$$K_m^{acoa_{mito}} = K_0^{acoa_{mito}} \cdot \left(1 + \frac{succoa_{mito}}{K_i^{succoa_{mito}}}\right)$$

$K_i^{coa_{mito}} = 0.067$

$K_i^{atp_{mito}} = 0.95$

$K_i^{succoa_{mito}} = 0.13$

$K_0^{acoa_{mito}}$ =0.006

Aconitase

$$\mathrm{v}_{ac} = V_{max}^{ac} \cdot \left(\frac{cit_{mito} - {}^{1}/_{K_{eq}^{ac}} \cdot isocit_{mito}}{1 + \frac{cit_{mito}}{K_m^{cit_{mito}}} + \frac{isocit_{mito}}{K_m^{isocit_{mito}}}}\right)$$

V_{max}^{ac} for numerical value see Supplemental Table II

$K_{eq}^{ac} = 0.1$

$K_m^{cit_{mito}} = 0.62$

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

NAD-dependent isocitrate dehydrogenase

$$v_{idh_{nad}} = V_{max}^{idh_{nad}} \cdot \left(\frac{isocit_{mito}^n}{isocit_{mito}^n + \left(K_m^{isocit_{mito}}\right)^n} \right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}} \right)$$

$V_{max}^{idh_{nad}}$ for numerical value see Supplemental Table II

$$K_m^{isocit_{mito}} = K_0^{isocit_{mito}} \cdot \left(1 - n_{adp_{mito}} \frac{adp_{mito}}{adp_{mito} + K_a^{adp_{mito}}}\right) \cdot \left(1 - n_{cit_{mito}} \frac{cit_{mito}}{cit_{mito} + K_a^{cit_{mito}}}\right)$$

$K_0^{isocit_{mito}} = 0.21$

$n = 3$

$n_{adp_{mito}} = 0.67$

$K_a^{adp_{mito}} =0.1$

$n_{cit_{mito}} = 0.85$

$K_a^{cit_{mito}} = 0.033$

$$K_m^{nad_{mito}} = K_0^{nad_{mito}} \cdot \left(1 + \frac{nadh_{mito}}{K_i^{nadh_{mito}}}\right)$$

$K_0^{nad_{mito}} = 0.06$

$K_i^{nadh_{mito}} = 0.0043$

NADP-dependent isocitrate dehydrogenase

$$v_{idh_{nadph}} = V_{max}^{idh_{nadp}} \cdot \left(\frac{isocit_{mito}}{isocit_{mito} + K_m^{isocit_{mito}}} \right) \cdot \left(\frac{nadp_{mito}}{nadp_{mito} + K_m^{nad_{mito}}} \right)$$

$V_{max}^{idh_{nadp}}$ for numerical value see Supplemental Table II

$$K_m^{isocit_{mito}} = K_0^{isocit_{mito}} \cdot \left(1 + \frac{cit_{mito}}{K_i^{cit_{mito}}}\right) \cdot \left(1 + \frac{akg_{mito}}{K_i^{akg_{mito}}}\right)$$

$K_0^{isocit_{mito}} = 0.045$

$$K_m^{nadp_{mito}} = K_0^{nadp_{mito}} \cdot \left(1 + \frac{nadph_{mito}}{K_i^{nadph_{mito}}}\right)$$

$K_0^{nadp_{mito}} = 0.046$

$K_i^{nadph_{mito}} = 0.125$

$K_i^{cit_{mito}} = 0.159$

$K_i^{akg_{mito}} = 0.08$

α-ketogluterate dehydrogenase

$$v_{kgdhc} = V_{mx}^{kgdhc} \cdot \left(\frac{akg_{mito}}{akg_{mito} + K_m^{akg_{mito}} \cdot \left(1 + \frac{nadh_{mito}}{K_{i2}^{nadh_{mito}}}\right)}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad} \cdot \left(1 + \frac{nadh_{mito}}{K_i^{nadh_{mito}}}\right)}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_m^{coa_{mito}} \cdot \left(1 + \frac{succoa_{mito}}{K_i^{succoa_{mito}}}\right)}\right)$$

V_{mx}^{kgdhc} for numerical value see Supplemental Table II

$K_{i2}^{nadh_{mito}} = 0.0127$

$K_m^{akg_{mito}}$ =0.6

$K_m^{nad_{mito}} = 0.021$

$K_i^{nadh_{mito}} = 0.0045$

$K_m^{coa_{mito}} = 0.0027$

$K_i^{succoa_{mito}} = 0.0069$

Succinyl-Coa synthetase

$$v_{scs-atp} = V_{max}^{scs-atp} \cdot \left(\frac{succoa_{mito} \cdot adp_{mito} \cdot p_{mito} - {}^{1}\!/\!_{K_{eq}^{scs-atp}} \cdot suc_{mito} \cdot coa_{mito} \cdot atp_{mito}}{\left(1 + \frac{succoa_{mito}}{K_m^{succoa_{mito}}}\right) \cdot \left(1 + \frac{adp_{mito}}{K_m^{adp_{mito}}}\right) \cdot \left(1 + \frac{p_{mito}}{K_m^{p_{mito}}}\right) + \left(1 + \frac{suc_{mito}}{K_m^{suc_{mito}}}\right) \cdot \left(1 + \frac{coa_{mito}}{K_m^{coa_{mito}}}\right) \cdot \left(1 + \frac{atp_{mito}}{K_m^{atp_{mito}}}\right) - 1}\right)$$

$$V_{max}^{scs-atp} = V_0^{scs-atp} \cdot \left(\frac{p_{mito}^n}{p_{mito}^n + K_a^{p\,n}}\right)$$

$V_0^{scs-atp}$ for numerical value see Supplemental Table II

$K_a^{p^n} = 2.3$

$n = 2.4$

$K_{eq}^{scs-atp} = 1/0.27$

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

$K_m^{adp_{mito}} = 0.25$

$K_m^{p_{mito}} = 0.72$

$K_m^{suc_{mito}} = 5.1$

$K_m^{coa_{mito}} = 0.032$

$K_m^{atp_{mito}} = 0.055$

$$v_{scs-gtp} = V_{max}^{scs-gtp} \cdot \left(\frac{succoa_{mito} \cdot gdp_{mito} \cdot p_{mito} - {}^{1}\!/\!{}_{K_{eq}^{scs-atp}} \cdot suc_{mito} \cdot coa_{mito} \cdot gtp_{mito}}{\left(1 + \frac{succoa_{mito}}{K_m^{succoa_{mito}}}\right) \cdot \left(1 + \frac{gdp_{mito}}{K_m^{gdp_{mito}}}\right) \cdot \left(1 + \frac{p_{mito}}{K_m^{p_{mito}}}\right) + \left(1 + \frac{suc_{mito}}{K_m^{suc_{mito}}}\right) \cdot \left(1 + \frac{coa_{mito}}{K_m^{coa_{mito}}}\right) \cdot \left(1 + \frac{gtp_{mito}}{K_m^{gtp_{mito}}}\right) - 1} \right)$$

$V_{max}^{scs-gtp} = V_0^{scs-gtp} \cdot \left(\frac{p_{mito}^n}{p_{mito}^n + K_a^{p^n}} \right)$

$V_0^{scs-gtp} = 0.11 \cdot V_0^{scs-atp}$

$K_a^{p_{mito}} = 2.3$

$n = 2.4$

$K_{eq}^{scs-gtp} = 1/0.27$

$K_m^{succoa_{mito}} = 0.086$

$K_m^{gdp_{mito}} = 0.007$

$K_m^{p_{mito}} = 2.26$

$K_m^{suc_{mito}} = 0.49$

$K_m^{coa_{mito}} = 0.036$

$K_m^{gtp_{mito}} = 0.036$

Succinate dehydrogenase

$$v_{succdh} = V_{max}^{succdh} \cdot \left(\frac{suc_{mito} \cdot q_{mm} - {}^{1}\!/_{K_{eq}^{succdh}} \cdot fum_{mito} \cdot qh_{2_{mm}}}{\left(suc_{mito} + K_m^{suc_{mito}}\right) \cdot \left(q_{mm} + K_m^{q_{mm}}\right)} \right)$$

V_{max}^{succdh} for numerical value see Supplemental Table II

$$K_{eq}^{succdh} = \exp\left(\frac{E_0^{fum_{mito}/suc_{mito}} - E_0^{q_{mm}/qh2_{mm}}}{R \cdot T} \cdot F \right)$$

$$E_0^{fum_{mito}/suc_{mito}} - E_0^{q_{mm}/qh2_{mm}} = 25\ mV$$

$$K_0^{suc_{mito}} = 1.3$$

$$K_m^{suc_{mito}} = K_0^{suc_{mito}} \cdot \left(1 + \frac{mal_{mito}}{K_i^{mal_{mito}}}\right)$$

$$K_i^{mal_{mito}} = 2.2$$

$$K_m^{q_{mm}} = 0.0005$$

Fumarase

$$v_{fum} = V_{max}^{fum} \cdot \left(\frac{fum_{mito} - {}^{1}\!/_{K_{eq}^{fum}} \cdot mal_{mito}}{1 + \frac{fum_{mito}}{K_m^{fum_{mito}}} + \frac{mal_{mito}}{K_m^{mal_{mito}}}} \right)$$

V_{max}^{fum} for numerical value see Supplemental Table II

$$K_{eq}^{fum} = 4.2$$

$$K_m^{fum_{mito}} = 0.333$$

$$K_m^{mal_{mito}} = 0.59$$

Malate dehydrogenase (mitochondrial)

$$v_{mdh_{mito}} = V_{max}^{mdh_{mito}} \cdot \left(\frac{mal_{mito} \cdot nad_{mito} - {}^{1}\!/_{K_{eq}^{mdh_{mito}}} \cdot oaa_{mito} \cdot nadh_{mito}}{\left(1 + \frac{mal_{mito}}{K_m^{mal_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{oaa_{mito}}{K_m^{oaa_{mito}}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) - 1} \right)$$

$V_{max}^{mdh_{mito}}$ for numerical value see Supplemental Table II

$K_{eq}^{mdh_{mito}} = 1 \cdot 10^{-5} \cdot \left(\frac{h_{cyt}}{h_{mito}}\right)$

$K_{m}^{mal_{mito}} = 0.4$

$K_{m}^{nad_{mito}} = 0.06$

$K_{m}^{oaa_{mito}} = 0.017$

$K_{m}^{nadh_{mito}} = 0.044$

Transdehydrogenase

$$v_{tdh} = V_{max}^{tdh} \cdot \left(nadh_{mito} \cdot nadp_{mito} - {}^{1}\!/_{K_{eq}^{tdh}} \cdot nad_{mito} \cdot nadph_{mito}\right)$$

$V_{max}^{tdh_{mito}}$ for numerical value see Supplemental Table II

$$K_{eq}^{tdh_{mito}} = K_{0}^{tdh} \cdot \exp\left(-\frac{v_{mm} \cdot F}{R \cdot T}\right) \cdot \left(\frac{h_{cyt}}{h_{mito}}\right)$$

$K_{0}^{tdh} = 1.5$

<u>Mitochondrial electrophysiology and ATP synthesis</u>

Chloride

$$I_{cl_{ed}} = P_{cl} \cdot A_m \cdot U \cdot F \cdot \left(\frac{cl_{cyt} - cl_{mito} \cdot exp(-U)}{1 - exp(-U)}\right)$$

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

$P_{cl} = 5 \cdot 10^{-10}\ m/s$

Sodium

$$I_{na}^{pump} = V_{max}^{Na-pump} \cdot \left(\frac{na_{cyt} \cdot h_{mito} - na_{mito} \cdot h_{cyt}}{1 + \frac{na_{cyt}}{K_m^{na}} + \frac{na_{mito}}{K_m^{na}}}\right)$$

$V_{max}^{Na-pump}$ for numerical value see Supplemental Table II

$K_m^{na} = 32.4$

$$I_{na_{ed}} = P_{na} \cdot A_m \cdot U \cdot F \cdot \left(\frac{na_{cyt} - na_{mito} \cdot exp(U)}{exp(U) - 1}\right)$$

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

$P_{na} = 1 \cdot 10^{-10} m/s$

$I_{na} = I_{na}^{pump} + I_{na_{ed}}$

Potassium

$I_K^{pump} = V_{max}^{K-pump} \cdot \left(k_{cyt} \cdot h_{mito} - k_{mito} \cdot h_{cyt}\right)$

V_{max}^{K-pump} for numerical value see Supplemental Table II

$I_{k_{ed}} = P_k \cdot A_m \cdot U \cdot F \cdot \left(\frac{k_{cyt} - k_{mito} \cdot exp(U)}{exp(U) - 1}\right)$

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

$P_K = 5 \cdot 10^{-10} m/s$

$I_k = I_k^{pump} + I_{k_{ed}}$

F0F1 synthetase

$$v_{F0F1} = V_{max}^{F0F1} \cdot \left(\frac{adp_{mito} \cdot p_{mito} - {}^{1}\!/\!_{K_{eq}^{F0F1}} \cdot atp_{mito}}{\left(K_m^{adp_{mito}} + adp_{mito}\right) \cdot \left(K_m^{p_{mito}} + p_{mito}\right)}\right)$$

$$V_{max}^{F0F1} = V_{F0F1} \cdot \left(0.114 + 0.886 \, \frac{(|V_{mm}|)^n}{(|V_{mm}|)^n + \left(K_m^{V_{mm}}\right)^n}\right)$$

V_{F0F1} for numerical value see Supplemental Table II

$n = 10$

$K_m^{V_{mm}} = 140$ mV

$$K_{eq}^{F0F1} = exp\left(\left(\frac{-E_0^{ATP}}{R \cdot T}\right) - n_H \cdot \left(\frac{V_{mm} \cdot F}{R \cdot T}\right)\right) \cdot \left(\frac{H_{cyt}}{H_{mito}}\right)^{n_H} mM^{-1}$$

$n_H = 3$

$E_0^{ATP} = 30500$ J/mol

$K_m^{adp_{mito}} = 0.025$

$K_m^{p_{mito}} = 6.1$

ATP-ADP nucleotide exchanger

$$v_{nex} = V_{max}^{nex} \cdot \left(\frac{1 - \frac{atp_{cyt} \cdot adp_{mito}}{adp_{cyt} \cdot atp_{mito}} \cdot exp\left(\frac{v_{mm} \cdot F}{R \cdot T}\right)}{\left(1 + \frac{atp_{cyt}}{adp_{cyt}} \cdot exp\left(f \cdot \frac{v_{mm} \cdot F}{R \cdot T}\right) \cdot \left(1 + \frac{adp_{mito}}{atp_{mito}}\right)\right)} \right)$$

V_{max}^{nex} for numerical value see Supplemental Table II

f =0.2

Phosphate exchanger

$$v_{P-ex} = V_{max}^{P-ex} \cdot \left(\frac{p_{cyt} \cdot h_{cyt} - p_{mito} \cdot h_{mito}}{\left(p_{cyt} + K_m^{p_{cyt}}\right)} \right)$$

V_{max}^{P-ex} for numerical value see Supplemental Table II

$K_m^{p_{cyt}} = 1.89$

Complex I

$$v_{cxI} = V_{max}^{cxI} \cdot \left(\frac{nadh_{mito} \cdot q_{mm} - {1}/{K_{eq}^{cxI}} \cdot nad_{mito} \cdot qh_{2_{mm}}}{\left(nadh_{mito} + K_m^{nadh_{mito}}\right) \cdot \left(q_{mm} + K_m^{q_{mm}}\right)} \right)$$

V_{max}^{cxI} for numerical value see Supplemental Table II

$$K_{eq}^{cxI} = \exp\left(\frac{\left(n \cdot E_0^{nadh/nad} + n \cdot E_0^{Q/QH_2} + n_H \cdot V_{mm}\right) \cdot F}{R \cdot T} \right) \cdot \left(\frac{h_{mito}}{h_{cyt}}\right)^{n_H}$$

$n = 2$

$E_0^{nadh/nad} = 320$ mV

$E_0^{Q/QH_2} = 87mV$

$n_H = 4$

$K_m^{nadh_{mito}} = 0.0017$

$K_m^{q_{mm}} = 0.013$

Complex II

see succinate dehydrogenase

Complex III

$$v_{cxIII} = V_{max}^{cxIII} \cdot \left(\frac{qh2_{mm} \cdot cytc_{ox_{mm}} - {}^{1}\!/_{K_{eq}^{cxIII}} \cdot q_{mm} \cdot cytc_{red_{mm}}}{\left(qh2_{mm} + K_m^{qh2_{mm}}\right) \cdot \left(cytc_{ox_{mm}} + K_m^{cytc_{ox}}\right)^2} \right)$$

V_{max}^{cxIII} for numerical value see Supplemental Table II

$$K_{eq}^{cxIII} = \exp\left(\frac{\left(-n \cdot E_0^{Q/QH_2} + n \cdot E_0^{cytC_{ox}/cytC_{red}} + n \cdot v_{mm}\right) \cdot F}{R \cdot T} \right) \cdot \left(\frac{h_{mito}}{h_{\emptyset}}\right)^{n_{h_{mito}}} \cdot \left(\frac{h_{\emptyset}}{h_{cyt}}\right)^{n_{h_{cyt}}}$$

$n = 2$

$E_0^{cytC_{ox}/cytC_{red}} = 255\ mV$

$E_0^{Q/QH_2} = 87\ mV$

$n_{h_{mito}} = 2$

$n_{h_{cyt}} = 4$

$h_{\emptyset} = 10^{-4} mM \overset{\text{def}}{=} \text{pH } 7$

$K_m^{qh_{2mm}} = 0.013$

$K_m^{cytc_{ox}} = 0.014$

Complex IV

$$v_{cxIV} = V_{max}^{cxIV} \cdot \left(\frac{cytc_{red}}{cytc_{red} + K_m^{cytc_{red}}}\right) \cdot \left(\frac{O_2}{O_2 + K_m^{O_2}}\right)$$

$$V_{max}^{cxIV} = V_0^{cxIV} \cdot \exp\left(-\frac{dGp \cdot F}{R \cdot T}\right)$$

$$dGp = -v_{mm} + \frac{R \cdot T}{F} \cdot \log\left(\frac{h_{cyt}}{h_{mito}}\right)$$

V_0^{cxIV} for numerical value see Supplemental Table II

$K_m^{cytc_{red}} = 0.007$

$$K_m^{O_2} = 2\ mmHg$$

Adenylate kinase

$$v_{ak_{cyt}} = V_{max}^{ak_{cyt}} \cdot \left(\frac{atp_{cyt} \cdot amp_{cyt} - 1/_{K_{eq}^{ak}} \cdot adp_{cyt} \cdot adp_{cyt}}{\left(1 + \frac{atp_{cyt}}{K_m^{atp_{cyt}}}\right) \cdot \left(1 + \frac{amp_{cyt}}{K_m^{amp_{cyt}}}\right) + \left(1 + \frac{adp_{cyt}}{K_m^{adp_{cyt}}}\right)^2 - 1} \right)$$

$V_{max}^{ak_{cyt}}$ for numerical value see Supplemental Table II

$K_{eq}^{ak} = 1$

$K_m^{atp_{cyt}} = 0.039$

$K_m^{adp_{cyt}} = 0.112$

$K_m^{amp_{cyt}} = 0.026$

Pyrophosphatase

$$v_{ppase} = V_{max}^{ppase} \cdot \left(\frac{pp_{cyt}}{pp_{cyt} + K_m^{pp_{cyt}}} \right)$$

V_{max}^{ppase} for numerical value see Supplemental Table II

$K_m^{pp_{cyt}} = 0.016$

ATP usage

$$v_{atp-usage} = V_{max}^{atp-usage} \cdot \left(\frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \right) \cdot (1 + k_{load})$$

$V_{max}^{atp-usage}$ for numerical value see Supplemental Table II

$K_m^{atp_{cyt}} = 2$

O_2 diffusion

$$v_{O_{2diff}} = V_{max}^{O_2-diff} \cdot (o2_{ext} - o2_{cyt})$$

$V_{max}^{O_2-diff}$ for numerical value see Supplemental Table II

Proton fluxes

$$I_H^{pump} = 4 \cdot v_{cxI} + 2 \cdot v_{cxIII} + 4 \cdot v_{cxIV}$$

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

$$P_H = 3 \cdot 10^{-4} m/s$$

Mitochondrial membrane potential

$$v_{V_{mm}} = \frac{10^{-1}}{c_m \cdot A_m} \cdot \left(-I_{C_{ed}} + I_{K_{ed}} + I_{H_{ed}} + I_{Na_{ed}} + I_H^{pump} + v_{nex} + 3 \cdot v_{syn} + F \cdot 10 \cdot v_{pepT} \cdot Vol_{cyt}\right)$$

Glycolysis

Glut1 glucose transporter (Glut1)

$$v_{gluT1} = V_{max}^{gluT1} \cdot \frac{glc_{ext} - glc_{cyt}}{1 + \frac{glc_{ext}}{K_m^{glc_{ext}}} + \frac{glc_{cyt}}{K_m^{glc_{cyt}}}}$$

$$V_{max}^{gluT1} = V_0^{gluT1} \cdot \left(1 - \frac{c16_{ext}^n}{c16_{ext}^n + K_i^{c16_{ext}}}\right)$$

V_0^{gluT1} for numerical value see Supplemental Table II

$n = 2$

$K_i^{c16_{ext}} = 0.2$

$K_m^{glc_{cyt}} = 5$

$K_m^{glc_{ext}} = 5$

Glut4 glucose transporter (Glut4)

$$v_{gluT4} = V_{max}^{gluT4} \cdot \frac{glc_{ext} - glc_{cyt}}{1 + \frac{glc_{ext}}{K_m^{glc_{ext}}} + \frac{glc_{cyt}}{K_m^{glc_{cyt}}}}$$

$$V_{max}^{gluT4} = V_0^{gluT4} \cdot \left(1 - \frac{c16_{ext}^n}{c16_{ext}^n + K_i^{c16_{ext}}}\right) \cdot \left(1 - \gamma \cdot \left(1 - \frac{epi_{ext}}{epi_{ext} + K_a^{epi_{ext}}}\right) \cdot \left(1 - \frac{amp_{cyt}}{amp_{cyt} + K_a^{amp_{cyt}}}\right)\right)$$

V_0^{gluT4} for numerical value see Supplemental Table II

$n = 2$

$K_i^{c16_{ext}} = 0.2$

$K_a^{epi_{ext}} = 200\ pM$

$K_a^{amp_{cyt}} = 0.2$

$K_m^{glc_{cyt}} = 5$

$K_m^{glc_{ext}} = 5$

Hexokinase A

$$v_{hkA} = V_{max}^{hkA} \cdot \left(\frac{glc_{cyt}}{glc_{cyt} + K_m^{glc_{cyt}}}\right) \cdot \left(\frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}}\right)$$

$$V_{max}^{hkA} = \frac{V_0^{hkA}}{1 + \frac{glc6p_{cyt}}{K_i^{hk}}}$$

V_0^{hkA} for numerical value see Supplemental Table II

$K_i^{glc_{cyt}} = 0.05$

$K_m^{glc_{cyt}} = 0.25$

$$K_m^{atp_{cyt}} = K_0^{atp_{cyt}} \cdot \left(1 + \frac{glc6p_{cyt}}{K_i^{glc6p_{cyt}}}\right) \cdot \left(1 + \frac{adp_{cyt}}{K_i^{adp_{cyt}}}\right)$$

$K_0^{atp_{cyt}} = 0.75$

$K_i^{adp_{cyt}} = 0.22$

$K_i^{glc6p_{cyt}} = 0.021$

Hexokinase 1

$$v_{hkB} = V_{max}^{hkB} \cdot \left(\frac{glc_{cyt}}{glc_{cyt} + K_m^{glc_{cyt}}}\right) \cdot \left(\frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}}\right)$$

$$V_{max}^{hkB} = \frac{V_0^{hkB}}{1 + \frac{glc6p_{cyt}}{K_i^{hk}}}$$

$V_0^{hkB} = 10 \cdot V_0^{hkA}$

$K_i^{hk} = 0.05$

$K_m^{glc_{cyt}} = 0.02$

$K_m^{atp_{cyt}} = K_0^{atp_{cyt}} \cdot \left(1 + \frac{glc6p_{cyt}}{K_i^{glc6p_{cyt}}}\right) \cdot \left(1 + \frac{adp_{cyt}}{K_i^{adp_{cyt}}}\right)$

$K_0^{atp_{cyt}} = 0.44$

$K_i^{adp_{cyt}} = 0.62$

$K_i^{glc6p_{cyt}} = 0.02$

D-Glucose-6-phosphate isomerase (Gpi)

$$v_{gpi} = V_{max}^{gpi} \cdot \frac{glc6p_{cyt} - \frac{fru6p_{cyt}}{K_{eq}^{gpi}}}{1 + \frac{glc6p_{cyt}}{K_m^{glc6p_{cyt}}} + \frac{fru6p_{cyt}}{K_m^{fru6p_{cyt}}}}$$

V_{max}^{gpi} for numerical value see Supplemental Table II

$K_{eq}^{Gpi} = 0.3$

$K_m^{glc6p_{cyt}} = 0.55$

$K_m^{fru6p_{cyt}} = 0.12$

Phosphofructokinase 2 (Pfk2)

$v_{pfk2} = V_{max}^{pfk2_{native}} \cdot \left(1 - \gamma^{Pfk2}\right) \cdot v_{pfk2}^{native} + V_{max}^{pfk2_p}\left(\gamma^{pfk2} \cdot v_{pfk2}^{p}\right)$

$\gamma^{pfk2} = \gamma \cdot (1 - \gamma^{amp})$

$V_{max}^{pfk2_{native}}$ for numerical value see Supplemental Table II

$V_{max}^{pfk2_p} = 2.3 \cdot V_{max}^{pfk2_{native}}$

$$v_{pfk2}^{native} = \frac{fru6p_{cyt}}{fru6p_{cyt} + K_m^{fru6p_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \cdot \left(1 - \frac{cit_{cyt}}{cit_{cyt} + K_i^{cit_{cyt}}}\right)$$

$K_m^{fru6p_{cyt}} = 0.121$

$K_m^{atp_{cyt}} = 0.63$

$K_i^{cit_{cyt}} = 0.029$

$$v_{pfk2}^{p} = \frac{fru6p_{cyt}}{fru6p_{cyt} + K_m^{fru6p_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \cdot \left(1 - \frac{cit_{cyt}}{cit_{cyt} + K_i^{cit_{cyt}}}\right)$$

$K_m^{fru6p_{cyt}} = 0.061$

$K_m^{atp_{cyt}} = 0.63$

$K_i^{cit_{cyt}} = 0.061$

Fructose-2,6-bisphosphatase (FBP2)

$v_{fbp2} = V_{max}^{fbp2_{phospho}} \cdot \gamma^{fbp2} \cdot v_{fbp2}^{p}$

$\gamma^{fbp2} = \gamma \cdot (1 - \gamma^{amp})$

$V_{max}^{fbp2_{phospho}} = V_{max}^{fbp2_{native}}$

$$v_{fbp2}^{p} = \frac{fru26bp_{cyt}}{fru26bp_{cyt} + K_m^{fru26bp_{cyt}}}$$

$K_m^{fru26p_{cyt}} = 0.026$

Phosphofructokinase 1 (Pfk1):

$v_{pfk1} = V_{max}^{pfk1} \cdot \left(\left(1 - \gamma^{Pfk1}\right) \cdot v_{pfk1}^{native} + \gamma^{pfk1} \cdot v_{pfk1}^{p}\right)$

$\gamma^{pfk1} = \gamma \cdot (1 - \gamma^{amp})$

V_{max}^{pfk1} for numerical value see Supplemental Table II

$$v_{pfk1}^{native} = \frac{fru26_{cyt}^{n}}{fru26_{cyt}^{n} + \left(K_a^{fru26_{cyt}}\right)^{n}} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \cdot \left(1 - f_{atp} \frac{atp_{cyt}^{n_{atp}}}{atp_{cyt}^{n_{atp}} + \left(K_i^{atp_{cyt}}\right)^{n_{atp}}}\right) \cdot \left(1 - f_{cit} \frac{cit_{cyt}^{n_{cit}}}{cit_{cyt}^{n_{cit}} + \left(K_i^{cit_{cyt}}\right)^{n_{cit}}}\right) \cdot \frac{\left(fru6p_{cyt}\right)^{n_{fru6p_{cyt}}}}{\left(fru6p_{cyt}\right)^{n_{fru6p_{cyt}}} + \left(K_m^{fru6p_{cyt}}\right)^{n_{fru6p_{cyt}}}}$$

$n = 2$

$$K_a^{fru26_{cyt}} = K_0^{fru26_{cyt}} \cdot \left(\frac{atp_{cyt}^{n_{fru26}}}{atp_{cyt}^{n_{fru26}} + \left(K_{i_{fru26}}^{atp_{cyt}} \cdot \left(1 + \frac{cit_{cyt}}{cit_{cyt} + K_{i_{atp}}^{cit_{cyt}}}\right)\right)^{n_{fru26}}}\right)$$

$K_0^{fru26_{cyt}} = 0.010$

$n_{fru26} = n_0 - \frac{cit_{cyt}}{cit_{cyt}+K_{cit}^{n_{fru26}}}$

$n_0 = 5$

$K_{cit}^{n_{fru26}} = 0.05$

$K_{i_{fru26}}^{atp_{cyt}} = 3.4$

$K_{i_{atp}}^{cit_{cyt}} = 0.065$

$K_m^{atp_{cyt}} = 0.2$

$f_{atp} = 0.95$

$n_{atp} = 6$

$K_i^{atp_{cyt}} = 1.3$

$n_{cit} = 4$

$f_{cit} = 0.485$

$K_i^{cit_{cyt}} = 0.192$

$$K_m^{fru6p_{cyt}} = K_0 \cdot \left(1 - \frac{fru26_{cyt}}{fru26_{cyt} + K_{a_{fru6p}}^{fru26_{cyt}}}\right) \cdot \left(1 - \frac{p_{cyt}}{p_{cyt} + K_{a_{fru6p}}^{p_{cyt}}}\right) \cdot \left(1 + f_{atp} \frac{atp_{cyt}^{n_{atp}}}{atp_{cyt}^{n_{atp}} + \left(K_{i_{atp}}^{fru26}\right)^{n_{atp}}}\right) \cdot \left(1 + k_{cit} \frac{cit_{cyt}^{n_{cit}}}{cit_{cyt}^{n_{cit}} + \left(K_i^{cit_{cyt}}\right)^{n_{cit}}}\right)$$

$K_0 = 7$

$K_{a_{fru6p}}^{fru26_{cyt}} = 0.00015$

$K_{a_{fru6p}}^{p_{cyt}} = 0.15$

$n_{atp} = 2$

$K_{i_{atp}}^{fru26} = 0.2$

$f_{atp} = 2$

$k_{cit} = 8$

$n_{cit} = 4$

$K_i^{cit_{cyt}} = 0.13$

$$n_{fru6p_{cyt}} = n_0 \cdot \left(1 - f \frac{fru26_{cyt}}{fru26_{cyt} + K_{n_{fru6p}}^{fru26_{cyt}}}\right) \cdot \left(1 + \left(f_{atp} \frac{atp_{cyt}}{atp_{cyt} + K_{n_{fru6p}}^{fatp}}\right) \cdot \left(1 - \frac{fru6p_{cyt}}{fru6p_{cyt} + K_{n_{fru6p}}^{fru6}}\right) \cdot \left(1 - \frac{p_{cyt}}{p_{cyt} + K_{n_{fru6p}}^{p}}\right)\right)$$

$n_0 = 1$

$f = 0.66$

$f_{atp} = 2.75$

$K_{n_{fru6p}}^{fru26_{cyt}} = 0.0001$

$K_{n_{fru6p}}^{atp} = 0.1$

$K_{n_{fru6p}}^{fru6} = 0.4$

$K_{n_{fru6p}}^{p} = 0.5$

$$v_{pfk1}^{p} = \frac{fru26_{cyt}^{n}}{fru26_{cyt}^{n} + \left(K_a^{fru26_{cyt}}\right)^n} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \cdot \left(1 - f_{atp} \frac{atp_{cyt}^{n_{atp}}}{atp_{cyt}^{n_{atp}} + \left(K_i^{atp_{cyt}}\right)^{n_{atp}}}\right) \cdot \left(1 - f_{cit} \frac{cit_{cyt}^{n_{cit}}}{cit_{cyt}^{n_{cit}} + \left(K_i^{cit_{cyt}}\right)^{n_{cit}}}\right) \cdot \frac{\left(fru6p_{cyt}\right)^{n_{fru6p_{cyt}}}}{\left(fru6p_{cyt}\right)^{n_{fru6p_{cyt}}} + \left(K_m^{fru6p_{cyt}}\right)^{n_{fru6p_{cyt}}}}$$

$n = 2$

$$K_a^{fru26_{cyt}} = K_0^{fru26_{cyt}} \cdot \left(\frac{atp_{cyt}^{n_{fru26}}}{atp_{cyt}^{n_{fru26}} + \left(K_{i_{fru26}}^{atp_{cyt}} \cdot \left(1 + \frac{cit_{cyt}}{cit_{cyt} + K_{i_{atp}}^{cit_{cyt}}}\right)\right)^{n_{fru26}}}\right)$$

$K_0^{fru26_{cyt}} = 0.01$

$n_{fru26} = n_0 - \frac{cit_{cyt}}{cit_{cyt} + K_{cit}^{n_{fru26}}}$

$n_0 = 5$

$K_{cit}^{n_{fru26}} = 0.05$

$K_{i_{fru26}}^{atp_{cyt}} = 3.4$

$K_{i_{atp}}^{cit_{cyt}} = 0.065$

$K_m^{atp_{cyt}} = 0.2$

$f_{atp} = 0.95$

$n_{atp} = 5$

$K_i^{atp_{cyt}} = 0.9$

$n_{cit} = 2$

$f_{cit} = 0.55$

$K_i^{cit_{cyt}} = 0.18$

$$K_m^{fru6p_{cyt}} = K_0 \cdot \left(1 - \frac{fru26_{cyt}}{fru26_{cyt} + K_{a_{fru6p}}^{fru26_{cyt}}}\right) \cdot \left(1 - \frac{p_{cyt}}{p_{cyt} + K_{a_{fru6p}}^{p_{cyt}}}\right) \cdot \left(1 + f_{atp} \frac{atp_{cyt}^{n_{atp}}}{atp_{cyt}^{n_{atp}} + \left(K_{i_{atp}}^{fru26}\right)^{n_{atp}}}\right) \cdot \left(1 + k_{cit} \frac{cit_{cyt}^{n_{cit}}}{cit_{cyt}^{n_{cit}} + \left(K_i^{cit_{cyt}}\right)^{n_{cit}}}\right)$$

$K_0 = 5$

$K_{a_{fru6p}}^{fru26_{cyt}} = 0.00015$

$K_{a_{fru6p}}^{p_{cyt}} = 0.15$

$n_{atp} = 2$

$K_{i_{atp}}^{fru26} = 0.2$

$f_{atp} = 2$

$k_{cit} = 8$

$n_{cit} = 4$

$K_i^{cit_{cyt}} = 0.13$

$$n_{fru6p_{cyt}} = n_0 \cdot \left(1 - f \frac{fru26_{cyt}}{fru26_{cyt} + K_{n_{fru6p}}^{fru26_{cyt}}}\right) \cdot \left(1 + \left(f_{atp} \frac{atp_{cyt}}{atp_{cyt} + K_{n_{fru6p}}^{fatp}}\right) \cdot \left(1 - \frac{fru6p_{cyt}}{fru6p_{cyt} + K_{n_{fru6p}}^{fru6}}\right) \cdot \left(1 - \frac{p_{cyt}}{p_{cyt} + K_{n_{fru6p}}^{p}}\right)\right)$$

$n_0 = 1$

$f = 0.66$

$f_{atp} = 2.75$

$K_{n_{fru6p}}^{fru26_{cyt}} = 0.0001$

$K_{n_{fru6p}}^{atp} = 0.1$

$K_{n_{fru6p}}^{fru6} = 0.4$

$K_{n_{fru6p}}^{p} = 0.5$

Fructose-1,6-bisphosphatase (Fbp1)

$$v_{fbp1} = V_{max}^{fbp1} \cdot \left(\left(1 - \gamma^{fbp1}\right) \cdot v_{fbp1}^{native} + \gamma^{fbp1} \cdot v_{fbp1}^{p}\right)$$

$$\gamma^{fbp1} = \gamma \cdot (1 - \gamma^{amp})$$

V_{max}^{fbp1} for numerical value see Supplemental Table II

$$v_{fbp1}^{native} = \frac{fru16bp_{cyt}}{fru16bp_{cyt} + K_m^{fru16bp_{cyt}}} / \left(1 + \frac{fru26bp_{cyt}^n}{\left(K_i^{fru26bp_{cyt}}\right)^n}\right)$$

$K_m^{fru16bp_{cyt}} = 0.0029$

$K_i^{fru26p_{cyt}} = 0.00113$

$n = 1.26$

$$v_{fbp1}^{p} = \frac{fru16bp_{cyt}}{fru16bp_{cyt} + K_m^{fru16bp_{cyt}}} / \left(1 + \frac{fru26bp_{cyt}^n}{\left(K_i^{fru26bp_{cyt}}\right)^n}\right)$$

$K_m^{fru16bp_{cyt}} = 0.0019$

$K_i^{fru26bp_{cyt}} = 0.00113$

$n = 1.26$

Aldolase (Ald)

$$v_{ald} = v_{max}^{ald} \cdot \frac{fru16bp_{cyt} - \frac{1}{K_{eq}^{ald}} grap_{cyt} \cdot dhap_{cyt}}{\left(1 + \frac{fru16bp_{cyt}}{K_m^{fru16bp_{cyt}}}\right) + \left(1 + \frac{grap_{cyt}}{K_m^{grap_{cyt}}}\right) \cdot \left(1 + \frac{dhap_{cyt}}{K_m^{dhap_{cyt}}}\right) - 1}$$

v_{max}^{ald} for numerical value see Supplemental Table II

$K_{eq}^{ald} = 0.099$

$K_m^{fru16bp_{cyt}} = 0.004$

$K_m^{grap_{cyt}} = 0.48$

$K_m^{dhap_{cyt}} = 0.38$

Triosephosphate isomerase (Tpi)

$$v_{tpi} = v_{max}^{tpi} \cdot \frac{dhap_{cyt} - \frac{grap_{cyt}}{K_{eq}^{tpi}}}{1 + \frac{dhap_{cyt}}{K_m^{dhap_{cyt}}} + \frac{grap_{cyt}}{K_m^{grap_{cyt}}}}$$

v_{max}^{tpi} for numerical value see Supplemental Table II

$K_{eq}^{tpi} = 0.04545$

$K_m^{dhap_{cyt}} = 0.58$

$K_m^{grap_{cyt}} = 0.4$

D-Glyceraldehyde-3-phosphate:NAD$^+$ oxidoreductase (Gapdh)

$$v_{gapdh} = v_{max}^{Gapdh} * \frac{nad_{cyt} \cdot grap_{cyt} \cdot p_{cyt} - \frac{1}{K_{eq}^{gapdh}} \cdot bpg13_{cyt} \cdot nadh_{cyt}}{\left(1 + \frac{nad_{cyt}}{K_m^{nad_{cyt}}}\right) \cdot \left(1 + \frac{grap_{cyt}}{K_m^{grap_{cyt}}}\right) \cdot \left(1 + \frac{p_{cyt}}{K_m^{p_{cyt}}}\right) + \left(1 + \frac{nadh_{cyt}}{K_m^{nadh_{cyt}}}\right) \cdot \left(1 + \frac{bpg13_{cyt}}{K_m^{bpg13_{cyt}}}\right) - 1}$$

v_{max}^{Gapdh} for numerical value see Supplemental Table II

$K_{eq}^{gapdh} = 10^{-4} mM^{-1}$

$K_m^{nad_{cyt}} = 0.09$

$K_m^{grap_{cyt}} = 0.044$

$K_m^{p_{cyt}} = 3.8$

$K_m^{nadh_{cyt}} = 0.006$

$K_m^{bpg13_{cyt}} = 0.01$

Phosphoglycerate kinase (Pgk)

$$v_{pgk} = v_{max}^{pgk} \cdot \frac{adp_{cyt} \cdot bpg13_{cyt} - \frac{1}{K_{eq}^{pgk}} \cdot atp_{cyt} \cdot pg3_{cyt}}{\left(1 + \frac{adp_{cyt}}{K_m^{adp_{cyt}}}\right) \cdot \left(1 + \frac{bpg13_{cyt}}{K_m^{bpg13_{cyt}}}\right) + \left(1 + \frac{atp_{cyt}}{K_m^{atp_{cyt}}}\right) \cdot \left(1 + \frac{pg3_{cyt}}{K_m^{pg3_{cyt}}}\right) - 1}$$

v_{max}^{pgk} for numerical value see Supplemental Table II

$K_{eq}^{pgk} = 1830$

$K_m^{adp_{cyt}} = 0.35$

$K_m^{bpg13_{cyt}} = 0.0022$

$K_m^{atp_{cyt}} = 0.151$

$K_m^{pg3_{cyt}} = 1.397$

2-Phospho-D-glycerate 2,3 phosphomutase (Pgm)

$$v_{pgm} = v_{max}^{pgm} \cdot \frac{pg3_{cyt} - \frac{1}{K_{eq}^{pgm}} pg2_{cyt}}{pg3_{cyt} + K_m^{pg3_{cyt}} \cdot \left(1 + \frac{pg2_{cyt}}{K_m^{pg2}}\right)}$$

v_{max}^{pgm} for numerical value see Supplemental Table II

$K_{eq}^{pgm} = 0.1725$

$K_m^{pg3_{cyt}} = 0.52$

$K_m^{pg2} = 0.24$

2-Phospho-D-glycerate hydrolase (Eno)

$$v_{eno} = v_{max}^{eno} \cdot \frac{pg2_{cyt} - \frac{1}{K_{eq}^{eno}} \cdot pep_{cyt}}{1 + \frac{pg2_{cyt}}{K_m^{pg2_{cyt}}} + \frac{pep_{cyt}}{K_m^{pep_{cyt}}}}$$

v_{max}^{eno} for numerical value see Supplemental Table II

$K_{eq}^{eno} = 1.7$

$K_m^{pg2_{cyt}} = 0.12$

$K_m^{pep_{cyt}} = 0.37$

Pyruvate kinase (Pk)

$$v_{pk} = v_{max}^{Pk} \frac{pep_{cyt}}{pep_{cyt} + K_m^{pep_{cyt}}} \cdot \frac{adp_{cyt}}{adp_{cyt} + K_m^{adp_{cyt}}}$$

v_{max}^{Pk} for numerical value see Supplemental Table II

$K_m^{pep_{cyt}} = 0.08$

$K_m^{adp_{cyt}} = 0.3$

Pyruvate carboxylase

$$v_{pc} = v_{max}^{Pc} \cdot \frac{atp_{mito} \cdot pyr_{mito}}{\left(atp_{mito} + k_m^{atp_{mito}}\right) \cdot \left(pyr_{mito} + k_m^{pyr_{mito}}\right)}$$

v_{max}^{Pc} for numerical value see Supplemental Table II

$k_m^{atp_{mito}} = 0.14$

$k_m^{pyr_{mito}} = 0.33$

Lactate dehydrogenase (Ldh):

$$v_{ldh} = v_{max}^{ldh} * \frac{pyr_{cyt} \cdot nadh_{cyt} - \frac{1}{K_{eq}^{ldh}} \cdot lac_{cyt} \cdot nad_{cyt}}{\left(1 + \frac{nadh_{cyt}}{K_m^{nadh_{cyt}}}\right) \cdot \left(1 + \frac{pyr_{cyt}}{K_m^{pyr_{cyt}}}\right) + \left(1 + \frac{lac_{cyt}}{K_m^{lac_{cyt}}}\right) \cdot \left(1 + \frac{nad_{cyt}}{K_m^{nad_{cyt}}}\right) - 1}$$

v_{max}^{ldh} for numerical value see Supplemental Table II

K_{eq}^{ldh} =9000

$K_m^{nadh_{cyt}} = 0.0121$

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

$K_m^{lac_{cyt}} = 4.4$

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

Lactate transport (LacT):

$$v_{lacT} = v_{max}^{lacT} \cdot \frac{lac_{ext} - lac_{cyt}}{1 + \frac{lac_{cyt}}{K_m^{lac_{cyt}}} + \frac{lac_{ext}}{K_m^{lac_{ext}}}}$$

v_{max}^{lacT} for numerical value see Supplemental Table II

$K_m^{lac_{cyt}} = 2.5$

$K_m^{lac_{ext}} = 2.5$

Pyruvate transport (PyrT):

$$v_{lacT} = v_{max}^{pyrT} \cdot \frac{pyr_{ext} - pyr_{cyt}}{1 + \frac{pyr_{cyt}}{K_m^{pyr_{cyt}}} + \frac{pyr_{ext}}{K_m^{pyr_{ext}}}}$$

v_{max}^{pyrT} for numerical value see Supplemental Table II

$K_m^{pyr_{ext}} = 0.1$

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

Mitochondrial pyruvate transport:

$$v_{pyrT_{mito}} = v_{max}^{pyrT_{mito}} \cdot \frac{pyr_{cyt} \cdot h_{cyt} - pyr_{mito} \cdot h_{mito}}{1 + \frac{pyr_{cyt}}{K_m^{pyr_{cyt}}} + \frac{pyr_{mito}}{K_m^{pyr_{mito}}}}$$

$v_{max}^{PyrT_{mito}}$ for numerical value see Supplemental Table II

$K_m^{pyr_{cyt}}$ =0.15

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

Mitochondrial malate-phosphate transport

$$v_{malpT} = v_{max}^{malpT} \cdot \left(\frac{mal_{mito} \cdot p_{cyt} - mal_{cyt} \cdot p_{mito}}{\left(1 + \frac{mal_{mito}}{K_m^{mal_{mito}}}\right) \cdot \left(1 + \frac{p_{cyt}}{K_m^{p_{cyt}}}\right) + \left(1 + \frac{mal_{cyt}}{K_m^{mal_{cyt}}}\right) \cdot \left(1 + \frac{p_{mito}}{K_m^{p_{mito}}}\right) - 1} \right)$$

v_{max}^{malpT} for numerical value see Supplemental Table II

$K_m^{p_{cyt}} = 1.41$

$K_m^{mal_{mito}} = 0.4$

$K_m^{p_{mito}} = 1.41$

$K_m^{mal_{cyt}} = 0.4$

Malate-pyruvate antiport (MalPyrT)

$$v_{mal-pyrT} = v_{max}^{mal-pyrT} * \left(\frac{mal_{mito} \cdot pyr_{cyt} - mal_{cyt} \cdot pyr_{mito}}{\left(1 + \frac{mal_{mito}}{K_m^{mal_{mito}}}\right) \cdot \left(1 + \frac{pyr_{cyt}}{K_m^{pyr_{cyt}}}\right) + \left(1 + \frac{mal_{cyt}}{K_m^{mal_{cyt}}}\right) \cdot \left(1 + \frac{pyr_{mito}}{K_m^{pyr_{mito}}}\right) - 1} \right)$$

$v_{max}^{MalPyrT}$ for numerical value see Supplemental Table II

$K_m^{pyr_{cyt}} = 0.84$

$K_m^{mal_{cyt}} = 0.7$

$K_m^{pyr_{mito}} = 0.84$

$K_m^{mal_{cyt}} = 0.7$

Cytosolic malate dehydrogenase (Mdh)

$$v_{mdh} = v_{max}^{Mdh} \cdot \frac{mal_{cyt} \cdot nad_{cyt} - \frac{1}{K_{eq}^{mdh_{cyt}}} \cdot oaa_{cyt} \cdot nadh_{cyt}}{\left(1 + \frac{mal_{cyt}}{K_m^{mal_{cyt}}}\right) \cdot \left(1 + \frac{nad_{cyt}}{K_m^{nad_{cyt}}}\right) + \left(1 + \frac{oaa_{cyt}}{K_m^{oaa_{cyt}}}\right) \cdot \left(1 + \frac{nadh_{cyt}}{K_m^{nadh_{cyt}}}\right) - 1}$$

v_{max}^{Mdh} for numerical value see Supplemental Table II

$K_{eq}^{mdh_{cyt}} = 10^{-5}$

$K_m^{mal_{cyt}} = 0.47$

$K_m^{nad_{cyt}} = 0.099$

$K_m^{oaa_{cyt}} = 0.042$

$K_m^{nadh_{cyt}} = 0.027$

NADP-dependent malic enzyme (cytosol)

$$v_{me} = V_{max}^{me} \cdot \left(\frac{mal_{cyt} \cdot nadp_{cyt} - {}^{1}\!/_{K_{eq}^{me}} \cdot pyr_{cyt} \cdot nadph_{cyt} \cdot hco3_{cyt}}{\left(1 + \frac{mal_{cyt}}{K_m^{mal_{cyt}}}\right) \cdot \left(1 + \frac{nadp_{cyt}}{K_m^{nadp_{cyt}}}\right) + \left(1 + \frac{pyr_{cyt}}{K_m^{pyr_{cyt}}}\right) \cdot \left(1 + \frac{nadph_{cyt}}{K_m^{nadph_{cyt}}}\right) \cdot \left(1 + \frac{hco3_{cyt}}{K_m^{hco3_{cyt}}}\right)} \right)$$

V_{max}^{me} for numerical value see Supplemental Table II

$K_{eq}^{me} = 34.4$

$K_m^{mal_{cyt}} = 0.12$

$K_m^{nadp_{cyt}} = 0.0092$

$K_m^{pyr_{cyt}} = 8$

$K_m^{nadph_{cyt}} = 0.0053$

$K_m^{hco3_{cyt}} = 13$

Nucleoside diphosphokinase (cytosolic)

$$v_{ndk_{cyt}} = V_{max}^{ndk_{cyt}} \cdot \left(\frac{atp_{cyt} \cdot gdp_{cyt} - {}^{1}\!/_{K_{eq}^{ndk}} \cdot adp_{cyt} \cdot gtp_{cyt}}{\left(1 + \frac{atp_{cyt}}{K_m^{atp_{cyt}}}\right) \cdot \left(1 + \frac{gdp_{cyt}}{K_m^{gdp_{cyt}}}\right) + \left(1 + \frac{adp_{cyt}}{K_m^{adp_{cyt}}}\right) \cdot \left(1 + \frac{gtp_{cyt}}{K_m^{gtp_{cyt}}}\right) - 1} \right)$$

$V_{max}^{ndk_{cyt}}$ for numerical value see Supplemental Table II

$K_{eq}^{ndk} = 1$

$K_m^{atp_{cyt}} = 1.8$

$K_m^{gdp_{cyt}} = 0.049$

$K_m^{adp_{cyt}} = 0.066$

$K_m^{gtp_{cyt}} = 0.15$

Nucleoside diphosphokinase (mito)

$$v_{ndk_{mito}} = V_{max}^{ndk_{mito}} \cdot \left(\frac{atp_{mito} \cdot gdp_{mito} - {}^{1}\!/_{K_{eq}^{ndk}} \cdot adp_{mito} \cdot gtp_{mito}}{\left(1 + \frac{atp_{mito}}{K_m^{atp_{mito}}}\right) \cdot \left(1 + \frac{gdp_{mito}}{K_m^{gdp_{mito}}}\right) + \left(1 + \frac{adp_{mito}}{K_m^{adp_{mito}}}\right) \cdot \left(1 + \frac{gtp_{mito}}{K_m^{gtp_{mito}}}\right) - 1} \right)$$

$V_{max}^{ndk_{mito}}$ for numerical value see Supplemental Table II

$K_{eq}^{ndk} = 1$

$K_m^{atp_{mito}} = 1.66$

$K_m^{gdp_{mito}} =0.036$

$K_m^{adp_{mito}} =0.073$

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

Glycogen metabolism

Alpha-D-Glucose 1-phosphate 1,6-phosphomutase:

$$v_{gpm} = v_{max}^{gpm} \cdot \frac{glc1p_{cyt} - \frac{1}{K_{eq}^{gpm}} \cdot glc6p_{cyt}}{1 + \frac{glc1p_{cyt}}{K_m^{glc1p_{cyt}}} + \frac{glc6p_{cyt}}{K_m^{glc6p_{cyt}}}}$$

v_{max}^{gpm} for numerical value see Supplemental Table II

$K_{eq}^{gpm} = 16.2$

$K_m^{glc1p_{cyt}} = 0.045$

$K_m^{glc6p_{cyt}} = 0.67$

UTP:Glucose-1-phosphate uridylyltransferase (UPGase):

$$v_{upgase} = v_{max}^{upgase} \cdot \frac{utp_{cyt} \cdot glc1p_{cyt} - \frac{1}{K_{eq}^{upgase}} \cdot udpglc_{cyt} \cdot pp_{cyt}}{\left(1 + \frac{utp_{cyt}}{K_m^{utp_{cyt}}}\right) \cdot \left(1 + \frac{glc1p_{cyt}}{K_m^{glc1p_{cyt}}}\right) + \left(1 + \frac{udpglc_{cyt}}{K_m^{udpglc_{cyt}}}\right) \cdot \left(1 + \frac{pp_{cyt}}{K_m^{pp_{cyt}}}\right) - 1}$$

v_{max}^{UPGase} for numerical value see Supplemental Table II

$K_{eq}^{upgase} = 0.3122$

$K_m^{utp_{cyt}} = 0.2$

$K_m^{glc1p_{cyt}} = 0.055$

$K_m^{udpglc_{cyt}} = 0.06$

$K_m^{pp_{cyt}} = 0.084$

Glycogen synthase (GS):

$$v_{gs} = V_{max}^{gs} \cdot \left((1 - \gamma^{gs}) \cdot v_{gs}^{native} + \gamma^{gs} \cdot v_{gs}^{p} \right)$$

$$\gamma^{gs} = 1 - \gamma \cdot \left(1 - \frac{epi_{ext}}{epi_{ext} + K_i^{epi}} \right)$$

$K_i^{epi} = 200\ pM$

$$V_{max}^{gs} = V_0^{gs} \frac{(store - glyglc)}{(store - glyglc) + 10mM}$$

V_0^{gs} for numerical value see Supplemental Table II

$store = 5\ mM$

$$v_{gs}^{native} = \left(\frac{udpglc_{cyt}}{udpglc_{cyt} + K_{m-native}^{udpglc_{cyt}}} \right) \cdot \left(\frac{glc6p_{cyt}}{glc6p_{cyt} + K_a^{glc6p_{cyt}}} \right)$$

$$K_{m-native}^{udpglc_{cyt}} = K_{0-native}^{udpglc_{cyt}} \cdot \left(1 - \frac{glc6p_{cyt}}{glc6p_{cyt} + K_{a2}^{glc6p_{cyt}}} \right) + K_{b-native}^{udpglc_{cyt}}$$

$K_{0-native}^{udpglc_{cyt}} = 0.9$

$K_a^{glc6p_{cyt}} = 0.004$

$K_{a2}^{glc6p_{cyt}} = 0.004$

$K_{b-native}^{udpglc_{cyt}} = 0.2$

$$v_{gs}^{p} = \left(\frac{udpglc_{cyt}}{udpglc_{cyt} + K_{m-p}^{udpglc_{cyt}}} \right) \cdot \left(\frac{glc6p_{cyt}}{glc6p_{cyt} + K_a^{glc6p_{cyt}}} \right)$$

$K_{m-p}^{udpglc_{cyt}} = K_{0-p}^{udpglc_{cyt}}$

$K_{0-p}^{udpglc_{cyt}} = 0.9$

$K_a^{glc6p_{cyt}} = 2$

Glycogen phosphorylase (GP):

$$v_{gp} = \left((1-\gamma^{gp}) \cdot v_{gp}^{native} + \gamma^{gp} \cdot v_{gp}^{p}\right)$$

$$\gamma^{gp} = \gamma^{gs}$$

$$v_{gp}^{native} = V_{max}^{gp-native} \cdot \frac{glyglc \cdot p_{cyt} - \frac{1}{K_{eq}^{gp}} \cdot glc1p_{cyt}}{\left(1+\frac{glyglc}{K_{m-native}^{glycogen}}\right) \cdot \left(1+\frac{p_{cyt}}{K_{m-native}^{p_{cyt}}}\right) + \left(1+\frac{glc1p_{cyt}}{K_{m-native}^{glc1p_{cyt}}}\right) - 1}$$

$$V_{max-native}^{gp} = \frac{V_0^{gp}}{K_{m-native}^{p_{cyt}} \cdot K_{m-native}^{glyglc}} \cdot \left(\frac{amp_{cyt}}{amp_{cyt} + K_{a-native}^{amp_{cyt}}}\right) \cdot \left(\frac{glyglc}{glyglc + 0.1 \cdot store}\right)$$

V_0^{gp} for numerical value see Supplemental Table II

$$store = 5\, mM$$

$$K_{a-native}^{amp} = 0.0022$$

$$K_{eq}^{gp} = 0.21 (mM)^{-1}$$

$$K_{m-native}^{glyglc} = 2.5$$

$$K_{m-native}^{p_{cyt}} = 500$$

$$K_{m-native}^{glc1p_{cyt}} = K_0^{glc1p} \cdot \left(1 - \frac{amp_{cyt}}{amp_{cyt} + K_{a-glc1p}^{amp_{cyt}}}\right)$$

$$K_0^{glc1p} = 250$$

$$K_{a-glc1p}^{amp_{cyt}} = 0.5$$

$$v_{gp}^{p} = V_{max-p}^{gp} \cdot \frac{glyglc \cdot p_{cyt} - \frac{1}{K_{eq}^{gp}} \cdot glc1p_{cyt}}{\left(1+\frac{glyglc}{K_{m-p}^{glycogen}}\right) \cdot \left(1+\frac{p_{cyt}}{K_{m-p}^{p_{cyt}}}\right) + \left(1+\frac{glc1p_{cyt}}{K_{m-p}^{glc1p_{cyt}}}\right) - 1}$$

$$V_{max-p}^{gp} = \frac{V_0^{gp}}{K_{m-p}^{p} \cdot K_{m-p}^{glyglc}} \cdot \left(k_1 + \frac{amp_{cyt}}{amp_{cyt} + K_{a-p}^{amp_{cyt}}}\right) \cdot \left(\frac{glyglc}{glyglc + 0.1 \cdot store}\right)$$

$$k_1 = 0.5$$

$$K_{a-native}^{amp} = 0.22$$

$$K_{m-p}^{glyglc} = 0.27$$

$$K_{m-p}^{p_{cyt}} = 3.8$$

$K_{m-p}^{glc1p_{cyt}} = 0.7$

Nucleoside diphosphokinase (cytosolic) (udp)

$$v_{ndk_{cyt}} = V_{max}^{ndk_{cyt}} \cdot \left(\frac{atp_{cyt} \cdot udp_{cyt} - 1/K_{eq}^{ndk} \cdot adp_{cyt} \cdot utp_{cyt}}{\left(1 + \frac{atp_{cyt}}{K_m^{atp_{cyt}}}\right) \cdot \left(1 + \frac{udp_{cyt}}{K_m^{udp_{cyt}}}\right) + \left(1 + \frac{adp_{cyt}}{K_m^{adp_{cyt}}}\right) \cdot \left(1 + \frac{utp_{cyt}}{K_m^{utp_{cyt}}}\right) - 1} \right)$$

$V_{max}^{ndk_{cyt}}$ for numerical value see Supplemental Table II

$K_{eq}^{ndk} = 1$

$K_m^{atp_{cyt}} = 0.5$

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

$K_m^{adp_{cyt}} = 0.07$

$K_m^{utp_{cyt}} = 0.15$

Malate-Aspartate shuttle

Aspartate–amino transferase (mitochondrial)

$$v_{asat_{mito}} = V_{max}^{asat} \cdot \left(\frac{asp_{mito} \cdot akg_{mito} - 1/K_{eq}^{asat} \cdot oaa_{mito} \cdot glu_{mito}}{\left(1 + \frac{asp_{mito}}{K_m^{asp_{mito}}}\right) \cdot \left(1 + \frac{akg_{mito}}{K_m^{akg_{mito}}}\right) + \left(1 + \frac{oaa_{mito}}{K_m^{oaa_{mito}}}\right) \cdot \left(1 + \frac{glu_{mito}}{K_m^{glu_{mito}}}\right) - 1} \right)$$

V_{max}^{asat} for numerical value see Supplemental Table II

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

$K_m^{asp_{mito}} = 0.35$

$K_m^{akg_{mito}} = 1.1$

$K_m^{oaa_{mito}}$=1.84

$K_m^{glu_{mito}}$=0.48

Aspartate–amino transferase (cytosolic)

$$v_{asat} = V_{max}^{asat} \cdot \left(\frac{asp_{cyt} \cdot akg_{cyt} - 1/K_{eq}^{asat} \cdot oaa_{cyt} \cdot glu_{cyt}}{\left(1 + \frac{asp_{cyt}}{K_m^{asp_{cyt}}}\right) \cdot \left(1 + \frac{akg_{cyt}}{K_m^{akg_{cyt}}}\right) + \left(1 + \frac{oaa_{cyt}}{K_m^{oaa_{cyt}}}\right) \cdot \left(1 + \frac{glu_{cyt}}{K_m^{glu_{cyt}}}\right) - 1} \right)$$

V_{max}^{asat} for numerical value see Supplemental Table II

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

$K_m^{asp_{cyt}} = 3.9$

$K_m^{akg_{cyt}} = 0.57$

$K_m^{oaa_{cyt}}$=2.05

$K_m^{glu_{cyt}}$=0.38

Aspartate–glutamate carrier

$$v_{agc} = V_{max}^{agc} \cdot \left(\frac{asp_{mito} \cdot glu_{cyt} - 1/K_{eq}^{agc} \cdot asp_{cyt} \cdot glu_{mito}}{\left(1 + \frac{asp_{mito}}{K_m^{asp_{mito}}}\right) \cdot \left(1 + \frac{glu_{cyt}}{K_m^{glu_{cyt}}}\right) + \left(1 + \frac{asp_{cyt}}{K_m^{asp_{cyt}}}\right) \cdot \left(1 + \frac{glu_{mito}}{K_m^{glu_{mito}}}\right) - 1} \right)$$

V_{max}^{asat} for numerical value see Supplemental Table II

$$K_{eq}^{asat} = exp\left(\frac{-V_{mm} \cdot F}{R \cdot T}\right) \cdot \left(\frac{H_{cyt}}{H_{mito}}\right)$$

$$K_m^{asp_{mito}} = K_0^{asp_{mito}} \cdot \left(1 + \frac{glu_{mito}}{K_i^{glu_{mito}}}\right)$$

$K_0^{asp_{mito}} = 0.05$

$K_i^{glu_{mito}} = 0.5$

$$K_m^{asp_{cyt}} = K_0^{asp_{cyt}} \cdot \left(1 + \frac{glu_{cyt}}{K_i^{glu_{cyt}}}\right)$$

$K_0^{asp_{cyt}} = 0.043$

$K_i^{glu_{cyt}} = 0.5$

$K_m^{glu_{mito}} = 3$

$K_m^{glu_{cyt}} = 3.2$

Malate – α-ketogluterate carrier

$$v_{mac} = V_{max}^{mac} \cdot \left(\frac{mal_{cyt} \cdot akg_{mito} - {}^{1}/_{K_{eq}^{mac}} \cdot mal_{mito} \cdot akg_{cyt}}{\left(1 + \frac{mal_{cyt}}{K_m^{mal_{cyt}}}\right) \cdot \left(1 + \frac{akg_{mito}}{K_m^{akg_{mito}}}\right) + \left(1 + \frac{mal_{mito}}{K_m^{mal_{mito}}}\right) \cdot \left(1 + \frac{akg_{cyt}}{K_m^{akg_{cyt}}}\right) - 1} \right)$$

V_{max}^{mac} for numerical value see Supplemental Table II

$K_{eq}^{mac} = 1$

$K_m^{mal_{cyt}} = 0.7$

$K_m^{akg_{mito}} = 0.17$

$K_m^{mal_{mito}} = 1.4$

$K_m^{akg_{cyt}} = 0.3$

Glycerol-3-phosphate dehydrogenase (cytosolic)

$$v_{g3pdh} = V_{max}^{g3pdh_{cyt}} \cdot \left(\frac{dhap_{cyt} \cdot nadh_{cyt} - {}^{1}/_{K_{eq}^{g3pdh}} \cdot g3p_{cyt} \cdot nad_{cyt}}{\left(1 + \frac{dhap_{cyt}}{K_m^{dhap_{cyt}}}\right) \cdot \left(1 + \frac{nadh_{cyt}}{K_m^{nadh_{cyt}}}\right) + \left(1 + \frac{g3p_{cyt}}{K_m^{g3p_{cyt}}}\right) \cdot \left(1 + \frac{nad_{cyt}}{K_m^{nad_{cyt}}}\right) - 1} \right)$$

$V_{max}^{g3pdh_{cyt}}$ for numerical value see Supplemental Table II

$K_{eq}^{g3pdh_{cyt}} = \frac{1}{3 \cdot 10^{-4}}$

$K_m^{dhap_{cyt}} = 0.2$

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

$K_m^{g3p_{cyt}} = 0.17$

$K_m^{nad_{cyt}} = 0.063$

Glycerol-3-phosphate dehydrogenase (mitochondrial)

$$v_{g3pdh_{mito}} = V_{max}^{g3pdh_{mito}} \cdot \left(\frac{dhap_{cyt} \cdot qh2_{mm} - {}^{1}/_{K_{eq}^{g3pdh}} \cdot g3p_{cyt} \cdot q_{mm}}{\left(1 + \frac{dhap_{cyt}}{K_m^{dhap_{cyt}}}\right) + \left(1 + \frac{g3p_{cyt}}{K_m^{g3p_{cyt}}}\right) - 1} \right)$$

$V_{max}^{g3pdh_{mito}}$ for numerical value see Supplemental Table II

$$K_{eq}^{g3pdh_{mito}} = K_{eq}^{g3pdh_{cyt}} \cdot exp\left(\frac{\left(n \cdot E_0^{nad/nadh} + n \cdot E_0^{QH_2/Q}\right) \cdot F}{R \cdot T}\right)$$

$K_m^{dhap_{cyt}} = 0.23$

$K_m^{g3p_{cyt}} = 1.8$

$E_0^{nad/nadh} = -320mV$

$E_0^{QH_2/Q} = -87mV$

$n = 2$

Pentose phosphate shunt

Glucose-6-phosphate dehydrogenase

$$v_{g6pdh} = V_{max}^{g6pdh} \cdot \left(\left(\frac{glc6p_{cyt}}{glc6p_{cyt} + K_m^{glc6p_{cyt}} \cdot \left(1 + \frac{c16coa_{cyt}}{K_i^{c16coa_{cyt}}}\right)}\right) \cdot \left(\frac{nadp_{cyt}}{nadp_{cyt} + K_m^{nadp_{cyt}} \cdot \left(1 + \frac{nadph_{cyt}}{K_i^{nadph_{cyt}}}\right)}\right)\right)$$

V_{max}^{g6pdh} for numerical value see Supplemental Table II

$K_m^{glc6p_{cyt}}$ =0.013

$K_i^{c16coa_{cyt}} = 0.029$

$K_m^{nadp_{cyt}} = 0.013$

$K_i^{nadph_{cyt}}$ =0.01

6-Phosphogluconolactase

$$v_{pgls} = V_{max}^{pgls} \cdot \left(\frac{pgl6_{cyt}}{pgl6_{cyt} + K_m^{pgl6_{cyt}}} \right)$$

V_{max}^{pgls} for numerical value see Supplemental Table II

$K_m^{pgl6_{cyt}} = 0.7$

6-Phosphogluconate dehydrogenase

$$v_{pgdh} = V_{max}^{pgdh} \cdot \left(\frac{nadp_{cyt} \cdot pg6_{cyt} - 1/K_{eq}^{pgdh} \cdot ru5p_{cyt} \cdot nadph_{cyt}}{\left(1 + \frac{nadp_{cyt}}{K_m^{nadp_{cyt}} \cdot \left(1 + \frac{nadph_{cyt}}{K_i^{nadph_{cyt}}}\right)}\right) \cdot \left(1 + \frac{pg6_{cyt}}{K_m^{pg6_{cyt}}}\right) + \left(1 + \frac{ru5p_{cyt}}{K_m^{ru5p_{cyt}}}\right) \cdot \left(1 + \frac{co2_{cyt}}{K_m^{co2_{cyt}}}\right) \cdot \left(1 + \frac{nadph_{cyt}}{K_m^{nadph_{cyt}}}\right) - 1} \right)$$

V_{max}^{pgdh} for numerical value see Supplemental Table II

$K_{eq}^{pgdh} = 74$

$K_m^{nadp_{cyt}} = 0.028$

$K_i^{nadph} = 0.02$

$K_m^{pg6_{cyt}} = 0.071$

$K_m^{co2_{cyt}} = 5$

$K_m^{nadph_{cyt}} = 0.001$

$K_m^{ru5p_{cyt}} = 0.123$

Ribulose-phosphate-3-epimerase

$$v_{rpe} = V_{max}^{rpe} \cdot \left(\frac{ru5p_{cyt} - 1/K_{eq}^{rpe} \cdot x5p_{cyt}}{1 + \frac{ru5p_{cyt}}{K_m^{ru5p_{cyt}}} + \frac{x5p_{cyt}}{K_m^{x5p_{cyt}}}} \right)$$

V_{max}^{rpe} for numerical value see Supplemental Table II

$K_{eq}^{rpe} = 1.5$

$K_m^{ru5p_{cyt}} = 0.2$

$K_m^{x5p_{cyt}} = 0.5$

Ribose-phosphate-isomerase

$$v_{rpi} = V_{max}^{rpi} \cdot \left(\frac{r5p_{cyt} - {}^{1}\!/\!{}_{K_{eq}^{rpi}} \cdot ru5p_{cyt}}{1 + \frac{r5p_{cyt}}{K_m^{r5p_{cyt}}} + \frac{ru5p_{cyt}}{K_m^{ru5p_{cyt}}}} \right)$$

V_{max}^{rpi} for numerical value see Supplemental Table II

$K_{eq}^{rpi} = 0.32$

$K_m^{r5p_{cyt}} = 9.1$

$K_m^{ru5p_{cyt}} = 0.78$

Transladolase

$$v_{taldo} = V_{max}^{taldo} \cdot \left(\frac{s7p_{cyt} \cdot grap_{cyt} - {}^{1}\!/\!{}_{K_{eq}^{taldo}} \cdot e4p_{cyt} \cdot fru6p_{cyt}}{\left(1 + \frac{s7p_{cyt}}{K_m^{s7p_{cyt}}}\right) \cdot \left(1 + \frac{grap_{cyt}}{K_m^{grap_{cyt}}}\right) + \left(1 + \frac{e4p_{cyt}}{K_m^{e4p_{cyt}}}\right) \cdot \left(1 + \frac{fru6p_{cyt}}{K_m^{fru6p_{cyt}}}\right) - 1} \right)$$

V_{max}^{tado} for numerical value see Supplemental Table II

K_{eq}^{taldo} =0.95

$K_m^{s7p_{cyt}}$ =0.17

$K_m^{grap_{cyt}}$ =0.038

$K_m^{e4p_{cyt}} = 0.13$

$K_m^{fru6p_{cyt}} = 0.3$

Transketolase 1

$$v_{tketo1} = V_{max}^{tketo1} \cdot \left(\frac{s7p_{cyt} \cdot grap_{cyt} - 1/_{K_{eq}^{tketo1}} \cdot r5p_{cyt} \cdot x5p_{cyt}}{\left(1 + \frac{s7p_{cyt}}{K_m^{s7p_{cyt}}}\right) \cdot \left(1 + \frac{grap_{cyt}}{K_m^{grap_{cyt}}}\right) + \left(1 + \frac{r5p_{cyt}}{K_m^{r5p_{cyt}}}\right) \cdot \left(1 + \frac{x5p_{cyt}}{K_m^{x5p_{cyt}}}\right) \cdot -1} \right)$$

V_{max}^{tketo1} for numerical value see Supplemental Table II

$K_{eq}^{tketo1} = 0.845$

$K_m^{s7p_{cyt}} = 0.285$

$K_m^{grap_{cyt}} = 0.38$

$K_m^{r5p_{cyt}} = 0.066$

$K_m^{x5p_{cyt}} = 0.15$

Transketolase 2

$$v_{tketo2} = V_{max}^{tketo1} \cdot \left(\frac{fru6p_{cyt} \cdot grap_{cyt} - 1/_{K_{eq}^{tketo2}} \cdot e4p_{cyt} \cdot x5p_{cyt}}{\left(1 + \frac{fru6p_{cyt}}{K_m^{fru6p_{cyt}}}\right) \cdot \left(1 + \frac{grap_{cyt}}{K_m^{grap_{cyt}}}\right) + \left(1 + \frac{e4p_{cyt}}{K_m^{e4p_{cyt}}}\right) \cdot \left(1 + \frac{x5p_{cyt}}{K_m^{x5p_{cyt}}}\right) \cdot -1} \right)$$

V_{max}^{tketo2} for numerical value see Supplemental Table II

$K_{eq}^{tketo2} = 0.084$

$K_m^{fru6p_{cyt}} = 0.34$

$K_m^{grap_{cyt}} = 0.38$

$K_m^{e4p_{cyt}} = 0.044$

$K_m^{x5p_{cyt}} = 0.16$

Fatty acid synthesis

Citrate-malate exchanger

$$v_{cit-mal} = \frac{V_{max}^{cit-mal}}{K_m^{cit_{mito}} \cdot K_m^{mal_{cyt}}}$$

$$\cdot\left(\frac{cit_{mito}\cdot mal_{cyt}-{}^{1}\!/_{K_{eq}^{cit-mal}}\cdot cit_{cyt}\cdot mal_{mito}}{\left(1+\frac{cit_{mito}}{K_m^{cit_{mito}}}\right)\cdot\left(1+\frac{mal_{cyt}}{K_m^{mal_{cyt}}}\right)+\left(1+\frac{cit_{cyt}}{K_m^{cit_{cyt}}}\right)\cdot\left(1+\frac{mal_{mito}}{K_m^{mal_{mito}}}\right)\cdot-1}\right)$$

$$V_{max}^{cit-mal}=V_0^{cit-mal}\cdot\left(1-\frac{\left(c16coa_{cyt}\right)^n}{\left(c16coa_{cyt}\right)^n+\left(K_i^{c16coa_{cyt}}\right)^n}\right)$$

$V_0^{cit-mal}$ for numerical value see Supplemental Table II

$K_i^{c16coa_{cyt}}=0.033$

$n=3$

$K_{eq}^{cit-mal}=1$

$$K_m^{cit_{mito}}=K_0^{cit_{mito}}\cdot\left(1+\frac{suc_{mito}}{K_i^{suc_{mito}}}\right)\cdot\left(1+\frac{isocit_{mito}}{K_i^{isocit_{mito}}}\right)\cdot\left(1+\frac{pep_{mito}}{K_i^{pep_{mito}}}\right)$$

$K_0^{cit_{mito}}=0.14$

$K_i^{suc_{mito}}=2.5$

$K_i^{isocit_{mito}}=0.08$

$K_i^{pep_{mito}}=0.18$

$K_m^{mal_{cyt}}=0.76$

$$K_m^{cit_{cyt}}=K_0^{cit_{cyt}}\cdot\left(1+\frac{pep_{cyt}}{K_i^{pep_{cyt}}}\right)$$

$K_0^{cit_{cyt}}=0.039$

$K_i^{pep_{cyt}}=0.18$

$K_m^{mal_{mito}}=0.76$

ATP dependent citrate lyase

$$v_{cit-lys}=V_{max}^{cit-lys}\cdot\left(\left(1-\gamma^{cit-lys}\right)\cdot v_{cit-lys}^{native}+\gamma^{cit-lys}\cdot v_{cit-lys}^{phospho}\right)$$

$\gamma^{cit-lys}=\gamma$

$V_{max}^{cit-lys}$ for numerical value see Supplemental Table II

$$v_{cit-lys}^{native} = \frac{cit_{cyt}^{n}}{cit_{cyt}^{n} + \left(K_m^{cit_{cyt}}\right)^n} \cdot \frac{coa_{cyt}}{coa_{cyt} + K_m^{coa_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}}$$

$K_m^{cit_{cyt}} = 0.154$

$n = 0.65$

$K_m^{coa_{cyt}} = 0.0026$

$K_m^{atp_{cyt}} = 0.041$

$$v_{cit-lys}^{phospho} = \frac{cit_{cyt}^{n}}{cit_{cyt}^{n} + \left(K_m^{cit_{cyt}}\right)^n} \cdot \frac{coa_{cyt}}{coa_{cyt} + K_m^{coa_{cyt}}} \cdot \frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}}$$

$K_m^{cit_{cyt}} = 0.103$

$n = 0.91$

$K_m^{coa_{cyt}} = 0.002$

$K_m^{atp_{cyt}} = 0.041$

Acetyl-CoA carboxylase 1

$$v_{acc1} = \gamma \cdot v_{acc1-p} + (1-\gamma) \cdot v_{acc1-up}$$

$$v_{acc1-p} = V_{max}^{acc1-p} \cdot \left(\frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}}\right) \cdot \left(\frac{acoa_{cyt}}{acoa_{cyt} + K_m^{acoa_{cyt}}}\right) \cdot \left(\frac{hco3_{cyt}}{hco3_{cyt} + K_m^{hco3_{cyt}}}\right)$$

$$V_{max}^{acc1-p} = V_{acc1-p} \cdot \left(\frac{cit_{cyt}}{cit_{cyt} + K_a^{cit_{cyt}}}\right) \cdot \left(1 - \frac{malcoa_{cyt}}{malcoa_{cyt} + K_i^{malcoa_{cyt}}}\right) \cdot \left(1 - \frac{c16coa_{cyt}}{c16coa_{cyt} + K_i^{c16coa_{cyt}}}\right)$$

V_{acc1-p} for numerical value see Supplemental Table II

$K_i^{c16coa_{cyt}} = 0.002$

$K_a^{cit_{cyt}} = 2.3$

$K_i^{malcoa_{cyt}} = 0.0106$

$K_m^{atp_{cyt}} = 0.057$

$K_m^{acoa_{cyt}} = 0.18$

$K_m^{hco3_{cyt}} = 2.25$

$$v_{acc1-up} = V_{max}^{acc1-up} \cdot \left(\frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}}\right) \cdot \left(\frac{acoa_{cyt}}{acoa_{cyt} + K_m^{acoa_{cyt}}}\right) \cdot \left(\frac{hco3_{cyt}}{hco3_{cyt} + K_m^{hco3_{cyt}}}\right)$$

$$V_{max}^{acc1-up} = V_{acc1-up} \cdot \left(1 + n_{up} \frac{cit_{cyt}}{cit_{cyt} + K_a^{cit_{cyt}}}\right) \cdot \left(1 - \frac{malcoa_{cyt}}{malcoa_{cyt} + K_i^{malcoa_{cyt}}}\right)$$

$V_{acc1-up} = 2.5 \cdot V_{acc1-p}$

$n_{up} = 1.4$

$K_a^{cit_{cyt}} = 0.8$

$K_m^{atp_{cyt}} = 0.057$

$K_m^{acoa_{cyt}} = 0.18$

$K_i^{malcoa_{cyt}} = 0.0106$

$K_m^{hco3_{cyt}} = 2.25$ [63]

Malonyl-CoA decarboxylase

$$v_{mcdc} = V_{max}^{mcdc} \cdot \left(\frac{malcoa_{cyt}}{malcoa_{cyt} + K_m^{malcoa_{cyt}}}\right)$$

$K_m^{malcoa_{cyt}} = 0.04$

Acetyl-CoA hydrolase

$$v_{acoah} = V_{max}^{acoah} \cdot \left(\frac{acoa_{cyt}}{acoa_{cyt} + K_m^{acoa_{cyt}}}\right)$$

$K_m^{acoa_{cyt}} = 0.153$

<u>TAG synthesis</u>

Glycerol-uptake

$$v_{glycT} = V_{max}^{glycT} \cdot \left(\frac{glyc_{ext} - glyc_{cyt}}{1 + \frac{glyc_{ext}}{K_m^{glyc_{ext}}} + \frac{glyc_{cyt}}{K_m^{glyc_{cyt}}}}\right)$$

V_{max}^{glycT} for numerical value see Supplemental Table II

$K_m^{glyc_{ext}} = 0.012$

$K_m^{glyc_{cyt}} = 0.012$

Glycerol kinase

$$v_{glycK} = V_{max}^{glycK} \cdot \left(\frac{glyc_{cyt}}{glyc_{cyt} + K_m^{glyc_{cyt}} \cdot \left(1 + \frac{g3p_{cyt}}{K_i^{g3p_{cyt}}}\right)} \right) \cdot \left(\frac{atp_{cyt}}{atp_{cyt} + K_m^{atp_{cyt}}} \right)$$

V_{max}^{glycK} for numerical value see Supplemental Table II

$K_m^{glyc_{cyt}} = 0.003$

$K_i^{g3p_{cyt}} = 0.58$

$K_m^{ATP_{cyt}} = 0.058$

Glycerophosphate acyltransferase

$$v_{gpat} = V_{max}^{gpat} \cdot \left(\frac{g3p_{cyt}}{g3p_{cyt} + K_m^{g3p_{cyt}}} \right) \cdot \left(\frac{c16coa_{cyt}}{c16coa_{cyt} + K_m^{c16coa_{cyt}}} \right)$$

V_{max}^{gpat} for numerical value see Supplemental Table II

$K_m^{g3p_{cyt}} = 0.67$

$K_m^{c16coa_{cyt}} = 0.02$

Acetyl glycerol-3-phosphate acyltransferase

$$v_{agpat} = V_{max}^{agpat} \cdot \left(\frac{lpa_{er}}{lpa_{er} + K_m^{lpa_{er}}} \right) \cdot \left(\frac{c16coa_{cyt}}{c16coa_{cyt} + K_m^{c16coa_{cyt}}} \right)$$

V_{max}^{agpat} for numerical value see Supplemental Table II

$K_m^{lpa_{er}} = 0.0065$

$K_m^{c16coa_{cyt}}$ =0.004

Phosphatidic acid phosphatase

$$v_{pap} = V_{max}^{pap} \cdot \left(\frac{pa_{er}^{n}}{pa_{er}^{n} + \left(K_m^{pa_{er}}\right)^{n}} \right)$$

V_{max}^{pap} for numerical value see Supplemental Table II

$K_m^{pa_{er}} = 0.35$

$$n = 2.2$$

Diacylglycerol acyltransferase

$$v_{dgat} = V_{max}^{dgat} \cdot \left(\frac{dag_{er}}{dag_{er} + K_m^{dag_{er}}} \right) \cdot \left(\frac{c16coa_{cyt}}{c16coa_{cyt} + K_m^{c16coa_{cyt}}} \right)$$

V_{max}^{dgat} for numerical value see Supplemental Table II

$K_m^{dag_{cyt}} = 0.03$

$K_m^{c16coa_{cyt}} = 0.1$

ATGL

$$v_{ATGL}^{tag} = V_{max-tag}^{ATGL} \cdot Sur_{ld} \cdot \gamma \cdot \left(\frac{tag_{ld}}{tag_{ld} + K_m^{tag_{ld}}} \right)$$

$V_{max-tag}^{ATGL}$ for numerical value see Supplemental Table II

$K_m^{tag_{ld}} = 10$

$$Sur_{ld} = \left(tag_{ld} + \frac{2}{3} \cdot dag_{ld} + \frac{1}{3} \cdot mag_{ld} + \frac{2}{3} ce_{ld} \right)^{\frac{2}{3}}$$

Hormone sensitive lipase (HSL) (dag)

$$v_{HSL}^{tag} = V_{max-tag}^{HSL} \cdot Sur_{ld} \cdot \gamma \cdot \left(\frac{dag_{ld}}{dag_{ld} + K_m^{dag_{ld}}} \right)$$

$V_{max-tag}^{HSL}$ for numerical value see Supplemental Table II

$K_m^{dag_{ld}} = 10$

$$Sur_{ld} = \left(tag_{ld} + \frac{2}{3} \cdot dag_{ld} + \frac{1}{3} \cdot mag_{ld} + \frac{2}{3} ce_{ld} \right)^{\frac{2}{3}}$$

Monoaclyglycerol lipase

$$v_{magl} = V_{max}^{magl} \cdot Sur_{ld} \cdot \left(\frac{mag_{ld}}{mag_{ld} + K_m^{mag_{ld}}} \right)$$

V_{max}^{magl} for numerical value see Supplemental Table II

$K_m^{mag_{ld}} = 0.51$

$$Sur_{ld} = \left(tag_{ld} + \frac{2}{3} \cdot dag_{ld} + \frac{1}{3} \cdot mag_{ld} + \frac{2}{3} ce_{ld} \right)^{\frac{2}{3}}$$

Cholesterol ester esterase

$$v_{cee} = V_{max}^{cee} \cdot Sur_{ld} \cdot \gamma \cdot \left(\frac{ce_{ld}}{ce_{ld} + K_m^{ce_{ld}}} \right)$$

V_{max}^{cee} for numerical value see Supplemental Table II

$K_m^{ce_{ld}} = 5$

$$Sur_{ld} = \left(tag_{ld} + \frac{2}{3} \cdot dag_{ld} + \frac{1}{3} \cdot mag_{ld} + \frac{2}{3} ce_{ld} \right)^{\frac{2}{3}}$$

Ketone body utilization

B-Hydroxy butyrate dehydrogenase

$$v_{\beta hdh} = V_{max}^{\beta hdh} \cdot \left(\frac{acac_{mito} \cdot nadh_{mito} - 1 / K_{eq}^{\beta hdh} \cdot bhbut_{mito} \cdot nad_{mito}}{\left(1 + \frac{acac_{mito}}{K_{m_{mito}}^{acac}}\right) \cdot \left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) + \left(1 + \frac{bhbut_{mito}}{K_m^{bhbut_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) - 1} \right)$$

$V_{max}^{\beta hdh}$ for numerical value see Supplemental Table II

$K_{eq}^{\beta hdh} = 20.3 \cdot \frac{h_{mito}}{h_{cyt}}$

$K_m^{acac_{mito}} = 0.204$

$$K_m^{nadh_{mito}} = K_0^{nadh_{mito}} \cdot \left(1 + \frac{nad_{mito}}{K_i^{nad_{mito}}} \right)$$

$K_0^{nadh_{mito}} = 0.017$

$K_i^{nad_{mito}} = 0.121$

$K_m^{hbut_{mito}} = 1.604$ [64]

$$K_m^{nad_{mito}} = K_0^{nad_{mito}} \cdot \left(1 + \frac{nadh_{mito}}{K_i^{nadh_{mito}}}\right)$$

$K_0^{nad_{mito}} = 0.067$

$K_i^{nadh_{mito}} = 0.066$

Succinyl-CoA-oxaloacid CoA transferase

$$v_{scot} = V_{max}^{scot} \cdot \left(\frac{acac_{mito} \cdot succoa_{mito} - {}^{1}/_{K_{eq}^{scot}} \cdot kc4coa_{mito} \cdot succ_{mito}}{\left(1 + \frac{acac_{mito}}{K_{m\,mito}^{\,acac}}\right) \cdot \left(1 + \frac{succoa_{mito}}{K_m^{succoa_{mito}}}\right) + \left(1 + \frac{kc4coa_{mito}}{K_m^{kc4coa_{mito}}}\right) \cdot \left(1 + \frac{succ_{mito}}{K_m^{succ_{mito}}}\right) - 1} \right)$$

V_{max}^{scot} for numerical value see Supplemental Table II

$K_{m\,mito}^{\,acac} = 0.44$

$$K_m^{succoa_{mito}} = K_0^{succoa_{mito}} \cdot \left(1 + \frac{succ_{mito}}{K_i^{succ_{mito}}}\right)$$

$K_0^{succ_{mito}} = 0.28$

$K_i^{succ_{mito}} = 0.72$

$$K_m^{kc4coa_{mito}} = K_0^{kc4coa_{mito}} \cdot \left(1 + \frac{acac_{mito}}{K_i^{acac_{mito}}}\right)$$

$K_0^{kc4coa_{mito}} = 0.04$

$K_i^{acac_{mito}} = 3.7$

$K_m^{succ_{mito}} = 34$

Acetoacetate transport (mitochondrial)

$$v_{acacT} = V_{max}^{acacT} \cdot \left(\frac{acac_{mito}}{acac_{mito} + K_m^{acac_{mito}}}\right)$$

V_{max}^{acacT} for numerical value see Supplemental Table II

$K_m^{acac_{mito}} = 0.56$

B-Hydroxy butyrate transport (mitochondrial)

$$v_{\beta hbT} = V_{max}^{\beta hbT} \cdot \left(\frac{bhbut_{mito}}{bhbut_{mito} + K_m^{bhbut_{mito}}} \right)$$

$V_{max}^{\beta hbT}$ for numerical value see Supplemental Table II

$K_m^{bhbut_{mito}} = 0.8$

Acetoacetate export (MCT1/MCT2)

$$v_{acac-ex} = V_{max}^{acac-ex} \cdot \left(\frac{acac_{ext} - acac_{cyt}}{1 + \frac{acac_{cyt}}{K_m^{acac_{cyt}}} + \frac{acac_{ext}}{K_m^{acac_{ext}}}} \right)$$

$V_{max}^{acac-ex}$ for numerical value see Supplemental Table II

$K_m^{acac_{cyt}} = 1.2$

$K_m^{acac_{ext}} = 1.2$

B-Hydroxy butyrate export (MCT1/MCT2)

$$v_{\beta hb-ex} = V_{max}^{\beta hb-ex} \cdot \left(\frac{bhbut_{ext} - bhbut_{cyt}}{1 + \frac{bhbut_{cyt}}{K_m^{bhbut_{cyt}}} + \frac{bhbut_{ext}}{K_m^{bhbut_{ext}}}} \right)$$

$V_{max}^{\beta hb-ex}$ for numerical value see Supplemental Table II

$K_m^{bhbut_{cyt}} = 0.8$

$K_m^{bhbut_{ext}} = 0.8$

Branched chain amino acid metabolism

Valine transport

$$v_{valT} = V_{max}^{valT} \cdot \left(\frac{val_{ext} - val_{cyt}}{1 + \frac{val_{ext}}{K_m^{val_{ext}}} + \frac{val_{cyt}}{K_m^{val_{cyt}}}} \right)$$

V_{max}^{valT} for numerical value see Supplemental Table II

$K_m^{val_{ext}} = 0.124$

$K_m^{val_{cyt}} = 0.124$

Leucine transport

$$v_{leuT} = V_{max}^{leuT} \cdot \left(\frac{leu_{ext} - leu_{cyt}}{1 + \frac{leu_{ext}}{K_m^{leu_{ext}}} + \frac{leu_{cyt}}{K_m^{leu_{cyt}}}} \right)$$

V_{max}^{leuT} for numerical value see Supplemental Table II

$K_m^{leu_{ext}} = 0.119$

$K_m^{leu_{cyt}} = 0.119$

Isoleucine transport

$$v_{isoleuT} = V_{max}^{isoleuT} \cdot \left(\frac{isoleu_{ext} - isoleu_{cyt}}{1 + \frac{isoleu_{ext}}{K_m^{isoleu_{ext}}} + \frac{isoleu_{cyt}}{K_m^{isoleu_{cyt}}}} \right)$$

$V_{max}^{isoleuT}$ for numerical value see Supplemental Table II

$K_m^{isoleu_{ext}} = 0.0967$

$K_m^{isoleu_{cyt}} = 0.0967$

Branched chain amino acid aminotransferase valine

$$v_{BCAAT-val} = V_{max}^{BCAAT-val} \cdot \left(\frac{val_{cyt} \cdot akg_{cyt} - {}^{1}\!/_{K_{eq}^{BCAAT-val}} \cdot aKIVA_{cyt} \cdot glu_{cyt}}{\left(1 + \frac{val_{cyt}}{K_m^{val_{cyt}}}\right) \cdot \left(1 + \frac{akg_{cyt}}{K_m^{akg_{cyt}}}\right) + \left(1 + \frac{aKIVA_{cyt}}{K_m^{aKIVA_{cyt}}}\right) \cdot \left(1 + \frac{glu_{cyt}}{K_m^{glu_{cyt}}}\right) - 1} \right)$$

$V_{max}^{BCAAT-val}$ for numerical value see Supplemental Table II

$K_{eq}^{BCAAT-val} = 1$

$K_m^{val_{cyt}} = 0.62$

$K_m^{akg_{cyt}} = 0.63$

$$K_m^{aKIVA_{cyt}} = K_0^{aKIVA_{cyt}} \cdot \left(1 + \frac{aKICA_{cyt}}{K_i^{aKICA_{cyt}}}\right) \cdot \left(1 + \frac{KMeVA_{cyt}}{K_i^{KMeVA_{cyt}}}\right)$$

$K_0^{aKIVA_{cyt}} = 0.11$

$K_i^{aKICA_{cyt}} = 2.1$

$K_i^{KMeVA_{cyt}} = 1.57$

$K_m^{glu_{cyt}} = 3.6$

Branched chain amino acid aminotransferase leucine

$$v_{BCAAT-leu} = V_{max}^{BCAAT-leu} \cdot \left(\frac{leu_{cyt} \cdot akg_{cyt} - {}^{1}\!/_{K_{eq}^{BCAAT-leu}} \cdot aKICA_{cyt} \cdot glu_{cyt}}{\left(1 + \frac{leu_{cyt}}{K_m^{leu_{cyt}}}\right) \cdot \left(1 + \frac{akg_{cyt}}{K_m^{akg_{cyt}}}\right) + \left(1 + \frac{aKICA_{cyt}}{K_m^{aKICA_{cyt}}}\right) \cdot \left(1 + \frac{glu_{cyt}}{K_m^{glu_{cyt}}}\right) - 1} \right)$$

$V_{max}^{BCAAT-leu}$ for numerical value see Supplemental Table II

$K_{eq}^{BCAAT-leu} = 1.75$

$K_m^{leu_{cyt}} = 3.8$

$K_m^{akg_{cyt}} = 0.63$

$$K_m^{aKIVA_{cyt}} = K_0^{aKIVA_{cyt}} \cdot \left(1 + \frac{aKICA_{cyt}}{K_i^{aKICA_{cyt}}}\right) \cdot \left(1 + \frac{KMeVA_{cyt}}{K_i^{KMeVA_{cyt}}}\right)$$

$K_0^{aKICA_{cyt}} = 0.14$

$K_i^{aKIVA_{cyt}} = 4.19$

$K_i^{KMeVA_{cyt}} = 1.57$

$K_m^{glu_{cyt}} = 6.65$

Branched chain amino acid aminotransferase isoleucine

$$v_{BCAAT-isoleu} = V_{max}^{BCAAT-isoleu} \cdot \left(\frac{isoleu_{cyt} \cdot akg_{cyt} - {}^{1}\!/_{K_{eq}^{BCAAT-leu}} \cdot KMeVA_{cyt} \cdot glu_{cyt}}{\left(1 + \frac{isoleu_{cyt}}{K_m^{isoleu_{cyt}}}\right) \cdot \left(1 + \frac{akg_{cyt}}{K_m^{akg_{cyt}}}\right) + \left(1 + \frac{KMeVA_{cyt}}{K_m^{KMeVA_{cyt}}}\right) \cdot \left(1 + \frac{glu_{cyt}}{K_m^{glu_{cyt}}}\right) - 1} \right)$$

$V_{max}^{BCAAT-isoleu}$ for numerical value see Supplemental Table II

$K_{eq}^{BCAAT-isoleu} = 1$

$K_m^{isoleu_{cyt}} = 3.8$

$K_m^{akg_{cyt}} = 0.63$

$$K_m^{KMeVA_{cyt}} = K_0^{KMeVA_{cyt}} \cdot \left(1 + \frac{aKICA_{cyt}}{K_i^{aKICA_{cyt}}}\right) \cdot \left(1 + \frac{aKIVA_{cyt}}{K_i^{aKICV_{cyt}}}\right)$$

$K_0^{KMeVA_{cyt}} = 0.07$

$K_i^{aKIVA_{cyt}} = 4.19$

$K_i^{aKICA_{cyt}} = 2.1$

$K_m^{glu_{cyt}} = 2.45$

A-ketoisovalerate transport (mitochondrial)

$$v_{aKIVAT_{mito}} = V_{max}^{aKIVAT_{mito}} \cdot \left(\frac{aKIVA_{cyt} - aKIVA_{mito}}{aKIVA_{cyt} + K_m^{aKIVA_{cyt}}}\right)$$

$V_{max}^{aKIVAT_{mito}}$ for numerical value see Supplemental Table II

$K_m^{aKIVA_{cyt}} = 0.025$

A-ketoisocaproate transport (mitochondrial)

$$v_{aKICAT_{mito}} = V_{max}^{aKICAT_{mito}} \cdot \left(\frac{aKICA_{cyt} - aKICA_{mito}}{aKICA_{cyt} + K_m^{aKICA_{cyt}}}\right)$$

$V_{max}^{aKICAT_{mito}}$ for numerical value see Supplemental Table II

$K_m^{aKICA_{cyt}} = 0.01$

A-ketomethylvalerate transport (mitochondrial)

$$v_{KMeVAT_{mito}} = V_{max}^{KMeVAT_{mito}} \cdot \left(\frac{KMeVA_{cyt} - KMeVA_{mito}}{KMeVA_{cyt} + K_m^{KMeVA_{cyt}}}\right)$$

$V_{max}^{KMeVAT_{mito}}$ for numerical value see Supplemental Table II

$K_m^{KMeVA_{cyt}} = 0.01$

Branched chain keto-amino acid dehydrogenase (aKIVA)

$$v_{bckadh-aKIVA} = V_{max}^{bckadh-aKIVA} \cdot \left(\frac{aKIVA_{mito}}{aKIVA_{mito} + K_m^{aKIVA_{mito}}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_m^{coa_{mito}}}\right)$$

$V_{max}^{bckadh-aKIVA}$ for numerical value see Supplemental Table II

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

$K_m^{nad_{mito}} = 0.04$

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

Branched chain keto-amino acid dehydrogenase (aKIVA)

$$v_{bckadh-aKICA} = V_{max}^{bckadh-aKICA} \cdot \left(\frac{aKICA_{mito}}{aKICA_{mito} + K_m^{aKICA_{mito}}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_m^{coa_{mito}}}\right)$$

$V_{max}^{bckadh-aKICA}$ for numerical value see Supplemental Table II

$K_m^{aKICA_{mito}} = 0.038$

$K_m^{nad_{mito}} = 0.04$

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

Branched chain keto-amino acid dehydrogenase (aKIVA)

$$v_{bckadh-KMeVA} = V_{max}^{bckadh-KMeVA} \cdot \left(\frac{KMeVA_{mito}}{aKICA_{mito} + K_m^{aKICA_{mito}}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_m^{coa_{mito}}}\right)$$

$V_{max}^{bckadh-KMeVA}$ for numerical value see Supplemental Table II

$K_m^{KMeVA_{mito}} = 0.035$

$K_m^{nad_{mito}} = 0.04$

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

2-methylacyl-CoA dehydrogenase (isobutyryl-CoA)

$$v_{MBCoADH-IsoButCoA} = V_{max}^{MBCoADH} \cdot \left(\frac{IsoButCoA_{mito}}{IsoButCoA_{mito} + K_m^{IsoButCoA_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{MBCoADH}$ for numerical value see Supplemental Table II

$K_m^{IsoButCoA_{mito}} = 0.013$

$K_m^{etffad_{mito}} = 0.0083$

2-methylacyl-CoA dehydrogenase (methylbutyryl-CoA)

$$v_{MBCoADH-MeButCoA} = V_{max}^{MBCoADH} \cdot \left(\frac{MeButCoA_{mito}}{MeButCoA_{mito} + K_m^{MeButCoA_{mito}}}\right) \cdot \left(\frac{etffad_{mito}}{etffad_{mito} + K_m^{etffad_{mito}}}\right)$$

$V_{max}^{MBCoADH}$ for numerical value see Supplemental Table II

$K_m^{MeButCoA_{mito}} = 0.027$

$K_m^{etffad_{mito}} = 0.0083$

Enoyl-CoA hydratase (methyl acrylyl CoA)

$$v_{ECoAH-MeAcrCoA} = V_{max}^{ECoAH-MeACrCoA} \cdot \left(\frac{MeAcrCoA_{mito}}{MeAcrCoA_{mito} + K_m^{MeAcrCoA_{mito}}}\right)$$

$V_{max}^{ECoAH-MeACrCoA}$ for numerical value see Supplemental Table II

$K_m^{MeAcrCoA_{mito}} = 0.001$

Enoyl-CoA hydratase (Tiglyl CoA)

$$v_{ECoAH-TigCoA} = V_{max}^{ECoAH-TigCoA} \cdot \left(\frac{TigCoA_{mito}}{TigCoA_{mito} + K_m^{TigCoA_{mito}}}\right)$$

$V_{max}^{ECoAH-TigCoA}$ for numerical value see Supplemental Table II

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

3-hydroxyisobutyryl-CoA hydrolase

$$v_{HibCoAhyd} = V_{max}^{HibCoAhyd} \cdot \left(\frac{HibCoA_{mito}}{HibCoA_{mito} + K_m^{HibCoA_{mito}}}\right)$$

$V_{max}^{HibCoahyd}$ for numerical value see Supplemental Table II

$K_m^{HibCoA_{mito}} = 0.006$

3-hydroxyisobutyrate dehydrogenase

$$v_{HibDh} = V_{max}^{HibDh} \cdot \left(\frac{Hib_{mito}}{Hib_{mito} + K_m^{Hib_{mito}}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}}\right)$$

V_{max}^{HibDh} for numerical value see Supplemental Table II

$K_m^{Hib_{mito}} = 0.061$

$K_m^{nad_{mito}} = K_0^{nad_{mito}} \cdot \left(1 + \frac{nadh_{mito}}{K_i^{nadh_{mito}}}\right)$

$K_0^{nad_{mito}} = 0.023$

$K_i^{nadh_{mito}} = 0.0057$

Methylmalonate-semialdehyde dehydrogenase

$$v_{mmsdh} = V_{max}^{mmsd} \cdot \left(\frac{mmsald_{mito}}{mmsald_{mito} + K_m^{mmsald_{mito}}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_m^{coa_{mito}}}\right)$$

V_{max}^{mmsd} for numerical value see Supplemental Table II

$K_m^{mmsald_{mito}} = 0.0053$

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

$K_m^{coa_{mito}} = 0.03$

3-hydroxy-2-methylbutyryl-CoA dehydrogenase

$$v_{HMBCDH} = V_{max}^{HMBCDH} \cdot \left(\frac{MeHButCoA_{mito}}{MeHButCoA_{mito} + K_m^{MeHButCoA_{mito}}}\right) \cdot \left(\frac{nad_{mito}}{nad_{mito} + K_m^{nad_{mito}}}\right)$$

V_{max}^{HMBCDH} for numerical value see Supplemental Table II

$K_m^{MeHButCoA_{mito}} = 0.005$

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

acetyl-CoA C-acyltransferase

$$v_{MAACT} = V_{max}^{MAACT} \cdot \left(\frac{MeAACoA_{mito}}{MeAACoA_{mito} + K_m^{MeAACoA_{mito}}}\right) \cdot \left(\frac{coa_{mito}}{coa_{mito} + K_m^{coa_{mito}}}\right)$$

V_{max}^{MAACT} for numerical value see Supplemental Table II

$K_m^{MeAACoA_{mito}} = 0.008$

$K_m^{coa_{mito}} = 0.02$

isovaleryl-CoA dehydrogenase

$$\mathrm{v_{IVCoADh}} = \mathrm{V_{max}^{IVCoADh}} \cdot \left(\frac{\mathrm{IsoValCoA_{mito}}}{\mathrm{IsoValCoA_{mito}} + \mathrm{K_m^{IsoValCoA_{mito}}}}\right) \cdot \left(\frac{\mathrm{etffad_{mito}}}{\mathrm{etffad_{mito}} + \mathrm{K_m^{etffad_{mito}}}}\right)$$

$V_{max}^{IVCoADh}$ for numerical value see Supplemental Table II

$K_m^{IsoValCoA_{mito}} = 0.014$

$K_m^{etffad_{mito}} = 0.0083$

Methylcrotonoyl-CoA carboxylase

$$\mathrm{v_{MECCC}} = \mathrm{V_{max}^{MECCC}} \cdot \left(\frac{\mathrm{MeCroCoA_{mito}}}{\mathrm{MeCroCoA_{mito}} + \mathrm{K_m^{MeCroCoA_{mito}}}}\right) \cdot \left(\frac{\mathrm{atp_{mito}}}{\mathrm{atp_{mito}} + \mathrm{K_m^{atp_{mito}}}}\right)$$

V_{max}^{MECCC} for numerical value see Supplemental Table II

$K_m^{MeCroCoA_{mito}} = 0.0747$

$K_m^{atp_{mito}} = 0.045$

Methylglutaconyl-CoA hydratase

$$\mathrm{v_{MEGCCH}} = \mathrm{V_{max}^{MEGCCH}} \cdot \left(\frac{\mathrm{MeGCCoA_{mito}}}{\mathrm{MeGCCoA_{mito}} + \mathrm{K_m^{MeGCCoA_{mito}}}}\right)$$

V_{max}^{MEGCCH} for numerical value see Supplemental Table II

$K_m^{MeGCCoA_{mito}} = 0.0083$

Hydroxymethylglutaryl-CoA lyase

$$\mathrm{v_{HMGCL}} = \mathrm{V_{max}^{HMGCL}} \cdot \left(\frac{\mathrm{HMeGCoA_{mito}}}{\mathrm{HMeGCoA_{mito}} + \mathrm{K_m^{HMeGCoA_{mito}}}}\right)$$

V_{max}^{HMGCL} for numerical value see Supplemental Table II

$K_m^{HMeGCoA_{mito}} = 0.0448$

Propionyl-CoA carboxylase

$$\mathrm{v_{PCC}} = \mathrm{V_{max}^{PCC}} \cdot \left(\frac{\mathrm{ProCoA_{mito}}}{\mathrm{ProCoA_{mito}} + \mathrm{K_m^{ProCoA_{mito}}}}\right) \cdot \left(\frac{\mathrm{atp_{mito}}}{\mathrm{atp_{mito}} + \mathrm{K_m^{atp_{mito}}}}\right)$$

V_{max}^{PCC} for numerical value see Supplemental Table II

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

$K_m^{atp_{mito}} = 0.08$

Methylmalonyl-CoA mutase

$$\mathrm{v_{MMCM}} = \mathrm{V_{max}^{MMCM}} \cdot \left(\frac{\mathrm{MeMalCoA_{mito}}}{\mathrm{MeMalCoA_{mito}} + \mathrm{K_m^{MeMalCoA_{mito}}}}\right)$$

V_{max}^{MMCM} for numerical value see Supplemental Table II

$K_m^{MeMalCoA_{mito}} = 0.133$

Glutamate transport

$$v_{gluT_{mito}} = V_{max}^{gluT_{mito}} \cdot \left(\frac{glu_{cyt} \cdot h_{cyt} - glu_{mito} \cdot h_{mito}}{1 + \frac{glu_{cyt}}{K_m^{glu_{cyt}}} + \frac{glu_{mito}}{K_m^{glu_{mito}}}} \right)$$

$V_{max}^{gluT_{mito}}$ for numerical value see Supplemental Table II

$K_m^{glu_{cyt}} = 5$

$K_m^{glu_{mito}} = 0.25$

Glutamate dehydrogenase (nad-dependent)

$$v_{gdh} = V_{max}^{gdh} \cdot \left(\frac{glu_{mito} \cdot nad_{mito} - 1/K_{eq}^{gdh} \cdot akg_{mito} \cdot nadh_{mito} \cdot nh3_{mito}}{\left(1 + \frac{glu_{mito}}{K_m^{glu_{mito}}}\right) \cdot \left(1 + \frac{nad_{mito}}{K_m^{nad_{mito}}}\right) + \left(1 + \frac{akg_{mito}}{K_m^{akg_{mito}}}\right)\left(1 + \frac{nadh_{mito}}{K_m^{nadh_{mito}}}\right) \cdot \left(1 + \frac{nh3_{mito}}{K_m^{nh3_{mito}}}\right)} \right)$$

$$V_{max}^{gdh} = V_0^{gdh} \cdot \left(1 - \frac{c16coa_{mito}}{c16coa_{mito} + K_i^{c16coa_{mito}}}\right) \cdot \left(A_0 + (1 - A_0)\left(1 - \frac{mal_{mito}}{mal_{mito} + K_i^{mal_{mito}}}\right)\right) \cdot$$

V_0^{gdh} for numerical value see Supplemental Table II

$K_i^{c16coa_{mito}} = 0.0001$

$A_0 = 0.7$

$K_i^{mal_{mito}} = 2$

$K_{eq}^{gdh} = 0.00387 mM$

$$K_m^{glu_{mito}} = K_0^{glu_{mito}} \cdot \left(1 + \frac{akg_{mito}}{K_i^{akg_{mito}}}\right) \cdot \left(1 + \frac{nh3_{mito}}{K_i^{nh3_{mito}}}\right)$$

$K_0^{glu_{mito}} = 4.61$

$K_i^{akg_{mito}} = 1.49$

$K_i^{nh3_{mito}} = 3.1$

$$K_m^{nad_{mito}} = K_0^{nad_{mito}} \cdot \left(1 + \frac{nadh_{mito}}{K_i^{nadh_{mito}}}\right)$$

$K_0^{nad_{mito}} = 0.364$

$K_i^{nadh_{mito}}$ =0.0086

$K_m^{akg_{mito}}$ =0.18

$K_m^{nadh_{mito}}$ =0.03

$K_m^{nh3_{mito}} = 20$

Stoichiometric matrix

$$\frac{d}{dt}acac_{cyt} = +\frac{Vol_{mito}}{Vol_{cyt}} \cdot v_{acacT} + v_{acac-ex}$$

$$\frac{d}{dt}acac_{ext} = 0$$

$$\frac{d}{dt}acac_{mito} = -v_{scot} - v_{\beta hdh} - v_{acacT} + v_{HMGCL}$$

$$\frac{d}{dt}acetate_{cyt} = +v_{acoah} + v_{aceT}$$

$$\frac{d}{dt}acoa_{cyt} = +v_{cit-lys} - v_{acc1} + v_{mcdc} + v_{acoah} + v_{HMGCL} + v_{MAACT}$$

$$\frac{d}{dt}acoa_{mito} = +2 \cdot v_{3kt}^{kc4coa} + 2 \cdot v_{3ktII}^{kc4coa} + v_{3kt}^{kc6coa} + v_{3kt}^{kc8coa} + v_{3kt}^{kc10coa} + v_{3kt}^{kc12coa} + v_{3kt}^{kc14coa} + v_{3kt}^{kc16coa} + v_{pdhc} - v_{cs}$$

$$\frac{d}{dt}adp_{cyt} = -\frac{v_{nex}}{10 \cdot F \cdot Vol_{cyt}} + v_{ndk_{cyt}} + 2 \cdot v_{ak_{cyt}} + v_{atp-usage} + v_{hkA} + v_{hkB} + v_{ndk_{cyt}}^{udp} + v_{pfk2} - v_{pfk1} - v_{pgk} - v_{pk} + v_{cit-lys} + v_{acc1} + v_{glycK}$$

$$\frac{d}{dt}adp_{mito} = -v_{scs-atp} - \frac{v_{F0F1}}{10 \cdot F \cdot Vol_{mito}} + \frac{v_{nex}}{10 \cdot F \cdot Vol_{mito}} + v_{ndk_{mito}} + v_{pc} + v_{PCC} + v_{MECCC}$$

$$\frac{d}{dt}akg_{cyt} = -v_{asat} + v_{mac} - v_{BCAAT-val} - v_{BCAAT-leu} - v_{BCAAT-isoleu}$$

$$\frac{d}{dt}akg_{mito} = +v_{idh_{nad}} + v_{idh_{nadp}} - v_{kgdhc} - v_{asat_{mito}} - \frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{mac} + v_{gdh}$$

$$\frac{d}{dt}aKICA_{cyt} = +v_{BCAAT-val} - v_{aKICAT}$$

$$\frac{d}{dt}aKICA_{mito} = +v_{aKICAT} \cdot \frac{Vol_{mito}}{Vol_{cyt}} - v_{bckadh-aKICA}$$

$$\frac{d}{dt}aKIVA_{cyt} = +v_{BCAAT-leu} - v_{aKIVAT}$$

$$\frac{d}{dt}aKIVA_{mito} = +v_{aKIVAT} \cdot \frac{Vol_{mito}}{Vol_{cyt}} - v_{bckadh-aKIVA}$$

$$\frac{d}{dt}amp_{cyt} = +v_{ACS1} + v_{FAB1} + v_{FAB4} - v_{ak_{cyt}}$$

$$\frac{d}{dt}asp_{cyt} = -v_{asat} + v_{agc}$$

$$\frac{d}{dt}asp_{mito} = -v_{asat_{mito}} - \frac{Vol_{cyt}}{Vol_{er}} \cdot v_{agc}$$

$$\frac{d}{dt}atp_{cyt} = -v_{ACS1} - v_{FAB1} - v_{FAB4} + \frac{v_{nex}}{10 \cdot F \cdot Vol_{cyt}} - v_{ndk_{cyt}} - v_{atp-usage} - v_{hkA} - v_{hkB} - v_{pfk2} - v_{pfk1} + v_{pgk} + v_{pk} - v_{ndk_{cyt}}^{udp} - v_{cit-lys} - v_{acc1} - v_{glycK} - v_{ak_{cyt}}$$

$$\frac{d}{dt}atp_{mito} = +v_{scs-atp} + \frac{v_{F0F1}}{10 \cdot F \cdot Vol_{mito}} - \frac{v_{nex}}{10 \cdot F \cdot Vol_{mito}} - v_{ndk_{mito}} - v_{pc} - v_{PCC} - v_{MECCC}$$

$$\frac{d}{dt}bhbut_{cyt} = +\frac{Vol_{mito}}{Vol_{cyt}} \cdot v_{\beta hbT} + v_{\beta hb-ex}$$

$$\frac{d}{dt}bhbut_{ext} = 0$$

$$\frac{d}{dt}bhbut_{mito} = +v_{\beta hdh} - v_{\beta hbT}$$

$$\frac{d}{dt}bpg13_{cyt} = +v_{gapdh} - v_{pgk}$$

$$\frac{d}{dt}c10coa_{mito} = -v_{c10coa-mcdh} - v_{c10coa-lcdh} + v_{3kt}^{kc12coa}$$

$$\frac{d}{dt}c12coa_{mito} = -v_{c12coa-mcdh} - v_{c12coa-lcdh} + v_{3kt}^{kc14coa}$$

$$\frac{d}{dt}c14coa_{mito} = -v_{c14coa-lcdh} + v_{3kt}^{kc16coa}$$

$$\frac{d}{dt}c16car_{cyt} = +v_{CPT1} - v_{CACT}$$

$$\frac{d}{dt}c16car_{mito} = +\frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{CACT} - v_{CPT2}$$

$$\frac{d}{dt}c16coa_{cyt} = +v_{ACS1} + v_{FATP1} + v_{FATP4} - v_{CPT1} - v_{gpat} - v_{agpat} - v_{dgat}$$

$$\frac{d}{dt}c16coa_{mito} = +v_{CPT2} - v_{c16coa-lcdh}$$

$$\frac{d}{dt}c16_{cyt} = +v_{CD36} - v_{ACS1} - v_{FATP1} - v_{FATP4} + \frac{Vol_{ld}}{Vol_{cyt}} \cdot v_{HSL}^{dag} + \frac{Vol_{ld}}{Vol_{cyt}} \cdot v_{ATGL}^{tag} + \frac{Vol_{ld}}{Vol_{cyt}} \cdot v_{magl}$$

$$\frac{d}{dt}c16_{ext} = 0$$

$$\frac{d}{dt}c4coa_{mito} = -v_{c4coa-scdh} + v_{3kt}^{kc6coa}$$

$$\frac{d}{dt}c6coa_{mito} = -v_{c6coa-mcdh} + v_{3kt}^{kc8coa}$$

$$\frac{d}{dt}c8coa_{mito} = -v_{c8coa-mcdh} + v_{3kt}^{kc10coa}$$

$$\frac{d}{dt}car_{cyt} = -v_{CPT1} + v_{CACT}$$

$$\frac{d}{dt}car_{mito} = -\frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{CACT} + v_{CPT2}$$

$$\frac{d}{dt}cit_{cyt} = +\frac{Vol_{mito}}{Vol_{cyt}} \cdot v_{cit-mal} - v_{cit-lys}$$

$$\frac{d}{dt}cit_{mito} = +v_{cs} - \mathrm{v_{ac}} - v_{cit-mal}$$

$$\frac{d}{dt}cl_{cyt} = 0$$

$$\frac{d}{dt}cl_{mito} = +\frac{I_{cl_{ed}}}{10 \cdot F \cdot Vol_{mito}}$$

$$\frac{d}{dt}coa_{cyt} = -v_{FABP1} - v_{FABP4} - v_{ACS1} + v_{CPT1} - v_{cit-lys} + v_{acoah} + v_{gpat} + v_{agpat} + v_{dgat}$$

$$\frac{d}{dt}coa_{mito} = -v_{CPT2} - v_{3kt}^{kc4coa} - v_{3ktII}^{kc4coa} - v_{3kt}^{kc6coa} - v_{3kt}^{kc8coa} - v_{3kt}^{kc10coa} - v_{3kt}^{kc12coa} - v_{3kt}^{kc14coa} - v_{3kt}^{kc16coa} - v_{pdhc} + v_{cs} - v_{kgdhc} + v_{scs-atp} + v_{scs-gtp} - v_{bckadh-aKICA} - v_{bckadh-aKIVA} - v_{bckadh-KMeVA} - v_{HibDh} - v_{mmsdh} - v_{MAACT}$$

$$\frac{d}{dt}co2_{cyt} = 0$$

$$\frac{d}{dt}co2_{mito} = 0$$

$$\frac{d}{dt}cytc_{ox_{mm}} = -\frac{2 \cdot v_{cxIII}}{10 \cdot F \cdot Vol_{membrane}} + \frac{v_{cxIV}}{10 \cdot F \cdot Vol_{membrane}}$$

$$\frac{d}{dt}cytc_{red_{mm}} = +\frac{2 \cdot v_{cxIII}}{10 \cdot F \cdot Vol_{membrane}} - \frac{v_{cxIV}}{10 \cdot F \cdot Vol_{membrane}}$$

$$\frac{d}{dt}dag_{er} = +\frac{Vol_{cyt}}{Vol_{er}} \cdot v_{pap} - \frac{Vol_{cyt}}{Vol_{er}} \cdot v_{dgat}$$

$$\frac{d}{dt}dag_{ld} = +v_{ATGL}^{tag} - v_{HSL}^{dag}$$

$$\frac{d}{dt}dhap_{cyt} = +v_{ald} - v_{tpi} - v_{g3pdh} - v_{g3pdh_{mito}}$$

$$\frac{d}{dt}ec10coa_{mito} = +v_{c10coa-mcdh} + v_{c10coa-lcdh} - v_{ehyd-ec10}$$

$$\frac{d}{dt}ec12coa_{mito} = +v_{c12coa-mcdh} + v_{c12coa-lcdh} - v_{ehyd-ec12}$$

$$\frac{d}{dt}ec14coa_{mito} = +v_{c14coa-lcdh} - v_{ehyd-ec14}$$

$$\frac{d}{dt}ec16coa_{mito} = +v_{c16coa-lcdh} - v_{ehyd-ec16}$$

$$\frac{d}{dt}ec4coa_{mito} = +v_{c4coa-scdh} - v_{ehyd-ec4}$$

$$\frac{d}{dt}ec6coa_{mito} = +v_{c6coa-mcdh} - v_{ehyd-ec6}$$

$$\frac{d}{dt}ec8coa_{mito} = +v_{c8coa-mcdh} - v_{ehyd-ec8}$$

$$\frac{d}{dt}e4p_{cyt} = +v_{taldo} + v_{tketo2}$$

$$\begin{aligned}\frac{d}{dt}etffad_{mito} = &-v_{c4coa-scdh} - v_{c6coa-mcdh} - v_{c8coa-mcdh} - v_{c10coa-mcdh} - v_{c12coa-mcdh} \\ &- v_{c10coa-lcdh} - v_{c12coa-lcdh} - v_{c14coa-lcdh} - v_{c16coa-lcdh} + v_{ETF-FAD} \\ &- v_{MBCoADH-IsoButCoA} - v_{MBCoADH-MeButCoA} - v_{IVCoADh}\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}&etffadh2_{mito} \\ &= +v_{c4coa-scdh} + v_{c6coa-mcdh} + v_{c8coa-mcdh} + v_{c10coa-mcdh} + v_{c12coa-mcdh} \\ &+ v_{c10coa-lcdh} + v_{c12coa-lcdh} + v_{c14coa-lcdh} + v_{c16coa-lcdh} - v_{ETF-FAD} \\ &+ v_{MBCoADH-IsoButCoA} + v_{MBCoADH-MeButCoA} + v_{IVCoADh}\end{aligned}$$

$$\frac{d}{dt}etfq_{mito} = -v_{ETF-FAD} + v_{ETF-QO}$$

$$\frac{d}{dt}etfqh2_{mito} = +v_{ETF-FAD} - v_{ETF-QO}$$

$$\frac{d}{dt}fru16bp_{cyt} = +v_{pfk1} - v_{fbp1} - v_{ald}$$

$$\frac{d}{dt}fru26bp_{cyt} = +v_{pfk2} - v_{fbp2}$$

$$\frac{d}{dt}fru6p_{cyt} = +v_{gpi} - v_{pfk2} + v_{fbp2} - v_{pfk1} + v_{fbp1} + v_{taldo} - v_{tketo2}$$

$$\frac{d}{dt}fum_{mito} = +v_{succdh} - v_{fum}$$

$$\frac{d}{dt}g3p_{cyt} = +v_{g3pdh} + v_{g3pdh_{mito}} + v_{glycK} - v_{gpat}$$

$$\frac{d}{dt}gdp_{cyt} = -v_{ndk_{cyt}} + v_{pepck}$$

$$\frac{d}{dt}gdp_{mito} = -v_{scs-gtp} - v_{ndk_{mito}}$$

$$\frac{d}{dt}glc_{cyt} = +v_{gluT1} + v_{gluT4} - v_{hkA} - v_{hkB}$$

$$\frac{d}{dt}glc_{ext} = 0$$

$$\frac{d}{dt}glc1p_{cyt} = -v_{gpm} - v_{upgase} + v_{gp}$$

$$\frac{d}{dt}glc6p_{cyt} = +v_{hkA} + v_{hkB} - v_{gpi} + v_{gpm} - v_{g6pdh}$$

$$\frac{d}{dt}glu_{cyt} = +v_{asat} - v_{agc} - v_{gluT_{mito}} + v_{BCAAT-val} + v_{BCAAT-leu} + v_{BCAAT-isoleu}$$

$$\frac{d}{dt}glu_{ext} = 0$$

$$\frac{d}{dt}glu_{mito} = +v_{asat_{mito}} + \frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{agc} - v_{gdh} + \frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{gluT_{mito}}$$

$$\frac{d}{dt}glyc_{cyt} = +v_{glycT} - v_{glycK} + \frac{Vol_{ld}}{Vol_{cyt}} \cdot v_{magl}$$

$$\frac{d}{dt}glyc_{ext} = 0$$

$$\frac{d}{dt}glyglc = + v_{gs} - v_{gp}$$

$$\frac{d}{dt}gra_{ext} = 0$$

$$\frac{d}{dt}grap_{cyt} = +v_{ald} + v_{tpi} - v_{gapdh} - v_{taldo} - v_{tketo1} - v_{tketo2}$$

$$\frac{d}{dt}gtp_{cyt} = +v_{ndk_{cyt}} - v_{pepck}$$

$$\frac{d}{dt}gtp_{mito} = +v_{scs-gtp} + v_{ndk_{mito}}$$

$$\frac{d}{dt}h_{cyt} = 0$$

$$\frac{d}{dt}h_{mito} = +\frac{-I_H^{pump} + I_{H_{ed}} + v_{P-ex} - I_k^{pump} - I_{na}^{pump} + 3 \cdot v_{F0F1}}{10 \cdot F \cdot Vol_{mito}}$$

$$\frac{d}{dt}hco3_{cyt} = 0$$

$$\frac{d}{dt}hco3_{mito} = 0$$

$$\frac{d}{dt}hib_{mito} = +v_{HibCoAhyd} - v_{HibDh}$$

$$\frac{d}{dt}HibCoA_{mito} = +v_{ECoAH-MeAcrCoA} - v_{HibCoAhyd}$$

$$\frac{d}{dt}HMeGCoA_{mito} = +v_{MEGCCH} - v_{HMGCL}$$

$$\frac{d}{dt}IsoButCoA_{mito} = +v_{bckadh-aKIVA} - v_{MBCoADH-IsoButCoA}$$

$$\frac{d}{dt}isoleu_{cyt} = +v_{isoleuT} - v_{BCAAT-isoleu}$$

$$\frac{d}{dt}isoleu_{ext} = 0$$

$$\frac{d}{dt}isocit_{mito} = +\mathrm{v}_{\mathrm{ac}} - v_{idh_{nad}} - v_{idh_{nadp}}$$

$$\frac{d}{dt}IsoValCoA_{mito} = +v_{bckadh-aKICA} - v_{IVCoADh}$$

$$\frac{d}{dt}kc10coa_{mito} = +v_{3hdh-lc10} - v_{3kt}^{kc10coa}$$

$$\frac{d}{dt}kc12coa_{mito} = +v_{3hdh-lc12} - v_{3kt}^{kc12coa}$$

$$\frac{d}{dt}kc14coa_{mito} = +v_{3hdh-lc14} - v_{3kt}^{kc14coa}$$

$$\frac{d}{dt}kc16coa_{mito} = +v_{3hdh-lc16} - v_{3kt}^{kc16coa}$$

$$\frac{d}{dt}kc4coa_{mito} = +v_{3hdh-lc4} - v_{3kt}^{kc4coa} - v_{3ktII}^{kc4coa} + v_{scot}$$

$$\frac{d}{dt}kc6\,coa_{mito} = +v_{3hdh-lc6} - v_{3kt}^{kc6coa}$$

$$\frac{d}{dt}kc8coa_{mito} = +v_{3hdh-lc8} - v_{3kt}^{kc8coa}$$

$$\frac{d}{dt}k_{cyt} = 0$$

$$\frac{d}{dt}k_{mito} = +\frac{I_K^{pump} + I_{k_{ed}}}{10 \cdot F \cdot Vol_{mito}}$$

$$\frac{d}{dt}KMeVA_{cyt} = +v_{BCAAT-isoleu} - v_{KMeVAT}$$

$$\frac{d}{dt}KMeVA_{mito} = +v_{KMeVAT} \cdot \frac{Vol_{mito}}{Vol_{cyt}} - v_{bckadh-KMeVA}$$

$$\frac{d}{dt}lc10coa_{mito} = +v_{ehyd-ec10} - v_{3hdh-lc10}$$

$$\frac{d}{dt}lc12coa_{mito} = +v_{ehyd-ec12} - v_{3hdh-lc12}$$

$$\frac{d}{dt}lc14coa_{mito} = +v_{ehyd-ec14} - v_{3hdh-lc14}$$

$$\frac{d}{dt}lc16coa_{mito} = +v_{ehyd-ec16} - v_{3hdh-lc16}$$

$$\frac{d}{dt}lc4coa_{mito} = +v_{ehyd-ec4} - v_{3hdh-lc4}$$

$$\frac{d}{dt}lc6coa_{mito} = +v_{ehyd-ec6} - v_{3hdh-lc6}$$

$$\frac{d}{dt}lc8coa_{mito} = +v_{ehyd-ec8} - v_{3hdh-lc8}$$

$$\frac{d}{dt}lac_{cyt} = +v_{ldh} + v_{lacT}$$

$$\frac{d}{dt}lac_{ext} = 0$$

$$\frac{d}{dt}leu_{cyt} = +v_{leuT} - v_{BCAAT-leu}$$

$$\frac{d}{dt}leu_{ext} = 0$$

$$\frac{d}{dt}lpa_{er} = +\frac{Vol_{cyt}}{Vol_{er}} \cdot v_{gpat} - \frac{Vol_{cyt}}{Vol_{er}} \cdot v_{agpat}$$

$$\frac{d}{dt}mag_{ld} = -v_{magl} + v_{HSL}^{dag}$$

$$\frac{d}{dt}mal_{cyt} = +v_{malpT} + v_{mal-pyrT} - v_{mdh} - v_{mac} - \frac{Vol_{mito}}{Vol_{cyt}} \cdot v_{cit-mal} - v_{me}$$

$$\frac{d}{dt}mal_{mito} = +v_{fum} - v_{mdh_{mito}} - \frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{malpT} - \frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{mal-pyrT} + \frac{Vol_{cyt}}{Vol_{mito}} \cdot v_{mac} + v_{cit-mal}$$

$$\frac{d}{dt}malcoa_{cyt} = +v_{acc1} - v_{mcdc}$$

$$\frac{d}{dt}MeAACoA_{mito} = +v_{HMBCDH} - v_{MAACT}$$

$$\frac{d}{dt}MeAcrCoA_{mito} = +v_{MBCoADH-IsoButCoA} - v_{ECoAH-MeAcrCoA}$$

$$\frac{d}{dt}MeButCoA_{mito} = +v_{bckadh-KMeVA} - v_{MBCoADH-MeButCoA}$$

$$\frac{d}{dt}MeCroCoA_{mito} = +v_{IVCoADh} - v_{MECCC}$$

$$\frac{d}{dt}MeGCCoA_{mito} = +v_{MECCC} - v_{MEGCCH}$$

$$\frac{d}{dt}MeHButCoA_{mito} = +v_{ECoAH-TigCoA} - v_{HMBCDH}$$

$$\frac{d}{dt}MeMalCoA_{mito} = +v_{PCC} - v_{MMCM}$$

$$\frac{d}{dt}mmsald_{mito} = +v_{HibDh} - v_{mmsdh}$$

$$\frac{d}{dt}na_{cyt} = 0$$

$$\frac{d}{dt}na_{mito} = +\frac{I_{na}^{pump} + I_{na_{ed}}}{10 \cdot F \cdot Vol_{mito}}$$

$$\frac{d}{dt}nad_{cyt} = -v_{gapdh} + v_{ldh} - v_{mdh} + v_{g3pdh}$$

$$\begin{aligned}\frac{d}{dt}nad_{mito} = {} & -v_{3hdh-lc4} - v_{3hdh-lc6} - v_{3hdh-lc8} - v_{3hdh-lc10} - v_{3hdh-lc12} - v_{3hdh-lc14} \\ & - v_{3hdh-lc16} - v_{pdhc} - v_{idh_{nad}} - v_{kgdhc} - v_{mdh_{mito}} + v_{tdh} + \frac{v_{cxI}}{10 \cdot F \cdot Vol_{mito}} \\ & + v_{\beta hdh} - v_{bckadh-aKICA} - v_{bckadh-aKIVA} - v_{bckadh-KMeVa} - v_{HibDh} - v_{mmsdh} \\ & - v_{HMBCDH} - v_{gdh}\end{aligned}$$

$$\frac{d}{dt}nadh_{cyt} = +v_{gapdh} - v_{ldh} + v_{mdh}$$

$$\begin{aligned}\frac{d}{dt}nadh_{mito} = {} & +v_{3hdh-lc4} + v_{3hdh-lc6} + v_{3hdh-lc8} + v_{3hdh-lc10} + v_{3hdh-lc12} + v_{3hdh-lc14} \\ & + v_{3hdh-lc16} + v_{pdhc} + v_{idh_{nad}} + v_{kgdhc} + v_{mdh_{mito}} - v_{tdh} - \frac{v_{cxI}}{10 \cdot F \cdot Vol_{mito}} \\ & - v_{\beta hdh} + v_{bckadh-aKICA} + v_{bckadh-aKIVA} + v_{bckadh-KMeVa} + v_{HibDh} - v_{mmsdh} \\ & + v_{HMBCDH} + v_{gdh}\end{aligned}$$

$$\frac{d}{dt}nadp_{cyt} = -v_{g6pdh} - v_{pgdh} - v_{me} + v_{nadph-use}$$

$$\frac{d}{dt} nadp_{mito} = -v_{tdh} - v_{idh_{nadp}}$$

$$\frac{d}{dt} nadph_{cyt} = +v_{g6pdh} + v_{pgdh} + v_{me} - v_{nadph-use}$$

$$\frac{d}{dt} nadph_{mito} = +v_{tdh} + v_{idh_{nadp}}$$

$$\frac{d}{dt} o2_{cyt} = -\frac{1}{4} \cdot \frac{v_{cxIV}}{10 \cdot F \cdot Vol_{cyt}} + v_{O_{2diff}}$$

$$\frac{d}{dt} o2_{ext} = 0$$

$$\frac{d}{dt} oaa_{cyt} = v_{mdh} + v_{asat} + v_{cit-lys}$$

$$\frac{d}{dt} oaa_{mito} = +v_{mdh_{mito}} + v_{pc} + v_{asat_{mito}} - v_{cs}$$

$$\frac{d}{dt} p_{cyt} = -\frac{v_{P-ex}}{10 \cdot F \cdot Vol_{cyt}} + 2 \cdot v_{ppase} + v_{atp-usage} + v_{fbp2} + v_{fbp1} - v_{gapdh} - v_{malpT} - v_{gp} + v_{cit-lys} + v_{acc1} + v_{pap}$$

$$\frac{d}{dt} p_{mito} = -v_{scs-atp} - v_{scs-gtp} - \frac{v_{F0F1}}{10 \cdot F \cdot Vol_{mito}} + \frac{v_{P-ex}}{10 \cdot F \cdot Vol_{mito}} + v_{pc} + \frac{Vol_{cell}}{Vol_{mito}} \cdot v_{malpT} + v_{PCC} + v_{MECCC}$$

$$\frac{d}{dt} pa_{er} = +\frac{Vol_{cyt}}{Vol_{er}} \cdot v_{agpat} - \frac{Vol_{cyt}}{Vol_{er}} \cdot v_{pap}$$

$$\frac{d}{dt} pep_{cyt} = +v_{eno} - v_{pk}$$

$$\frac{d}{dt} pg2_{cyt} = +v_{pgm} - v_{eno}$$

$$\frac{d}{dt} pg3_{cyt} = +v_{pgk} - v_{pgm}$$

$$\frac{d}{dt} pg6_{cyt} = +v_{pgls} - v_{pgdh}$$

$$\frac{d}{dt} pgl6_{cyt} = +v_{g6pdh} - v_{pgls}$$

$$\frac{d}{dt} pp_{cyt} = +v_{ACS1} + v_{FAB1} + v_{FAB4} - v_{ppase} + v_{upgase}$$

$$\frac{d}{dt} propcoa_{mito} = +v_{mmsdh} + v_{MAACT} - v_{PCC}$$

$$\frac{d}{dt} pyr_{cyt} = +v_{pk} - v_{ldh} - v_{mal-pyrT} + v_{pyrT} - v_{pyrT_{mito}} + v_{me}$$

$$\frac{d}{dt}pyr_{ext} = 0$$

$$\frac{d}{dt}pyr_{mito} = -v_{pdhc} - v_{pc} + \frac{Vol_{cell}}{Vol_{mito}} \cdot v_{pyrT} + \frac{Vol_{cell}}{Vol_{mito}} \cdot v_{mal-pyrT}$$

$$\frac{d}{dt}q_{mm} = -\frac{Vol_{mito}}{Vol_{membrane}} \cdot v_{ETF-QO} - \frac{Vol_{mito}}{Vol_{membrane}} \cdot v_{succdh} - \frac{v_{cxI}}{10 \cdot F \cdot Vol_{membrane}} + \frac{v_{cxIII}}{10 \cdot F \cdot Vol_{membrane}} + \frac{Vol_{cyt}}{Vol_{membrane}} v_{g3pdh_{mito}}$$

$$\frac{d}{dt}qh2_{mm} = +\frac{Vol_{mito}}{Vol_{membrane}} \cdot v_{ETF-QO} + \frac{Vol_{mito}}{Vol_{membrane}} \cdot v_{succdh} + \frac{v_{cxI}}{10 \cdot F \cdot Vol_{membrane}} - \frac{v_{cxIII}}{10 \cdot F \cdot Vol_{membrane}} - \frac{Vol_{cyt}}{Vol_{membrane}} v_{g3pdh_{mito}}$$

$$\frac{d}{dt}r5p_{cyt} = -v_{rpi} + v_{tketo1}$$

$$\frac{d}{dt}ru5p_{cyt} = +v_{pgdh} - v_{rpe} + v_{rpi}$$

$$\frac{d}{dt}s7p_{cyt} = -v_{taldo} - v_{tketo1}$$

$$\frac{d}{dt}suc_{mito} = +v_{scs-atp} + v_{scs-gtp} - v_{succdh} + v_{scot}$$

$$\frac{d}{dt}succoa_{mito} = +v_{kgdhc} - v_{scs-atp} - v_{scs-gtp} - v_{scot} + v_{MMCM}$$

$$\frac{d}{dt}tag_{er} = +\frac{Vol_{cyt}}{Vol_{er}} \cdot v_{dgat} - v_{LD-syn-tag}$$

$$\frac{d}{dt}tag_{ld} = +\frac{Vol_{er}}{Vol_{ld}} \cdot v_{LD-syn-tag} - v_{ATGL}^{tag}$$

$$\frac{d}{dt}TigCoA_{mito} = +v_{MBCoADH-MeButCoA} - v_{ECoAH-TigCoA}$$

$$\frac{d}{dt}udp_{cyt} = -v_{ndk_{cyt}}^{udp} + v_{gs}$$

$$\frac{d}{dt}udpglc_{cyt} = +v_{upgase} - v_{gs}$$

$$\frac{d}{dt}utp_{cyt} = +v_{ndk_{cyt}}^{udp} - v_{upgase}$$

$$\frac{d}{dt}val_{cyt} = +v_{valT} - v_{BCAAT-val}$$

$$\frac{d}{dt}val_{ext} = 0$$

$$\frac{d}{dt}v_{mm} = \frac{10^{-1}}{c_m \cdot A_m} \cdot \left(-I_{C_{ed}} + I_{K_{ed}} + I_{H_{ed}} + I_{Na_{ed}} + I_H^{pump} + v_{ex} + 3 \cdot v_{syn}\right)$$

$$\frac{d}{dt}x5p_{cyt} = +v_{rpe} + v_{tketo1} + v_{tketo2}$$

Supplement S2: Information to external conditions and transfer functions

Glucose-Insulin

The plasma concentrations of the hormone insulin determines the phosphorylation state of the inter-convertible enzymes. Insulin is secreted by the pancreas into the portal vein and the secretion rate is mainly controlled by the glucose concentration of the blood. Therefore, we used the empirical glucose hormone transfer function (GHT), which describes the relationship between the plasma level of glucose and the plasma levels of insulin established in Bulik et al., 2016[65] (Supplemental Figure I):

$$\mathrm{Ins} = 1.55\ \mathrm{nM} * \frac{(\mathrm{Glc_{ext}})^{5.7}}{(\mathrm{Glc_{ext}})^{5.7} + (7.7\ \mathrm{mM})^{5.7}}$$

Enzyme phosphorylation state

The concentration of insulin determines the phosphorylation state of the interconvertible enzymes.[65] The phosphorylation state γ of interconvertible enzymes (Supplemental Figure II) is given by:

$$\gamma = 1 - \frac{Ins^{0.65}}{Ins^{0.65} + (0.4\,nM)^{0.65}}.$$

AMP-dependent phosphorylation

In addition to hormone dependent phosphorylation, phosphorylation in dependence of the energetic state of the cell is achieved by the AMP-dependent kinase. Therefore, we introduced AMP-dependent phosphorylation by

$$\gamma_{AMP} = \frac{AMP}{AMP + 0.04}.$$

Glucose-fatty acids

The plasma concentration of fatty acids (FA) is largely determined by the rate of triglyceride lipolysis in the adipose tissue, which is mainly controlled by insulin and glucagon through the activity of the hormone sensitive lipases (HSL). Based on measured relations between the plasma levels of plasma and FA, we constructed an empirical glucose-FA transfer function (GFT) (Supplemental Figure III):

$$tfa_{plasma} = 1.2mM - 1.1mM \frac{Glc_{ext}^4}{Glc_{ext}^4 + (6.5mM)^4}$$

Conversion of total plasma fatty acids to free plasma fatty acids

Plasma fatty acids are largely bound to plasma albumin or lipoproteins, but only free fatty acids are taken up by the heart. We calculated the free fatty acid concentration (ffa_{plasma}) from total plasma fatty acid concentration (tfa_{plasma}) assuming a linear relationship between the two. In this way, we can recapitulate hyperbolic saturation kinetics in the cardiac fatty acid uptake rates when depicted against total plasma fatty acid concentration or against free fatty acid plasma concentration:

$$ffa_{plasma} = 3.125 \cdot 10^{-4} \cdot tfa_{plasma}$$

Epinephrine

The plasma concentrations of the hormone epinephrine is an important determinant for the activity of glucose transport capacity in cardiomyocytes. As epinephrine increases cardiac pacing,[66] we describe epinephrine levels in dependence of cardia pacing (load) by a transfer function (Supplemental Figure IV).

Supplement S3: Model calibration and validation

All model parameters except V_{max}-values (e.g. kinetic rate constants, substrate affinities, affinities to allosteric regulators) were taken from reported kinetic studies of the isolated enzyme obtained from mammalian cardiac tissue. The V_{max} values, which give the maximal activity of each enzyme and that may vary due to variable protein expression, were estimated by fitting the model to measurements of exchange fluxes and internal metabolites obtained in different experimental setups. The validity of the model was checked by comparing simulated exchange fluxes and metabolite concentrations with experimental data. As the heart switches its substrate uptake rates in dependence of substrate availability, we performed different simulations with variable substrate availability.

Glucose uptake

First, we simulated the glucose uptake of cardiac muscle in dependence of glucose availability. To match experimental conditions, we assumed that glucose and oxygen are the only available substrates, assumed that there are no hormones present and that the ATP demand is constant with a moderate demand. All external conditions are given in Supplemental Table III.

Supplemental Figure V shows the cardiac glucose uptake rate in dependence of plasma glucose concentrations obtained by systematically varying the external glucose concentration. The heart takes up glucose until saturation is reached at around 20 mM. This is much higher than the typical blood plasma concentration. At physiological glucose concentrations (<10 mM), glucose uptake increases with increasing plasma glucose levels.

Lactate uptake

The next most abundant carbohydrate available to the heart is lactate. Therefore, we used the model to investigate the utilization of this important fuel, when the supply with alternative substrate is limited. We varied the external availability of lactate between 0 mM and 12 mM, keeping the glucose concentration at a low value of 2 mM and putting the fatty acid concentration to 0.1 mM (Supplemental Table IV). Supplemental Figure VI shows the ratio of lactate to oxygen consumption rate (OCR). Lactate to OCR ratio increases up to 4 mM plasma lactate concentration when saturation is reached. This means that in the physiological range (<2 mM) lactate uptake is limited by substrate availability.

Fatty acid uptake

Next, we checked the ability of the model to recapitulate fatty acid uptake. We monitored the fatty acid uptake when systematically varying the plasma fatty acid concentrations between 0 and 2 mM while assuming a moderate ATP demand (Supplemental Table V). As the majority of fatty acids in the plasma are bound to albumin, but only free fatty acids are taken up by the heart, we used the transfer function depicted in Supplement S2 to calculate the free fatty acid concentration from the plasma fatty acid concentration.

Supplemental Figure VII shows the cardiac fatty acid uptake rate in dependence of total plasma fatty acid concentration and unbound free fatty acid concentration (insert). Fatty acid uptake reaches saturation at around 1 mM total plasma fatty acids.

Suppression of glucose uptake by plasma fatty acids

After checking that the model correctly recapitulates the substrate utilization for glucose and fatty acids in the absence of the other substrate, the next step was to investigate the interplay of the different substrates. Therefore, we simulated the uptake of glucose in the presence of varying fatty acid concentrations in the plasma (Supplemental Table VI).

Supplemental Figure VIII shows the suppression of glucose utilization by fatty acid concentrations in the plasma. With increasing fatty acid availability, the model correctly recapitulates the replacement of glucose with fatty acids. This strongly supports the view that fatty acids are the preferred substrate for the heart, and that glucose is used only when fatty acid availability is limited.

Ketone body utilization

Ketone bodies represent an important substrate for the heart especially during fasting conditions when glucose and lactate are not available or need to be saved for the utilization by other organs (i.e. gluconeogenesis form lactate in the liver or glycolysis in the brain).

Assuming moderate glucose levels and moderate load, we systematically varied the plasma ketone body concentration (β-hydroxybuterate) from 0 to 5.5 mM and monitored the ketone body uptake rates (Supplemental Table VII). Supplemental Figure IX shows that ketone body uptake increases with increasing ketone body availability, not reaching saturation at physiological plasma ketone body concentrations.

Substrate utilization in the human heart

Next, we tested whether the model correctly recapitulates substrate uptake of the human heart under physiological conditions when all substrates (glucose, lactate, fatty acids, ketone bodies and branched chain amino acids) are present at the same time (Supplemental Table VIII).

We simulated the substrate utilization rates of the human heart at rest and moderate pacing in an overnight fasted state and compared the simulated rates to experimental data for the human heart. Supplemental Figure X shows that the model calculations recapitulate the substrate uptake profile of the normal human heart as reported in several *in vivo* studies[37, 38, 40-43, 45] (Supplemental Figure XA). At rest, lactate is utilized with the highest rate, followed by fatty acids and ketone bodies. Increased energy demand during pacing is predominantly fueled by increased uptake by carbohydrates (glucose, lactate, pyruvate), while fatty acid utilization remains almost constant. Branched chain amino acids do not contribute significantly to the energy expenditure of the heart (<1%).

SUPPLEMENTAL TABLES

Supplemental Table I: Metabolite concentrations

Metabolite		Location	Mammalian		Modeled		References
			min [mM]	max [mM]	min [mM]	max [mM]	
ACoA	Acetyl coenzyme A	cell	<0.01	0.11	0.0061	0.0673	5, 67-72
Acyl-CoA	Acyl coenzyme A	cell	<0.01	0.11	0.02	0.05	5, 69, 72
CoA_{mito}	Coenzyme A	mito	0.05	2.26	0.0213	1.1477	73, 74
NAD+	Nicotinamide adenine dinucleotide	cell	0.59	1.45	1.13	1.14	67, 75
$NAD+_{cyt}$	Nicotinamide adenine dinucleotide	cyt	0.51	1.39	1.13	1.13	76
$NAD+_{mito}$	Nicotinamide adenine dinucleotide	mito	0.19	0.87	0.026	0.05	74, 76
NADH	Reduced nicotinamide adenine dinucleotide	cell	0.02	0.36	<0.01	0.0042	67, 77
$NADH_{cyt}$	Reduced nicotinamide adenine dinucleotide	cyt	<0.01	0.01	<0.01	<0.01	76
$NADH_{mito}$	Reduced nicotinamide adenine dinucleotide	mito	0.05	0.20	<0.01	0.024	76
P	Phosphate	cell	2.25	20.50	11.37	21. 7	5, 78-80
P_{cyt}	Phosphate	cyt	2.18	7.81	5.45	15.25	80, 81
AMP	Adenosine monophosphate	cell	0.07	2.62	0.02	3.89	5, 75, 82, 83
ADP	Adenosine diphosphate	cell	0.69	4.49	0.34	2.67	5, 67, 75, 82-84
ADP_{cyt}	Adenosine diphosphate	cyt	0.32	0.93	0.34	2.66	80
ATP	Adenosine triphosphate	cell	4.05	28.29	3.28	9.32	5, 67, 71, 77, 78, 82, 84-90
GDP	Guanosine diphosphate	cell	0.11	0.21	0.04	0.61	75
GTP	Guanosine triphosphate	cell	0.31	0.59	0.47	1.04	75
Glc6P	Glucose 6-phosphate	cell	0.10	0.93	0.05	0.34	5, 91
Fru6P	Fructose-6-phosphate	cell	0.03	0.23	<0.01	0.08	5, 82, 91
Fru26P2	Fructose-2,6-bisphosphate	cell	<0.01	0.01	<0.01	0.01	82
Fru16P2	Fructose-1,6-bisphosphate	cell	0.01	0.13	<0.01	<0.01	5, 82, 91, 92
DHAP	Dihydroxyacetone phosphate	cell	0.01	0.14	0.01	0.037	5, 82
GAP	Glyceraldehyde 3-phosphate	cell	0.02	0.09	<0.01	0.02	5, 91

13BPG	1,3-Bisphosphoglycerate	cell	<0.01	<0.01	<0.01	<0.01	[92]
3PG	3-Phosphoglycerate	cell	0.03	0.57	0.06	0.21	[5, 91, 92]
2PG	2-Phosphoglycerate	cell	<0.01	0.03	<0.01	0.036	[5, 91]
PEP	Phosphoenolpyruvate	cell	0.01	0.04	0.01	0.01	[5, 91, 92]
Pyr	Pyruvate	cell	0.01	6.00	0.02	1.5	[5, 67, 71, 91, 92]
Gly3P	Glycerol 3-phosphate	cell	<0.01	0.25	<0.01	0.09	[5, 91, 92]
Glc1P	Glucose 1-phosphate	cell	0.01	0.16	<0.01	0.02	[5, 92]
UDP-Glc	Uridine diphosphate glucose	cell	0.26	0.72	<0.01	2.1	[5, 81]
Cit	Citrate	cell	0.19	1.42	0.04	0.1	[5, 67, 93]
IsoCit	Isocitrate	cell	0.02	0.07	<0.01	<0.01	[5, 93]
aKG	Alpha-ketoglutarate	cell	0.05	0.29	<0.01	0.05	[5, 67, 93]
aKG_{mito}	Alpha-ketoglutarate	mito	0.13	0.21	0.02	0.15	[74]
Suc	Succinate	cell	0.26	4.42	<0.01	0.06	[5, 67, 71]
Fum	Fumarate	cell	0.11	0.72	0.5	0.66	[5, 67]
Mal	Malate	cell	0.13	0.49	0.11	0.99	[5, 67, 93]
OA	Oxaloacetate	cell	0.02	0.05	<0.01	0.04	[5]
Asp	Aspartate	cell	3.01	10.78	<0.01	4.74	[5, 93, 94]
Gln	Glutamine	cell	10.38	26.24	10.33	10.33	[95, 96]
Glu	Glutamate	cell	4.63	18.72	<0.01	1.09	[5, 93, 94, 96]
IsoLeu	Isoleucine	cell	<0.01	0.23	0.18	0.2	[94-96]
Leu	Leucine	cell	0.07	0.37	0.33	0.39	[94, 95]
Val	Valine	cell	0.23	0.36	0.35	0.4	[94]
Acyl-Carn	Acylcarnitine	cell	0.01	0.94	0.03	0.14	[74, 97]
$Acyl\text{-}Carn_{cyt}$	Acylcarnitine	cyt	0.03	0.38	0.01	0.08	[73]
$Acyl\text{-}Carn_{mito}$	Acylcarnitine	mito	0.00	0.22	0.08	0.44	[73]
Carn	Carnitine	cell	0.74	4.24	0.78	0.89	[5, 79, 98]
$Carn_{cyt}$	Carnitine	cyt	2.56	2.65	0.32	0.39	[73]
$Carn_{mito}$	Carnitine	mito	1.84	2.03	2.66	3.02	[73]
TAG	Triacylglycerol	cell	3.34	9.78	1.4	2.77	[5, 99]
DAG	Diacyl-glycerol	cell	0.03	0.43	0.51	0.51	[5, 99]

MalCoA	Malonyl coenzyme A	cell	<0.01	0.02	<0.01	0.01	[68, 70, 72, 100-102]
C4CoA	Butyryl coenzyme A	cell	<0.01	0.01	<0.01	<0.01	[103]
C6CoA	Hexanoyl coenzyme A	cell	<0.01	0.01	<0.01	<0.01	[104]
C8CoA	Octanoyl coenzyme A	cell	<0.01	0.01	<0.01	<0.01	[104]
C10CoA	Decanoyl coenzyme A	cell	0.01	0.02	<0.01	<0.01	[104]
C14CoA	Myristoyl coenzyme A	cell	<0.01	<0.01	<0.01	<0.01	[69]
C16CoA	Palmitoyl coenzyme A	cell	<0.01	0.01	<0.01	<0.01	[69]

Supplemental Table II: V_{max} values

Short Name	Long Name	EC/TCDB Number	Estimated v_{max} value [µmol/g/h]
v_CD36	fatty acid translocase	TCDB 4.C.1.1	4.20E+01
v_acs1	(Long-chain) acyl-coa synthetase 1	EC 6.2.1.3	2.80E+00
v_fatp1	fatty acid transport protein 1	TCDB 4.C.1.1	1.04E-01
v_fatp4	fatty acid transport protein 4	TCDB 4.C.1.1	1.35E-01
v_CPT1	Carnitine O-palmitoyltransferase 1, liver isoform	EC 2.3.1.21	7.50E-02
v_CACT	Carnitin-Acylcarnitin translocase	TCDB 2.A.29.8	5.00E+00
v_CPT2	Carnitine O-palmitoyltransferase 2, mitochondrial	EC 2.3.1.21	5.00E+01
v_c4coa_scdh	Short chain acyl-coa dehydrogenase (c4)	EC 1.3.8.1	5.00E+00
v_c6coa_mcdh	medium chain acyl-coa dehydrogenase (c6)	EC 1.3.8.7	5.25E+01
v_c8coa_mcdh	medium chain acyl-coa dehydrogenase (c8)	EC 1.3.8.7	6.25E+01
v_c10coa_mcdh	medium chain acyl-coa dehydrogenase (c10)	EC 1.3.8.7	1.20E+01
v_c12coa_mcdh	medium chain acyl-coa dehydrogenase (c12)	EC 1.3.8.7	9.75E+00
v_c10coa_lcdh	long chain acyl-coa dehydrogenase (c10)	EC 1.3.8.8	1.20E+00
v_c12coa_lcdh	long chain acyl-coa dehydrogenase (c12)	EC 1.3.8.8	9.75E-01
v_c14coa_lcdh	long chain acyl-coa dehydrogenase (c14)	EC 1.3.8.8	5.25E-01

v_c16coa_lcdh	long chain acyl-coa dehydrogenase (c16)	EC 1.3.8.8	1.20E-01
v_etf	ETF-FAD	-	2.50E+02
v_etfq	ETF-QO	-	1.25E+03
v_E_hyd_C4_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec4)	EC 4.2.1.17	2.50E+03
v_E_hyd_C6_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec6)	EC 4.2.1.17	3.20E+04
v_E_hyd_C8_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec8)	EC 4.2.1.17	2.28E+04
v_E_hyd_C10_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec10)	EC 4.2.1.17	1.35E+04
v_E_hyd_C12_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec12)	EC 4.2.1.17	4.00E+03
v_E_hyd_C14_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec14)	EC 4.2.1.17	2.17E+03
v_E_hyd_C16_CoA_MC	Enoyl-coa hydratase (Crontonase) (ec16)	EC 4.2.1.17	1.00E+03
v_3HdH_C4_CoA	3-hydroxyacyl-coa dehydrogenase (lc4)	EC 1.1.1.35	5.75E+10
v_3HdH_C6_CoA	3-hydroxyacyl-coa dehydrogenase (lc6)	EC 1.1.1.35	5.75E+10
v_3HdH_C8_CoA	3-hydroxyacyl-coa dehydrogenase (lc8)	EC 1.1.1.35	5.75E+10
v_3HdH_C10_CoA	3-hydroxyacyl-coa dehydrogenase (lc10)	EC 1.1.1.35	5.75E+10
v_3HdH_C12_CoA	3-hydroxyacyl-coa dehydrogenase (lc12)	EC 1.1.1.35	5.75E+10
v_3HdH_C14_CoA	3-hydroxyacyl-coa dehydrogenase (lc14)	EC 1.1.1.35	5.75E+10
v_3HdH_C16_CoA	3-hydroxyacyl-coa dehydrogenase (lc16)	EC 1.1.1.35	5.75E+10
v_3KT_C4_I	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	2.50E+00
v_3KT_C4_II	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	2.50E+01
v_3KT_C6	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	6.00E+00
v_3KT_C8	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	5.50E+00
v_3KT_C10	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	5.75E+00
v_3KT_C12	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	5.25E+00
v_3KT_C14	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	4.25E+00
v_3KT_C16	3-ketoacyl-coa thiolase (kc4)	EC 2.3.1.16	2.50E+00
v_pdhc	Pyruvate dehydrogenase complex	EC 1.2.4.1; EC 1.8.1.4; EC 2.3.1.12	1.00E-01
v_cs	Citrate synthase, mitochondrial	EC 2.3.3.1	8.00E+01
v_ac	Aconitase	EC 4.2.1.3	9.00E+04
v_icdh_nad	NAD-dependent isocitrate dehydrogenase	EC 1.1.1.41	2.70E+01
v_icdh_nadp	NADP-dependent isocitrate dehydrogenase	EC 1.1.1.42	4.50E+00

v_akdhc	α-ketogluterate dehydrogenase	EC 1.2.4.2; EC 1.8.1.4; EC 2.3.1.61	4.50E+02
v_succoas_atp	Succinyl-Coa Synthetase (ATP)	EC 6.2.1.4; EC 6.2.1.5; EC 6.2.1.5	2.25E+04
v_succoas_gtp	Succinyl-Coa Synthetase (GTP)	EC 6.2.1.4; EC 6.2.1.4; EC 6.2.1.5	2.48E+03
v_succdh	Succinate dehydrogenase	EC 1.3.5.1	9.00E+03
v_fum	Fumerase	EC 4.2.1.2	1.80E+05
v_mdh	Malate dehydrogenase, mitochondrial	EC 1.1.1.37	9.00E+04
v_tdh	NAD(P) transhydrogenase, mitochondrial	EC 1.6.1.2	3.60E+03
v_ATP_use	ATP usage	-	1.20E-01
v_Phos	Phosphate carrier protein, mitochondrial	TCDB 2.A.29.4.2	7.72E+10
v_syn	F0F1 synthetase	EC 3.6.3.14	6.40E-06
v_ex	ATP-ADP nucleotide exchanger	TCDB 2.A.29	7.20E-07
v1	Complex I	EC 1.6.5.3	6.72E-07
v3	Complex III	EC 1.10.2.2	2.40E-06
v4	Complex IV	EC 1.9.3.1	9.60E-04
v_ak_cyt	Adenylate kinase	EC 2.7.4.3	8.00E+03
v_o2_diff	O2 diffusion	-	8.00E+01
v_ppase	Pyrophosphatase	EC 3.6.1.1	8.00E-02
I_C_ED	Chloride electro diffusion	-	8.00E-01
I_K_P	Sodium pump	-	2.40E-05
I_K_ED	Sodium electro diffusion	-	8.00E-01
I_Na_P	Potassium pump	-	1.60E-04
I_Na_ED	Sodium electro diffusion	-	8.00E-01
I_H_ED	Mitochondrial uncoupling protein	TC 2.A.29.24.1; TC 2.A.29.24.3; TC 2.A.29.3.2; TC 2.A.29.3.4; TC 2.A.29.3.5	8.00E-01
v_gpi	Glucose-6-phosphate isomerase	EC 5.3.1.9	3.51E+03
v_ald	Fructose-bisphosphate aldolase B	EC 4.1.2.13	1.17E+03
v_tpi	Triosephosphate isomerase 1	EC 5.3.1.1	1.17E+03
v_gapdh	Glyceraldehydephosphate dehydrogenase	EC 1.2.1.12	1.76E+05
v_pgk	Phosphyglyceratekinase (Pgk)	EC 2.7.2.3	5.85E+02
v_pgm	2-Phospho-D-glycerate 2,3 phosphomutase (Pgm)	EC 5.4.2.1	5.85E+05

v_eno	2-Phospho-D-glycerate hydrolase (Eno)	EC 4.2.1.11	1.17E+03
v_glcT1	Glucose transporter type 1	TC 2.A.1.1	4.15E-04
v_glcT4	Glucose transporter type 4	TC 2.A.1.1	6.31E-03
v_hk1	Hexokinase	EC 2.7.1.1	4.68E-02
v_hk2	Hexokinase	EC 2.7.1.1	4.68E-03
v_fbp2	Phosphofructokinase 2 (FBP2)	EC 2.7.1.105; EC 3.1.3.46; EC 3.1.3.46	4.68E-03
v_pfk2	Phosphofructokinase 2 (Pfk2)	EC 2.7.1.105; EC 3.1.3.46; EC 3.1.3.46	1.17E-02
v_fbp1	Fructose-1,6-bisphosphatase (Fbp1)	EC 3.1.3.11	1.17E+00
v_pfk1	Phosphofructokinase 1 (Pfk1)	EC 2.7.1.11	5.85E-01
v_pk	Pyruvate kinase (Pk)	EC 2.7.1.40	5.85E-02
v_pc	Pyruvate carboxylase; mitochondrial	EC 6.4.1.1	1.17E-02
v_mal_pyrT	Malate-pyruvate antiport (MalPyrT)	-	4.68E-01
v_me_nadp	Identifier nicht gefunden	-	1.17E+01
v_ldh	Lactate dehydrogenase	EC 1.1.1.27	1.17E+05
v_mdh_cyt	Malate dehydrogenase, cytoplasmic	EC 1.1.1.37	1.17E+03
v_lacT	Lactate transport (LacT)	TCDB 2.A.1.13.1; TCDB 2.A.1.13.5; TCDB 2.A.1.13.6; TCDB 2.A.1.13.7; TCDB 2.A.1.13.9	1.17E-02
v_pyrT	pyruvate transport (pyrT)	TCDB 2.A.1.13.1	1.17E-02
v_pyrT_mito	Mitochondrial pyruvate transport	TCDB 2.A.1.13.1	1.17E+05
v_ndk_cyt	Nudiki (cytosolic)	EC 2.7.4.6	1.17E+04
v_ndk_mito	Nudiki (mitochondrial)	EC 2.7.4.6	1.17E+06
v_ASAT_mito	Aspartate aminotransferase, mitochondrial	EC 2.6.1.1	1.50E+02
v_ASAT_in	Aspartate aminotransferase, cytoplasmic	EC 2.6.1.1	1.50E+02
v_asp_glu_T	aspartate –glutamate carrier	TCDB 2.A.29.14.1	2.25E-01
v_mal_akg_T	Malate – α-ketogluterate carrier	TCDB 2.A.29.2.13	1.50E+06
v_g3pdh_cyt	Glycerol-3-phosphate dehydrogenase (cytosolic)	EC 1.1.1.8	1.50E+06
v_g3pdh_mito	Glycerol-3-phosphate dehydrogenase (mitochondrial)	EC 1.1.5.3	3.00E-10
v_g6pd	Glucose-6-phosphate 1-dehydrogenase	EC 1.1.1.49	5.00E-06
v_pglase	6-phosphogluconolactonase	EC 3.1.1.31	3.00E-05
v_pgdh	6-phosphogluconate dehydrogenase; decarboxylating	EC 1.1.1.44	1.00E-01

v_rpe	Ribulose-phosphate 3-epimerase	EC 5.1.3.1	5.00E-03
v_rpi	Ribose-5-phosphate isomerase	EC 5.3.1.6	1.00E-02
v_taldo	Transaldolase	EC 2.2.1.2	1.00E-02
v_tkl1	Transketolase 1	EC 2.2.1.1	1.00E+02
v_tkl2	Transketolase 2	EC 2.2.1.1	1.00E+00
v_Cit_Mal	Citrate-malate exchanger	TCDB 2.A.29.7.2	3.00E-03
v_Cit_Lys	ATP dependent citrate lyase	EC 2.3.3.8	1.00E-05
v_ACC1	Acetyl-CoA carboxylase 1	EC 6.4.1.2	1.40E-05
v_Mal_CoA_dc	Malonyl-CoA decarboxylase	EC 4.1.1.9	1.00E-06
v_glycerol_uptake	Glycerol-uptake		7.50E-03
v_glycerol_kinase	Glycerol kinase	EC 2.7.1.30	3.60E-03
v_gpat	Glycerol-3-phosphate acyltransferase	EC 2.3.1.15	3.00E-03
v_agpat	Acetyl glycerol-3-phosphate acyltransferase	EC 2.3.1.51	4.50E-03
v_PAP	Phosphatidic acid phosphatase	EC 3.1.3.4	9.00E-03
v_dgat	Diacylglycerol acyltransferase	EC 2.3.1.20	1.05E-02
v_ld_syn	LD synthesis (tag)	-	3.00E-03
v_atgl	ATGL	EC 3.1.1.3	3.00E-04
v_hsl	Hormone-sensitive lipase	EC 3.1.1.79	3.00E-04
v_magl	Monoacylglycerol lipase	EC 3.1.1.23	3.00E-04
v_g16pi	alpha-D-Glucose 1-phosphate 1,6-phosphomutase	EC 5.4.2.2	1.20E+04
v_upgase	UTP:Glucose-1-phosphate uridylyltransferase (UPGase)	EC 2.7.7.9	9.00E+00
v_ndkutp	Nudiki (cytosolic) (udp)	EC 2.7.4.6	6.00E+01
v_gs	Glycogen synthase (GS)	EC 2.4.1.11	3.00E-04
v_gp	Glycogen-phosphorylase (GP)	EC 2.4.1.1	1.80E-02
v_acac_cytT	Acetoacetate export (MCT1/MCT2)	TCDB 2.A.1.13.1; TCDB 2.A.1.13.5; TCDB 2.A.1.13.6; TCDB 2.A.1.13.7; TCDB 2.A.1.13.9	2.85E-02
v_bhbut_cytT	B-Hydroxy butyrate export (MCT1/MCT2)	TCDB 2.A.13.1	2.85E-02
v_acac_mito_ex	Acetoacetate transport (mitochondrial)	TCDB 2.A.13.1	8.55E-02
v_bhbut_mito_ex	B-Hydroxy butyrate transport (mitochondrial)	TCDB 2.A.13.1	8.55E-02
v_bHBDH	D-beta-hydroxybutyrate dehydrogenase, mitochondrial	EC 1.1.1.30	5.70E+03

v_scot	Succinyl-CoA:3-ketoacid coenzyme A transferase 1, mitochondrial	EC 2.8.3.5	5.70E+01
v_valT	valine transporter	-	1.00E-01
v_leuT	leucine transporter	-	1.00E-01
v_isoleuT	isoleucine transporter		1.00E-01
v_BCAAT_val	Branched-chain-amino-acid aminotransferase	EC 2.6.1.42	1.00E-01
v_BCAAT_leu	Branched-chain-amino-acid aminotransferase	EC 2.6.1.42	1.00E-01
v_BCAAT_isoleu	Branched-chain-amino-acid aminotransferase	EC 2.6.1.42	1.00E-01
v_BCKADH_aKIVA	Branched-chain alpha-keto acid dehydrogenase	EC 1.2.4.4	1.00E-01
v_BCKADH_aKICA	Branched-chain alpha-keto acid dehydrogenase	EC 1.2.4.4	1.00E-01
v_BCKADH_KMeVA	Branched-chain alpha-keto acid dehydrogenase	EC 1.2.4.4	1.00E-01
v_MBCoADH_IsoButCoA	2-methylacyl-CoA dehydrogenase	EC 1.3.99.12	1.00E+01
v_MBCoADH_MeButCoA	2-methylacyl-CoA dehydrogenase	EC 1.3.99.12	1.00E+01
v_ECoAH_MeAcrCoA	Enoyl-CoA hydratase, mitochondrial	EC 4.2.1.17	1.00E+03
v_ECoAH_TigCoA	Enoyl-CoA hydratase, mitochondrial	EC 4.2.1.17	1.00E+01
v_HibCDA_HibCoA	3-hydroxyisobutyryl-CoA hydrolase, mitochondrial	EC 3.1.2.4	1.00E+01
v_HibCDH_HBA	3-hydroxyisobutyryl-CoA hydrolase, mitochondrial	EC 3.1.2.4	1.00E+01
v_MMSDH_MMSALD	Methylmalonate-semialdehyde dehydrogenase, mitochondrial	EC 1.2.1.27	1.00E+01
v_HMBCDH_MeHButCoA	Methylmalonate-semialdehyde dehydrogenase, mitochondria	EC 1.2.1.27	1.00E+01
v_MAACT_MeAACoA	3-ketoacyl-CoA thiolase, mitochondrial	EC 2.3.1.16	1.00E+01
v_IVCoADH_isoValCoA	Isovaleryl-CoA dehydrogenase, mitochondrial	EC 1.3.8.4	1.00E+01
v_MECCC_MeCroCoA	Methylcrotonoyl-CoA carboxylase, mitochondrial	EC 6.4.1.4	1.00E+01
v_MEGCCH_MeGCCoA	Methylglutaconyl-CoA hydratase, mitochondrial	EC 4.2.1.18	1.00E+01
v_HMGCL_HMeGCoA	Hydroxymethylglutaryl-CoA lyase, mitochondrial	EC 4.1.3.4	1.00E+01
v_PCC_PropCoa	Propionyl-CoA carboxylase, mitochondrial	EC 6.1.4.3	1.00E+01
v_MMCM_MeMalCoa	Methylmalonyl-CoA mutase, mitochondrial	EC 5.4.99.2	1.00E+01

Supplemental Table III: External conditions for simulation of cardiac glucose uptake

Glucose [mM]	0.5-25	Valine [mM]	0
Lactate[mM]	0	Leucine [mM]	0
Fatty acids [mM]	0.1	Isoleucine [mM]	0
B-hydroxybuterate [mM]	0	Insulin [nM]	0-1500 TF (Supplement S2)
Acetoacetate [mM]	0	k-load	5

Supplemental Table IV: External conditions for simulation of cardiac lactate uptake

Glucose [mM]	2	Valine [mM]	0
Lactate[mM]	0.2-12	Leucine [mM]	0
Fatty acids [mM]	0.1	Isoleucine [mM]	0
B-hydroxybuterate [mM]	0	Insulin [nM]	1 TF (Supplement S2)
Acetoacetate [mM]	0	k-load	0

Supplemental Table V: External conditions for simulation of cardiac fatty acid uptake

Glucose [mM]	7.63	Valine [mM]	0
Lactate[mM]	1	Leucine [mM]	0
Fatty acids [mM]	0-2	Isoleucine [mM]	0
B-hydroxybuterate [mM]	0	Insulin [nM]	757 TF (Supplement S2)
Acetoacetate [mM]	0	k-load	5

Supplemental Table VI: External conditions for simulation of the uptake of glucose in the presence of varying fatty acid concentrations in the plasma.

Glucose [mM]	5.8	Valine [mM]	0
Lactate[mM]	0.8	Leucine [mM]	0

Fatty acids [mM]	0-1.2	Isoleucine [mM]	0
B-hydroxybuterate [mM]	0	Insulin [nM]	257 TF (Supplement S2)
Acetoacetate [mM]	0	k-load	2

Supplemental Table VII: External conditions for simulation of the ketone body uptake

Glucose [mM]	4	Valine [mM]	0
Lactate[mM]	0	Leucine [mM]	0
Fatty acids [mM]	0	Isoleucine [mM]	0
B-hydroxybuterate [mM]	0-5	Insulin [nM]	36 TF (Supplement S2)
Acetoacetate [mM]	0	k-load	3

Supplemental Table VIII: External conditions for simulation of the substrate utilization rates of the human heart.

Glucose [mM]	5.8	Valine [mM]	0.2
Lactate[mM]	0.8	Leucine [mM]	0.15
Fatty acids [mM]	0.5	Isoleucine [mM]	0.06
B-hydroxybuterate [mM]	0.08	Insulin [nM]	100 TF (Supplement S2)
Acetoacetate [mM]	004	k-load	0.5/3

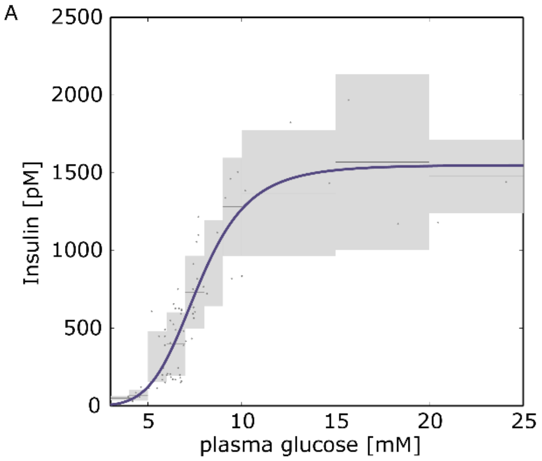
Supplemental Table IX: Univariate rank correlation analysis

Spearman correlation	**rho**	**p-value**	**rho**	**p-value**
	NYHA stage	**NYHA stage**	**delta NYHA**	**delta NYHA**
max glucose uptake [µmol/g/h]	0,06042146	0,68662206	0,04819485	0,80392941
max lactate uptake [µmol/g/h]	0,01120792	0,93527217	-0,42659854	0,01060146
max fa uptake [µmol/g/h]	-0,01506064	0,91309669	-0,06126284	0,72663757
max val uptake [µmol/g/h]	0,12001814	0,3827748	0,17392669	0,31767967
max leu uptake [µmol/g/h]	0,12176937	0,3758194	0,17392669	0,31767967
max isoleu uptake [µmol/g/h]	0,12001814	0,3827748	0,17392669	0,31767967
max bhbut uptake [µmol/g/h]	0,09067518	0,51029546	-0,23802854	0,16853131
max acac uptake [µmol/g/h]	0,06137114	0,6562428	-0,11191674	0,52212178
glucose uptake at max load [µmol/g/h]	0,21979975	0,1068696	0,21292572	0,21941718

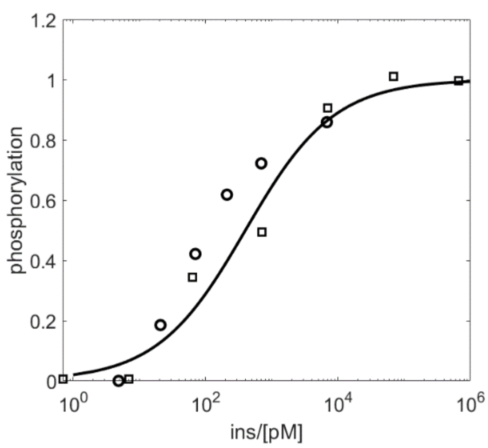
lactate uptake at max load [µmol/g/h]	0,05658443	0,68156265	-0,3729562	0,02734142
fa uptake at max load [µmol/g/h]	0,04599917	0,73877199	-0,22144274	0,20109571
val uptake at max load [µmol/g/h]	-0,10635848	0,43960862	0,27149896	0,11464054
leu uptake at max load [µmol/g/h]	-0,09627914	0,48439462	0,24340771	0,15883029
isoleu uptake at max load [µmol/g/h]	-0,10931613	0,42691944	0,28673996	0,09491045
ketone body uptake at max load [µmol/g/h]	0,17905429	0,19087286	-0,33948577	0,04602315
o2 consumption at max load [µmol/g/h]	0,05413269	0,69466976	-0,38356513	0,02293154
ATP consumption at max load [µmol/g/h]	-0,03673707	0,79002249	-0,39148447	0,02003839

SUPPLEMENTAL FIGURES

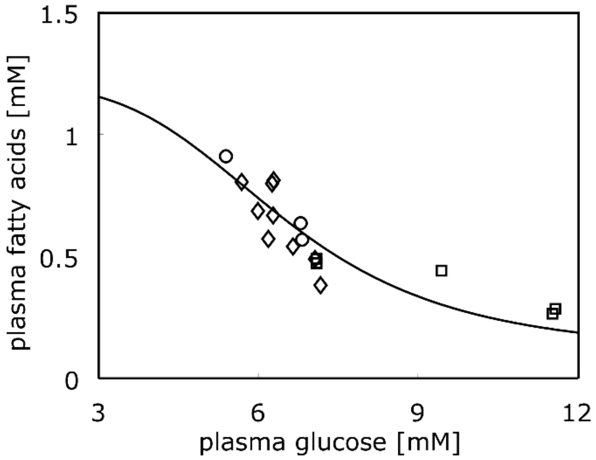
Supplemental Figure I



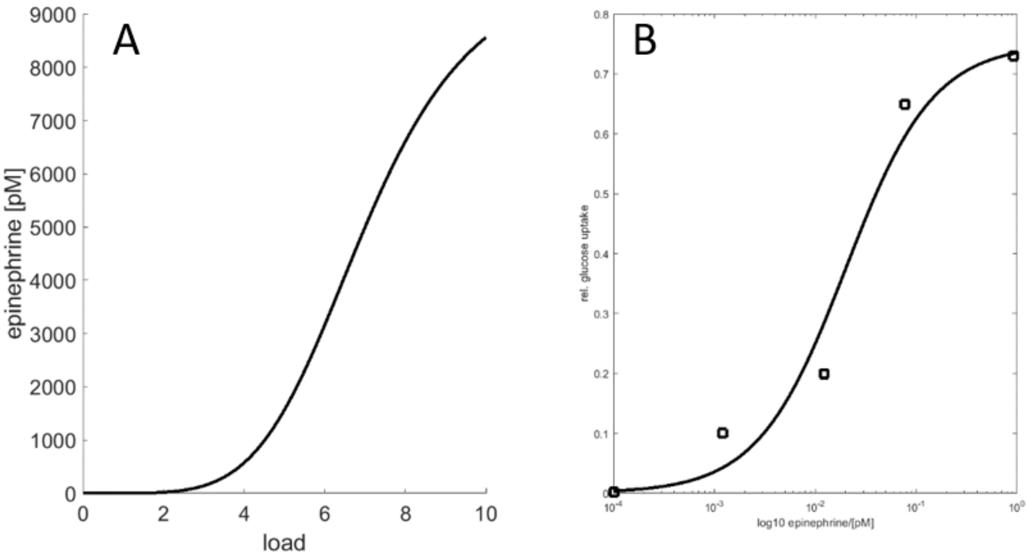
Supplemental Figure II



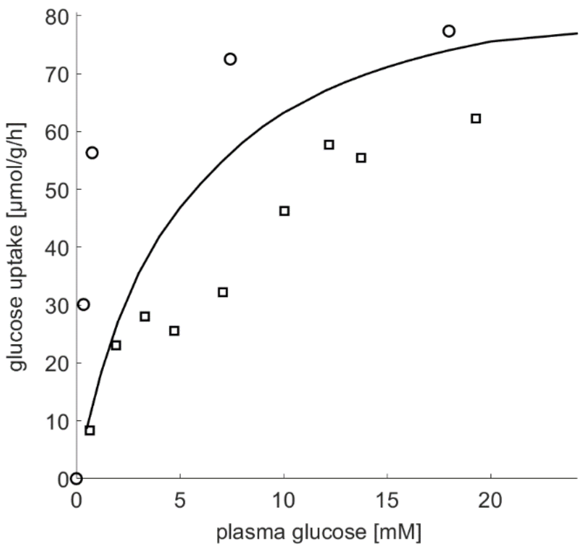
Supplemental Figure III



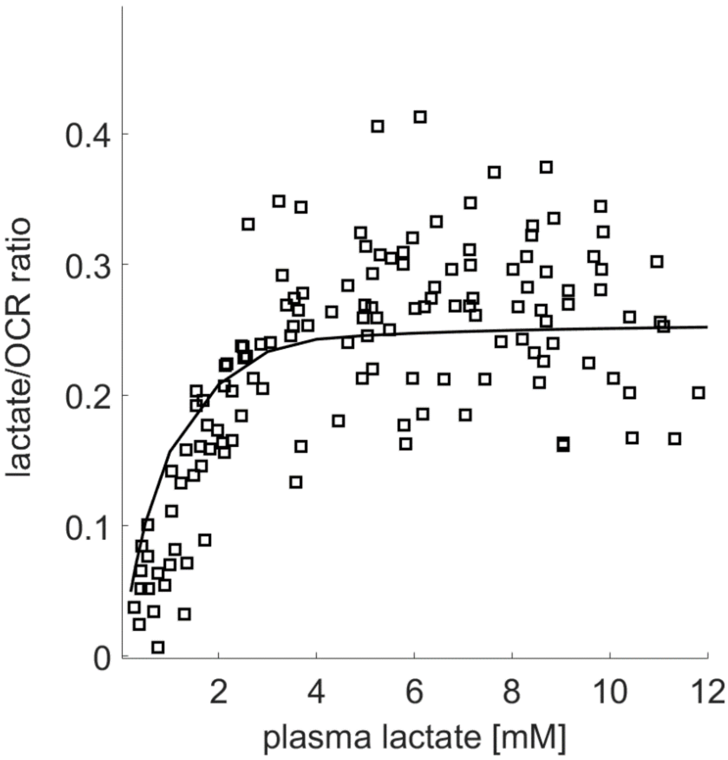
Supplemental Figure IV



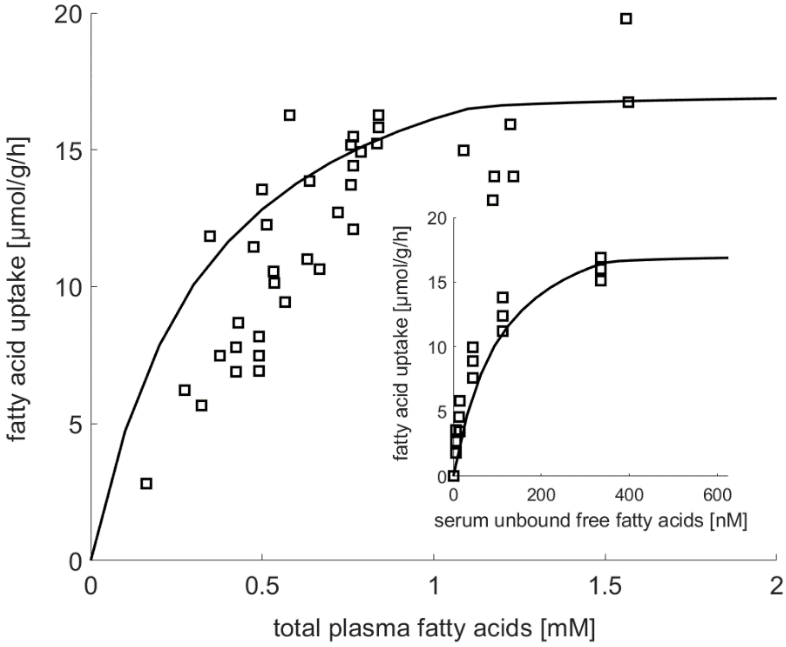
Supplemental Figure V



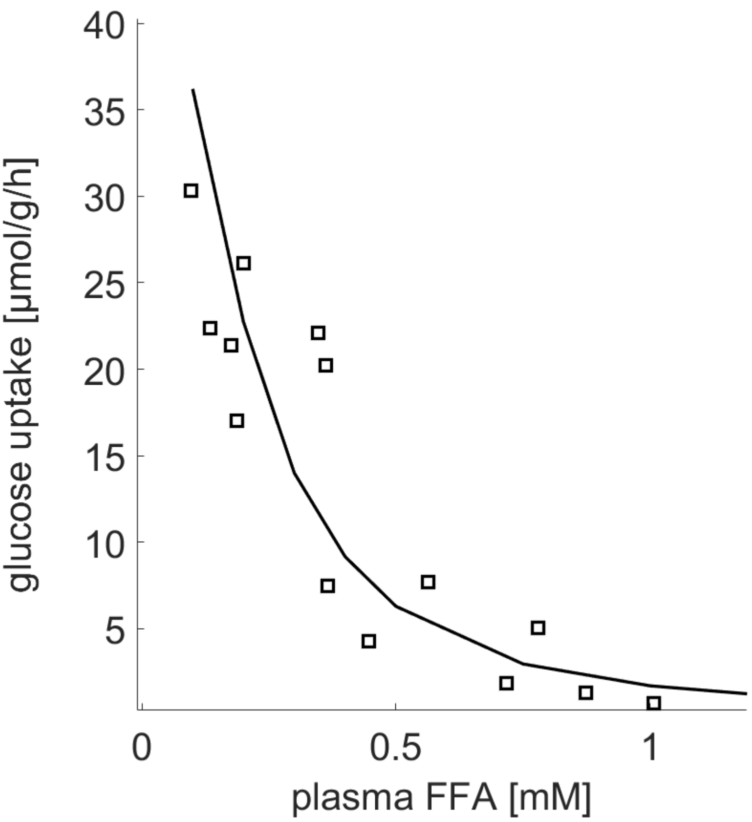
Supplemental Figure VI



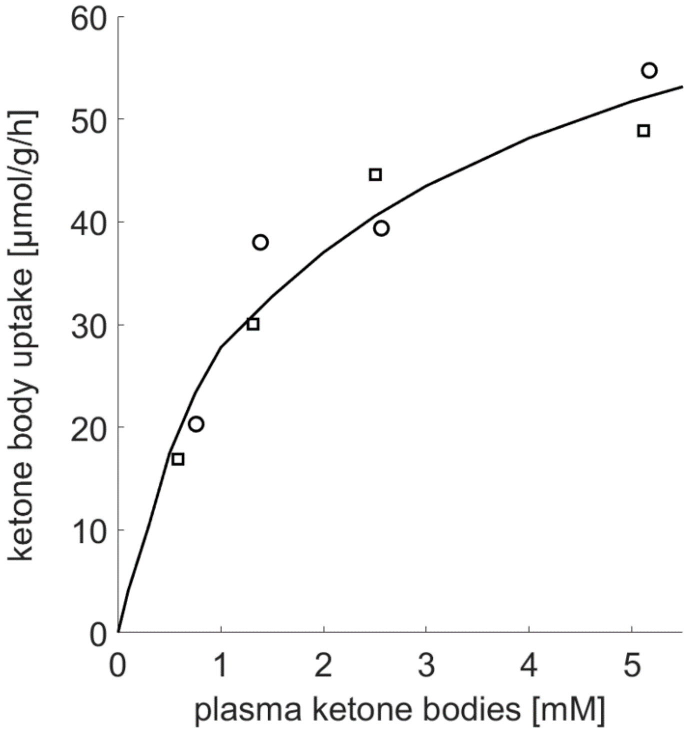
Supplemental Figure VII



Supplemental Figure VIII



Supplemental Figure IX



Supplemental Figure X

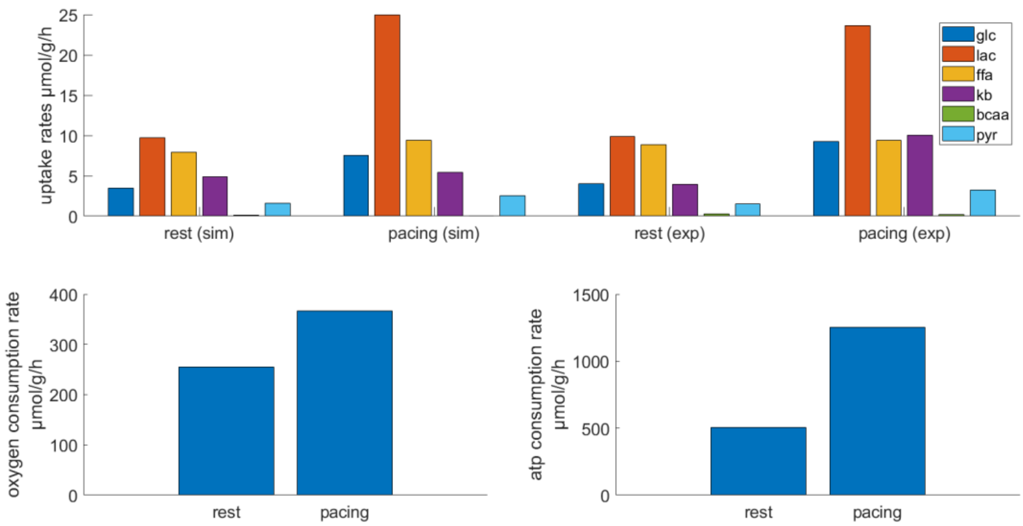


FIGURE LEGENDS

Supplemental Figure I

The GHT functions describe the dependence of plasma insulin on plasma glucose levels. Experimentally determined plasma concentrations of glucose and hormone (grey dots) from various sources (insulin)[105-107] were pooled (black lines – mean values, light grey boxes – standard deviations). A Hill-type function was used to fit the data by least-square minimization yielding the GHT function.

Supplemental Figure II

Hormone phosphorylation function γ. Bold lines depict the function γ used to relate the level of insulin to the phosphorylated form of enzymes regulated by eversible phosphorylation. Data taken from Stuenaes et al., 2010 and Ramachandran et al., 1982.[108, 109]

Supplemental Figure III

Glucose to fatty acids transfer (GFT) functions for the dependence of total plasma (tfa) levels from plasma glucose level (glc_plasma). Experimentally determined plasma concentration values of glucose and fatty acids from various sources.[110-112] Hill-type transfer functions were fitted to the data by least-square minimization yielding the GFT.

Supplemental Figure IV

(A) Relation between epinephrine and load parameter. (B) Effect of epinephrine on cardiac glucose transport. Data taken from Clark and Patten, 1984.[113]

Supplemental Figure V

Cardiac glucose utilization rate in dependence of external glucose concentration. Data taken from Henderson et al., 1961 and Morgan et al., 1961.[114, 115]

Supplemental Figure VI

Lactate-oxygen ratio in dependence of lactate availability. Lactate uptake increases with lactate availability until saturation is reached at ~ 2.5 mM plasma lactate concentration. Experimental data taken from Drake and al., 1980.[116]

Supplemental Figure VII

Fatty acid utilization in dependence of plasma free (not bound to albumin) fatty acid concentration. Insert: Fatty acid utilization in dependence of plasma total fatty acid concentration. Data taken from Vyska et al., 1991 and Stremmel, 1988.[117, 118]

Supplemental Figure VIII

Suppression of glucose utilization by fatty acids. Increasing availability of fatty acids in the plasma lead to a progressive replacement of glucose with fatty acids as energy delivering substrate. Data taken from Nuutila et al., 1994.[44]

Supplemental Figure IX

Ketone body uptake in dependence of plasma ketone body concentration. Data taken from Sultan, 1992.[119]

Supplemental Figure X

Substrate utilization rates of the human heart under overnight fasted conditions at rest and moderate pacing. (A) Simulated and experimentally determined uptake rates for glucose (glc), lactate (lac), fatty acids (ffa), ketone bodies (kb), branched chain amino acids (bcaa) and pyruvate (pyr) at rest and during moderate pacing. Ketone body uptake utilization in dependence of plasma ketone body concentration. Experimental data represent averaged values taken from Data taken from literature.[37, 38, 40-43, 45]