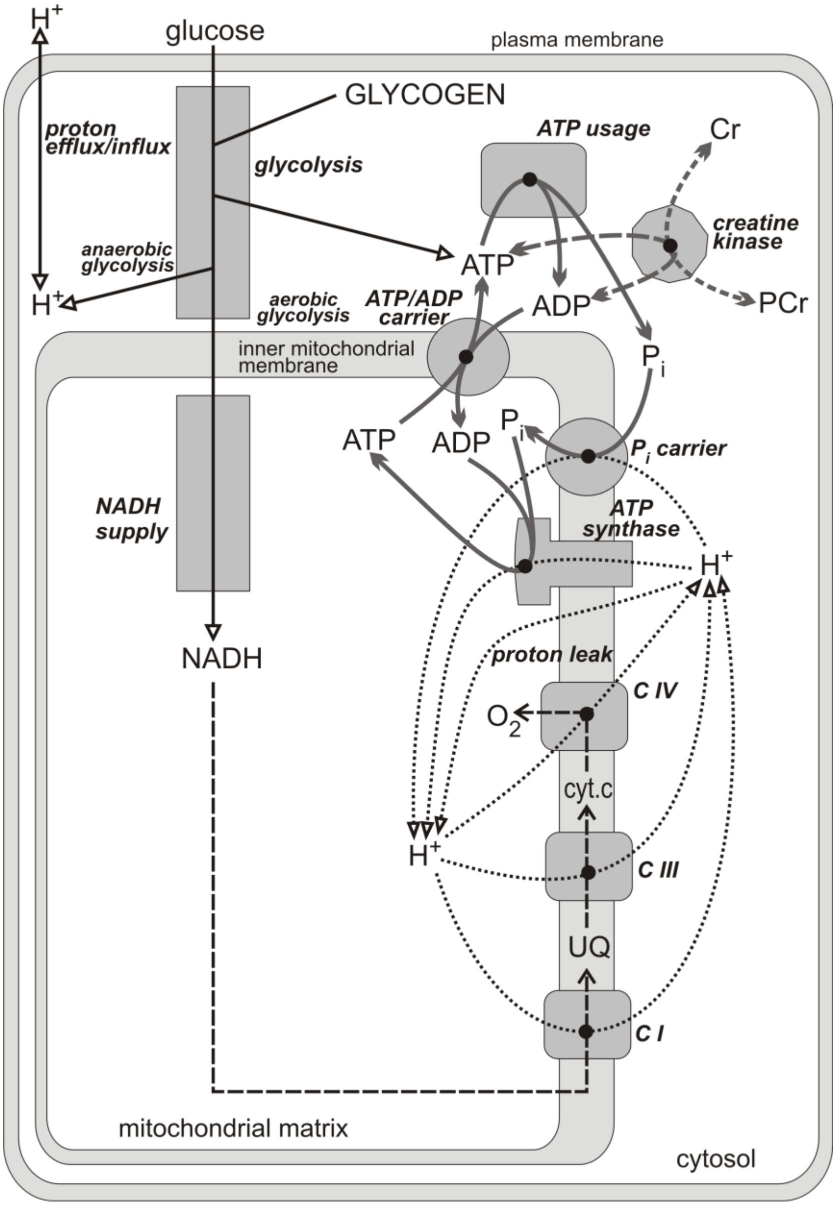
Kinetic description of the dynamic model of the heart cell bioenergetic system.



Subscripts: e, external (cytosolic); i, internal (mitochondrial); t, total; f, free; m, magnesium complex; j, monovalent.
All metabolite concentrations in μM. All rates/fluxes in μM min^{-1}.
DH, NADH supply; C1, complex I; C3, complex III; C4, complex IV; SN, ATP synthase; EX, ATP/ADP carrier; PI, P_i carrier; UT, ATP usage; LK, proton leak; CK, creatine kinase; AK, adenylate kinase; GL, glycolysis; EF, proton exfflux/influx to/from blood.

Constants

k_{DH}= 96293 μM min^{-1}
K_{mN} =100
p_D=0.8

k_{C1}= 819.61 μM mV^{-1} min^{-1}

k_{C3}= 467.90 μM mV^{-1} min^{-1}

k_{C4}= 12.348 μM^{-1} min^{-1}
K_{mO} =120 μM (mechanistic K_m for O_2, much higher than apparent K_m)

k_{SN}= 117706 μM min^{-1}
n_A = 2.5 (phenomenological H^+/ATP stoichiometry of ATP syntahse)

k_{EX}= 187185 μM min^{-1}
K_{mADP} =3.5 μM

k_{PI}= 238.11 μM^{-1} min^{-1}

k_{UT}= 13280 μM min^{-1} (low work) - 69000 μM min^{-1} (high work)
K_{mA}=150 μM

k_{LK1}= 8.575 μM min^{-1}
k_{LK2} = 0.038 mV^{-1}

k_{fAK}= 2957 μM^{-1} min^{-1}
k_{bAK}= 78.02 μM^{-1} min^{-1}

k_{fCK} = 6.0606 μM^{-2} min^{-1}
k_{bCK} = 0.0030 μM^{-1} min^{-1}

k_{EF} = 10000 μM min^{-1}
pH_0 = 7.0

k_{GL} = 32.19 min^{-1}
H^+_{rest} = 0.1 μM

k_{DTe} = 24 μM (magnesium dissociation constant for external ATP)
k_{DDe} = 347 μM (magnesium dissociation constant for external ADP)
k_{DTi} = 17 μM (magnesium dissociation constant for internal ATP)
k_{DDi} = 282 μM (magnesium dissociation constant for internal ADP)

R_{cm} = 4.35 (cell volume/mitochondria volume ratio)
B_N = 5 (buffering capacity coefficient for NAD)

T = 298
R = 0.0083 $kJ_{*}mol^{-1}{}_{*}K^{-1}$
F = 0.0965 $kJ_{*}mol^{-1}{}_{*}mV^{-1}$
S = $2.303_{*}R_{*}T$
Z = $2.303_{*}R_{*}T/F$

$u = 0.861$ (= $\Delta\Psi/\Delta p$)

$c_{buffi} = 0.022$ M H^+/pH unit (buffering capacity for H^+ in matrix)
$c_{buffe} = 0.025$ M H^+/pH unit (buffering capacity for H^+ in cytosol)

$pK_a = 6.8$

$\Delta G_{P0} = 31.9$ kJ $*$mol^{-1}

$E_{mN0} = -320$ mV
$E_{mU0} = 85$ mV
$E_{mc0} = 250$ mV
$E_{ma0} = 540$ mV

Constant metabolite concentrations

$O_2 = 240$ μM

$c_t = 270$ μM (= $c^{2+} + c^{3+}$, total concentration of cytochrome c)
$U_t = 1350$ μM (= $UQH_2 + UQ$, total concentration of ubiquinone)
$N_t = 2970$ μM (= NADH + NAD^+, total concentration of NAD)
$a_t = 135$ μM

$Mg_{fe} = 4000$ μM (free external magnesium concentration)
$Mg_{fi} = 380$ μM (free internal magnesium concentration)

$A_{iSUM} = 16260$ μM (= $ATP_{ti} + ADP_{ti}$, total internal adenine nucleotide concentration)
$A_{eSUM} = 6700$ μM (= $ATP_{te} + ADP_{te} + AMP_e$, total external adenine nucleotide concentration)
$C_{SUM} = 25000$ μM (= Cr + PCr, total creatine concentration)

Values of independent variables, respiration rate (v_{C4}) and AMP_e at <u>low work</u>

$v_{C4} = 2533$ μM min^{-1}
NADH = 828.41 μM
$UQH_2 = 1142.91$ μM
$c^{2+} = 60.850$ μM
$O_2 = 240.00$ μM
ATPti = 6965.3
$Pi_{ti} = 6902.7$ μM
$H_i = 0.037244$ μM
$ATP_{te} = 6668.25$ μM
$ADP_{te} = 31.574$ μM
($AMP_e = 0.4187$ μM)
$Pi_{te} = 2561.8$ μM
PCr = 12241.1 μM
$H_e = 0.1000$ μM

Calculations

$c^{3+} = c_t - c^{2+}$
$UQ = U_t - UQH_2$
$NAD^+ = N_t - NADH$

$Cr = C_{SUM} – PCr$

$AMP_e = A_{eSUM} - ATP_{te} - ADP_{te}$
$ADP_{ti} = A_{iSUM} - ATP_{ti}$

$ATP_{fe} = ATP_{te}/(1+Mg_{fe}/k_{DTe})$
$ATP_{me} = ATP_{te} - ATP_{fe}$
$ADP_{fe} = ADP_{te}/(1+Mg_{fe}/k_{DDe})$
$ADP_{me} = ADP_{te} - ADP_{fe}$

$ATP_{fi} = ATP_{ti}/(1+Mg_{fi}/k_{DTi})$
$ATP_{mi} = ATP_{ti} - ATP_{fi}$
$ADP_{fi} = ADP_{ti}/(1+Mg_{fi}/k_{DDi})$
$ADP_{mi} = ADP_{ti} - ADP_{fi}$

$pH_i = -\log(H_i/10^6)$ (H_i expressed in μM)
$pH_e = -\log(H_e/10^6)$ (H_e expressed in μM)
ΔpH (mV) $= Z\ (pH_i-pH_e)$
Δp (mV) $= 1/(1-u)\ \Delta pH$
$\Delta\Psi$ (mV) $= -\ (\Delta p - \Delta pH)$
Ψi (mV) $= 0.65*\Delta\Psi$
Ψe (mV) $= -\ 0.35*\Delta\Psi$

$c_{0i} = (10^{-pHi}-10^{-pHi-dpH})/dpH$ (‘natural’ buffering capacity for H^+ in matrix)
$dpH = 0.001$
$r_{buffi} = c_{buffi}/c_{0i}$ (buffering capacity coefficient for H^+ in matrix)

$c_{0e} = (10^{-pHe}-10^{-pHe-dpH})/dpH$ (‘natural’ buffering capacity for H^+ in cytosol)
$dpH = 0.001$
$r_{buffe} = c_{buffe}/c_{0e}$ (buffering capacity coefficient for H^+ in cytosol)

$Pi_{je} = Pi_{te}/(1+10^{pHe-pKa})$
$Pi_{ji} = Pi_{ti}/(1+10^{pHi-pKa})$

$\Delta G_{SN} = n_A*\Delta p - \Delta G_P$ (thermodynamic span of ATP synthase)
$\Delta G_P = \Delta G_{P0}/F + Z * \log(10^6*ATP_{ti}/(ADP_{ti}*Pi_{ti}))$ (concentrations expressed in μM)

$E_{mN} = E_{mN0}+Z/2 * \log(NAD^+/NADH)$ (NAD redox potential)
$E_{mU} = E_{mU0}+Z/2 * \log(UQ/UQH_2)$ (ubiquinone redox potential)
$E_{mc} = E_{mc0}+Z * \log(c^{3+}/c^{2+})$ (cytochrome c redox potential)
$E_{ma} = E_{mc}+\Delta p*(2 + 2u)/2$ (cytochrome a_3 redox potential)

$A_{3/2} = 10^{(Ema-Ema0)/Z}$ (a^{3+}/a^{2+} ratio)
$a^{2+} = a_t/(1 + A_{3/2})$ (concentration of reduced cytochrome a_3)

$\Delta G_{C1} = E_{mU}-E_{mN}-\Delta p*4/2$ (thermodynamic span of complex I)
$\Delta G_{C3} = E_{mc}-E_{mU}-\Delta p*(4-2u)/2$ (thermodynamic span of complex III)

$s = 0.7-(pH-6.0)*0.5$ (net stoichiometry of proton consumption/production by creatine kinase when coupled with ATP consumption/production, respectively; Lohman reaction)

Kinetic equations

Substrate dehydrogenation:

$$v_{DH} = k_{DH} \frac{1}{\left(1 + \frac{K_{mN}}{NAD^{+} / NADH}\right)^{p_D}}$$

Complex I:

$$v_{C1} = k_{C1} \cdot \Delta G_{C1}$$

Complex III:

$$v_{C3} = k_{C3} \cdot \Delta G_{C3}$$

Complex IV:

$$v_{C4} = k_{C4} \cdot a^{2+} \cdot c^{2+} \frac{1}{1 + \frac{K_{mO}}{O_2}}$$

ATP synthase:

$$v_{SN} = k_{SN} \frac{\gamma - 1}{\gamma + 1},$$

$$\gamma = 10^{\Delta G_{SN} / Z}$$

ATP/ADP carrier:

$$v_{EX} = k_{EX} \cdot \left(\frac{ADP_{fe}}{ADP_{fe} + ATP_{fe} \cdot 10^{-\Psi_e / Z}} - \frac{ADP_{fi}}{ADP_{fi} + ATP_{fi} \cdot 10^{-\Psi_i / Z}} \right) \cdot \left(\frac{1}{1 + K_{mADP} / ADP_{fe}} \right)$$

Phosphate carrier:

$$v_{PI} = k_{PI} \cdot \left(Pi_{je} \cdot H_e - Pi_{ji} \cdot H_i \right)$$

ATP usage:

$$v_{UT} = k_{UT} \frac{1}{1 + \frac{K_{mA}}{ATP_{te}}}$$

Proton leak:

$$v_{LK} = k_{LK1} \cdot \left(e^{k_{LK2} \cdot \Delta p} - 1 \right)$$

Adenylate kinase:

$$v_{AK} = k_{fAK} \cdot ADP_{fe} \cdot ADP_{me} - k_{bAK} \cdot ATP_{me} \cdot AMP_e$$

Creatine kinase:

$$v_{CK} = k_{fCK} \cdot ADP_{te} \cdot PCr \cdot H_e^{+} - k_{bCK} \cdot ATP_{te} \cdot Cr$$

Proton efflux:

$$v_{EF} = k_{EF} \cdot \left(pH_0 - pH_e \right)$$

Glycolysis:

$v_{GL} = k_{GL} \cdot \left(ADP_{te} + AMP_{e} \right)\left(H_{rest}^{+} / H^{+} \right)$ (anaerobic glycolysis present)

or

$v_{GL} = 0.2 \cdot v_{DH}$ (anaerobic glycolysis absent)

Set of differential equations

$$\overset{\bullet}{NADH} = \left(v_{DH} - v_{C1} \right) \cdot R_{cm} / B_{N}$$

$$\overset{\bullet}{UQH_{2}} = \left(v_{C1} - v_{C3} \right) \cdot R_{cm}$$

$$\overset{\bullet}{c^{2+}} = \left(v_{C3} - 2 \cdot v_{C4} \right) \cdot 2 \cdot R_{cm}$$

$\overset{\bullet}{O_{2}} = 0$ (constant saturated oxygen concentration = 240 μM) or $\overset{\bullet}{O_{2}} = -v_{C4}$

$$\overset{\bullet}{H_{i}^{+}} =$$
$$-\left(2 \cdot \left(2 + 2 \cdot u \right) \cdot v_{C4} + \left(4 - 2 \cdot u \right) \cdot v_{C3} + 4 \cdot v_{C1} - n_{A} \cdot v_{SN} - u \cdot v_{EX} - \left(1 - u \right) \cdot v_{PI} - v_{LK} \right) \cdot R_{cm} /$$
$$r_{buffi}$$

$$\overset{\bullet}{ATP_{ti}} = \left(v_{SN} - v_{EX} \right) \cdot R_{cm}$$

$$\overset{\bullet}{Pi_{ti}} = \left(v_{PI} - v_{SN} \right) \cdot R_{cm}$$

$$\overset{\bullet}{ATP_{te}} = \left(v_{EX} - v_{UT} + v_{AK} + v_{CK} + v_{GL} \right) \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

$$\overset{\bullet}{ADP_{te}} = \left(v_{UT} - v_{EX} - 2 \cdot v_{AK} - v_{CK} - v_{GL} \right) \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

$$\overset{\bullet}{Pi_{te}} = \left(v_{UT} - v_{PI} - v_{GL} \right) \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

$$\overset{\bullet}{PCr} = -v_{CK} \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

$$\overset{\bullet}{H_{e}^{+}} =$$
$$\left(\begin{array}{l} 2 \cdot \left(2 + 2 \cdot u \right) \cdot v_{C4} + \left(4 - 2 \cdot u \right) \cdot v_{C3} + 4 \cdot v_{C1} - n_{A} \cdot v_{SN} - u \cdot v_{EX} - \left(1 - u \right) \cdot v_{PI} - v_{LK} - \\ s \cdot v_{CK} - v_{EF} + v_{GL} - 0.2 \cdot v_{DH} \end{array} \right) /$$
$$r_{buffe} \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

Simulations of work transitions (low-to-high work transitions)

See:

Korzeniewski B, Noma A, Matsuoka S. Regulation of oxidative phosphorylation in intact mammalian heart in vivo. *Biophys Chem* 116: 145-157, 2005.

Korzeniewski B. Oxygen consumption and metabolite concentrations during transitions between different work intensities in heart. *Am J Physiol* 291: H1466-474, 2006.