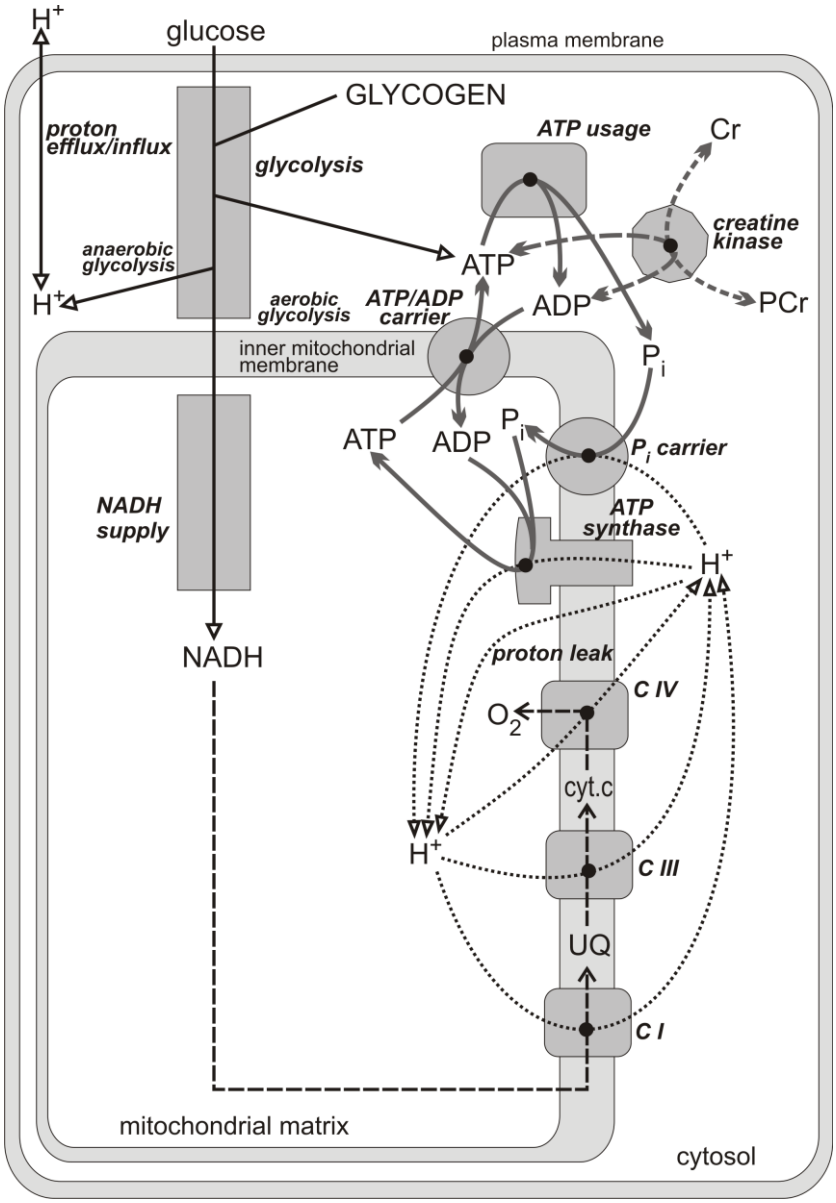
Kinetic description of the dynamic model of the skeletal muscle cell bioenergetic system.



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}= 28074 μM min^{-1}
K_{mN} =100
p_D=0.8

k_{C1}= 238.95 μM mV^{-1} min^{-1}

k_{C3}= 136.41 μM mV^{-1} min^{-1}

k_{C4}= 3.600 μM^{-1} min^{-1}
K_{mO} =120 μM (mechanistic K_m for O_2, much higher than apparent K_m)

k_{SN}= 34316 μM min^{-1}
n_A = 2.5 (phenomenological H^+/ATP stoichiometry of ATP syntahse)

k_{EX}= 54572 μM min^{-1}
K_{mADP} =3.5 μM

k_{PI}= 69.421 μM^{-1} min^{-1}

k_{UT}= 781.97 μM min^{-1} (resting state)
K_{mA}=150 μM

k_{LK1}= 2.500 μM min^{-1}
k_{LK2} = 0.038 mV^{-1}

k_{fAK}= 862.10 μM^{-1} min^{-1}
k_{bAK}= 22.747 μM^{-1} min^{-1}

k_{fCK} = 1.9258 μM^{-2} min^{-1}
k_{bCK} = 0.00087538 μM^{-1} min^{-1}

k_{EF} = 10000 μM min^{-1}
pH_0 = 7.0

k_{GL} = 17.4 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)

Rc_m = 15 (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

$O_2 = 30$ 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)
$C_{SUM} = 35000$ μM (= Cr + PCr, total creatine concentration)

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

$v_{C4} = 287$ μM min^{-1}
$NADH = 1669.5$ μM
$UQH_2 = 1145.3$ μM
$c^{2+} = 53.79$ μM
$O_2 = 240.00$ μM
$ATPti = 13580$
$Pi_{ti} = 15613$ μM
$H_i = 0.03536$ μM
$ATP_{te} = 6693.6$ μM
$ADP_{te} = 6.599$ μM
($AMP_e = 0.0182$) μM
$Pi_{te} = 2823.3$ μM
$PCr = 28761$ 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)
$\Delta pH\ (mV) = Z\ (pH_i - pH_e)$
$\Delta p\ (mV) = 1/(1-u)\ \Delta pH$
$\Delta\Psi\ (mV) = -\ (\Delta p - \Delta pH)$
$\Psi i\ (mV) = 0.65 * \Delta\Psi$
$\Psi e\ (mV) = -\ 0.35 * \Delta\Psi$

$c_{0i} = (10^{-pHi} - 10^{-pHi-dpH})/dpH$ ('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

$$\dot{NADH} = \left(v_{DH} - v_{C1} \right) \cdot R_{cm} / B_N$$

$$\dot{UQH}_2 = \left(v_{C1} - v_{C3} \right) \cdot R_{cm}$$

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

$\dot{O}_2 = 0$ (constant saturated oxygen concentration = 240 μM) or $\dot{O}_2 = -v_{C4}$

$$\dot{H}^+_i = -\left(2 \cdot \left(2 + 2 \cdot u \right) \cdot v_{C4} + \left(4 - 2 \cdot u \right) \cdot v_{C3} + 4 \cdot v_{C1} - n_A \cdot v_{SN} - u \cdot v_{EX} - \left(1 - u \right) \cdot v_{PI} - v_{LK} \right) \cdot R_{cm} / r_{buffi}$$

$$\dot{ATP}_{ti} = \left(v_{SN} - v_{EX} \right) \cdot R_{cm}$$

$$\dot{Pi}_{ti} = \left(v_{PI} - v_{SN} \right) \cdot R_{cm}$$

$$\dot{ATP}_{te} = \left(v_{EX} - v_{UT} + v_{AK} + v_{CK} + 1.5 \cdot v_{GL} \right) \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

$$\dot{ADP}_{te} = \left(v_{UT} - v_{EX} - 2 \cdot v_{AK} - v_{CK} - 1.5 \cdot v_{GL} \right) \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

$$\dot{Pi}_{te} = \left(v_{UT} - v_{PI} - 1.5 \cdot v_{GL} \right) \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

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

$$\dot{H}^+_e = \begin{pmatrix} 2 \cdot \left(2 + 2 \cdot u \right) \cdot v_{C4} + \left(4 - 2 \cdot u \right) \cdot v_{C3} + 4 \cdot v_{C1} - n_A \cdot v_{SN} - u \cdot v_{EX} - \left(1 - u \right) \cdot v_{PI} - v_{LK} - \\ s \cdot v_{CK} - v_{EF} + v_{GL} - 0.2 \cdot v_{DH} \end{pmatrix} / r_{buffe} \cdot R_{cm} / \left(R_{cm} - 1 \right)$$

Simulations of work transitions (rest-work-rest transitions)

See:

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