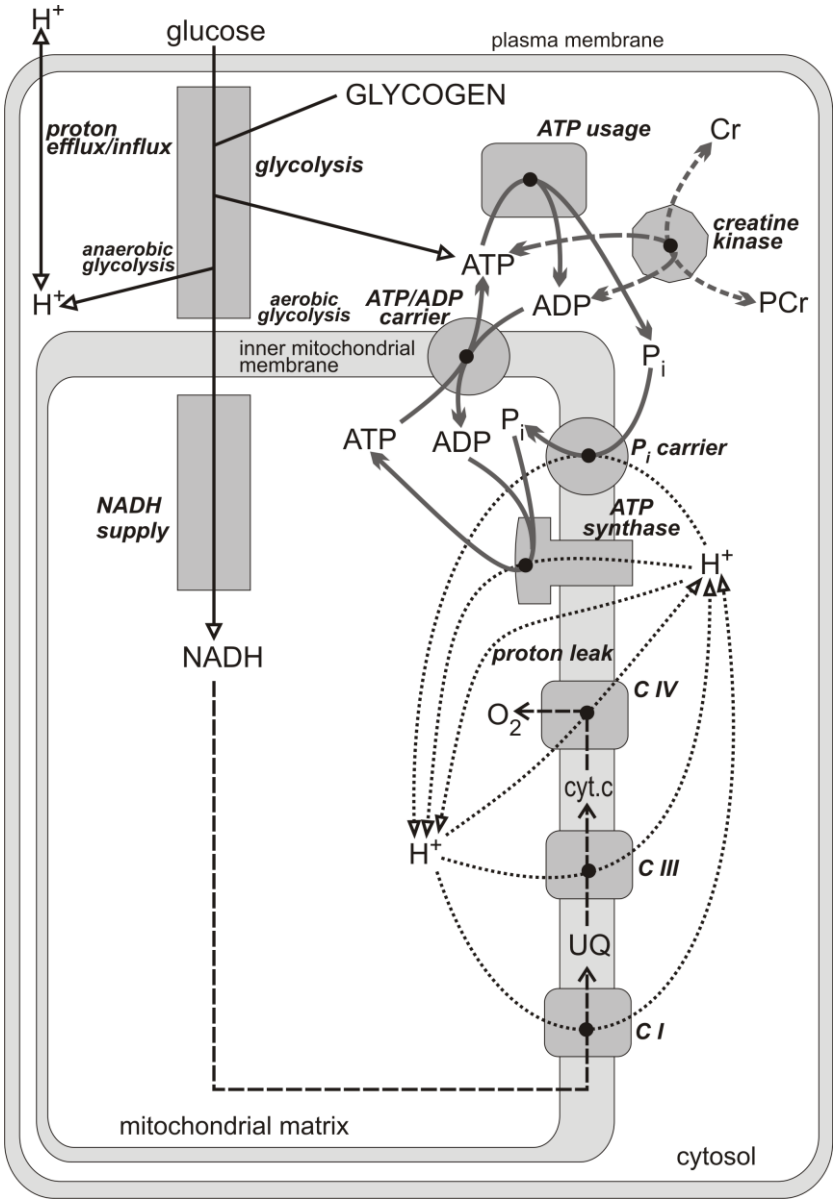
Kinetic description of the dynamic model of the skeletal muscle cell bioenergetic system.



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_{add} = 0.2 $mM^{-0.5}$
Pi_{crit} = 18 mM
t_a = 2 min
Pi_{peak} = 25 mM (termination of exercise)

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

$O_2 = 30\ \mu M$

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

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

$A_{iSUM} = 16260\ \mu M$ (= $ATP_{ti} + ADP_{ti}$, total internal adenine nucleotide concentration)
$A_{eSUM} = 6700\ \mu M$ (= $ATP_{te} + ADP_{te} + AMP_e$, total external adenine nucleotide concentration)
$C_{SUM} = 35000\ \mu M$ (= Cr + PCr, total creatine concentration)

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

$v_{C4} = 287\ \mu M\ min^{-1}$
$NADH = 1669.5\ \mu M$
$UQH_2 = 1145.3\ \mu M$
$c^{2+} = 53.79\ \mu M$
$O_2 = 240.00\ \mu M$
ATPti = 13580
$Pi_{ti} = 15613\ \mu M$
$H_i = 0.03536\ \mu M$
$ATP_{te} = 6693.6\ \mu M$
$ADP_{te} = 6.599\ \mu M$
$(AMP_e = 0.0182)\ \mu M$
$Pi_{te} = 2823.3\ \mu M$
$PCr = 28761\ \mu M$
$H_e = 0.1000\ \mu M$

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:

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

Additional ATP usage

$$v_{add} = k_{add} \cdot v_{UT} \cdot (P_i - P_{i_{crit}})^{0.5} \cdot e^{-t_a / t_{add}}$$

t_{add}, time after the onset of exercise

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 $\dot{O}_2 = -v_{C4}$

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

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

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

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

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

$$\dot{Pi}_{te} = (v_{UT} + v_{add} - v_{PI} - 1.5 \cdot v_{GL}) \cdot \frac{R_{cm}}{(R_{cm} - 1)}$$

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

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

Computer simulations

The above description is only the core of the standard model version. Particular simulations, frequently using modified parameter values, are described in detail in relevant articles. Some of them are enumerated below:

Korzeniewski B, Zoladz JA. Slow V'O_2 off-kinetics in skeletal muscle is associated with fast PCr off-kinetics – and inversely. *J Appl Physiol* 115: 605-612, 2013.

Korzeniewski B. Regulation of oxidative phosphorylation during work transitions results from its kinetic properties. *J Appl Physiol* 116: 83-94, 2014.

Korzeniewski B. Regulation of oxidative phosphorylation in different muscles and various experimental conditions. *Biochem J* 375: 799-804, 2003.

Korzeniewski B, Rossiter HB. Each-step activation of oxidative phosphorylation is necessary to explain muscle metabolic kinetic responses to exercise and recovery in humans. *J Physiol* 593: 5255-5268, 2015.

Korzeniewski B (2017) Regulation of oxidative phosphorylation through each-step activation: evidences from computer modeling. ***Prog Biophys Mol Biol*** 125, 1-23.

Korzeniewski B (2018) Regulation of oxidative phosphorylation is different in electrically- and cortically-stimulated skeletal muscle. ***PLoS One*** 13(4): e0195620..

Korzeniewski B (2018) Muscle VO_2-power output nonlinearity in constant-power, step-incremental, and ramp-incremental exercise: magnitude and underlying mechanisms. ***Phys Rep*** 6(21), e13915.

Korzeniewski B, Rossiter HB (2020) Exceeding a "critical" muscle P_i: implications for VO_2 and metabolite slow components, muscle fatigue and power-duration relationship. ***Eur J Appl Physiol*** 120, 1609-1619.

Korzeniewski B, Rossiter HB (2021) Factors determining training-induced changes in VO_{2max}, critical power and VO_2 on-kinetics in skeletal muscle. ***J Appl Physiol*** 130: 498-507.

Korzeniewski B (2021) Mechanisms of the effect of oxidative phosphorylation deficiencies on the skeletal muscle bioenergetic system in patients with mitochondrial myopathies. ***J Appl Physiol*** 131: 768-777.

Korzeniewski B, Rossiter HB (2022) Skeletal muscle biochemical origin of exercise intensity domains and their relation to whole-body VO_2 kinetics. ***Biosci Rep*** 42: BSR20220798.

Korzeniewski B (2023) Sensitivity of VO_{2max}, critical power and VO_2 on-kinetics in skeletal muscle. ***Resp Physiol Neurobiol*** 307: 103977.

Korzeniewski B (2023) VO_2 (non-)linear increase in ramp-incremental exercise vs. VO_2 slow component in constant-power exercise: Underlying mechanisms. ***Resp Physiol Neurobiol*** 311: 104023.