Kinetic description of the dynamic model of oxidative phosphorylation in isolated skeletal muscle mitochondria respiring on pyruvate.

Subscripts: e, external (suspension); i, internal (mitochondrial); t, total; f, free; m, magnesium complex; j, monovalent; a.u., arbitrary units.
Respiration rate (vC4) scaled to 100 a.u. in state 3. All metabolite concentrations in μM.
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; AK, adenylate kinase.

Constants

k_{DH} = 997.5 a.u.
K_{mN} =100
p_D=0.8

k_{C1} = 8.287 a.u.

k_{C3} = 4.731 a.u.

k_{C4} = 0.1215 a.u.
K_{mO} =120 μM (mechanistic K_m for O_2, much higher than apparent K_m)

k_{SN}= 1070 a.u.
n_A = 2.5 (phenomenological H^+/ATP stoichiometry of ATP syntahse)

k_{EX} = 2112 a.u.
K_{mADP} =3.5 μM

k_{PI} = 1.502 a.u.
pK_a = 6.8

k_{UT}= 0 a.u. (state 4), 275 a.u. (state 3.5, 50 % of state 3 respiration), 900 a.u. (state 3)
K_{mA}=150 μM

k_{LK1} = 0.1456 a.u.
k_{LK2} = 0.038 mV^{-1}

k_{fAK} = 139.2 a.u.
k_{bAK} = 3.673 a.u.

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_{sm} = 340 (suspension 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)

ΔG_{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

pH_e = 6.9

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} = 2000 μM (= $ATP_{te} + ADP_{te} + AMP_e$, total external adenine nucleotide concentration)

Initial values of independent variables (μM), respiration rate (v_{C4}, a.u.) and AMP_e (μM)

State:	State 4 (k_{UT} = 0)	State 3.5 (k_{UT} = 275)	State 3 (k_{UT} = 900)
v_{C4} (= vO_2)	10.48	50.02	99.86
NADH	1643.7	425.4	180.4
UQH_2	1150.1	1160.3	1194.4
c^{2+}	54.913	63.137	58.152
H^+_i	0.0446	0.0492	0.0529
ATP_{ti}	15410	8662	1890
Pi_{ti}	56501	33460	27901
ATP_{te}	1999.868	1977.605	238.605
Pi_{te}	9939	10050	13239
ADP_{te}	0.132	21.726	347.130
AMP_e	0.0000244	0.668	1414.3

Calculations

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

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

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

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

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

$pH_i = -\log(H_i/10^6)$ (H_i expressed in μM)
ΔpH (mV) = Z (pH_i-pH_e)
Δp (mV) = 1/(1-u) ΔpH
$\Delta\Psi$ (mV) = - (Δp - ΔpH)
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)

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

$\Delta G_{SN} = n_A * \Delta p - \Delta G_P$ (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)

Kinetic equations
(All reaction rates are expressed in a.u.).

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:

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

Set of differential equations

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

$$\dot{UQH_2} = \left(v_{C1} - v_{C3} \right) \cdot R_{sm}$$

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

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

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

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

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

$$\dot{ATP}_{te} = v_{EX} - v_{UT} + v_{AK}$$

$$\dot{ADP}_{te} = v_{UT} - v_{EX} - 2 \cdot v_{AK}$$

$$\dot{Pi}_{te} = v_{UT} - v_{PI}$$
