

Concise complete kinetic description of the dynamic model of oxidative phosphorylation in intact skeletal muscle. Subscripts: e, external (cytosolic); i, internal (mitochondrial); t, total; f, free; m, magnesium complex; j, monovalent.

KINETIC EQUATIONS

(All reaction rates are expressed in $\mu\text{M min}^{-1}$).

Substrate dehydrogenation:

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

$$k_{DH} = 28074 \mu\text{M min}^{-1}, K_{mN} = 100, p_D = 0.8$$

Complex I:

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

$$k_{C1} = 238.95 \mu\text{M mV}^{-1} \text{ min}^{-1}$$

Complex III:

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

$$k_{C3} = 136.41 \mu\text{M mV}^{-1} \text{ min}^{-1}$$

Complex IV:

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

$$k_{C4} = 3.600 \mu\text{M}^{-1} \text{ min}^{-1}, K_{mO} = 120 \mu\text{M} \text{ (apparent } K_{mO} = 0.8 \mu\text{M)}$$

ATP synthase:

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

$$k_{SN} = 34316 \mu\text{M min}^{-1}, \gamma = 10^{\Delta G_{SN}/Z}$$

ATP/ADP carrier:

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

$$k_{EX} = 54572 \mu\text{M min}^{-1}, K_{mADP} = 3.5 \mu\text{M}$$

Phosphate carrier:

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

$$k_{PI} = 69.421 \mu\text{M}^{-1} \text{min}^{-1}$$

ATP usage:

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

$$k_{UT} = 686.50 \mu\text{M min}^{-1} \text{ (resting state)}, K_{mA} = 150 \mu\text{M}$$

Proton leak:

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

$$k_{LK1} = 2.500 \mu\text{M min}^{-1}, k_{LK2} = 0.038 \text{ mV}^{-1}$$

Adenylate kinase:

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

$$k_{fAK} = 862.10 \mu\text{M}^{-1} \text{min}^{-1}, k_{bAK} = 22.747 \mu\text{M}^{-1} \text{min}^{-1}$$

Creatine kinase:

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

$$k_{fCK} = 1.9258 \mu\text{M}^{-2} \text{min}^{-1}, k_{bCK} = 0.00087538 \mu\text{M}^{-1} \text{min}^{-1}$$

Proton efflux:

$$v_{EFF} = k_{EFF} \cdot (pH_0 - pH_e)$$

$$k_{EFF} = 10000 \mu\text{M min}^{-1}, pH_0 = 7.0$$

SET OF DIFFERENTIAL EQUATIONS

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

$$U\dot{Q}H_2 = (v_{C1} - v_{C3}) \cdot R_{cm}$$

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

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

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

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

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

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

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

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

$$\dot{PCr} = -v_{CK}$$

$$\dot{H}_e^+ = \frac{\left(2 \cdot (2 + 2 \cdot u) \cdot v_{C4} + (4 - 2 \cdot u) \cdot v_{C3} + 4 \cdot v_{C1} - n_A \cdot v_{SN} - u \cdot v_{EX} - (1 - u) \cdot v_{PI} - v_{LK} - \left(v_{CK} - v_{EFF}\right)\right)}{r_{buffe}}$$

$R_{cm} = 15$ (cell volume/mitochondria volume ratio)

$B_N = 5$ (buffering capacity coefficient for NAD)

CALCULATIONS

$$c^{3+} = c_t - c^{2+}$$

$$c_t = 270 \mu\text{M} \quad (= c^{2+} + c^{3+}, \text{ total concentration of cytochrome c})$$

$$UQ = U_t - UQH_2$$

$$U_t = 1350 \mu\text{M} \quad (= UQH_2 + UQ, \text{ total concentration of ubiquinone})$$

$$NAD^+ = N_t - NADH$$

$$N_t = 2970 \mu\text{M} \quad (= NADH + NAD^+, \text{ total concentration of NAD})$$

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

$$A_{eSUM} = 6700.2 \mu\text{M} \quad (= ATP_{te} + ADP_{te} + AMP_e, \text{ total external adenine nucleotide concentration})$$

$$ADP_{ti} = A_{iSUM} - ATP_{ti}$$

$$A_{iSUM} = 16260 \mu\text{M} \quad (= ATP_{ti} + ADP_{ti}, \text{ total internal adenine nucleotide concentration})$$

$$Cr = C_{SUM} - PCr$$

$$C_{SUM} = 35000 \mu\text{M} \quad (= Cr + PCr, \text{ total creatine concentration})$$

$$P_{SUM} = 55659 \mu\text{M} \quad (= PCr + 3ATP_{te} + 2ADP_{te} + AMP_e + Pi_{te} + (3ATP_{ti} + 2ADP_{ti} + Pi_{ti})/R_{cm}, \text{ total phosphate pool})$$

$$Mg_{fe} = 4000 \mu\text{M} \quad (\text{free external magnesium concentration})$$

$$ATP_{fe} = ATP_{te}/(1 + Mg_{fe}/k_{DTe})$$

$$k_{DTe} = 24 \mu\text{M} \quad (\text{magnesium dissociation constant for external ADP})$$

$$ATP_{me} = ATP_{te} - ATP_{fe}$$

$$ADP_{fe} = ADP_{te}/(1 + Mg_{fe}/k_{DDe})$$

$$k_{DDe} = 347 \mu\text{M} \quad (\text{magnesium dissociation constant for external ATP})$$

$$ADP_{me} = ADP_{te} - ADP_{fe}$$

$$Mg_{fi} = 380 \mu\text{M} \quad (\text{free internal magnesium concentration})$$

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

$$k_{DTi} = 17 \mu\text{M} \quad (\text{magnesium dissociation constant for internal ATP})$$

$$\text{ATP}_{mi} = \text{ATP}_{ti} - \text{ATP}_{fi}$$

$$\text{ADP}_{fi} = \text{ADP}_{ti} / (1 + \text{Mg}_{fi} / k_{DDi})$$

$$k_{DDi} = 282 \mu\text{M} \quad (\text{magnesium dissociation constant for internal ADP})$$

$$\text{ADP}_{mi} = \text{ADP}_{ti} - \text{ADP}_{fi}$$

$$T = 298$$

$$R = 0.0083 \text{ kJ} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$$

$$F = 0.0965 \text{ kJ} \cdot \text{mol}^{-1} \cdot \text{mV}^{-1}$$

$$S = 2.303 \cdot R \cdot T$$

$$Z = 2.303 \cdot R \cdot T / F$$

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

$$\text{pH}_e = -\log(H_e / 1000000) \quad (H_e \text{ expressed in } \mu\text{M})$$

$$\text{pH}_i = -\log(H_i / 1000000) \quad (H_i \text{ expressed in } \mu\text{M})$$

$$\Delta\text{pH} = Z (\text{pH}_i - \text{pH}_e)$$

$$\Delta p = 1 / (1 - u) \Delta\text{pH}$$

$$\Delta\Psi = - (\Delta p - \Delta\text{pH})$$

$$\Psi_i = 0.65 \cdot \Delta\Psi$$

$$\Psi_e = - 0.35 \cdot \Delta\Psi$$

$$c_{0i} = (10^{-\text{pH}_i} - 10^{-\text{pH}_i - \Delta\text{pH}}) / \Delta\text{pH} \quad (\text{'natural' buffering capacity for } H^+ \text{ in matrix})$$

$$\Delta\text{pH} = 0.001$$

$$\Gamma_{\text{buffi}} = c_{\text{buffi}} / c_{0i} \quad (\text{buffering capacity coefficient for } H^+ \text{ in matrix})$$

$$c_{\text{buffi}} = 0.022 \text{ M } H^+ / \text{pH unit} \quad (\text{buffering capacity for } H^+ \text{ in matrix})$$

$$c_{0e} = (10^{-\text{pH}_e} - 10^{-\text{pH}_e - \Delta\text{pH}}) / \Delta\text{pH} \quad (\text{'natural' buffering capacity for } H^+ \text{ in cytosol})$$

$$\Delta\text{pH} = 0.001$$

$$\Gamma_{\text{buffe}} = c_{\text{buffe}} / c_{0e} \quad (\text{buffering capacity coefficient for } H^+ \text{ in cytosol})$$

$$c_{\text{buffe}} = 0.025 \text{ M } H^+ / \text{pH unit} \quad (\text{buffering capacity for } H^+ \text{ in cytosol})$$

$$P_{i_e} = P_{i_t} / (1 + 10^{\text{pHe} - \text{pKa}})$$

$$P_{i_j} = P_{i_t} / (1 + 10^{\text{pHi} - \text{pKa}})$$

$$\text{pKa} = 6.8$$

$$\Delta G_{\text{SN}} = n_A \cdot \Delta p - \Delta G_P \quad (\text{thermodynamic span of ATP synthase})$$

$$\Delta G_P = \Delta G_{P0} / F + Z \cdot \log(1000000 \cdot \text{ATP}_t / (\text{ADP}_t \cdot \text{Pi}_t)) \quad (\text{concentrations expressed in } \mu\text{M})$$

$$n_A = 2.5 \quad (\text{phenomenological } \text{H}^+/\text{ATP} \text{ stoichiometry of ATP synthase})$$

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

$$E_{\text{mN}} = E_{\text{mN0}} + Z/2 \cdot \log(\text{NAD}^+/\text{NADH}) \quad (\text{NAD redox potential})$$

$$E_{\text{mN0}} = -320 \text{ mV}$$

$$E_{\text{mU}} = E_{\text{mU0}} + Z/2 \cdot \log(\text{UQ}/\text{UQH}_2) \quad (\text{ubiquinone redox potential})$$

$$E_{\text{mU0}} = 85 \text{ mV}$$

$$E_{\text{mc}} = E_{\text{mc0}} + Z \cdot \log(c^{3+}/c^{2+}) \quad (\text{cytochrome c redox potential})$$

$$E_{\text{mc0}} = 250 \text{ mV}$$

$$E_{\text{ma}} = E_{\text{mc}} + \Delta p \cdot (2 + 2u)/2 \quad (\text{cytochrome } a_3 \text{ redox potential})$$

$$A_{3/2} = 10^{(E_{\text{ma}} - E_{\text{ma0}})/Z} \quad (a^{3+}/a^{2+} \text{ ratio})$$

$$a^{2+} = a_t / (1 + A_{3/2}) \quad (\text{concentration of reduced cytochrome } a_3)$$

$$a^{3+} = a_t - a^{2+}$$

$$a_t = 135 \mu\text{M}$$

$$E_{\text{ma0}} = 540 \text{ mV}$$

$$\Delta G_{\text{C1}} = E_{\text{mU}} - E_{\text{mN}} - \Delta p \cdot 4/2 \quad (\text{thermodynamic span of complex I})$$

$$\Delta G_{\text{C3}} = E_{\text{mc}} - E_{\text{mU}} - \Delta p \cdot (4 - 2u)/2 \quad (\text{thermodynamic span of complex III})$$
