Dear Erich,

these are my comments to the manuscript version 44. Comments are under the screenshot.

B. Ahn, M.G. Alves, D.A. Beard, D. Ben-Shachar, D. Bishop, S. Breton, G.C. Brown, R.A. Brown, G.R. Buettner, A. Bumsoo, Z. Cervincova, A.J. Chicco, P.M. Coen, J.L. Collins, L.

Z. Cervinkova

Page 1: wrong spelling

powerhouses of the cell contain the coenzyme ubiquinone and cytochrome *b*, *c*, aa_3 redox systems, ~~and~~ ATP synthase or alternative oxidases, ion transporters including proton pumps, mi-

Page 6: delete and

1. Introduction

Every study of mitochondrial function and disease is faced with **E**volution, **A**ge, **G**ender ~~and sex~~, **L**ifestyle, and **E**nvironment (EAGLE) as essential background conditions characteriz-

Page 4: delete and sex

dria are largely maintained. The plasma membrane separates the cytosol, nucleus and organelles (the intracellular compartment) from the environment ~~of the cell~~. The plasma membrane con-

Page 9: delete of the cell.

Reprogramming [of] mitochondrial pathways may be considered as a switch of gears (stoichiometry) rather than uncoupling (loosening the stoichiometry).

Page 11: add of

Until page 25 – all definitions are clear, the manuscript is readable and understandable.

The understandability is difficult from page 26, the real problem to understand starts for me on page 28. The Table 5 and explanations in Table 5 legend are confusing.

Table 5. Power, exergy, force, flow, and advancement.

Expression	Symbol	Definition	Unit	Notes
Power	P_{tr}	$P_{tr} = I_{tr} \cdot F_{tr} = \partial_{tr}G \cdot \partial t$	$W = J \cdot s^{-1}$	Eq. 4
Force, isomorphic	F_{tr}	$F_{tr} = \partial G \cdot \partial_{tr}\xi^{-1}$ [tr]	$J \cdot X^{-1}$	Eq. 5

Eq. 5: $\partial_{tr}G$ [J] is the partial Gibbs energy change (exergy) in the advancement of transformation tr.

Page 28: add consistency to table Eq. 5 and explanation Eq. 5 (tr)

~~Number~~ concentration, C_{NX}: The experimental *number concentration* of sample in the case of cells or animals, *e.g.*, nematodes is $C_{NX}=N_X/V$ [X·L^{-1}], where N_X is the number of cells or organisms in the chamber (**Table 6**).

Flow per sample entity, $I_{X,O2}$: A special case of normalization is encountered in respiratory studies with permeabilized (or intact) cells. If respiration is expressed per cell, the O_2 flow per measurement system is replaced by the O_2 flow per cell, $I_{cell,O2}$ (**Table 6**). O_2 flow can be calculated from volume-specific O_2 flux, $J_{V,O2}$ [nmol·s^{-1}·L^{-1}] (per V of the measurement chamber [L]), divided by the ~~number~~ concentration of cells, $C_{Nce}=N_{ce}/V$ [cell·L^{-1}], where N_{ce} is the

Page 38: The term number concentration is very strange. Cell number concentration is more understandable. But anyway - it is just concentration of cells in the chamber.

Expression of respiration in amol.s^{-1}.cell^{-1} looks fine for me.