Dear Dr. Gnaiger,

I read the manuscript with great interest. Since there is no option of using the Track Changes function I decided to list my comments in this file in the order of their flow in the text.

1. Contents – I have a minor suggestion regarding Sections 2 and 3. Each paragraph of these Sections talks about respiratory states and rates. However, Section 2 mainly introduces definitions and description of the states (OxPhos, Leak, etc), while Section 3 explains the functional cooperation and interdependency of the states. Wouldn't you think reasonable to slightly reformulate the Section 3 title to highlight the mutuality of respiratory states and rates?

2. Page 6 – This page provides a sum of unique features of mitochondria as a cellular organelle. I would add to the list of characteristics exclusive to mitochondria the presence of cardiolipin in the mitochondria membrane, which is directly connected to the mitochondria respirometric activity [*Paradies, G., et al., Functional role of cardiolipin in mitochondrial bioenergetics. Biochim Biophys Acta, 2014. 1837(4): p. 408-17*].

   "Mitochondria membrane contains cardiolipin, which is not present in any other cellular membranes. This non-bilayer phospholipid promotes assembling of respiratory proteins in high order supercomplexes to ensure maximal efficacy of energetic processes"

3. Page 19 – For the States 2 and 3 designating 100-300μM ADP, which induces transient stimulation of respiration only, a High Concentration ("High ADP") would sound confusing for inexperienced researchers. (In our experimental settings, this range is even smaller (10-70μM) for mitochondria preparations from some types of cultured cells. While this information is out of scope of the manuscript, I would like to share that we noticed that mitochondria isolated from cells grown as monolayer population acquire more reticulated mitochondria and upon isolation behave differently than those from tissues). Yet, later in the manuscript the readers learn about saturating concentrations of ADP (1-5mM), which are really high. Would it be reasonable to replace "High ADP" with something like "Activating ADP" to avoid "higher than high" phrases?

4. Page 32 – The Figure 7 in a very presentable way distinguishes terms Flow and Flux. These two terms are intensively used throughout the text. Although, their difference looks obvious, I would first introduce the simplistic definition of Flow (movement) and Flux (rate of flow) in one sentence in the beginning of Section 3 to prepare inexperienced readers to sophisticated expressions of these terms in following paragraphs.

5. Page 37 – I found the schematic a bit complicated at first glance, especially for those who are just entering the field of cellular physiology. However, the explanation in the text compensates. The effort to provide a definition to each and every component and condition for generalization purposes is encouraging.

6. Page 39 – The manuscript is supplied with many experimental values of sample amounts, rates, etc, which are invaluable as a starting point for those who are just entering the field. Table 8, for example, provides cell density (10^6 cells/ml) typically used and justified herein. The muscle samples 1.5 - 3mg were mentioned in Mass-Specific Flux paragraph. It would be helpful to indicate the typically used amount of mitochondria (0.1 mg/ml) either in Table 8 or in Sample Concentration paragraph, although it could vary depending on tissue type and experimental conditions.

   Some of my thoughts regarding the mitochondria structural organization I did not mention here. Many functional aspects are explainable from the point of the integral proteins and membrane architecture. I was not sure if this is necessary here, because from the point of terminological concept this manuscript is well focused and elaborated.

   Sincerely,
   Zulfiya