Overall comments_Donal O'Gorman

The intro is very nice but the section on Control and regulation/response are too complicated and require simplification. These are amongst the first sections readers come across in a long article. They do not need discouragement at such an early stage. The following sections on control states are much easier to follow and understand.

Line 246: I don't think the quote helps with the overall meaning and would suggest removing
Line 284: We should consider the amount of fuel available separately from the composition (ie substrates) and differentiate between 'oxygen availability' and 'oxygen supply' (eg. perfusion). Also to consider in this section is the efficiency of signalling pathways (eg insulin resistance will lead to decreased glucose uptake).
Line 302-304: This sentence is confusing – the term 'metabolic system or module' needs to be better defined. I would suggest using just one term 'metabolic system', but provide a definition as well as an example as this term will have a different meaning for a cell biologist and a physiologist. A different example for 'metabolic system' is provided in line 304 and this seems like a better example than 'ATP synthase in line 302 – no need to repeat though.

Respiratory control and response: ~~There is a difference between control by a fixed component of a metabolic system or module, e.g. ATP synthase, and the response to an experimental variable, *e.g.*, fuel substrate or ADP.~~ Whilst lack of control by a metabolic ~~module~~system~~,~~ (*e.g.* phosphorylation system)~~,~~ does mean that there will be no response to a variable activating it~~,~~ (*e.g.* [ADP]). However, the reverse is not true as the ~~; *i.e.*, lack~~absence of a response to [ADP] does not exclude the phosphorylation system from having some degree of control. The degree of control of a component of the OXPHOS system on an output variable of the system, such as oxygen flux, will in general be different from the degree of control on other outputs, such as phosphorylation flux or ~~, cytochrome redox states, protonmotive force, phosphorylation potential, and~~ proton leak flux (**Box 2**). As such, it is necessary to be specific as to which output is under consideration. Respiratory control is insufficiently specific in the context of specific interpretations (Fell 1997).

Kommentiert [DOG1]: Starting the section talking about a component of a system following by regulation of the system, then going back to a component of a system is confusing. I have suggested some editing but feel free to change

Kommentiert [DOG2]: Don't need all the examples as they are in Box 2

Kommentiert [DOG3]: This does not make sense

Respiratory coupling Control
Line 321-323: Start the section with this sentence – much better to get a definition first.

Coupling Control States
Really liked this section –easy to follow.

Phosphoylation and LEAK sections
Really enjoyed reading those

Coupling states and respiratory rates
Line 613: Suggest using just 'metabolic systems', as per previous comment.

Section 2.3 is Coupling States and Respiratory Rates and Section 3 is States and Rates – this could also lead to confusion.

Line 857: Should it be ‘energy’??

Section 4.1: Flux Chamber Volume
The section should start with a simple description outlining the current challenges and why it should be normalised.

Section 4.2 Extensive quantities and size specific normalisation
This heading is not clear – especially ‘extensive quantities’. I still didn’t fully understand when I read the explanatory text
Also challenging to fully understand normalisation of the ‘Flow per system’.

Section 4.4: Conversion: oxygen, proton and ATP flux
A simplified introduction would help the reader here. The average reader will struggle with all the equations without context.