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Peer Review

Review of: "Mechanisms of Glycolysis and Fermentation: A Non-Equilibrium Thermodynamics Perspective"

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The manuscript from Roosterman and Cottrell discussed glucose and lactic acid metabolism in the context of thermodynamics. The overall aim of this paper is to clarify the basic chemical and physical properties of glucose and lactic acid metabolism. I admire the authors' effort to carefully compare classical literature, such as Meyerhof's work in 1951, to current textbooks. The authors are scrutinizing mass and charge balances in biochemistry textbooks. Such an endeavor is absolutely necessary to make sure we understand and teach biochemistry in the correct way. Despite the good intentions of the authors, the description of their theory is far from being clear. There are flaws, some fatal in my humble opinion, hampering the goal of making glucose metabolism more scientifically accurate. I would like to list the following points to invite discussion from the authors and the readers.

1. I don't see how protons (H^+) can be considered as energy particles. This is a key concept the authors mentioned throughout the paper. For example, on Page 3 (of the PDF version), the first line, the authors claimed that "H^+ is the energy particle freed during burning (NADH-H^+)". It is noteworthy that the actual "energy particle" is not H^+ but is H^-, hydride, which is stored in NADH. The authors should understand that when NADH is converted to NAD^+, this is a reduction reaction. The electrons are donated by NADH to the substrate. H^+ has no electrons to donate. Therefore, a proton cannot reduce anything. It is not an energy particle by any means.
2. I think it is important to clarify that despite the fact that ATP synthase is powered by the proton gradient, the proton itself is not an energy particle. An analogy would be that a sugar cube can fall from the 8^{th} floor to the ground and release its gravitational potential energy. This form of

 doi.org/10.32388/ADW3T9

energy is different from the form of energy that can be extracted from the same sugar cube by combustion. A proton stores no biochemical energy; a proton gradient does.

3. The authors challenge the common idea that the demarcation between glycolysis and the tricarboxylic acid cycle is pyruvate. They propose lactic acid as the demarcation. I think pyruvate is a reasonable point separating glycolysis and the TCA cycle. This is because glycolysis happens in the cytoplasm and the TCA cycle happens in the mitochondria. Pyruvate is transported into the mitochondria through the mitochondrial pyruvate carrier (MPC). MPCs are important in all eukaryotes, from *Saccharomyces cerevisiae* to mammals. The Cori cycle describes the fact that glucose can be metabolized into lactic acid, which can circulate back to make glucose again through hepatic gluconeogenesis. Although lactic acid plays an important role as a circulating metabolite, pyruvate is a more reasonable demarcation between glycolysis and the TCA cycle in the context of carbon catabolism.
4. The first sentence of the abstract is catchy. However, the abstract is not clear in the message of what is wrong with the common understanding of biochemistry.
5. The introduction section is too metaphorical. The introduction talks about Maxwell's demon, then zombies. I don't know what zombies are supposed to mean, and I don't see the connection to biochemistry. It also talks about Phlogiston, an obsolete scientific term. I don't see how the introduction makes the central question more clear.
6. Page 10: "The difference between citric acid and citrate, pyruvate and lactic acid, as well as gold and lead, are three protons". I get that the authors are trying to say that protons are important in the sense of balancing mass and charge. However, their analogy is a bad one. Protons bind to carboxylic acid under low pH. This is a chemical equilibrium. The nuclei of Au and Pb are different not only in three protons but also in 5-7 neutrons. The nuclear reactions are fundamentally different from biochemical reactions.

In summary, I think the authors would benefit from a better definition of the question and refraining from too much metaphor to make the manuscript more accessible to average readers.

Declarations

Potential competing interests: No potential competing interests to declare.