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Peer Review

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

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The manuscript "Non-Equilibrium Thermodynamics-based Concept of the Pathways Glycolysis and Fermentation" by Roosterman and Cottrell considers various aspects of glycolysis from a non-equilibrium thermodynamic perspective.

General comment: While this article is presented as a review of the subject, it is really a hypothesis paper as it does not review the field, but rather presents alternative views. In general, the article is interesting, but it is not easy to follow the discussion. It would improve the organization if the authors first presented a concise synopsis of the current thinking and then presented their alternative views and contrasted them clearly.

Specific comments:

Abstract;

1. "Every single chemical formula of modern models of glycolysis violates two laws of nature."

It would be very helpful if these violations could be briefly listed in parentheses so that readers understand where the discussion is going.

2. "Recently, the well-established models of metabolism have collapsed by re-introducing hydrogen as the energy entity driving biological processes."

Some readers may be confused by this because the proton-motive force is obviously driven by hydrogen ions, and therefore classical mitochondrial metabolism involves hydrogen driving biological processes. You need to be clear here to avoid confusion. See the general comment above; state the current view and then contrast that with the author's alternate view.

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3. “Maxwell’s observation of the dissipation of energy in nature guided Thomson to the formulation of the thermodynamic demon hypothesis in 1879[2].”

To make the point clear to readers, the authors should mention the original context in which Maxwell envisioned the "demon". This was in the context of gas laws and how you could get a non-equilibrium situation if a demon controlled a trap door between two compartments of gas. If the demon only opened the trap door when a highly energetic molecule approached, then a non-equilibrium could be created. The point, as it relates to biology, is that selective energy dissipation would result in a non-equilibrium condition with reduced entropy in one compartment.

4. On page 2, glucose is mis-spelled as glycose in one place, and phlogiston is mis-spelled as phlogistron in several places.

5. Page 3: “Enzymes catalysing the burning of glucose are organized in complexes or metabolons[7][8].”

Additional references would be helpful here, for example:

Wu, Fei; Minteer, Shelley (2 February 2015). "Krebs Cycle Metabolon: Structural Evidence of Substrate Channeling Revealed by Cross-Linking and Mass Spectrometry". Angewandte Chemie International Edition. 54 (6): 1851–1854. doi:10.1002/anie.201409336. PMID 25537779.

6. Figure 1: It would be helpful if the proteins in the various figures were labeled.

7. Page 5: “Direct or water-free transfer of an intermediate within an enzyme complex is mathematically one molecule in zero Litre of water. 1 molecule of acid divided by 0 L of water is an infinite molarity.”

Once bound to an enzyme, a substrate is no longer a solute as it is not dissolved in water. This makes the concept of molarity inappropriate (rather than infinite). What is the molarity of iron atoms if a block of iron is submerged in water?

8. Page 6, Figure 3: Please include the contribution of water to the generation of HCO_3 in this figure.

9. Page 11: “The aims of this review are to (i) determine the glycolytic reactions generating the energy particle proton (H^+), (ii) trace the flow of protons driving the reduction of pyruvate to generate a lactate flow non-equilibrium...”

The authors appear to be focusing on the protons generated during glycolysis that are not carried by NADH. The authors need to be clear which specific protons they are discussing; the free protons generated, or those bound in NADH.

10. Page 12: "Glycolysis produces 2 H+ twice for storage as two sets of 2 ATP."

Each time, one proton is carried as NADH, and the other is released as a free proton. This should be made clear, and you should be clear that you are referring to the free protons so that readers can follow your logic.

11. Pages 14, 16, and 20, Pathways 1, 2, and 3: Please designate the proteins in these figures.

12. Page 17: "Thus, we suggest that obligate aerobe cells can regulate the switch to (aerobe) fermentation at a high ATP/ADP ratio to **pronounce** biosynthesis and proliferation."

By "pronounce," do you mean facilitate or increase?

13. Page 24, Figure 6: The figure legend should describe the proton flow in more detail.

14. A concise and brief summary paragraph at the end of the discussion would be very helpful.

Declarations

Potential competing interests: No potential competing interests to declare.