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Peer Review

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

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This review presents an ambitious and highly unconventional reinterpretation of glycolysis and fermentation through a non-equilibrium thermodynamics framework, proposing proton (H^+) flow as the central “energy entity” and challenging the stoichiometric and conceptual foundations of modern biochemical models; its strengths lie in its originality, deep engagement with historical literature (e.g., Meyerhof, Krebs, Cori), and its attempt to unify metabolism, signaling, and systems biology under a coherent energetic narrative centered on lactate flow non-equilibrium. However, the manuscript is polemical in tone, frequently asserting that current biochemical models “violate laws of nature” without rigorously demonstrating specific quantitative inconsistencies, and it often conflates established thermodynamic principles with speculative extensions such as a “4th law of thermodynamics,” which lacks broad scientific consensus. The arguments would be strengthened by clearly distinguishing hypothesis from established fact, providing explicit stoichiometric recalculations with stepwise mass and charge balances, reducing rhetorical language (e.g., references to “alchemy,” “zombies,” or scientific misconduct), and engaging more directly with contemporary biochemical evidence supporting mainstream models (including chemiosmotic coupling and mitochondrial proton gradients) rather than dismissing them. Greater structural clarity, schematic summaries comparing classical versus proposed pathways, and formal thermodynamic modeling would substantially improve readability and scientific credibility. With a more measured tone, clearer quantitative validation, and sharper differentiation between conceptual innovation and empirical evidence, the manuscript could contribute meaningfully to theoretical discussions on metabolic organization and non-equilibrium bioenergetics.

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Declarations

Potential competing interests: No potential competing interests to declare.