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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 unconventional reinterpretation of glycolysis and fermentation through non-equilibrium thermodynamics, highlighting proton flow as a central energy entity; however, the manuscript has several weaknesses that limit its scientific robustness and acceptance. First, many claims (e.g., that current glycolysis models violate conservation of mass or thermodynamic laws) are highly controversial and insufficiently supported by quantitative biochemical or experimental evidence; the arguments are largely theoretical and rely heavily on reinterpretation of historical literature rather than modern molecular, kinetic, or metabolomic validation. Second, the methodology is unclear for a review article because it introduces new mechanistic pathways without systematic literature selection criteria, structured comparison with established biochemical models, or critical evaluation of contradictory evidence. Third, the manuscript frequently uses metaphorical or philosophical explanations (e.g., thermodynamic demons, zombies, Newton's apple analogy), which reduces scientific clarity and may confuse readers. Fourth, the proposed biochemical pathways and stoichiometric modifications lack computational modeling, flux balance analysis, or experimental datasets to demonstrate feasibility. To strengthen the article, the authors should incorporate systematic literature review methodology, provide quantitative biochemical modeling or experimental validation, reduce speculative language, directly compare their model with established metabolic flux data, and clarify mechanistic pathways with standardized biochemical terminology and clear diagrams supported by empirical evidence.

Declarations

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Potential competing interests: No potential competing interests to declare.