

Peer Review

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

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This review presents a highly unconventional and ambitious reinterpretation of glycolysis and fermentation through the lens of non-equilibrium thermodynamics, proposing proton-driven energy flow as a central organizing principle of metabolic pathways. The manuscript demonstrates notable scholarly effort, integrates historical biochemical literature, and attempts to unify diverse biological phenomena—including metabolism, signaling, memory formation, and disease—under a common energetic framework. The conceptual perspective is intellectually stimulating and may encourage discussion regarding metabolon organization, lactate metabolism, and proton-coupled transport mechanisms. However, several claims—particularly the assertion that modern glycolytic models violate fundamental physical and chemical laws—are presented with strong language that exceeds the level of experimental or quantitative evidence currently provided. The manuscript would benefit from clearer differentiation between hypothesis-driven theoretical interpretation and experimentally validated biochemical mechanisms, as well as from the inclusion of quantitative thermodynamic modeling or empirical data supporting the proposed proton transport chain and revised stoichiometric relationships. Additionally, some sections rely heavily on philosophical or metaphorical arguments, which may reduce clarity for readers seeking mechanistic or experimentally testable conclusions. Overall, the article offers a provocative theoretical viewpoint with potential interdisciplinary relevance, but its scientific impact would be strengthened by moderating categorical claims, improving clarity, and providing stronger experimental or computational validation of the proposed metabolic model.

Declarations

Potential competing interests: No potential competing interests to declare.