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Peer Review

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

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The reviewed manuscript presents a bold and thought-provoking reevaluation of glycolytic metabolism, challenging long-standing biochemical paradigms with a framework grounded in physics and non-equilibrium thermodynamics. The author argues that contemporary models of glycolysis are in contradiction with foundational scientific laws formulated by Newton and Lavoisier and that early metabolic models, in contrast, were more aligned with natural laws. One of the most striking and innovative claims in the manuscript is the reintroduction of hydrogen, specifically as a redox unit, as a central energy entity driving the Krebs cycle and cellular metabolism more broadly. This concept proposes a radical shift in how we understand metabolic energy flow, moving beyond the classical ATP-centric view toward a model that emphasizes dynamic lactate flow and redox balance.

A key strength of the manuscript is its integrative perspective. By invoking principles from physics, chemistry, and thermodynamics, the author attempts to unify disparate fields under a single metabolic framework. This interdisciplinary approach is timely, especially in light of increasing recognition that metabolism plays a crucial role in diverse physiological and pathological states, including memory formation, obesity, exercise physiology, cancer metabolism, inflammation, and neuropsychiatric disorders such as schizophrenia. This conceptual unification is ambitious and commendable, as it challenges researchers to think beyond siloed biological mechanisms and consider metabolism as a central coordinating process in biology.

Another important contribution of the work is the proposed reinterpretation of lactate not as a waste product, but as a dynamic intermediate with functional and biosynthetic significance. The model emphasizes the continuous non-equilibrium flow of lactate, supporting the notion that lactic acid plays an active role in ATP recovery and energy redistribution. This is in line with emerging literature

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recognizing lactate as a metabolic signal and substrate in its own right, particularly in exercise physiology and cancer biology. The author's emphasis on the dual mitochondrial consumption of both pyruvate and lactate provides a mechanistic insight that may offer explanatory power across multiple biological contexts.

Despite these conceptual advances, the manuscript would benefit from a more detailed and structured presentation of the evidence supporting these claims. While the ideas are intellectually stimulating, many of the assertions are presented as established facts without adequate experimental or literature-based substantiation. For instance, the claim that current glycolysis models violate Newtonian or Lavoisierian principles is not supported with rigorous examples or clear mechanistic explanations. To strengthen the manuscript, the author should more precisely define what these violations entail and provide detailed comparisons with contemporary models.

The manuscript introduces the two-cell model of metabolism as a novel framework, yet it does not clearly delineate how this model is structurally or functionally distinct from the conventional compartmentalized view of cellular metabolism. The operational definition of "two-cell" is somewhat ambiguous—whether this refers to two metabolic states within one cell, two interacting cell types, or a theoretical construct is not immediately evident. A diagrammatic representation or conceptual schematic would greatly enhance clarity and comprehension for readers unfamiliar with the terminology.

In terms of scientific rigor, the manuscript would benefit from clearer differentiation between hypothesis, theory, and established evidence. Some sections make sweeping generalizations—such as the universal regulatory role of the redox unit (2H) or the permanent cellular memory of glycogenolysis —without sufficient empirical grounding. While these ideas are certainly intriguing and may inspire future research, they should be framed more cautiously, possibly as testable hypotheses rather than established principles.

From a methodological perspective, the manuscript lacks a clear description of how the proposed model was developed or validated. There is no mention of computational modeling, experimental validation, or systematic review of the literature. Including such methodological details would enhance the manuscript's scientific credibility and allow readers to assess the robustness of the claims. Furthermore, the incorporation of current experimental findings from metabolomics, redox biology, and mitochondrial dynamics could reinforce the proposed concepts and provide valuable context.

On the stylistic front, the writing is dense and at times opaque. The manuscript would benefit from more accessible language and a clearer organizational structure. Key terms such as "redox unit," "flow non-

equilibrium," and "informational metabolism" require operational definitions to ensure that the narrative is understandable to a broad interdisciplinary audience. Repetition of complex ideas without clear transitions occasionally hinders the flow of the argument.

One opportunity for future development would be to propose specific experimental designs or data types that could be used to validate the claims made in the manuscript. For example, metabolite flux analyses, isotope tracing, or single-cell redox imaging could be valuable tools to investigate dynamic lactate flow or redox storage mechanisms. Collaborations with experimentalists across disciplines could help bring the theoretical model closer to empirical application.

In conclusion, the manuscript presents an original and daring reevaluation of core metabolic processes through the lens of non-equilibrium thermodynamics and redox biology. It introduces several potentially transformative ideas, including the energetic role of hydrogen, the redefinition of lactate's function, and the conceptual unification of biological systems through metabolism. However, to fully realize its impact, the manuscript would benefit from a clearer exposition, stronger empirical grounding, and more precise framing of its theoretical constructs. With these improvements, the work could significantly contribute to the ongoing redefinition of metabolic research in systems biology and medicine.

Declarations

Potential competing interests: No potential competing interests to declare.