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Peer Review

Review of: "The Steady State Approximation in Enzyme Kinetics: Reflections in Its Centennial Year"

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Review Report

Manuscript Title- The Steady State Approximation in Enzyme Kinetics: Reflections in Its Centennial Year

This paper, titled *"The Steady State Approximation in Enzyme Kinetics: Reflections in Its Centennial Year,"* by Eric Barnsley, revisits the quasi-steady state (QSS) approximation introduced by Briggs and Haldane in 1925 for analyzing enzyme-catalyzed reactions. The author critiques the traditional application of the QSS approximation, particularly in reversible reaction schemes where product binding occurs, arguing that it can lead to ambiguities in interpreting kinetic constants like K_m and k_{cat}. Some of my comments are:

1. The article has many grammatical errors. So, they need to make grammatical

corrections to the article.

1. How does this critique affect the interpretation of Michaelis-Menten parameters in modern enzymology, particularly for reversible reactions? Discuss implications for enzyme engineering, drug inhibition studies, or metabolic modeling.
2. Has the author considered performing numerical simulations (e.g., using COPASI or KinTek Explorer) to support analytical claims? Include computational results for Schemes 1 & 2 to reinforce theoretical arguments.
3. How does this work significantly advance beyond previous critiques of the QSS approximation (e.g., Miller & Alberty, 1958; Walter & Morales, 1964)? Clearly state the unique insights of this paper compared to prior literature.

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4. Are the approximations (e.g., neglecting terms in Scheme 1) justified under realistic enzyme kinetics conditions? Include error analysis or sensitivity studies to validate assumptions.
5. Can the author propose specific enzyme systems (e.g., fumarase, invertase) where the revised kinetic constants could be experimentally verified? Suggest testable predictions or cite existing data supporting the revised model.
6. How does this critique affect the interpretation of Michaelis-Menten kinetics in modern biochemistry? Discuss implications for drug design, metabolic modeling, or enzyme engineering.
7. How does this analysis compare to more complex models (e.g., King-Altman, stochastic approaches)? Discuss whether the QSS issue persists in advanced frameworks.
8. If the Haldane Relationship is not universally valid, what thermodynamic constraints should replace it? Propose modified relationships or conditions for validity.
9. Should enzyme kinetics textbooks revise their presentation of the QSS approximation? Recommend specific updates for clarity (e.g., caveats, revised derivations).
10. What are the key limitations (e.g., applicability to multi-substrate enzymes)? Outline unresolved questions and suggest future computational/experimental work.
11. Would the paper benefit from better organization (e.g., subsections, graphical summaries)? Add a conceptual figure comparing QSS vs. equilibrium assumptions.

This paper has strong potential but needs:

1. Clearer novelty claims (vs. past critiques).
2. Numerical/experimental validation (even simulated data).
3. Better structure (subsections, conceptual figures).

Decision: Accept after Minor Revisions

This paper provides a rigorous and timely critique of the quasi-steady state (QSS) approximation in enzyme kinetics, highlighting its limitations in reversible reaction schemes. The author effectively revisits historical assumptions, demonstrates ambiguities in kinetic constants, and challenges the general validity of the Haldane Relationship. While the theoretical analysis is sound, the manuscript would benefit from clarifying its novelty compared to prior work, adding computational or experimental validation, and improving readability with structured subsections and visual aids. Once these revisions are addressed, the paper will make a valuable contribution to the field.

Attachments: available at https://doi.org/10.32388/8LD0PF

Declarations

Potential competing interests: No potential competing interests to declare.