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Peer Review

Review of: "False Assumptions in Derivations of the Henri-Michaelis-Menten Equation When Using the Quasi-Steady-State Assumption"

Paula Alexandra Pinto[1]

1. Universidade de Tras-os-Montes e Alto Douro, Portugal

The manuscript "False Assumptions in Derivations of the Henri-Michaelis-Menten Equation When Using the Quasi-Steady-State Assumption", by Eric Barnsley, constitutes a rigorous theoretical reanalysis that identifies and corrects a historical error attributed to J.B.S. Haldane: in the derivation of the Henri-Michaelis-Menten (HMM) equations for reversible enzymatic reactions under the quasi-steady-state (QSS) approximation, Haldane would have nullified the product concentration (p = 0), which, in fact, converted his analyses into models for irreversible reactions. The author's main conclusion is that, for reversible reactions, the parameters K₀ and k₀ of the HMM equation should, as a general rule, incorporate a term dependent on the product concentration present at the beginning of the QSS (p*), except in special cases (equilibrium of the intermediate or essentially irreversible reaction); This correction implies that classical analytical expressions for determining individual rate constants from experimental kinetic parameters lack generalized validity and that academic textbooks need pedagogical revision.

(Text in progress; approximate references to lines of document v3 from August 12, 2026)

The manuscript presents a valid research question of great historical and pedagogical relevance to enzyme kinetics: verifying the algebraic correctness of Haldane's derivations for reversible reactions (approx. lines 4–5, 10). The title is clear and concise, accurately indicating the theoretical focus of the work. The language is suitable for a specialized audience, although the algebraic density may put off readers less versed in handling differential equations. The main ideas are presented with progressive clarity: in section 2 (approx. lines 10–13), the author dismantles Haldane's error step by step, showing that

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setting p to zero in equations 2–5 converts Scheme 2 into an irreversible model—a flaw in reasoning that, as well argued, persists in textbooks and algorithms (line 10, mention of Cleland). This point is the strong core of the article and is logically well constructed.

In section 3 (approx. lines 13–21), the author presents a correct derivation under QSS, using the conservation of mass a<sub>sub> = a + x + y + p and the approximation a<sub>sub> ≈ a + p (line 15), which is consistent with the classical literature (Briggs & Haldane, Miller & Alberty). The introduction of p* as the product concentration at the "beginning" of the QSS is conceptually valid, and the author is careful to note that p* is not a constant, but depends on a<sub> (line 21). The methodology is, in this sense, described in sufficient detail for algebraic reproduction by expert peers.

However, significant limitations arise. The article is entirely lacking in figures and tables—a notable omission in a theoretical work where diagrams of the mechanisms and graphical representations of the p* vs. K<sub> relationships would greatly facilitate understanding. There is no numerical or experimental validation of the theoretical predictions; the author himself admits that "computations of this complexity are still awaited" (approx. line 28), which weakens the bridge between algebraic correctness and its practical applicability in the laboratory.

A flaw in the reasoning in the discussion lies in the generalization contained in the passage that states that "advances will depend entirely on modern physico-chemical methods" (approx. line 28). Although understandable as the opinion of an experienced researcher, this conclusion does not derive directly from the algebraic derivations presented; it is an interpretative extrapolation that goes beyond the empirical support of the manuscript. Similarly, the statement that "textbooks need revision" (approx. line 27), while reasonable, is not accompanied by a concrete proposal of how this revision should be implemented pedagogically, nor by an estimate of the magnitude of Haldane's error in real-world cases (e.g., simulations showing under what conditions p* is negligible).

The author states that "the consequences of using Haldane's erroneous assumption in analyses of more complex reactions is too broad a subject to be covered here" (approx. line 9), which constitutes an honestly stated limitation of scope, but which leaves the reader without tools to assess whether the error propagates critically in bi-substrate kinetics or inhibition, areas where the author claims the flaw persists (line 10). Regarding statistical controls and tests, they are not applicable in this purely theoretical context, which is acceptable, but it also means that the article does not demonstrate that the proposed correction significantly alters the determination of individual constants in real experimental data. Section 4 (approx. lines 22–23), with the "Scheme 3" and the alternative approach via assemblage (M), is elegant

and pedagogically valuable, but the identification of f<sub> and f<sub> requires, as the author notes, a return to the algebra of section 3, which limits its usefulness as a didactic shortcut.

The references are, in general, adequate and cover essential historical sources (Henri, Michaelis-Menten, Haldane, Briggs-Haldane, Van Slyke-Cullen) and contemporary works (Johnson, Choi et al.). No excessive or inappropriate citations are detected.

In short, the manuscript is a valuable and courageous theoretical exercise that corrects a centuries-old error with algebraic rigor. Its strengths lie in the clarity of the identification of the historical error and in the proposal of an alternative derivation. Its main weaknesses are the absence of numerical or experimental support, the lack of figures, and some generalisations in the discussion that extrapolate beyond the direct support of the theoretical results presented. To reinforce its impact, validation through computational simulation and a quantitative discussion of the practical magnitude of the p* term under typical enzymological conditions would be desirable.

Declarations

Potential competing interests: No potential competing interests to declare.