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This Week's Citation Classic™

Lineweaver H & Burk D. The determination of enzyme dissociation constants. *J. Amer. Chem. Soc.* **56**:658-66, 1934.
[Fertilizer Investigations Unit, Bureau of Chemistry and Soils, US Dept. Agriculture, Washington, DC]

Graphical methods are given for interpreting enzyme kinetic data in terms of postulated mechanisms and for obtaining characterizing enzyme-substrate and enzyme-inhibition dissociation constants. Kinetic equations resulting from postulated mechanisms are transposed into a form that gives linear graphs that can be readily extrapolated to yield the constants. [The *SCI*® indicates that this paper has been explicitly cited in over 8,000 publications since 1955.]

Hans Lineweaver
7045 Oak Leaf Drive
Santa Rosa, CA 95405

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The seed for this publication came from a course in contact (heterogeneous) catalysts being taught by Paul H. Emmett at George Washington University, where I was attending evening classes leading to a master's degree. He showed how kinetic data could be plotted in linear form to test hypotheses for catalytic mechanisms that involved adsorption of gases on catalytic surfaces. I noted the similarity of the classical Langmuir adsorption isotherm to the Michaelis-Menten[1] equation, $v = V_{max}(S)/(K_s + S)$, for enzyme action, and realized that similar linear test plots could be made of enzyme kinetic data to test hypotheses and to evaluate characterizing constants of enzymes. Burk, whom I was assisting in looking for enzymes involved in nitrogen fixation by the bacterium *Azotobacter*, suggested publication when I showed him how this could be done. At his insistence and with his considerable help, the paper was submitted to the *Journal of the American Chemical Society*, where it was rejected on the basis of the comments of three referees. The editor, Arthur B. Lamb, wrote: "In happier times, when we had a reasonable amount of space, I would have been inclined to accept this manuscript in spite of the lack of enthusiasm which these referees evince.... Please do not hesitate, however, to send me such rebuttals or any other comments you may care to make." Rebuttals and improvements were made in the manuscript, which was resubmitted and sent to three additional referees who were also unenthusiastic about the manuscript. However, Lamb commented that editorial privilege allowed him to accept it.

Of the three linear transformations that can be made of the Michaelis-Menten equation, the double-reciprocal plot ($1/v$ *vs.* $1/S$), frequently referred to as the Lineweaver-Burk plot or simply the double-reciprocal plot, has remained most popular.[2-4] Burk[2] recently discussed the three linear transformations along with historical comments about our paper after 50 years. It remains important that adequate attention be paid to changes in weighting that occur when transformations are made, especially if the error at individual substrate concentrations is high.

Why the many citations? The paper revealed no new fundamental concepts or profound results. It did describe, with examples, a simple treatment of enzyme kinetic data that yielded straight-line plots if the data are consistent with a postulated mechanism, and these can be extrapolated easily to yield characterizing constants of the enzyme. I like to think that its popularity and use in textbooks[3,4] is partly because it includes rather thorough yet concise comments naming limitations and precautions (not always applied by investigators) that must be considered when interpretations are drawn from the manipulation of kinetic data. It was perhaps serendipity that the paper was timely, having appeared just after interest in enzyme research was increased by the Nobel Prize-winning proof of John Northrop, Wendell Stanley, and James Sumner that enzymes are proteins rather than some phantom substance.

1. **Michaelis L & Menten M L.** Die Kinetik der Invertinwirkung. *Biochem. Z.* 49:333-69. 1913. (Cited 900 times since 1955.)
2. **Burk D.** Enzyme kinetic constants: the double reciprocal plot. *Trends Biochem. Sci.* 9:202-4, 1984.
3. **Lehninger A L.** *Principles of biochemistry.* New York: Worth, 1982. p. 213-17.
4. **Schwimmer S.** *Source book of food enzymology.* Westport, CT: AVI, 1981. 967 p.