The Biophysicist

Research on Students' Understanding of Michaelis-Menten Kinetics and Enzyme Inhibition: Implications for Instruction and Learning

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ABSTRACT We report a summary of the results from an education research project that investigated student reasoning related to Michaelis-Menten enzyme kinetics and enzyme inhibition. We have previously discussed students' mathematical reasoning related to rate laws and reaction order, student conceptions of different types of enzyme inhibition (competitive, noncompetitive, and uncompetitive), and student understanding of representations used to describe enzyme kinetics (Michaelis-Menten graphs, Lineweaver-Burk plots, reaction schemes). In this paper, we bring together the different publications that resulted from this project to emphasize the implications for instruction gleaned from each study and discuss the additional insight provided by synthesizing the results across studies. For this work, the results from this project have been framed according to the refined consensus model of pedagogical content knowledge, a framework from science education that defines the knowledge and skills needed to transform content knowledge into teaching.

KEY WORDS enzyme kinetics; chemistry education research; general audience

I. INTRODUCTION

As indicated in a topical literature review related to research on the teaching and learning of chemical kinetics, most work has been carried out in a general chemistry context with an emphasis on identifying students' alternative conceptions (1). On the basis of this body of research, students need more support regarding the empirical nature of rate laws and reaction order (2–6), they tend to conflate chemical kinetics and equilibrium ideas (2, 3, 7–9), and they have difficulty with graphical depictions of rate (4, 5, 8–10). As discussed by Becker et al. (2), a contributing factor associated with students' challenges when using these mathematical models lies in a need to use metamodeling ideas more productively, such as understanding the nature and purpose of models and having an appreciation for the role of testing and evaluating models. However, attributing these metamodeling ideas to equations and graphs is unlikely if students do not view them as models (11).

Focusing more specifically on mathematical models such as graphs across the physical sciences, interpreting the information provided in a graphical representation is complex, with mathematical ability and contextual complexity serving as potential barriers for students (12–15). Moreover, students tend to focus on and cue into surface features

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of graphs, such as an overemphasis on the shape of the graph (16) or inappropriately attributing time to the *x*-axis (17). There is a similar trend observed in the mathematics education research literature, in which students impose time on functions that did not have time as the independent variable (18). Focusing on the context of chemical kinetics, research indicates students have difficulty drawing connections between the particulate-level mechanism and the information represented in a graph (4, 5, 8–10, 19). Further compounding the issue, graphical representations used in chemical kinetics may be a source of anxiety for students (19), and the presentation of chemical kinetics concepts in textbooks do not adequately support students in drawing connections (20–22).

Relevant for the work discussed in this paper is the recent movement toward more chemistry education research carried out in upper-division contexts on advanced topics. However, most work has still been contextualized in general chemistry courses, suggesting the need for more research that provides insight regarding how to enhance and improve the teaching and learning of advanced topics in the chemistry curriculum (23, 24). In particular, chemical kinetics and enzyme kinetics have been identified as understudied topics in the growing body of education literature (1). A review of the literature reveals a large library of resources to help practitioners support student learning related to enzyme kinetics: (a) analogies that use familiar contexts to describe enzyme-substrate interactions, catalysis, and other facets of enzyme kinetics (25–36); (b) suggestions for framing and contextualizing enzyme kinetics content (33, 37–43); (c) laboratory experiments involving the collection of enzyme kinetics data and determining kinetics parameters (44–50); and (d) examples of software to generate enzyme kinetics data and model related processes (51–59). Despite the myriad of resources available, there is a lack of research to support claims regarding the efficacy of these resources, and the extent to which they influence student learning requires further evaluation. Nevertheless, a few contributions from the literature relate to particular topics that are relevant for this discussion. For example, previous work indicates students tend to focus on formal definitions of catalysts, evoking discussions of activation energy and increasing the rate of the reaction, but they tend to have difficulty drawing connections to how catalysts physically interact at the particulate level (4, 8, 9, 60). On a related note, students also tend to have difficulty reasoning about ideas related to enzyme-substrate interactions, such as the role of charge and shape (61–63). Therefore, students can be expected to find it challenging to discuss the physical mechanisms related to enzyme kinetics at the molecular level and relate it to mathematical models or macroscopic observations.

Building on our recent work in chemical kinetics that emphasized students' mathematical reasoning during problem solving (7, 16, 60, 64–66)—tersely summarized in a recent book chapter (67)—here, we focus on students' understanding of enzyme kinetics, guided by the overarching research question: *How do students reason about enzyme kinetics?* Addressing this question involves a brief overview of the themes that emerged from our enzyme kinetics project, which focused on students' mathematical reasoning related to rate laws and reaction order (68), student conceptions of enzyme inhibition and the associated mechanisms (69), and student understanding of representations such as Michaelis-Menten graphs, Lineweaver-Burk plots, and reaction schemes (70). After providing an overview of the results, we focus on the implications this work has for improving the teaching and learning of chemistry, using the refined consensus model of pedagogical content knowledge to frame the results for practitioners. All aspects of this project were completed in accordance with and were approved by Purdue University's Institutional Review Board.

II. PEDAGOGICAL CONTENT KNOWLEDGE

As originally described by Shulman (71), pedagogical content knowledge (PCK) is the knowledge that transforms discipline-specific

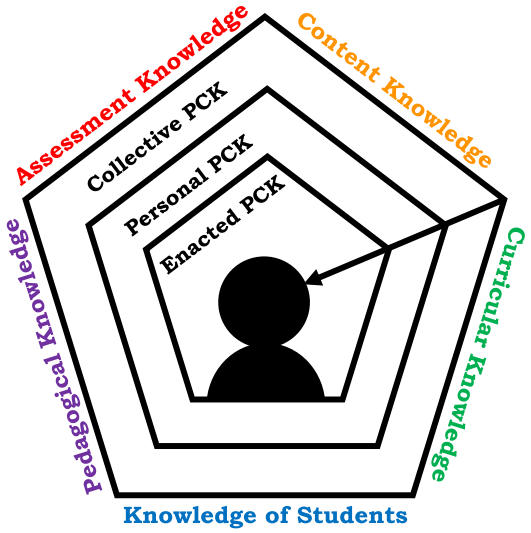


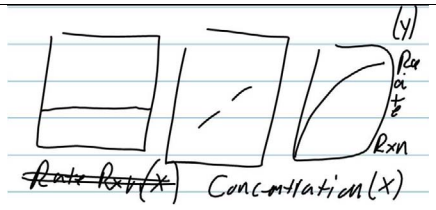
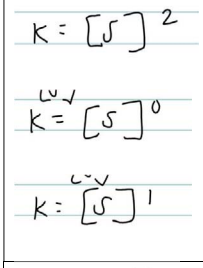
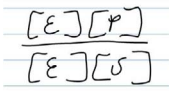
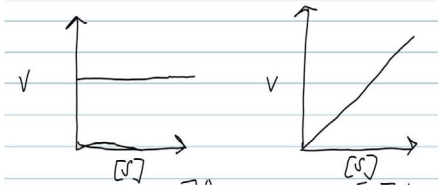
Fig 1. The refined consensus model of pedagogical content knowledge. Within the model, different knowledge bases comprise PCK, with the arrow highlighting the importance of moving knowledge from the community (collective PCK) to an individual instructor (personal and enacted PCK); reproduced from Rodriguez and Towns (83) with permission from the American Chemical Society.

content into effective teaching, an idea based on the observation that knowing the content is not enough to be able to teach and help students learn the content. Throughout the literature, multiple models for PCK have been described and used in a variety of contexts to frame research studies that focused on characterizing PCK and supporting instructors' development of PCK (72); many of these types of studies exist in chemistry education (73–81). More recently, an updated model of PCK has been presented, called the *refined consensus model of PCK* (82). This model describes the different knowledge bases that comprise PCK: (a) assessment knowledge, knowledge related to designing and taking action on the basis of formative and summative assessments; (b) content knowledge, knowledge related to key ideas in a discipline (disciplinary expertise); (c) curricular knowledge, knowledge related to the sequence and structure of a curriculum; (d) knowledge of students, knowledge related to students' understanding and associated challenges with a topic; and (e) pedagogical knowledge, general knowledge related to instruction and the classroom (72). Additionally, the refined consensus model of PCK characterizes 3 realms with respect to where the knowledge resides: collective PCK, knowledge held by a community; personal PCK, knowledge held by an individual; and enacted PCK, the application of an individual's personal PCK during planning, teaching, and reflecting (82). A summary of the refined consensus model of PCK is provided in Figure 1. For clarity, the research discussed in this paper was not designed within the PCK framework; rather, PCK was used to help frame the results and make the implications more practical for instructors (e.g., How does this research influence our assessment knowledge? How does this research influence our knowledge of students?) (83).

III. OVERVIEW OF RESULTS

This section provides a brief overview of the results of our research project, which will provide context for the discussion regarding how to improve instruction related to enzyme kinetics. The first paper reported describes students' mathematical reasoning related to rate laws and reaction order. The second paper presents the results regarding students' conceptualization of competitive, noncompetitive, and uncompetitive enzyme inhibition. In the final paper discussed, emphasis is placed on students' understanding of Michaelis-Menten graphs, Lineweaver-Burk plots, and reaction schemes. The data for this project came from semistructured interviews with second-year students ($n = 14$) in an introductory biochemistry course offered by a chemistry department at a large, research-intensive university in the Midwestern United States. During the interviews, students were provided a Michaelis-Menten graph, a reaction scheme, and a graph depicting enzyme inhibition; these were used as an opportunity to investigate students' reasoning related to enzyme kinetics. For more information regarding the methods, data collection, and analysis associated with this project, we direct readers to the individual papers cited and summarized in the following sections.

Table 1. Student reasoning about rate laws and reaction order.

Student	Rate Law	Reaction Order
Tim		
Claire	 	

A. Analyzing mathematical reasoning related to enzyme kinetics

When provided the Michaelis-Menten graph, students were asked additional follow-up questions, such as *What is reaction order? What are rate laws? How is that related to enzyme kinetics?* The student responses to these prompts are discussed in more detail in Rodriguez et al. (68). In short, student discussions of rate laws primarily involved surface-level connections, in which 4 of the 14 students tended to have an algebraic understanding of the rate law (rate = $k[A]^a$), focusing on the general surface features of the equation ($\square = \square\square^{\square}$). For example, as shown in Table 1, students Tim and Claire wrote equations that had a similar pattern to that of the rate law and had some of the expected terms, but the order of terms was mismatched. Similarly, when discussing the rate law, Claire also focused on surface-level features and wrote something reminiscent of an equilibrium expression. It should be noted that conflation of chemical kinetics and equilibrium ideas has been previously reported in the literature, such as confusing *rate laws* and *equilibrium expressions* or *rate* and *extent* (2, 7–9). Analogous to students' reasoning about rate laws, when discussing reaction order (Table 1), 5 of the 14 students focused on the pattern in the graph, associating the different orders with different graphical shapes with features such as the axis labels being prompted by the interviewer. The students' emphasis on the surface features of the equation and graphs limited their ability to draw connections to enzyme kinetics. The results of this study suggest students need more support integrating chemistry ideas with equations and graphs and viewing these representations as models of phenomena (11).

B. Characterizing student conceptions of enzyme inhibition

In another paper related to this dataset, emphasis was placed on student reasoning about the different inhibition types, including competitive inhibition, noncompetitive inhibition, and uncompetitive inhibition (69). For this analysis, *resource graphs* were used to indicate the connections between the ideas discussed by the students (84). For example, consider Lex

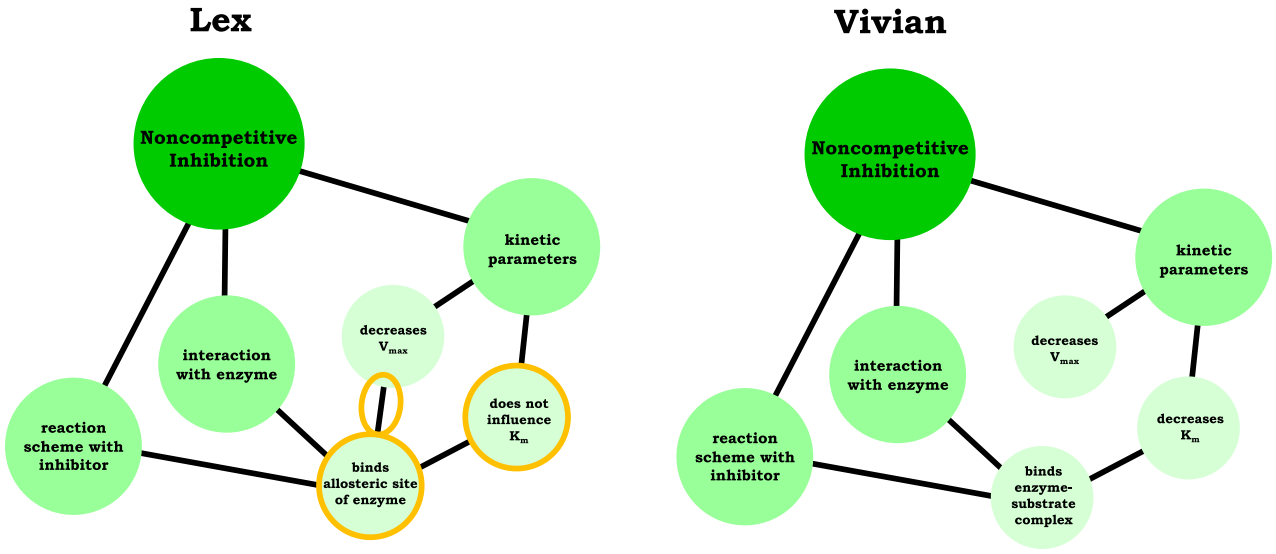


Fig 2. Comparison of Lex and Vivian's resource graphs; the differences between the graphs are highlighted in gold on Lex's resource graph.

and Vivian's resource graphs (Fig 2). Note that they had different ideas regarding how noncompetitive inhibitors bind and influence K_m: Lex stated noncompetitive inhibitors bind the allosteric site and do not influence K_m, whereas Vivian stated that noncompetitive inhibitors bind the enzyme-substrate complex and decrease K_m. Moreover, Lex's discussion reflected more sophisticated reasoning, drawing connections between the mechanism of binding and the changing kinetic parameters—Vivian, on the other hand, had more fragmented reasoning. We noted general trends in this study by comparing the resource graphs for each inhibition type for each student. By focusing on the ideas students discussed and the connections they made, one of the main themes that emerged was that students were able to attend to changing parameters when provided a Michaelis-Menten plot exhibiting enzyme inhibition and associate the correct changing parameters with an inhibition type. However, students had difficulty drawing connections between the particulate-level mechanism of enzyme-inhibitor binding and the changing parameters; for example, addressing the question: *Why does a competitive inhibitor increase K_m but not affect V_{max}?* Responding to this type of question involves more than simply memorizing and associating vocabulary terms with changing parameters, requiring students to bridge macroscopic observations related to measured changes in V_{max} and K_m with molecular interactions and behavior (i.e., location of inhibitor and substrate binding sites). Because of the similarly sounding names, it was also noted that students tended to conflate noncompetitive and uncompetitive inhibition, suggesting the need for more instructional support regarding the distinction between inhibition types.

C. Investigating student understanding of representations in enzyme kinetics

In the final paper published for this project, themes were discussed related to how students described the Michaelis-Menten graph, Lineweaver-Burk plot, and reaction scheme (i.e., $E + S \rightleftharpoons ES \rightarrow E + P$) (70). With respect to the Michaelis-Menten graphs, it was noted that 4 of the students in the sample implicitly or explicitly attributed *time* to the *x*-axis, with similar results discussed in other research related to students' understanding of reaction coordinate diagrams (17). More broadly in the mathematics education community, research has also noted students' tendency to impose time on functions not involving time (18). On a related note, 8 of the students (unprompted) mentioned V_0 (the graphs in the interview

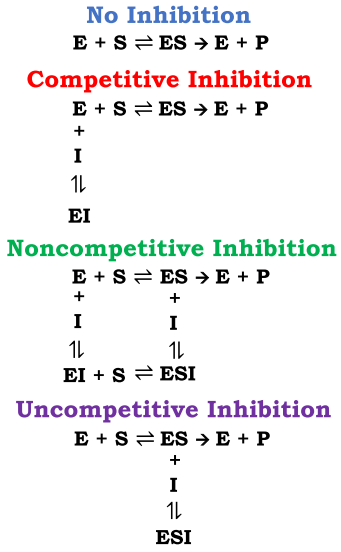


Fig 3. Reaction schemes in the presence of different inhibition types; adapted from Rodriguez et al. (70) with permission from the American Chemical Society.

prompts had V on the y-axis, not V_0), but further probing indicated students were unsure why it was labeled *initial velocity*, simply recalling seeing V_0 on graphs from class. Part of the confusion lay in the fact that an initial value such as V_0 or t_0 is typically a single value that is used as a constant, but in the Michaelis-Menten graph it is used as the dependent variable. For students to reconcile these ideas, they have to understand the process of constructing a Michaelis-Menten graph, in which each point corresponds to an initial velocity value for a [Product] vs. time graph carried out under specific conditions. Although students were not asked in the interviews about Lineweaver-Burk plots, with the exception of one student, all the students in the sample discussed the reciprocal relationship represented in Lineweaver-Burk plots. Furthermore, the students tended to discuss the utility of Lineweaver-Burk plots for determining the changes in kinetic parameters and identifying inhibition types. Lastly, when students discussed the reaction scheme, they tended to have difficulty regarding how the different inhibitors influenced the reaction scheme, with only a few students writing reaction schemes that were consistent with those presented in Figure 3.

IV. IMPLICATIONS FOR INSTRUCTION

In this section, the implications for instruction are discussed based on the results of our research. We find it useful to frame the implications for research within the professional knowledge bases related to the refined consensus model of PCK: assessment knowledge, content knowledge, curricular knowledge, knowledge of students, and pedagogical knowledge (83). For the purposes of this paper, we posit that the different knowledge bases are dynamic, in the sense that the different categories of knowledge overlap and interact; thus, representation of ideas is more important than strictly attempting to assign an idea or implication to a specific knowledge base. Moreover, in terms of considering how this research can be translated into the classroom, a logical progression of ideas involves first providing an overview of the topics with which students had challenges (i.e., knowledge of students), because the results of the overview serve as a context to consider how instruction can address these challenges. This discussion will then be followed by the implications of the research for pedagogical knowledge. Next, the implications will be discussed for the scope of the content presented and its relationship to the larger educational context (content knowledge and curricular knowledge, respectively). Finally, a discussion of the implications for assessment knowledge will be provided. Assessment was intentionally selected to discuss last because it naturally builds on the topics discussed in the other sections.

A. Knowledge of students: In what ways do students need more support?

The *knowledge of students* professional knowledge base involves considerations related to topics that provide difficulty for students, which were discussed above in relation to the outcomes of our research. In Table 2, we summarized the results related to ways in which students need more support. Looking

Table 2. Implications for instruction related to the professional knowledge base *knowledge of students*.

Knowledge of Students: In what ways do students need more support?	
Analyzing mathematical reasoning related to enzyme kinetics	• Relating reaction order and rate laws to enzyme kinetics • Integrating chemistry ideas with equations and graphs
Characterizing student conceptions of enzyme inhibition	• Drawing connections between changing kinetic parameters and particulate-level mechanism • Differentiating between inhibition types
Investigating student understanding of representations in enzyme kinetics	• Reasoning about how the Michaelis-Menten graph is constructed • Describing how inhibitors influence the reaction scheme

at the results across the different studies together, 2 larger themes emerge. First, students tended to have difficulty combining chemistry and mathematics ideas, focusing more on surface features of mathematical representations. We do not mean to imply that students do not have access to the appropriate ideas relevant for making connections, rather we posit that students' reasoning tends to be compartmentalized or siloed (67). Second, the way in which information is presented in biochemistry is distinct from its presentation and representation in general chemistry, which can be challenging for students. In some ways this is an issue of retention (focusing on the extent to which students remember the concepts they learned in general chemistry), but for students to draw connections with previous material, they have to recognize that they have seen the material previously, which is closely related to what is emphasized and assessed (85). As an additional note, it is important to keep in mind that it is not enough to simply know that students need more support with specific topics; the key point is finding ways to use this knowledge to influence and guide instruction. Practical suggestions based on this work are provided in the subsequent sections.

B. Pedagogical knowledge: What general knowledge may be useful for teaching?

Pedagogical knowledge can be framed as the general knowledge related to presenting content and managing a classroom, but it also involves theories related to learning. The research discussed in this paper was informed by the resource-based model of cognition, which emphasizes the manifold nature of cognitive structure and the context dependence of resources used to answer a question (86). This framework has important implications for instruction in the way it shifts the focus from what students do not know toward what students do know (87). Stated differently, the goal of instruction is not to identify and replace misconceptions; rather, the goal is to determine how students' ideas can be used productively. This shift requires intentionality and creativity in designing instructional activities, prompts, and assessment items that have the proper scaffolding to support students in cuing into relevant features and the productive use of cognitive resources (2, 88). Additionally, one other aspect of pedagogical knowledge involves providing alternative ways to frame and discuss content, such as the use of analogies. From the findings of this research, we designed an analogy to help students distinguish between the different inhibition types (89). One way to help students distinguish between the different mechanisms associated with inhibition is to use an analogy, framed as a race, in which each inhibitor plays by its own set of rules (i.e., binding conditions) to cross the finish line and win the prize (i.e., bind the enzyme). An overview of the analogy is provided in Figure 4.

C. Content knowledge: What are some ideas that should be emphasized?

One of the key considerations related to the *content knowledge* professional knowledge base is deciding how much detail to provide for a given topic. In recent efforts by the American Chemical Society Examinations Institute, summaries have been provided regarding the content that is relevant for general chemistry (90, 91), organic chemistry (92),

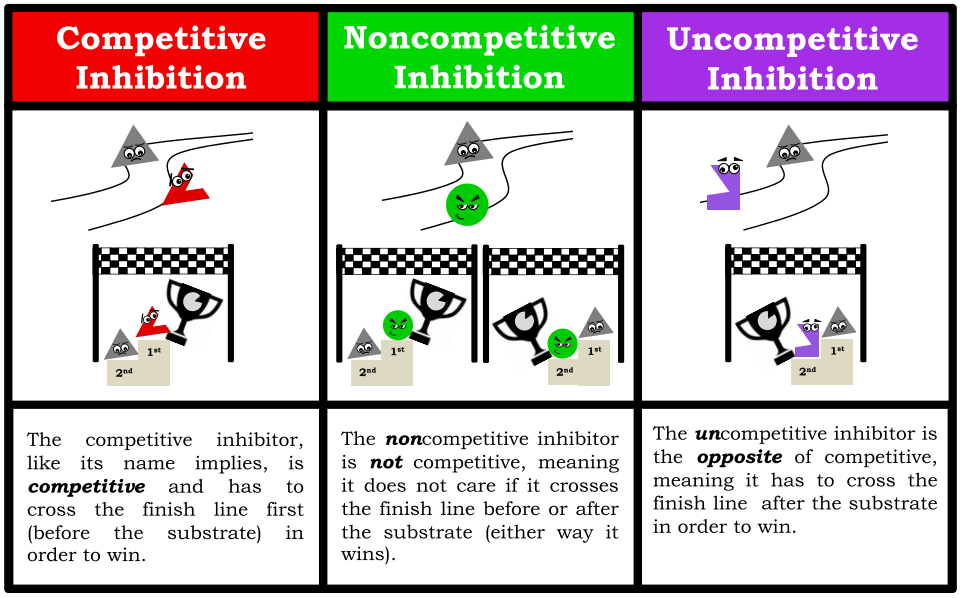


Fig 4. Analogy to help students distinguish between different inhibition types; figure reproduced from Rodriguez and Towns (89) with permission from the American Chemical Society.

inorganic chemistry (93), and physical chemistry (94), with biochemistry likely to be released in the near future. However, the overview of content provided is more descriptive than prescriptive, without formal statements regarding the necessary level of detail that should be discussed in a given course. Nevertheless, chemistry education research provides an avenue for evidence-based recommendations of *how* to teach and *what* to teach. In the context of a curriculum that is already dense with content, we recommend focusing on (i.e., assessing) fewer inhibition types. As is the case with typical biochemistry courses, the students in this study learned about competitive, noncompetitive, uncompetitive, and mixed inhibition (mixed inhibition was not emphasized in this project). The danger with presenting too much content is that exam questions tend to revolve around associating inhibition types with changing parameters, without requiring deeper levels of reasoning. If students were assessed on their ability to reason about fewer inhibition types, there would be space for students to make connections and comparisons and to prompt them with questions that

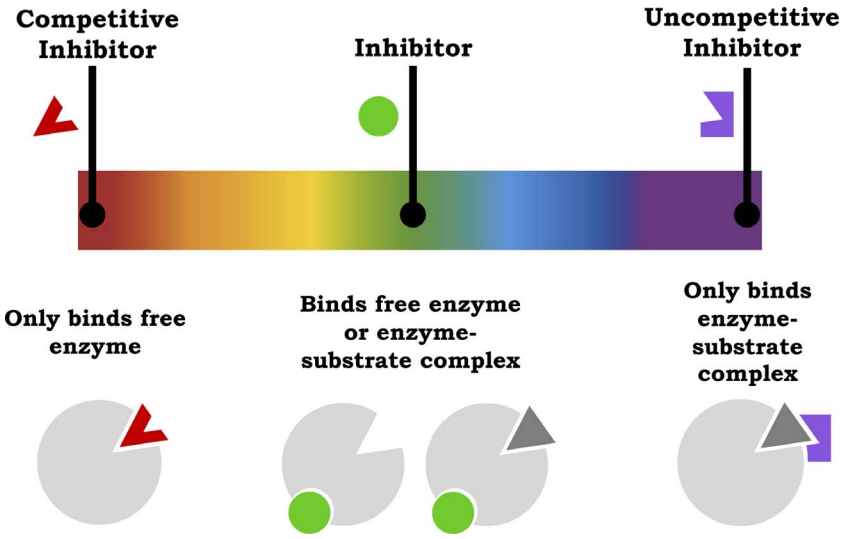


Fig 5. Enzyme inhibition can be framed as a spectrum with competitive, noncompetitive, and uncompetitive being special points on this continuum; figure reproduced from Rodriguez and Towns (69) with permission from the Royal Society of Chemistry.

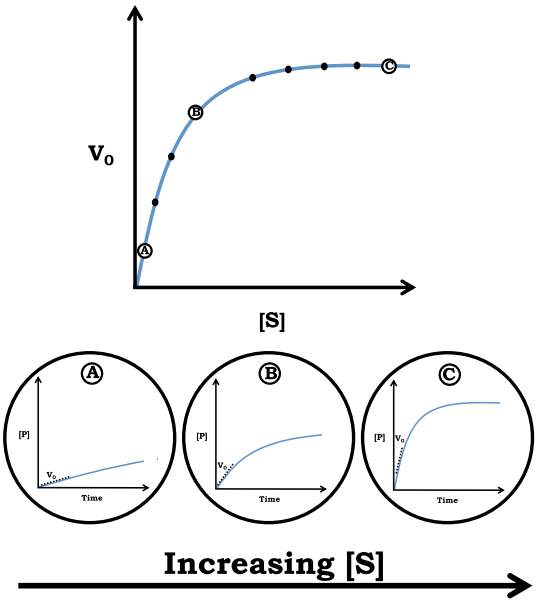


Fig 6. The Michaelis-Menten plot is a unique opportunity to discuss data collection and how it is represented with each point on the Michaelis-Menten graph corresponding to a set of kinetics data collected under varying substrate concentrations; figure reproduced from Rodriguez et al. (70) with permission from the American Chemical Society.

move beyond memorization. Additionally, when discussing enzyme inhibition, we suggest framing inhibition as a spectrum, in which inhibitors exhibit some affinity for both the free enzyme and the enzyme-inhibition complex, where competitive, noncompetitive, and uncompetitive inhibitors are simply special cases along this continuum (Fig 5). Lastly, we argue for the importance of discussing the construction of the Michaelis-Menten plot in more detail, because it provides an excellent opportunity for students to analyze and interpret data and develop a more sophisticated understanding of what is being modeled in the graph (Fig 6).

D. Curricular knowledge: How does enzyme kinetics relate to other topics?

Curricular knowledge allows instructors to place their course in the context of all the other courses students have taken and will take. Building on the idea of Michaelis-Menten graph construction from the previous section, the Michaelis-Menten graph encodes kinetics data in a way that is different from the kinetics graphs students typically see in general chemistry (Fig 7), which likely contributes to student difficulty in drawing connections between rate laws, reaction order, and enzyme kinetics (Fig 8). On a related note, the reaction scheme illustrating the mechanism between enzyme and substrate is different from how students were presented related content in general chemistry (Fig 9). Instructors should not assume

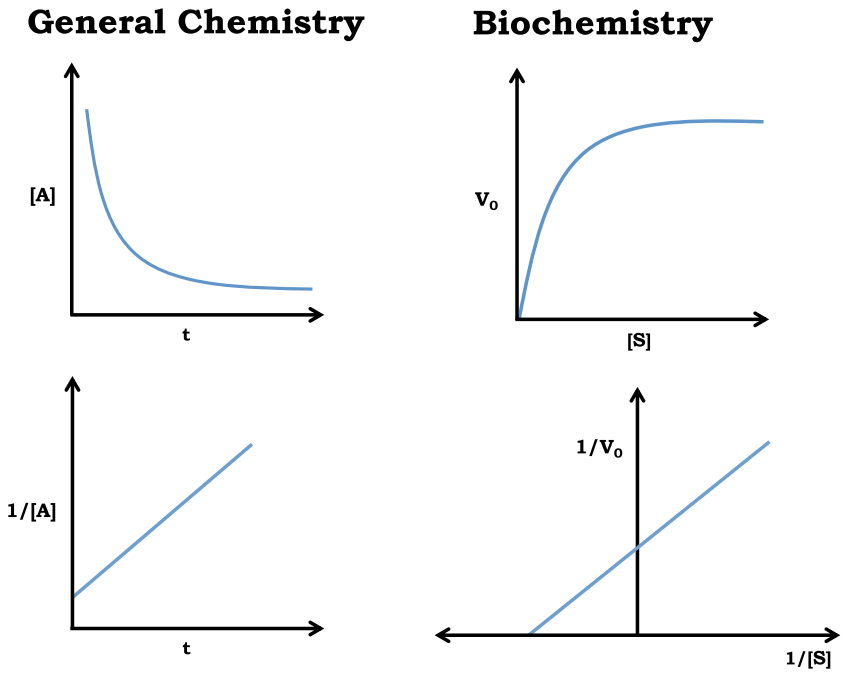


Fig 7. The way kinetics data are represented and discussed in biochemistry courses is distinct from its presentation in general chemistry; careful attention should be given to emphasizing these distinctions.

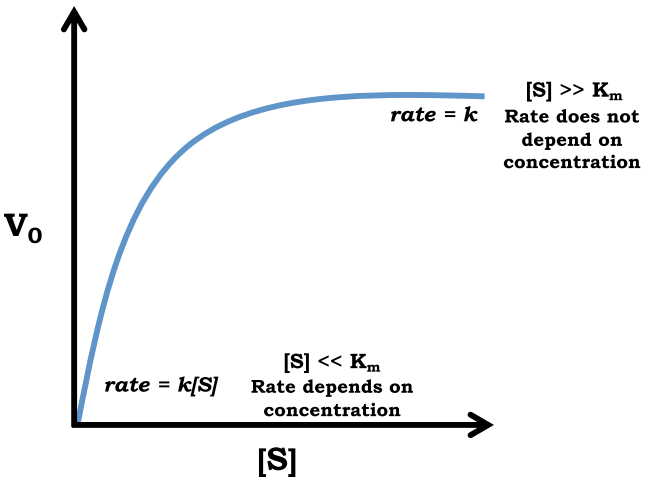


Fig 8. Students learn about rate laws and reaction order in general chemistry; in biochemistry, connections should be drawn between these ideas and enzyme kinetics.

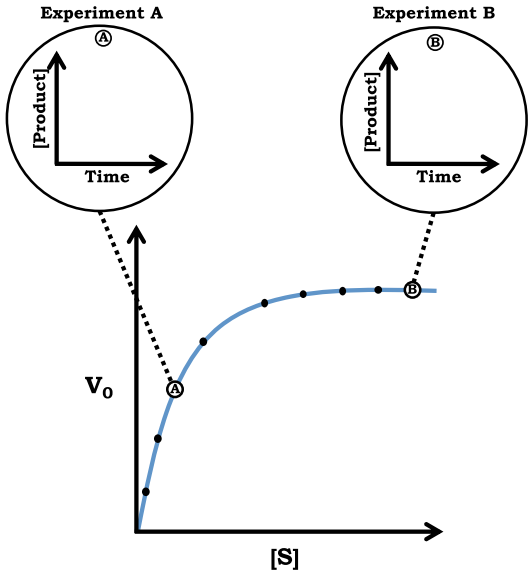
students are making these connections and should design instruction to support students in developing a more coherent and sophisticated understanding of the content.

E. Assessment knowledge: What are some specific assessment questions?

The role of assessment cannot be understated, because instructors communicate what is important when they place it on an exam (95). Therefore, if we want students to be able to draw connections between concepts across the curriculum (e.g., reaction order and enzyme kinetics) instructors have to be intentional about what they assess. One example of an exam question is based on making a simple change in wording for free response questions, which has a large effect on what the student is being asked to do—memorize changing parameters associated with inhibition types (e.g., *How does a competitive inhibitor influence* K_m?

General Chemistry	Biochemistry
(1) $E + S \rightleftharpoons ES$	$E + S \rightleftharpoons ES \rightarrow E + P$
(2) $ES \rightarrow E + P$	

Fig 9. The way in which reaction mechanisms are represented and discussed is different from their presentation in biochemistry; connections between different ways of representing the same phenomena should be made explicit.



(a) Using the space provided, draw the [Product] vs. Time graphs that correspond to Point A and Point B.
(b) Label V_0 on the graphs you drew in (a).
(c) Compare the relative amount of free enzyme (E) and enzyme-substrate complex (ES) at Point B. Which species has a higher concentration at Point B. Explain your reasoning.

Fig 10. Potential assessment question related to the construction of the Michaelis-Menten graph; figure reproduced from Rodriguez *et al.* (70) with permission from the American Chemical Society.

How does a noncompetitive inhibitor influence K_m)—or provide a particulate-level description of phenomena (e.g., *Why does a competitive inhibitor increase the* K_m *value but a noncompetitive inhibitor does not influence the* K_m *value?*). In Figures 10–12, some additional assessment questions for enzyme kinetics have been provided that were designed to address the ideas discussed in this paper. As shown in Figure 10, the task prompts students to consider how the Michaelis-Menten graph is constructed and reason through the implications for different points on the graph. In Figure 11, the different reaction schemes are presented, and rather than having the students draw them, students are prompted to use their understanding of the binding mechanism to consider which reactions would occur under the conditions provided. Figure 12 provides a graph that is closer to what students may have seen in general chemistry; it requires them to reason about the definition of rate and how

Different solutions containing enzyme, substrate, and inhibitors were prepared. For each of the conditions listed below indicate the reactions that occur in the solution. The first one, in which there is no inhibitor present, has been completed for you.

No Inhibition	
✓	E + S ⇌ ES
✓	ES → E + P
	E + I ⇌ EI
	ES + I ⇌ ESI

Competitive Inhibition	
	E + S ⇌ ES
	ES → E + P
	E + I ⇌ EI
	ES + I ⇌ ESI

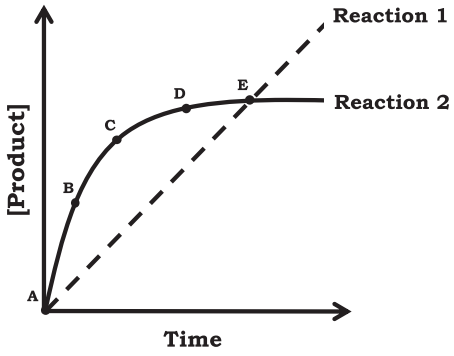
Noncompetitive Inhibition	
	E + S ⇌ ES
	ES → E + P
	E + I ⇌ EI
	ES + I ⇌ ESI

Fig 11. Potential assessment question related to student understanding of the reaction schemes.

concentration dependence dictates reaction order, which is determined empirically.

V. CONCLUSION

Although enzyme kinetics is a challenging topic for students, it serves as an opportunity to draw connections to students' prior knowledge and relate empirical data with particulate-level phenomena. This paper was not intended to be a comprehensive overview of our enzyme kinetics project; rather, the main focus was on how the research could be translated into classroom practice, aided by the PCK framework. To practitioners, we encourage the use of the resources provided in this paper, and it should be noted that the assessment items do not necessarily have to be used on an exam. The example assessment questions could also be used for different contexts, such as small group activities, in-class discussions, iClicker questions (an electronic student response system used in classrooms), homework assignments, and so on. Additionally, to researchers, we found the PCK framework to be a useful lens, and we suggest researchers use the PCK framework, not necessarily in the design of a study, but to help structure and frame the implications for instructors.



(a) Circle the point on the graph (A, B, C, D, E) where the rates of Reaction 1 and Reaction 2 are the same. Explain your reasoning for the point you selected.

(b) What conclusions can be made about the reaction order for Reaction 1? Explain your reasoning. Your response should draw a connection between the data and reaction order.

Fig 12. Potential assessment question related to reaction rate and order; figure adapted from Rodriguez and Towns (83) with permission from the American Chemical Society.

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AUTHOR CONTRIBUTIONS

J-MGR designed the research; collected, analyzed, and interpreted the data; wrote the manuscript; and created the figures. MHT designed the research, discussed the analysis and interpretation of the data, and edited the manuscript.

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